# Director's Report to the National Advisory Council on Drug Abuse - September, 2008

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## Research Findings - Cross-Divisional Research

### A NIDA DBNBR and DESPR Cross-Divisional Supported Study Highlights the CHRNA5-A3-B4 Region is a Risk Factor for Age-Dependent Nicotine Addiction

The research examined the hypothesis that associations between nicotinic acetylcholine receptor subunit gene variants and nicotine dependence assessed in adulthood would be stronger among smokers who began daily nicotine exposure during adolescence. This group examined 2,827 subjects from three European American cohorts with a mean age of 49.6 years. All were either current or previous daily cigarette smokers, with only 8% who had not smoked for at least 2 years prior to the study. Participants began daily smoking at a mean age of 17.3 and smoked 28.3 cigarettes per day for a mean of 30.7 years. The mean Fagerstrom Test of Nicotine Dependence test score was 5.7. Smokers were dichotomized into Òearly onsetÓ (age 16 or younger) and Òlate onsetÓ (age 17 or older). Using a candidate gene approach, the SNP panel screen included common coding variants and haplotypes detected in eight alpha and three beta nicotinic subunit receptor genes. Of the 2,827 long-term smokers examined, common susceptibility and protective haplotypes at the chromosome 15 CHRNA5-A3-B4 locus were associated with nicotine dependence severity (OR=1.82; 95%CI 1.39-2.39, p=2 x 10-5) in subjects who began daily smoking at or before the age of 16. This effect was not seen in subjects who began daily smoking after the age of 16, marking a period of exposure vulnerability that results in a more severe form of adult nicotine dependence. The interaction of a common genetic risk factor, age, and onset of daily smoking supports the notion that it is important to understand gene x environment x development factors. This finding needs independent replication, but it points to how genetic studies of complex disease phenotypes can bolster public health approaches to disorders such as addictions, because the risk is amenable to both intervention and prevention. Weiss, R.B., Baker, T.B., Cannon, D.S., von Niederhausern, A., Dunn, D.M., Matsunami, N., Singh, N.A., Baird, L., Coon, H., McMahon, W.M., Piper, M.E., Fiore, M.C., Scholand, M.B., Connett, J.E., Kanner, R.E., Gahring, L.C., Rogers, S.W., Hoidal, J.R., and Leppert, M.F. A Candidate Gene Approach Identifies the CHRNA5-A3-B4 Region as a Risk Factor for Age-Dependent Nicotine Addiction. PLOS Genetics, 4(7), pp. 1-11, 2008.

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# Director's Report to the National Advisory Council on Drug Abuse - September, 2008

## Research Findings - Basic Neuroscience Research

### Voluntary Oral

Nicotine Intake in Mice Down-Regulates Glur2 But Not Depression-Like Behaviors Dr. Marina Picciotto and her colleagues at Yale University have continued their studies on the adaptive changes in brain and behavior that accompany repeated exposure to nicotine. Some of these adaptive changes are thought to be mediated by glutamate receptors (GluR) and cAMP response element-binding protein (CREB) in the nucleus accumbens. Dr. Picciotto studied the effects of nicotine exposure via the drinking water on nicotine preference, locomotor activity, and anxiety and depression-like behaviors in inbred mice. She and her colleagues reported few behavioral changes following extended nicotine exposure, but clear down-regulation of GluR2 in the mesolimbic system. When given a choice between nicotine and control solutions, mice showed a significant preference for nicotine. Dr. Picciotto interpreted these findings to indicate that voluntary nicotine drinking induces nicotine preference in mice with accompanying down regulation of GluR, but that differences are not sufficient to explain preference for nicotine. Vieryra-Reyes, P. Picciotto, M., and Mineur, Y. Voluntary Oral Nicotine Intake in Mice Down-regulates GluR2 but Does Not Modulate Depression-like Behaviors. Neuroscience Letters, 434, pp. 18-22, 2008.

### Improved Synthesis of the ORL Antagonist, 1-[(3R, 4R)-1-Cyclooctylmethyl-3-ethoxycarbonyl-4-piperidinyl]-3-ethyl-1,3-dihydro-2H-benzimidazol-2-one (J-113397)

Four subtypes of opioid receptors have been identified based upon structural homology. These include the classical mu, delta, and kappa receptors (MOP, DOP, and KOP, respectively) and the more recently identified opioid-receptor-like-1 (ORL-1), which is termed NOP. The endogenous ligand for NOP is a heptapeptide named as nociceptin by one group of investigators and orphanin FQ (N/OFQ) by another group. Several studies have shown that NOP may be involved in pain regulation, drug dependence, anxiety and stress, depression, learning and memory, motor activity, epilepsy/seizures, cardiovascular effects, urinary incontinence, cough and immunoregulation. A number of ORL-1 (NOP) receptor agonists and antagonists have been synthesized and used to characterize the pharmacological effects of the NOP system. The first and most studied small molecule antagonist is 1-[(3R, 4R)-1-Cyclooctylmethyl-3-ethoxycarbonyl-4-piperidinyl]-3-ethyl-1,3-dihydro-2H-benzimidazol-2-one (J-113397). The synthesis of this molecule has been reported previously. In two reports the optical resolution of the racemate of J-113397 was achieved by chromatography with a chiral column, and in another report a new synthesis of (+)- and (-)- J-113397 was reported. In the present study the authors have avoided the expense of large scale chiral column and provided an alternate

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practical synthesis of (+/-)-J113397 by separating the racemic compound into individual (+) - and (-)-isomers using a chiral auxiliary. Carroll, F.I. and Brieaddy, L.E. Improved Synthesis of the ORL Antagonist 1-[(3R,4R)-1-Cyclooctylmethyl-3-ethoxycarbonyl-4-piperidinyl]-3-ethyl-1,3-dihydro-2H-benzimidazol-2-one (J-113397). Synthetic Communication, 38, pp. 1926-1930, 2008.

### Microchip Capillary Electrophoresis

Members of the mammalian family of proteins known as RGS proteins (regulators of G-protein signaling) serve as GTPase-activating proteins, since they can bind to G proteins, reduce the normal lifetime of the GTP-G complex by hydrolysis, and effectively "turn off" the associated G protein-coupled receptor (GPCR) signaling pathway. RGS proteins have become a target for the design of RGS inhibitors, in order to potentiate the effects of GPCRs activated by agonist drugs. Recently, Dr. Richard Neubig and his colleagues at the University of Michigan reported on the development and validation of a micro-fabricated channel electrophoresis device for the determination of GTP hydrolysis and enzyme kinetics, which promises to improve the capability of high throughput screening. The completed device was subjected to validation for intra- and inter-channel deviation. The microchip could demonstrate the acceleration of G GTPase activity by RGs (based on the increase in product BGDP), as well as a reduction in BGDP in the presence of an RGS4 inhibitor, such as the YJ34 peptide, or the small molecule inhibitor CCG-4986. The screening of RGS inhibitors could be done at the rate of 4300 samples/hour for one determination each, if a library of inhibitors were to be tested. Finally, the microchip could also be used to obtain a complete dose response curve, in this case, one that provides a determination of the EC50 for inhibition of basal BGTP hydrolysis by formation of a GTPgammaS-BGTP complex. Pei, J. Dishinger, D.L. Roman, C. Rungwanitcha, R.R. Neubig and Kennedy, R.T. Microfabricated Channel Array Electrophoresis for Characterization and Screening of Enzymes using RGS-G Protein Interactions as a Model System. Analytical Chemistry, 80(13), pp. 5225-5231, 2008.

### CD4+ T Lymphocytes Contribute To Spinal Nerve Transection-Induced Neuropathic Pain

Neuropathic pain is initiated or caused by a primary lesion or dysfunction in the nervous system. Current treatments for neuropathic pain are not effective and are often associated with various side effects such as physical dependence, hyperalgesia, tolerance, and sedation. Understanding the underlying mechanisms of neuropathic pain may help to develop novel, non-addictive analgesic agents. This study investigated the role of infiltrating T lymphocytes in the etiology of persistent pain by using a murine spinal nerve L5 transection (L5Tx) neuropathic pain model. T lymphocyte-deficient mice showed no evident mechanical hypersensitivity after day 3 of L5Tx compared to wild-type mice. Employing a Fluorescence Activated Cell Sorter (FACS) technique, these investigators observed significant leukocytic infiltration (CD45(hi)) into the lumbar spinal cord that peaked at day 7 post L5Tx. These infiltrating leukocytes contained predominantly CD4(+), but not CD8(+) T lymphocytes. B lymphocytes, natural killer cells, and macrophages were not detected at day 7 post L5Tx. No differences in the activation of peripheral CD4(+) T lymphocytes were detected in either the spleen or lumbar lymph nodes between L5Tx and sham surgery groups. Furthermore, CD4 KO mice displayed significantly decreased mechanical hypersensitivity after day 7 of L5Tx; adoptive transfer of CD4(+) leukocytes reversed this effect. Decreased immunoreactivity of glial fibrillary acidic protein observed in CD4 KO mice post L5Tx indicated possible T lymphocyte-glial interactions. These results suggest a contributing role of spinal cord-infiltrating CD4(+) T lymphocytes versus peripheral CD4(+) T

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lymphocytes in the maintenance of nerve injury-induced neuropathic pain. Approaches to reduce CD4+ T lymphocyte infiltration may reduce CD4+ T lymphocyte-mediated CNS responses after nerve injury and thus may be useful in chronic neuropathic pain management. Cao, L. and DeLeo, J.A. CNS-infiltrating CD4+ T Lymphocytes Contribute to Murine Spinal Nerve Transection-induced Neuropathic Pain. European Journal of Immunology, 38(2), pp. 448-458, 2008.

### The Endogenous Cannabinoid System Modulates Nicotine Reward and Dependence

A growing body of evidence suggests that the endogenous cannabinoid system modulates the addictive properties of nicotine, the main component of tobacco that produces rewarding effects. In this study, complementary transgenic and pharmacological approaches were used to test the hypothesis that the endocannabinoid system modulates nicotine reward and dependence. An acute injection of nicotine elicited normal analgesic and hypothermic effects in knockout (KO) mice lacking the cannabinoid-1 receptors (CB1) and mice treated with the CB1 antagonist Rimonabant. However, disruption of CB1 receptor signaling blocked nicotine reward, as assessed in the conditioned place preference (CPP) paradigm. Conversely, genetic deletion or pharmacological inhibition of fatty acid amide hydrolase (FAAH), the enzyme responsible for catabolism of the endocannabinoid anandamide, enhanced the expression of nicotine CPP. Although the expression of spontaneous nicotine withdrawal was unaffected in CB1 KO mice, acute administration of Rimonabant ameliorated somatic withdrawal signs in wild type mice. Increasing endogenous levels of anandamide through genetic or pharmacological approaches exacerbated the physical somatic signs of spontaneous nicotine withdrawal in a milder withdrawal model. Moreover, FAAH-compromised mice displayed increased conditioned place aversion in a mecamylamine-precipitated model of nicotine withdrawal. These findings suggested that endocannabinoids play a role in the rewarding properties of nicotine, as well as in nicotine dependence liability. Specifically, increasing endogenous cannabinoid levels magnifies, whereas disrupting CB1 receptor signaling attenuates, nicotine reward and withdrawal. Collectively, these results support the hypothesis that cannabinoid receptor antagonists may offer therapeutic advantages to treat tobacco dependence. Merritt, L.L. Martin, B.R., Walters, C., Lichtman, A.H., and Damaj, M.I. The Endogenous Cannabinoid System Modulates Nicotine Reward and Dependence. Journal of Pharmacology and Experimental Therapeutics, May 2008, E-pub ahead of print.

### Lithium Protects against Phencyclidine (PCP) Neurotoxicity

PCP, ketamine, and other N-methyl-D-aspartate (NMDA) receptor antagonists are known to produce neuroapoptosis when administered during early postnatal development in rats. Early treatment with NMDA antagonists (equivalent to exposure in humans in the prenatal third trimester) results in schizophrenia-like behaviors when the rats reach early adolescence and young adulthood. Lithium is clinically used to treat schizoaffective and bipolar disorders and has recently been shown to have neuroprotective properties. The present study used corticostriatal slices taken from postnatal day-2 rat pups to investigate the possible protective effect of lithium and the role of the phosphatidylinositol-3 kinase (PI-3K)/Akt and extracellular signal-regulated kinase (ERK) pathways in PCP-induced neuroapoptosis. It is known that PI-3K/Akt generally promotes cell survival by phosphorylating (and thus inhibiting) pro-apoptotic proteins such as caspase-9 and glycogen synthase kinase-3 (GSK-3). They found that lithium pretreatment dose-dependently reduced PCP-induced caspase-3 activation and DNA fragmentation in layer II-IV of the cortex. PCP elicited time-dependent inhibition of the ERK and PI-3K/Akt pathways, as indicated by dephosphorylation of ERK1/2 and Akt. GSK-3

was also dephosphorylated at serine 9 and thus activated by PCP. Lithium prevented PCP-induced inhibition of the two pathways and activation of GSK-3. Further, blocking either the PI-3K/Akt or ERK pathway abolished the protective effect of lithium, and inhibiting GSK-3 activity mimicked the protective effect of lithium. No crosstalk between the two pathways was found, and specific GSK-3 inhibition did not prevent PCP-induced dephosphorylation of Akt and ERK. These data indicate that the protective effect of lithium against PCP-induced neuroapoptosis is mediated through independent stimulation of the PI-3K/Akt and ERK pathways and suppression of GSK-3 activity. Xia, Y., Wang, C.Z., Liu, J., Anastasio, N.C., and Johnson, K.M. Lithium Protection of Phencyclidine-induced Neurotoxicity in Developing Brain: the Role of PI-3K/Akt and MEK/ERK Signaling Pathways. Journal of Pharmacology and Experimental Therapeutics, 2008 Jun 10 [E-pub ahead of print].

### Glutamate Release in the Nucleus Accumbens Core Is Necessary for Heroin Seeking

Although critical roles for glutamatergic neuroplasticity (i.e., the ability of glutamatergic synapses to change long-term as circumstances dictate) have been well described after exposure to the stimulants cocaine and amphetamine, roles for glutamate in opiate addiction are less established. However, very recent findings indicate that glutamatergic systems plasticity does indeed play critical roles in opiate addiction. Peter Kalivas' group showed, in rats trained to self-administer heroin and then extinguished, that reinstatement by either noncontingent heroin or cue (models of relapse) was accompanied by increased extracellular glutamate in the nucleus accumbens (NAc) core (NAcore). As has been shown for reinstatement of cocaine self-administration, the increase in glutamate during heroin-induced reinstatement was abolished by inhibiting glutamatergic afferents from the prelimbic cortex to the NAcore with the use of GABA agonists. Both cocaine and heroin reinstatement were blocked by inhibiting AMPA-type glutamate receptors in the NAcore. This new finding complements that of the Shaham lab at the NIDA IRP showing that activation of inhibitory mGluR2/3 autoreceptors in the NAcore or shell, which reduces glutamate release, prevents cue-induced reinstatement of heroin seeking (Bossert et al. 2006). LaLumiere, R.T. and Kalivas, P.W. Glutamate Release in the Nucleus Accumbens Core Is Necessary for Heroin Seeking. J. Neurosci., 28, pp. 3170-3177, 2008.

### Agonist-Directed Signaling of the Serotonin-2A Receptor Depends on -Arrestin-2 Interactions In Vivo

Visual and auditory hallucinations accompany certain neuropsychiatric disorders, such as schizophrenia, and they also can be induced by the use or abuse of certain drugs. The serotonin 2A receptors (5-HT2ARs) are molecular targets for drug-induced hallucinations. However, the cellular mechanisms by which the 5-HT2AR mediates these effects are not well understood. Drugs acting at the 5-HT2AR can trigger diverse signaling pathways that may be directed by the chemical properties of the drug. -arrestins are intracellular proteins that bind to these receptors and are a point where such divergences in ligand-directed functional signaling could occur. Dr. Laura Bohn at the Ohio State University College of Medicine compares the endogenous agonist, serotonin, to a synthetic 5-HT2AR hallucinogenic agonist, 2,5-dimethoxy-4-iodoamphetamine (DOI), in mice lacking -arrestin-2, as well as in cells lacking -arrestins. In mice, they find that serotonin induces a head twitch response by a -arrestin-2-dependent mechanism. However, DOI invokes the behavior independent of -arrestin-2. The two structurally distinct agonists elicit different signal transduction and trafficking patterns upon activation of 5-HT2AR, which hinge on the presence of -arrestins. Their study suggests that the 5-HT2AR--arrestin interaction may be particularly important in receptor function in response to endogenous serotonin levels, and this could have major

implications in drug development for treating neuropsychiatric disorders such as depression and schizophrenia. Schmid, C.L., Raehal, K.M., and Bohn, L.M. Agonist-directed Signaling of the Serotonin-2A receptor Depends on Beta-arrestin-2 Interactions In Vivo. Proceedings of the National Academy of Sciences USA, 105(3), pp. 1079-1084, 2008.

### Morphine-Induced Receptor Endocytosis in a Novel Knockin Mouse Reduces Tolerance and Dependence

Opioid drugs, such as morphine, are among the most effective analgesics available, but their utility for the treatment of chronic pain is limited by side effects including tolerance and dependence. Morphine acts primarily through the mu-opioid receptor (MOP-R), which is also a target of endogenous opioids. However, unlike endogenous ligands, morphine fails to promote substantial receptor endocytosis both in vitro and in vivo. Receptor endocytosis serves at least two important functions in signal transduction. First, desensitization and endocytosis act as an ''OFF'' switch by uncoupling receptors from G protein. Second, endocytosis functions as an ''ON'' switch, resensitizing receptors by recycling them to the plasma membrane. Thus, both the OFF and ON function of the MOP-R are altered in response to morphine compared to endogenous ligands. To examine whether the low degree of endocytosis induced by morphine contributes to tolerance and dependence, Dr. Whistler and her group at the Ernest Gallo Clinic and Research Center generated a knockin mouse that expresses a mutant MOP-R that undergoes morphine-induced endocytosis. Morphine remains an excellent antinociceptive agent in these mice. Importantly, these mice display substantially reduced antinociceptive tolerance and physical dependence. These data suggest that opioid drugs with a pharmacological profile similar to morphine but the ability to promote endocytosis could provide analgesia while having a reduced liability for promoting tolerance and dependence. Kim, J.A., Bartlett, S., He, L., Nielsen, C.K., Chang, A.M., Kharazia, V., Waldhoer, M., Ou, C.J., Taylor, S., Ferwerda, M., Cado, D., and Whistler, J.L. Morphine-induced Receptor Endocytosis in a Novel Knockin Mouse Reduces Tolerance and Dependence. Current Biology, 18(2), pp. 129-135, 2008.

### Anomalous Dopamine Release Associated with a Human Dopamine Transporter Coding Variant

Dopamine (DA) signaling at synapses is tightly coordinated through opposing mechanisms of vesicular fusion-mediated DA release and transporter-mediated DA clearance. Altered brain DA signaling is thought to underlie multiple brain disorders, including drug addiction, Parkinson's disease, and a number of psychiatric syndromes. Dr. Blakely and his group identified a pedigree containing two male children diagnosed with ADHD who share a rare human DA transporter (DAT; SLC6A3) coding variant, Ala559Val. Although hDAT Ala559Val supports normal DAT protein and cell surface expression, as well as normal DA uptake, the variant exhibits anomalous DA efflux from DA-loaded cells. That is, they appear to reverse transport at the DAT. Additionally, they also show that hDAT Ala599Val exhibits increased sensitivity to intracellular Na(+), but not intracellular DA, and displays exaggerated DA efflux at depolarized potentials. Remarkably, the two most common ADHD medications, amphetamine and methylphenidate, both block hDAT Ala559Val-mediated DA efflux, whereas these drugs have opposite actions at wild-type hDAT. Their findings reveal that DA efflux, typically associated with amphetamine-like psychostimulants, can be produced through a heritable change in hDAT structure. Because multiple gene products are known to coordinate to support amphetamine-mediated DA efflux, the properties of hDAT Ala559Val may have broader significance in identifying a new mechanism through which DA signaling disorders arise. Additionally, they suggest that block of inappropriate neurotransmitter efflux may be an unsuspected mechanism supporting the

therapeutic actions of existing transporter-directed medications. Mazei-Robison, M.S., Bowton, E., Holy, M., Schmudermaier, M., Freissmuth, M., Sitte, H.H., Galli, A. and Blakely, R.D., Journal of Neuroscience, 28(28), pp. 7040-7046, 2008.

### There is Metaplastic Control of the Endocannabinoid System At Inhibitory Synapses In Hippocampus

Endocannabinoids (eCBs) are important signaling molecules that modulate synaptic plasticity. This ability to induce additional modulation (plasticity) of neuronal plasticity responses has been termed metaplasticity. eCB system (eCB synthesis, release, transport) activation can occur either in response to increased intracellular Ca2+ concentrations, or through activation of G-protein coupled receptors including metabotropic glutamate receptors (mGluRs). This paper reports the identification of a novel calcium-dependent mechanism that regulates mGluR-dependent eCB system activation in the hippocampus. In this mechanism, a transient rise in intracellular Ca2+ concentration that does not activate the eCB system primes cells to release eCBs with a subsequent (not concurrent) activation of mGluRs. Conversely, calcium-dependent release of eCBs can be enhanced by prior mGluR activation. These results show that eCB system activation is also subject to metaplasticity, adding another layer of complexity to the regulation of neuronal activity within the hippocampus. Edwards, D.A., Zhang, L., and Alger, B.A. Metaplastic Control of the Endocannabinoid System at Inhibitory Synapses in Hippocampus. Proceedings of the National Academy of Sciences of the United States, 105, pp. 8142-8147, 2008.

### Increased Impulsivity during Withdrawal from Cocaine Self-Administration: Role for DFosB in the Orbitofrontal Cortex

Impulsivity is associated with the development and maintenance of addiction in which low prefrontal cortical activity is observed. It is not clear whether impulsivity is an antecedent or a consequence of addiction or both. Furthermore, most studies on impulsivity in cocaine addicts are done when addicts are abstinent and thus may reflect a consequence of withdrawal. Animal models using a 5-choice serial reaction time test (5CSRT) that measures impulsivity and cognitive performance permit scientists to tease out these possibilities. Eric Nestler and his colleagues examined the effect of cocaine self-administration on performance of the 5CSRT during acquisition and withdrawal from cocaine self-administration and determined whether the FosB induction in the orbital frontal cortex (OFC) would alter drug induced affects on impulse control. FosB is induced in many parts of the brain, including the OFC by chronic self-administration of cocaine. Rats self-administering cocaine developed tolerance to the initial errors of omissions and premature responses on the 5CSRT produced by cocaine. In contrast, rats during periods of withdrawal from cocaine showed increased premature responding. Over expression of FosB in the OFC attenuated errors of premature responses during acute self-administration of cocaine but dramatically increased the number of premature responses during cocaine withdrawal. Over expression of JunB (a dominant-negative antagonist of FosB) blocked the development of tolerance to the errors of omission and premature responses. These results suggest that FosB induction by cocaine plays a role in mediating the deficits in impulse control during withdrawal from chronic cocaine self-administration and acts a compensatory mechanism to produce tolerance to the errors produced by acute cocaine. One question remains is whether FosB mimics low prefrontal activity observed in cocaine addicts. While the paper suggests that chronic cocaine impairs impulse control in the withdrawn state, the paper does not address the question of how chronic self-administration of cocaine might affect animals displaying traits of high and low impulsivity as measured by 5CSRT. Thus, the cognitive deficits observed could still be both an antecedent and a consequence

of chronic cocaine self-administration. Winstanley, C.A., LaPlant, Q., Theobald, D.E., Green, T.A., Bachtell, R.K., Perrotti, L.I., DiLeone, R.J., Russo, S.J., Garth, W.J., Self, D.W., and Nestler, E.J. Journal of Neuroscience, 27(39), pp. 10497-10507, 2008; Winstanley C.A., Bachtell, R.K., Theobald, D.E.H., Laali, S., Green, T.A., Kumar, A., Chakravarty, S., Self, D.W. and Nestler, E.J. Increased Impulsivity during Withdrawal from Cocaine Self-Administration: Role for FosB in the Orbitofrontal Cortex. Cerebral Cortex., 2008 Jun 6. [E-pub ahead of print]

### EphB and EphrinB Are Charged for the Initiation of Synaptogenesis

During synaptogenesis the postsynaptic neuron sends out dendrites which form filopodia to explore and contact the presynaptic axon terminals. If a contact is made and recognized as partner, the cell adhesion triggers synaptogenesis. Until recently, how dendritic filopodial motility is linked to cell-cell interactions and the identity of molecules that regulate the filopodial motility and initiate synaptogenesis were not known. A team led by NIDA researcher Mathew Dalva, at University of Pennsylvania, reports that their new findings provide evidence for EphB-ephrinB, a receptor-ligand cell adhesion molecule pair, functioning as a unifying molecular mechanism that is able to control filopodia motility, cell-cell interactions, and induce synapse differentiation. Eph receptors are transmembrane signaling molecules and are the largest known family of receptor tyrosine kinases in the human genome. They are divided into A and B subclasses based on affinity for their membrane-associated ligands, ephrinA and ephrinB. A number of lines of evidence suggest that EphB receptors are a key regulator of synapse development and spine formation. In the present work, EphB knock-out mice cortical neurons showed the specific loss of synaptic specializations in dendritic protrusions, but not along dendritic shafts, demonstrating that EphBs selectively regulate the formation of many dendritic spine synapses. Expression of EphB2 in neurons that lack endogenous EphB1-3 was sufficient to rescue the phenotype, indicating that EphBs function in cell-autonomously. Moreover, immunostaining in sections from cortex of these animals revealed a ~40% decrease in the number of excitatory synapses. EphB tyrosine kinase activity can trigger intracellular signaling cascades that lead to actin remodeling and, as such, can influence movement and retraction of filopodia. Downstream signaling pathways, through Rho, Cdc42, and PAK, that link activation of EphB receptors to changes in spine morphology are elucidated. Strikingly, the combination of PAK and kinase inactive EphB2 rescues synaptogenesis, but deletion of the ephrin-binding domain from EphB2 precludes rescue, indicating that both motility and trans-cellular interactions are required for synaptic initiation. Thus, EphB-ephrin signaling and cell-cell interactions coordinate both the motility of dendritic filopodia exploration and synaptogenesis. Kayser, M.S., Nolt, M.K., and Dalva, M.B. EphB Receptors Couple Dendritic Filopodia Motility to Synapse Formation. Neuron 59, pp. 56-69, 2008.

### F-BAR

Cellular membrane and membrane remodeling are involved in every aspect of cell survival and function, including receptor-ligand signaling, metabolite transport, as well as drug uptake and degradation. However, a structural description of membrane associated macromolecules and their roles in regulating membrane structures are largely missing. The BAR (Bin, amphiphysin, Rvs) domain superfamily proteins have recently been found to be recruited from cytoplasm to the membrane, and trigger the formation of membrane extensions, invaginations, tubular organelles, transport intermediates and endocytic vesicles. To understand how BAR proteins play their roles, NIDA researcher Vinzenz Unger examined the structure and role of one subfamily of BAR protein, the F-BAR, using electron cryomicroscopy. He

reports that, during membrane tubule formation, the self segregated F-BAR proteins self assemble into a helical coat on the membrane, providing scaffolding for the folding of the membrane. The F-BAR modules readily bind to the originally flat membranes and generate membrane curvature de novo. By visualizing and following the F-BAR scaffolding, he observed the domain binds to the flat membrane via a surface other than the concave face, and therefore F-BAR helical coats are more than just curvature sensors or stabilizers. There is also no obvious need to invoke membrane curvature-mediated attractive forces since the dimers interact directly and extensively with each other. At the same time, the structural determinants of tubule formation serve to spatially segregate F-BAR activity from other membrane-binding domains. This work is an important first step toward a structural exploration of membrane remodeling during cell endocytosis. Frost, A., Perera, R., Rous A., Spasov, K., Destaing, O., Egelman, E.H., De Camilli, P., and Unger, V.M. Structural Basis of Membrane Invagination by F-BAR Domains. Cell, 132, pp. 807-817, 2008.

### Differences between Dorsal and Ventral Striatum in Drd1a Dopamine Receptor Coupling of Dopamine- and cAMP-Regulated Phosphoprotein-32 to Activation of Extracellular Signal-Regulated Kinase

The striatum of the brain plays a role in processing context-and reward-related information to shape learning and behavior. Dopaminergic signals carried from the substantia nigra to the striatum modulate synaptic plasticity of glutaminergi c corticostriatal neurons. Dysregulation of the above process has been implicated in psychostimulant addiction and movement disorders. Sensitization of dopamine D1 receptor (Drd1a) responses occurs in reaction to both psychostimulants and loss of dopamine input to the striatum, as seen in models of Parkinson's disease (PD). This sensitization is influenced by phosphorylation of extracellular signaling-regulated kinase 1/2 (ERK 1/2), whose activity, in turn, is amplified by dopamine receptor protein phosphatase inhibitor [dopamine- and cAMP-related phosphoprotein 32 (DARPP-32)]. Psychostimulant and Drd1a agonist induced Drd1a sensitization coincides with a large increase of phsphorylated ERK1/2 (pERK 1/2) within neurons in the ventral striatum and nucleus accumbens (NAc), but not within neurons of the dorsal striatum. In a dopamine-depleted model of PD, however, there is a significant amount of ERK 1/2 activation within the dorsal striatum. Dr. Paul Worley and colleagues determined that the specific mechanism of Drd1a sensitization associated with PD is not dependent on DARPP-32-induced amplification of ERK 1/2. In this study, the investigators demonstrate an identical marked increase of pERK 1/2 within dopamine-depleted dorsal striatum in both wild-type and DARPP-32 knock-out mice. In addition, the investigators assessed the potential role of DARPP-32 activation of ERK 1/2 L-DOPA-associated dyskinesias. No appreciable difference was observed in the number of pERK 1/2 immunoreactive neurons between wild-type or DARPP-32 KO mice treated with either Drd1a agonist or L-DOPA. These results indicate that the mechanism of DARPP-32 regulated activation of ERK 1/2 is confined to the ventral striatum and NAc. In addition, the above mechanism of dopamine sensitization is not evident in a dopamine-depleted model of PD. Gerfen, C.R., Paletzki, R., and Worley, P. Differences between Dorsal and Ventral Striatum in Drd1a Dopamine Receptor Coupling of Dopamine- and cAMP-Regulated Phosphoprotein-32 to Activation of Extracellular Signal-Regulated Kinase. Journal of Neuroscience, 28(28) pp. 7113-7120, 2008.

### Binding Sites For Cocaine and Dopamine In the Dopamine Transporter Overlap

The dopamine transporter (DAT) regulates dopaminergic signaling via reuptake of dopamine from the synaptic cleft. Cocaine binds to DAT with high affinity

and inhibits dopamine reuptake, which results in a large increase in extracellular dopamine levels. Previous studies have attempted to elucidate the cocaine binding site within the DAT; however, without an accurate molecular model of DAT, identifying these sites has been difficult. Recently, Loland et al. constructed molecular models for DAT binding of cocaine and the cocaine analog CFT ((-)-2-carbomethoxy-3-(4-fluorophenyl)tropane) based on a high-resolution crystallized structure of the bacterial transporter LeuT, a homolog within the neurotransmitter/Na+ symporter (NSS) family. The investigators report that cocaine and its analogs bind to a site located deep between the transmembrane domains (TMD) 1, 3, 6 and 8 of DAT, which overlaps extensively with the binding sites of dopamine. The model indicates that dopamine and the cocaine analog CFT both interact with the same protein side chains within DAT. For example, asparagine residue 79 within TMD1 interacts with the amine group of dopamine and CFT. Furthermore, both CFT and dopamine interact with hydrophobic and aliphatic residues located within TMD 1, 3, and 6. The above results were confirmed via mutation of residues that interacted with dopamine and cocaine/CFT. The docking model was further validated by introducing structural limitations at sites located extracellularly to cocaine/CFT in order to trap the radiolabeled ligand within its binding pocket. This study presents a complete and experimentally verified model of cocaine and dopamine binding sites within DAT and demonstrates that these sites extensively overlap. As a result, these findings may render the creation of a competitive inhibitor of cocaine that does not disrupt dopamine uptake unfeasible. Beuming, T., Kniazeff, J., Bergmann, M.L., Shi, L., Gracia, L., Raniszewska, K., Newman, A.H., Javitch, J.A., Weinstein, H., Gether, U., and Loland, C.J. The Binding Sites for Cocaine and Dopamine in the Dopamine Transporter Overlap. Nature Neuroscience, 11(7), pp. 780-789, 2008.

### Multiple Actions of Spinophilin Regulate Mu Opioid Receptor Function

Spinophilin is a ubiquitous, neuronal dendritic-spine enriched protein that interacts with and modulates the activity of several elements within the G-protein-coupled receptor (GPCR) signaling network. Recent studies have demonstrated that spinophilin modulates alpha-2-adrenergic signaling pathways, which are very similar to those involved with mu-opioid receptor (MOR) responses. In this study, Dr. Venetia Zachariou and colleagues evaluate the effects of spinophilin on the acute and chronic actions of opiates. Spinophilin indirectly promotes MOR internalization and recycling and regulates signal transduction events that are induced after MOR activation. Over expression of spinophilin within PC12 cells results in fast internalization of MOR within 30 minutes of exposure to morphine. Conversely, under control conditions exposure to morphine leads to delayed MOR endocytosis. Previous studies have demonstrated that MOR internalization is positively correlated with increased analgesic tolerance and opiate dependence. Thus, spinophilin modulates responses to chronic opiate exposure by preventing the development of tolerance and dependence. Deletion of the spinophilin gene results in an amplification of the consequences of repeated morphine exposure. When compared to normal wild-type mice, spinophilin knock out (KO) mice display decreased sensitivity to low morphine doses as determined by the 52*C hot plate test. In addition, spinophilin KO mice develop analgesic tolerance to morphine twice as quickly as wild-type mice (2 daily 20 mg/kg i.p. injections of morphine vs. 4 injections). Furthermore, mutant spinophilin mice show withdrawal symptoms that are two times as intense as compared to the wild-type controls. These findings describe the role of spinophilin in regulating MOR signaling pathways and the behavioral responses of opiate exposure. Spinophilin may serve as a target to aid in the investigation and development of opiate drugs that display effective analgesic actions while also limiting the adverse behavioral consequences of opiate exposure. Charlton, J.J., Allen, P.B., Psifogeorgou, K., Chakravarty, S., Gomes, I., Neve, R.L., Devi, L.A.,

Greengard, P., Nestler, E.J., and Zachariou, V. Multiple Actions of Spinophilin Regulate Mu Opioid Receptor Function. Neuron, 58(2), pp. 238-247, 2008.

### Rewarding Stimuli Regulate Chromatin Via A Protein Phosphatase Cascade

Drugs of abuse and natural rewards such as food enhance extracellular dopamine levels in the nucleus accumbens and other brain structures leading to reinforcement learning. The precise mechanisms by which these rewards lead to long term synaptic changes are of great scientific interest. A current paradigm is that dopamine D1 receptor activation leads to phosphorylation of the signaling molecule DARPP-32. This in turn leads to inhibition of protein phosphatase PP1 leading to increased phosphorylation of channels and other cytoplasmic molecules critical for synaptic plasticity in neurons. Although these cytoplasmic functions of DARPP-32 are understood, drug and food rewards can cause DARPP-32 to accumulate rapidly in the cell nucleus. The nuclear functions of DARPP-32 have not been well characterized. In this paper, Dr. Greengard and colleagues have found that phosphorylation of DARPP-32 specifically on serine 97 (S97) controls nuclear localization of DARPP-32. Phosphorylation of DARPP-32 S97 by the casein kinase 2 leads to cytoplasmic localization of DARPP-32, while dephosphorylation of S97 by protein phosphatase 2A leads to nuclear localization of DARPP-32. To test the functional consequences of this exquisite regulation of DARPP-32 localization, a team of researchers mutated serine 97 to alanine (S97A) such that DARPP-32 could no longer be phosphorylated at this position and was in large part localized to the nucleus. The S97A mutation had no effect on the initial responses of the animals to cocaine. However, in response to a second cocaine injection, S97A mice had reduced locomotor sensitivity to cocaine and rewarding effects of cocaine were not observed. S97A animals also had decreased motivation for food rewards. What does DARPP-32 do in the nucleus? DARPP-32 is known to inhibit the PP1 protein phosphatase and phosphorylation of the chromatin structural protein histone H3 on serine 10 (S10) which is known to be crucial for memory formation. Dr. Greengard and colleagues found that cocaine could induce phosphorylation of histone H3 S10 but this effect was blocked by the DARPP-32 S97A mutant as well as by a T34A mutation. This data reveals that DARPP-32 phosphorylation on threonine 34 is required to inhibit protein phosphatase PP1 function and allow phosphorylation of histone H3 S10. There is an additional layer of regulatory complexity through modulation of DARPP-32 levels in the nucleus. In this work Dr. Greengard and colleagues have linked DARPP-32 to the regulation of chromatin in the nucleus. This regulation presumably can lead to long term changes in gene expression in these neurons which ultimately are required for processes such as memory formation and the long term rewarding effects of drugs of abuse. A deeper understanding of the precise molecular steps in this process may lead to the identification of new therapeutic targets and agents to treat addiction. Stipanovich, A., Valjent, E., Matamales, M., Nishi, A., Ahn, J.H., Maroteaux, M., Bertran-Gonzalez, J., Brami-Cherrier, K., Enslen, H., Corbille, A.G., Filhol, O., Nairn, A.C., Greengard, P., Herve, D., Girault, J.A. A Phosphatase Cascade by Which Rewarding Stimuli Control Nucleosomal Response. Nature, 453, pp. 879-885, 2008.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2008

## Research Findings - Basic Behavioral Research

### Persistent Synaptic Potentiation Is Produced By the Self-Administration of Cocaine, But Not Natural Rewards

Relapse to drug-seeking and drug-taking behavior is a characteristic feature of addiction. A popular hypothesis suggests that drug addiction results from maladaptive co-option of the brain's natural reward-related learning and memory mechanism. In this study, Dr. Antonello Bonci and his colleagues examined whether long-term potentiation (LTP), a synaptic mechanism associated with learning and memory, could be elicited at excitatory synapses in ventral tegmental area (VTA) dopamine neurons following natural reward or cocaine self-administration training. Potentiation was assessed in electrophysiological experiments by measuring both the ratio of AMPA to NMDA glutamate receptors (indicating a postsynaptic change) and the frequency of miniature excitatory postsynaptic currents (mEPSCs, indicative of a presynaptic change). In all cases where LTP was found, both measures were elevated. LTP was induced by self-administration training for both natural reward (food or sucrose) and cocaine. However, the LTP produced by cocaine self-administration lasted for at least three months while that produced by natural rewards had dissipated by 21 days after training ceased. Interestingly, at 21 days, animals trained to respond for food, sucrose, or cocaine all continued to show high levels of reward seeking, as measured in progressive ratio tests. Thus, persistent LTP in VTA is not necessary for continued reward seeking per se, but in the case of cocaine, its persistence suggests that it may be involved in long-term vulnerability for relapse. In this regard, another important result from the study was that the LTP produced by cocaine self-administration was resistant to extinction. Rats trained to self-administer cocaine for 14 days followed by three weeks of daily two-hour extinction training, during which cocaine was not delivered to reinforce responding. One day after the last extinction session, half of the rats were sacrificed for electrophysiological experiments and the other half underwent a single cue-induced reinstatement session and were then sacrificed for electrophysiology. Both groups showed elevated AMPA:NMDA ratios and mEPSC frequencies similar to those of rats that had been abstinent from cocaine for 21 days after self-administration without extinction training. These data suggest that even when drug-seeking behaviors are extinguished, the enhancement in glutamate function induced by voluntary cocaine self-administration remains potentiated, and thus may be important in the resumption of the previously extinguished behavior, or relapse. The persistent potentiation of excitatory synapses in VTA dopamine neurons may represent a fundamental cellular phenomenon driving pathological drug-seeking behavior. Chen, B.T, Bowers, M.S., Martin, M., Hopf, F.W., Guillory, A.M., Carelli, R.M., Chou, J.K., and Bonci, A. Cocaine but Not Natural Reward Self-Administration nor Passive Cocaine Infusion Produces Persistent LTP in the VTA. Neuron, 59, pp. 288-297, 2008.

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### Novel Reactivity and Behavioral Inhibition: Inflexibility As A Vulnerability Phenotype?

Recently there has been great interest in using animal models to determine behavioral phenotypes that confer vulnerability to acquire or sustain drug abuse behavior, (e.g., drug self-administration). It has long been known that individual animals differ in basal activity levels and response to novel stimuli and environments. Animals with greater responses are those who more readily acquire drug self-administration. A number of other behavioral tests assay impulsivity and individual tasks may assess different components of impulsivity. While the link between addiction and impulsivity is clear, it is unknown whether impulsive behavior is antecedent to, or a consequence of, chronic exposure to drugs of abuse. Some studies suggest that animals high on impulsivity assessments are also more vulnerable to acquire self-administration, but other authors claim that impulsivity is more related to features of addiction such as compulsive drug taking and continued drug seeking in the face of adverse consequences. Thus there is an interest in determining if high novelty reactivity and impulsive behavior represent overlapping vulnerability phenotypes in animal models of drug abuse. Drs. Stoffel and Cunningham have been studying high and low-novel reactive rats (HR, LR) and animals that demonstrate impulsive behavior on an operant schedule called differential reinforcement of low-rate (DRL) responding. On this schedule, impulsive animals have difficulty withholding lever press responses for a specific interval in order to earn a reinforcer. On this task, animals can be separated into high disinhibition and low disinhibition phenotypes (HD and LD). In this study, the researchers found that (1) HR and HD animals were indistinguishable in their response patterns under the DRL schedule, indicating an overlap of phenotype, and (2) Both HR and HD rats showed less variability in responding on the DRL task, suggesting that a more rigid response typography is a common characteristic of this phenotype. This is an interesting observation, as chronic cocaine treatment has been associated with a narrowing of cognitive and behavioral flexibility. The finding from this animal model suggests that behavioral inflexibility may be a component of the vulnerability phenotype and deserves further investigation. Stoffel, E.C. and Cunningham, K.A. The Relationship Between the Locomotor Response to a Novel Environment and Behavioral Disinhibition in Rats. Drug and Alc. Dep., 92, pp. 69-78, 2008.

### Activation of Circadian Genes With Repeated Binge-Like Cocaine Self-Administration

Drugs of abuse disrupt homeostatic processes such as sleep and eating, and psychostimulants activate genes involved in the regulation of circadian rhythms. Circadian genes may also play a role in modulating cocaine reward, as sensitization in drosophila depends on the activation of genes such as Period 1, Period 2 and Clock. Additionally, circadian associated genes located outside of the suprachiasmatic nucleus are found in regions such as the dorsal striatum, known to be important for drug-related learning and the development of habitual behaviors in addiction. For example, in mice, Erg1, a circadian associated gene, is required for long-lasting associations between cocaine and the drug-related environment. Drs. Wendy Lynch and colleagues at Yale University have been studying circadian related genes in a rat model of i.v. cocaine self-administration to identify changes in neural pathways, produced by repeated drug administration, which may be responsible for homeostatic dysregulation and involved in neuroadaptations seen in addiction. Using a continuous access paradigm with discrete trial drug availability, they mimicked high levels of cyclical intake seen in human abusers. After seven days of binge administration, gene expression was assayed using a custom microarray chip

focused on growth factor signaling molecules, transcription factors and known classes of circadian or timekeeper genes. Profiles were compared to animals self-administering saline only. Genes found to be differentially upregulated in the striatum included transcription factors such as zinc finger genes, Fosl1 and CREB; growth factors such as Chgb; enzymes/kinases such as Camklg, Fdft1; receptors/signal transduction proteins (e.g., 5-HT2C, NMDA2A); and neurotransmitter signaling genes such as Park2. Twenty-seven genes with a known circadian function were also upregulated and additional validation using quantitative real-time PCR was performed for the self-administration group. They also assayed additional known circadian genes that were not represented on the gene array, using real-time PCR quantification of mRNA levels, to reveal differential regulation of Clock, Per2 and Cry1 in cocaine self-administering animals. In order to identify neural networks associated with self-administration, the investigators used functional network mapping software, GeneGo (MetaCore). Each of the cocaine-regulated genes were examined for their involvement in the circadian systems, focusing not only on the primary circadian genes (Arntl/Bmal1, Clock, Per1, Per2, Cry1, Cry2), but also genes that have been shown previously to be regulated by or associated with the circadian system. Thirty regulatory networks of significance were identified, suggesting inhibitory and activation interactions between genes important for circadian rhythms and related biological processes. The authors discuss common mechanisms by which cocaine-activated and circadian systems may be regulated (e.g., through D1-cAMP signaling pathways or NMDA regulation of Per1 gene expression, changes ERK/MAPK signaling pathways). Most importantly, results from this study suggest candidates for future investigation to manipulate these signaling pathways with specific inhibitors or activators and examine the consequence for behavior. Lynch, W.J., Girgenti, M.J., Breslin, F.J., Newton, S.S., and Taylor, J.R. Gene Profiling the Response to Repeated Cocaine Self-administration in Dorsal Striatum: A Focus on Circadian Genes. Brain Research, 1213, pp. 166-177, 2008.

### Two Classes of Neurons in the Rostral Ventromedial Medulla (RVM) Independently Modulate Pain

Studies have identified two classes of neurons (based on electrophysiological characterization) in the RVM, a region importantly involved with pain modulation. These cells are termed "on-cells" and "off-cells" and fire during pain and analgesia, respectively. In the current study, NIDA-grantee Dr. Mary Heinricher and colleagues (Oregon Health & Science University) examined if the activation of on-cells directly inhibits off-cells, as is generally believed to be the case. They recorded activity of on- and off-cells during heat-evoked paw or tail withdrawal in lightly anesthetized rats and precisely measured the onsets of the off-cell pause and the on-cell burst. Contrary to what would be expected if on-cells were inhibitory interneurons, off-cells typically ceased firing before on-cells began firing (mean 481 ms lag). This suggests that on-cell activity does not directly inhibit off-cell activity. These data help us better understand the brainstem circuitry involved with pain and analgesia and suggest that the on- and off-cells work more independently than previously thought in modulating pain. Clearly, D.R., Neubert, M.J., and Heinricher, M.M, Neuroscience, 151, pp. 564-571, 2008.

### Behavioral and Electrophysiological Indices of Negative Affect Predict Cocaine Self-Administration

The hypothesis that drug-associated cues can induce a negative affective state that would then induce drug taking was put forward more than 30 years ago. But the current study, a collaboration between Dr. Sue Grigson's and Dr. Regina Carelli's laboratories, is the first test of this hypothesis and its neurobiological basis in an animal model. In this study rats were given intraoral infusions of an orange or grape flavored saccharin solution. The rats were

conditioned to associate one of the flavors with the opportunity to self-administer cocaine and, on alternate days, to associate the other flavor with saline self-administration. Flavor conditioning sessions consisted of thirty 3.5s infusions over a 30 min session, followed by drug availability during self-administration five minutes later. Initially, the rats made stereotyped orofacial responses (licking and sideways tongue protrusions), which are associated with palatable taste stimuli, for both flavors However, as one of the flavors came to predict cocaine, they began to show selective aversive taste reactions to that flavor (gaping), identical to responses rats make for unpalatable tastes such as quinine. Analysis of the aversive taste reactivity measures and measures of drug seeking behavior showed that stronger aversive reactions to the cocaine-associated taste predicted shorter latency to the first cocaine infusion and more "drug loading" (number of cocaine infusions early in the session). Previous studies of neurophysiological responses in the nucleus accumbens (NAc) have shown that stimuli with positive hedonic values generally suppress NAc activity, while those with negative values generally excite NAc neurons. Consistent with this characterization, presentation of either flavor solution in naive rats inhibited about 75% of the neurons recorded and excited only about 25%. However, after conditioning, responses to the cocaine-associated flavor were reversed (about 60% excitatory), while those to the saline-associated flavor remained the same (i.e., mostly inhibitory). These neurophysiological data demonstrate a shift in patterned NAc neuronal firing that corresponds with the learned shift in affect and the increased cocaine-seeking behavior. This study provides strong support for the hypothesis that drug-associated cues can trigger an aversive affective state that drives drug-seeking behavior, and it provides a novel behavioral model to further investigate the neural mechanisms by which cues can exert control over drug self-administration. Wheeler, R.A., Twining, R.C., Jones, J.L., Slater, J.M., Grigson, P.S. and Carelli, R.M. Behavioral and Electrophysiological Indices of Negative Affect Predict Cocaine Self-administration. Neuron, 57, pp. 774-785, 2008.

### The Medial Prefrontal Cortex Mediates Differential Effects of Uncontrollable vs. Controllable Stress on Responses to Drugs of Abuse

A single session of uncontrollable (inescapable tailshock, IS), but not controllable (escapable tailshock, ES), stress enhances the conditioned place preference (CPP) response to morphine, even when the stressor and drug administration are separated temporally and spatially. Dr. Steven Maier and his colleagues have been systematically investigating the neural circuit that underlies this differential vulnerability to drug reward produced by controllable vs. uncontrollable stress. From previous studies, they knew that activation of serotonergic neurons in the dorsal raphe (DRN) during IS was necessary to potentiate dopamine efflux in the nucleus accumbens and enhance morphine CPP and also that activation of the ventral medial prefrontal cortex (mPFCv) can inhibit DRN activity. Thus, in this study, they investigated whether the mPFCv was a critical mediator of the effects of stressor controllability on morphine-CPP. In one experiment, they inactivated mPFCv just prior to stress exposure by microinjections of muscimol. This inactivation had no effect on the ability of IS to potentiate morphine CPP, but now ES also potentiated the behavior. In the second, complementary, experiment they microinjected picrotoxin to activate mPFCv. In this case, neither IS nor ES effectively enhanced morphine-CPP. Together, these results demonstrate that activation of mPFCv during stress is both necessary and sufficient to block stress-induced potentiation of morphine-CPP, regardless of the type of stressor. The results are consistent with a variety of other studies that implicate PFC hypoactivity in promoting addiction-related behaviors. The authors speculate that mPFCv may be responsible both for detecting stressor controllability and for dampening the stress-activated neural activity that increases drug reward and other deleterious behaviors. Rozeske, R.R., Der-Avakian, A., Bland, S.T., Beckley,

J.T., Watkins, L.R., and Maier, S.F. The Medial Prefrontal Cortex Regulates the Differential Expression of Morphine-conditioned Place Preference Following a Single Exposure to Controllable or Uncontrollable Stress. Neuropsychopharmacology, [E-pub ahead of print], 2008.

### Methylphenidate Disrupts Social Play Behavior in Adolescent Rats

Dr. Louk Vanderschuren and his colleagues at the University Medical Center Utrecht, Uterech, The Netherlands, report that low doses of methylphenidate, abolish social play behavior (i.e., pouncing and pinning which often involve boxing/wrestling and chasing) without altering general social interest (i.e, social exploration via sniffing, including anogenital) or locomotor behavior during social interactions in rats. This effect of methylphenidate did not depend upon the baseline level of social play and was not secondary to changes in locomotion. Furthermore, the play-suppressant effect of methylphenidate was not subject to tolerance or sensitization. Methylphenidate blocked both the initiation to play and the responsivity to play initiation. The effect of methylphenidate was mimicked by the noradrenaline reuptake inhibitor atomoxetine, which is also used for the treatment of ADHD, and was blocked by an alpha-2 adrenoceptor antagonist. In addition, combined administration of sub-effective doses of methylphenidate and atomoxetine suppressed social play. However, blockade of alpha-1 adrenoceptors, beta-adrenoceptors or dopamine receptors did not alter the effect of methylphenidate. These data show that methylphenidate selectively blocks the most vigorous part of the behavioral repertoire of adolescent rats, through a noradrenergic mechanism. The authors suggest that the effect of methylphenidate on social play is a reflection of its therapeutic effect in ADHD, i.e., improved behavioral inhibition. However, given the importance of social play for child development, these findings may also indicate a possible adverse side-effect of methylphenidate. Vanderschuren, L.J.M.J., Trezza, V., Griffioen-Roose, S., Schiepers, O.J.G., Van Leeuwen, N., De Vries, T.J., and Schoffelmeer, A.N.M. Methylphenidate Disrupts Social Play Behavior in Adolescent Rats. Neuropsychopharmacology, 2008 May 21 [E-pub ahead of print]. 10.1038/npp.2008.10. PMID: 18496520

### The Relative Abuse Potential of Oral Oxycodone, Hydrocodone and Hydromorphone in Healthy Non-Dependent Prescription Opioid Abusers

Epidemiological studies and law enforcement data suggest that the abuse, medical consequences and diversion of prescription opioids represent a growing public health problem in the United States. Various opioid drugs are prescribed for pain relief, such as hydrocodone (brands include Vicodin, Anexsia, Lorcet, Norco), oxycodone (brands include Oxycontin, Oxycet, Percocet, Percodan), hydromorphone (brands include Dilaudid, Hydrostat IR, Palladone), and morphine. It is commonly believed that these drugs differ in their relative risks for abuse with some having greater abuse potential than others; indeed, physicians are inclined to prescribe more frequently those drugs presumed to have lower abuse potential in order to reduce the risk of misuse. Hydrocodone, for example, is the most commonly prescribed opioid in the United States, accounting for approximately 47% of the total number of opioid prescriptions, and is also less stringently regulated under the Federal Controlled Substances Act. Despite the precipitous rise of abuse of prescription opioids in the United States over the last decade, there have been few controlled comparisons of the abuse liability of the most commonly used opioids. Dr. Sharon Walsh and her colleagues at the University of Kentucky conducted an outpatient study employing a double-blind, randomized, within-subject, placebo-controlled design to examine the relative abuse potential and potency of oral oxycodone (10, 20 & 40 mg), hydrocodone (15, 30 & 45 mg), hydromorphone (10, 17.5 & 25 mg) and placebo. Nine healthy adult volunteers with sporadic prescription opioid abuse participated in 11 experimental sessions (6.5 hr in duration)

conducted in a hospital setting. All three opioids produced a typical mu opioid agonist profile of subjective (increased ratings of liking, good effects, high and opiate symptoms), observer-rated, and physiological effects (miosis, modest respiratory depression, exophoria and decrements in visual threshold discrimination) that were generally dose-related. The overall profile of action did not differentiate these three drugs suggesting that they have similar abuse liability characteristics. Relative potency assays revealed that oxycodone was roughly equipotent to or slightly more potent than hydrocodone. Hydromorphone was only modestly more potent (less than two-fold) than either hydrocodone or oxycodone, which is inconsistent with prior estimates arising from analgesic studies. Estimates from prior studies based on the strength of these drugs to provide pain relief (rather than on their abuse-related, subjective features) have indicated that oxycodone and hydrocodone are approximately equally powerful analgesics and that hydromorphone is 4-7 more powerful than either. The present study suggests that the abuse liability profile and relative potency of these three commonly used opioids do not differ substantially from one another and that other factors may account for differential rates of abuse such as availability and/or formulation. These data also suggest that analgesic potency may not accurately reflect relative differences in the abuse liability of prescription opioids. Therefore, physicians who prescribe opioids should choose the drug which provides the best pain relief and side effect profile for a given patient while recognizing that these drugs may possess comparable risk for abuse. Walsh, S.L., Nuzzo, P.A., Lofwall, M.R., and Holtman, J.R., Jr. The Relative Abuse Liability of Oral Oxycodone, Hydrocodone and Hydromorphone Assessed in Prescription Opioid Abusers. Drug and Alcohol Dependence, 2008 Jul 5. [E-pub ahead of print]

### Menstrual Cycle Modulates Striatal Dopamine in Drug-Naive Cynomolgus Monkeys

Several studies have reported that the subjective effects of abused stimulants in women vary with the menstrual cycle. Given the role of the brain dopamine system in abused drugs, these menstrual cycle effects may be mediated by interactions between gonadal hormones and dopamine. Drs. Paul Czoty and Michael Nader and colleagues at Wake Forest University School of Medicine conducted the first non-human primate study to examine whether basal measures of DA D2 receptor availability vary with the menstrual cycle phase. They tested seven drug-naive, individually-housed female cynomolgus monkeys using the D2-like receptor ligand [18F]fluoroclebopride (FCP). Menstrual cycle phase was determined by serum progesterone levels on the day of the PET scan. In both the caudate nucleus and the putamen, D2 receptor availability was found to be lower during the follicular phase than in the luteal phase. Previous studies examining menstrual cycle effects on D2 receptor availability in female human subjects have reported mixed results, including effects consistent with the present results, opposite the present results, and a report of no effects. Drs. Czoty, Nader and colleagues note that there are several potential explanations for these discrepancies, including their use of monkeys with no drug history of any kind (other than veterinary care with ketamine) and their use of a state-of-the-art primate microPET camera with high resolution. Whether the lower D2 receptor availability observed in the follicular phase this study reflects lower D2 receptor densities or higher levels of extracellular dopamine in the follicular phase is unclear; however, the authors note that rodent studies have shown that estrogen, which is higher in the follicular phase than luteal, has been shown to increase dopamine release. Several studies have shown that D2 receptor availability is inversely related to vulnerability to the abuse-related effects of cocaine. The present data, therefore, suggest that such effects in females would be greater in the follicular phase, which is an outcome that has been observed in several studies examining the subjective effects of stimulants in humans. Also, NIDA grantee Dr. Nancy Mello of the Harvard Medical School reported in 2007 that a low dose

of cocaine produced a considerably greater progressive ratio breakpoint during the follicular phase than in the luteal phase in cynomolgus monkeys (Mello, N.K., Knudson, I.M., and Mendelson, J.H.. Sex and Menstrual Cycle Effects on Progressive Ratio Measures of Cocaine Self-Administration in Cynomolgus Monkeys. Neuropsychopharmacology, 32, pp. 1956-1966, 2007). Although only females were studied in the present study, data from a prior published study by these researchers examining D2 receptor availability in individually-housed male monkeys permitted an examination of sex differences. Results from that study indicated that D2 receptor availability in both the caudate nucleus and the putamen was lower than seen in females in either the luteal or follicular phase. This research highlights the need for models of the neurobiology of addiction to incorporate sex differences and the interactions of gonadal hormones and neurotransmitter systems underlying addiction. Czoty, P.W., Riddick, N.V., Gage, H.D., Sandridge, M., Nader, S.H., Garg, S., Bounds, M., Garg, P.K., and Nader, M.A. Effect of Menstrual Cycle Phase on Dopamine D2 Receptor Availability in Female Cynomolgus Monkeys.
Neuropsychopharmacology. 2008 Feb 6. [E-pub ahead of print]

### Developmental Differences In Cocaine-Induced Behavioral Sensitization In The Mouse

Although it is fairly well established that adolescent animals differ from adults in their behavioral and neurochemical sensitivity to drugs of abuse, less is known about the long-term neurobehavioral consequences of adolescent drug exposure. With rats, some investigators have found that adolescent cocaine exposure results in differential sensitivity to cocaine during adulthood, while others have failed to find this effect. The current experiment by Dr. M. Foster Olive sought to examine whether adolescent mice exposed to cocaine would be differentially sensitive to the behavioral and neurochemical effects of cocaine compared to mice similarly treated as adults. Initially, systemically administered cocaine produced increased locomotor activity in all mice, whereas saline had no effect. However, after 9 days of cocaine treatment, adolescent mice displayed higher levels of locomotor activity compared to comparably treated adults. Following 10 days of abstinence, a cocaine challenge produced higher levels of locomotor activity in adolescent mice with this cocaine history than in the adult group with similar prior drug exposure. Changes in central transmitter systems involved in motivational circuitry were assessed with in vivo microdialysis for dopamine and glutamate levels in the nucleus accumbens following the cocaine challenge. Compared to the mice previously treated with saline, mice with prior nine-day cocaine treatment tended to show larger increases in dopamine dialysate, and adult mice displayed greater peak dopamine dialysate levels as compared with the adolescents. There were no differences in levels of extracellular glutamate. The current findings reveal that although adolescent mice develop greater behavioral sensitization to the locomotor-stimulating effects of cocaine, this difference cannot be explained by age-related differences in limbic dopamine stimulation. Thus, the neurochemical mechanisms that account for greater locomotor sensitization in adolescent mice are yet to be determined. Camarini R, Griffin, W.C., Yanke, A.B., dos Santos, B.R. and Olive, M.R. Effects of Adolescent Exposure to Cocaine on Locomotor Activity and Extracellular Dopamine and Glutamate Levels in Nucleus Accumbens of DBA/2J mice. Brain Res. 1193, pp. 34-42, 2008.

### Distal Cues in the Environment Produce Cue Reactivity in Abstinent Smokers

Smoking research has primarily focused on proximal cues (cue directly linked to smoking behavior) alone, or proximal cues in the presence of distal cues. Dr. Cynthia Conklin and colleagues investigated differences in smoking cue reactivity produced by proximal cues versus those produced by distal cues

(indirectly linked, e.g., environmental cues). These cues were presented as pictorial stimuli, and featured either proximal or distal cues, but not both. The distal (environmental) cues included three smoking contexts and three non-smoking contexts. The proximal cues included three smoking cues (e.g., cigarette in ashtray, lighter, pack of cigarettes), and three nonsmoking cues. The six environmental cues were combined with the six proximal cues in a counter-balanced 12-trial cue reactivity paradigm. Adult smokers abstained from smoking for 6 hours prior to cue reactivity testing. During the session, heart rate and skin conductance were monitored, and following each pictorial stimuli presentation, subjective ratings were taken for craving, vividness, relevance, negative affect, positive affect, excited and calm. Both types of smoking cues elicited craving, with proximal cues eliciting higher craving ratings than distal cues. Smokers rated smoking cues as more vivid and more relevant than nonsmoking cues, and proximal cues were more vivid and more relevant than distal cues. Similar results were found with negative affect. Positive affect, on the other hand, was elicited by distal cues more than proximal cues. Although there was no main effect for excitement when comparing smoking and nonsmoking cues, there was a pairwise interaction that indicated that proximal cues elicited higher ratings on excitement as compared to distal cues. Results from this study indicate that it is possible to develop smoking environmental (distal) cues, using pictorial stimuli that successfully produce cue reactivity in abstinent smokers. In fact, smokers in this study were robustly reactive to the environmental cues and, to a lesser extent, proximal cues that are more often manipulated in craving and intervention research. Conklin, C.A., Robin, N., Perkins, K.A., Salkeld, R.P. and McClernon, F.J. Proximal Versus Distal Cues to Smoke: The Effects of Environments on Smokers' Cue-Reactivity. Exper. Clin. Psychopharm. 16(3), pp. 207-214, 2008.

### Chronic Nicotine Restricts Weight Gain and Alters Expression of Two Neuropeptides that are Markers for Activation of the Hypothalamic-Pituitary Axis (HPA)

Long-time NIDA grantee, Dr. Burt Sharp, is investigating possible mechanisms responsible for stress-induced effects of chronic nicotine. Dr. Sharp has examined corticotropin-releasing factor (CRF) and arginine vasopressin (AV) as indicators of a stress reactivity. He found that rats self-administering (SA) intravenous nicotine during a 23 hour access period ate less than free fed saline SA control animals. This restricted weight gain was not simply due to lower calorie intake, as pair-fed controls gained more weight (free fed > pair-fed> nicotine SA). During nicotine SA, antibody probes of CRF and AV were used to visualize mRNA expression. While no differences were found between free-fed and pair-fed rats, animals in the chronic nicotine group had decreased CRF levels in the paraventricular nucleus, and significant increases in AV mRNA. When nicotine SA was extinguished (e.g., nicotine no longer available as a consequence of lever pressing), there was a reversal of the mRNA findings, with no signal intensity differences between nicotine SA and saline SA rats. Since chronic nicotine enhances the HPA response to mild footshock stress (mFSS), an experiment was conducted to examine the responsiveness of a subset of PVN neurons under mFSS as compared to mFSS + nicotine. Rats were trained to lever press to SA nicotine for 20 sessions (one session per day), then mFSS was introduced. PVN+ AV neurons responded to mFSS with increased mRNA expression and chronic nicotine augmented this increase. Although mFSS increased mRNA expression of CRF, chronic nicotine did not promote further increases. However, when neurons expressed mRNA for both AV and CRF, the mFSS-induced increases were further augmented by chronic nicotine. These data suggest that chronic nicotine produces a stress-like behavioral phenotype, (e.g., lower weight gain not due solely to reduced calorie intake), and augments stress-induced mRNA increases indexed by two markers of HPA axis activation. Yu, G., Chen, H., Zhao, W., Matta, S.G. and Sharp, B.M. Nicotine Self-Administration Differentially Regulates Hypothalamic

Corticotropin-Releasing Factor and Arginine Vasopression mRNAs and Facilitates Stress-Induced Neuronal Activation. J. Neurosci. 28(1), pp. 2773-2782, 2008.

### Blocking the Toll-like Receptor 4 (TLR4) Eliminates Neuropathic Pain in Rats

NIDA-grantee Dr. Linda Watkins and colleagues (University of Colorado, Boulder) have been looking at the involvement of spinal microglia in pain and opioid analgesia. The present studies demonstrate that the TLR4 is critical for maintaining neuropathic pain following sciatic nerve chronic constriction injury (CCI) in rats. Established neuropathic pain was reversed by an intrathecally delivered TLR4 receptor antagonist derived from lipopolysaccharide. Additionally, (+)-naltrexone, (+)-naloxone, and (-)-naloxone, which were also shown to be TLR4 antagonists, completely reversed neuropathic pain with chronic infusion. Immunohistochemical analyses of spinal cord tissue following chronic infusion revealed suppression of CCI-induced microglial activation by (+)-naloxone and (-)-naloxone. Together, these data support the conclusion that neuron-to-glia signaling through the TLR4 is important for maintaining neuropathic pain. The finding with (+)-naloxone is of potential clinical relevance since (+)-naloxone is an antagonist that is inactive at neuronal mu-opioid receptors that produce analgesia. Thus, drugs like (+)-naloxone may be useful clinically to suppress glial activation and pain while not interfering with mu-opioid agonist's ability to also suppress pain. Hutchinson, M.R., Zhang, Y., Brown, K., Coats, B.D., Shridhar, M., Sholar, P.W., Patel, S.J., Crysdale, N.Y., Harrison, J.A., Maier S.F., Rice, K.C., and Watkins, L.R., European Journal of Neuroscience, pp. 1-10, 2008.

### Endocannabinoid Signaling Controls Anxiety in Hamsters

Available evidence suggests that endocannabinoid receptors and endogenous cannabinoids in the limbic system of the brain modulate emotional responding. NIDA investigators sought to investigate the existence of an endocannabinoid signaling system in the Syrian hamster using neuroanatomical, biochemical and pharmacological approaches. Using in vitro receptor binding and quantitative autoradiography they found a heterogeneous distribution of cannabinoid binding sites in hamster brain similar to that observed in rat. Dense binding was detected in basal ganglia and other motor structures, limbic structures including the hippocampus and cingulate cortex. Lower levels of binding were detected in the amygdala and brainstem. They also found that FAAH, the predominant enzyme that controls deactivation of the endogenous cannabinoid anandamide in other rodents plays a similar role in hamsters. They reported also that WIN55,212-2 induced CB1-mediated motor ataxia. Blockade of CB1 with rimonabant induced anxiogenic-like behavior in the elevated plus maze and stimulation of CB1 blocked anxiety in the plus maze. Finally, they found that neither unconditioned nor conditioned social defeat in the hamster is mediated by CB1 receptor activation. This research provides the first evidence that the hamster brain contain functional cannabinoid CB1 receptors, as well as FAAH, similar to that observed in non-hibernating rodent species. Moreover, this system serves naturally to modulate anxiety-like behavior in the hamster. Finally, the data suggest that cannabinoids and benzodiazepines differentially modulate anxiety. That is, although the benzodiazepine, diazepam, reduced anxiety-like behavior in the elevated plus maze and in the social defeat models, CB1 activation had no effect on social defeat. It did, however, induce anxiolytic effects in the plus maze. Moise, A.M., Eisenstein, S.A., Astarita, G., Piomelli, D., and Hohmann, A.G. An Endocannabinoid Signaling System Modulates Anxiety-like Behavior in Male Syrian Hamsters. Psychopharmacology, 2008, on-line publication.

### Stimulus-Reward Learning about Cocaine in Adolescents vs Adults

This study investigated the effects of cocaine self-administration on stimulus-reward learning in adult male rats depending upon whether the drug experience occurred during adolescence or adulthood. In addition, to assess the effects of contingent vs noncontingent (or passive) cocaine exposure, a triadic design (i.e., continent cocaine, noncontingent cocaine, saline) was used with both age groups. Following drug exposure, all rats were returned to their home cages for an 18 day drug free period. Then they were assessed in a conditioned cue preference apparatus where they learned to associate particular cues with a food reward or lack thereof. Results indicated first that cocaine self-administration behavior was similar in adolescent and adult rats. However, despite similarities in the amount of cocaine consumed in adult and adolescent rats, subsequent learning was affected differentially after the drug-free period. Rats contingently self-administering cocaine or passively exposed to cocaine during adulthood showed learning deficits in the conditioned cue preference task, indicating a deficit in the stimulus-reward learning function of the amygdala reward system. Rats exposed to contingent or noncontingent cocaine during adolescence, on the other hand, showed strong conditioned cue preference. This indicates that the stimulus-reward learning function of the amygdala memory system was intact after adolescent cocaine exposure. Under passive saline control conditions, the strength of conditioning was similar in rats for whom drug-onset began either in adolescence or adulthood. These findings support a view that similar intakes of cocaine can have different consequences when drug use begins during adolescence vs. adulthood. The authors further suggest that adolescent rats are not as vulnerable to cocaine-induced devaluation of natural rewards (i.e., the comparison of food reward relative to cocaine) compared to adult rats and that this reduced sensitivity protects them from later impairment in stimulus-reward learning. Kerstetter, K.A., and Kantak, K.M. Differential Effects of Self-administered Cocaine in Adolescent and Adult Rats on Stimulus-reward Learning. Psychopharmacology, 194, pp. 403-311, 2007.

### Neural Substrates Involved in Context Reinstatement of Cocaine Responding

Environmental cues associated with drugs of abuse contribute to the development, maintenance and relapse to addiction, but the neurobiological mechanisms responsible for these effects have yet to be fully elucidated. In the present report, Dr. Katherine Kantak and her colleagues investigated the role of the ventral hippocampus in regulating context and discrete cue-induced reinstatement of cocaine-seeking behavior. Animals were trained to self-administer cocaine in the presence of distinct contextual or discrete cues. Some animals had extensive exposure (21 days) to the drug associated contexts, whereas other had short-term exposure (3 days). To test the role of the hippocampus, half the animals in each training group were conditioned after infusion of lidocaine to inactivate the ventral hippocampus and half were trained following saline infusions into the same structure. Results showed that inactivation of the ventral hippocampus by lidocaine during conditioning blocked context-induced reinstatement in rats with short- but not long-term exposure to the contextual cues. These results suggest that hippocampal processing of drug-related information is still in progress after 3 pairings but not after 21 context-drug pairings. In contrast to the results for contextual cue-induced reinstatement, lidocaine did not affect reinstatement by discrete cues, even though rats had only 3 days of exposure, suggesting that either the ventral hippocampus isn't involved in processing of discrete cues, or that processing of these cues is completed after three days. Overall the findings suggest that the ventral hippocampus is involved in associative learning early in the development of cocaine addiction. Once the cocaine-paired cues are no longer novel, however, other brain areas, such as prefrontal cortex, may be

more relevant for processing the contextual cues. Arkins, A. L., Mashhoon, Y., and Kantak, K.M. Hippocampal Regulation of Contextual Cue-induced Reinstatement of Cocaine-seeking Behavior. Pharmacology, Biochemistry and Behavior, 90, pp. 981-491, 2008.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2008

## Research Findings - Behavioral and Brain Development Research

### Age of Methylphenidate Treatment Initiation in Children with ADHD and Later Substance Abuse: Prospective Follow-Up Into Adulthood

The purpose of this study was to investigate whether the development of substance abuse disorders is related to the age at which stimulate treatment begins in children with attention deficit hyperactivity disorder (ADHD). Using a prospective longitudinal design, 176 methylphenidate-treated children were followed. Some of these children had begun stimulant treatment as early as age 6 and for others, the treatment did not begin until age 12. These Caucasian male children who were diagnosed with ADHD, but without conduct disorder, were reassessed at late adolescence (mean age=18.4 years) and adulthood (mean age=25.3). The study also included one hundred seventy-eight comparison subjects. Childhood predictor variables used in the Cox proportional hazards model included: age at initiation of methylphenidate treatment, total cumulative dose of methylphenidate, treatment duration, IQ, severity of hyperactivity, socioeconomic status, and lifetime parental psychopathology. Separate models examined a number of lifetime outcome measures which included: any substance use disorder, alcohol use disorder, non-alcohol substance use disorder, stimulant use disorder, antisocial personality, mood, and anxiety disorders. The results indicated a significant positive relationship between age of treatment initiation and non-alcohol substance use disorder. Specifically, the chance of developing a substance use disorder was greater the later in age that stimulant treatment began. Additional post hoc analyses showed that the relationship between age at stimulant treatment initiation and later substance use disorder was explained by the development of antisocial personality disorder which is often comorbid with substance abuse disorders. No relationship was found between the age at first methylphenidate treatment and mood and anxiety disorders. The results found in this study did not find that beginning stimulant treatment relatively early in the life of children with ADHD is associated with an increased risk for negative outcomes. Mannuzza, S., Klein, R., Truong, N., Moulton, J., Roizen, E., Howell K., and Castellanos, F. Age of Methylphenidate Treatment Initiation in Children with ADHD and Later Substance Abuse: Prospective Follow-Up into Adulthood. The American Journal of Psychiatry, 165 (5), pp. 604-609, 2008.

### Fatty Acid Ethyl Esters in Meconium are Associated with Poorer Neurodevelopmental Outcomes to Two Years of Age

The aim of this study was to examine the relationship between fatty acid ethyl esters (FAEE) in meconium and neurodevelopment in infants at 6.5 months, 1 year, and 2 years of age who were exposed to alcohol in utero. The current

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study reports on a secondary analysis of the data collected in a prospective longitudinal study of high risk mothers and their infants. Meconium was collected from 219 newborns shortly after birth and neurodevelopment was assessed with the Bayley Scales of Infant Development (2nd edition) which included the Mental and Psychomotor scales. Increasing concentrations of FAEE were significantly correlated with poorer mental and psychomotor development at all follow-up visits even after controlling for a number of prenatal and maternal factors. The results of this study showed that elevated FAEE in meconium may be a marker in identifying newborn infants who may be at risk for mental and psychomotor delays from alcohol exposure in utero, but do not show the typical characteristic facies of FAS. Early intervention is critical in these children and the results of this study are important in that the meconium analysis described by these authors may be a reliable means of identifying these at-risk children at birth. Peterson, J., Kirchner, H., Xue, W., Minnes, S., Singer, L., and Bearer, C. Fatty Acid Ethyl Esters in Meconium are Associated with Poorer Neurodevelopmental Outcomes to Two Years of Age. Journal of Pediatrics, 152(6), pp. 788-792, June, 2008.

### Meaningful Differences in Maternal Smoking Behavior during Pregnancy: Implications for Infant Behavioral Vulnerability

Dr. Laurie Wakschlag and her colleagues used the 9-month-old sweep of the Millennium Cohort Study, a cohort of over 18,000 infants born in 2000-2, to examine the effects of smoking during pregnancy on problem behavior in offspring. Prior research has shown that the prenatal exposure to maternal smoking is associated with problem behavior in infants, but it is not clear whether these effects are associated with maternal characteristics that distinguish persistent smoking from quitting or whether they are due to teratological effects. In this study, mothers were classified as pregnancy non-smokers, quitters and light or heavy smokers. The Carey Infant Temperament Scale was used to assess temperamental positive mood, receptivity to novelty and regularity. Mothers who smoked heavily during pregnancy had infants with the lowest scores of easy temperament and low positive mood. In contrast, mothers who quit smoking during their pregnancy had infants with the highest scores of easy temperament. There also appeared to be a protective effect of quitting during pregnancy in that these mothers' infants had a decreased risk of distress to novelty and irregularity in comparison to those mothers who had never smoked. The results of this study suggest that offspring behavior associated with pregnancy smoking is complex and multi-determined. Future research is needed to elucidate the differences in maternal personality characteristics between quitters and persistent smokers and how these differences help to predict early vulnerabilities and offspring behavioral patterns over time. Pickett, K., Wood, C., Adamson, J., DeSouza, L., and Wakschlag, L. Meaningful Differences in Maternal Smoking Behavior during Pregnancy: Implications for Infant Behavioral Vulnerability. Journal of Epidemiology and Community Health, 62(4), pp. 318-324, 2008.

### Children's Cognitive-Behavioral Functioning at Age 6 and 7: Prenatal Drug Exposure and Caregiving Environment

This study examined the relationship of prenatal drug exposure (PDE) and caregiving environment to cognitive, academic, and behavioral performance. Participants included 111 with PDE that were part of a longitudinal randomized controlled trial of a home-based intervention among drug-using women and their infants. A total of 62 non-drug exposed children were recruited from the same community to serve as controls. At ages 6 and 7, children were administered the Stanford-Binet Intelligence Scales, Fourth Edition, the Wide Range Achievement Test and the Child Behavior Checklist. Numerous theoretically and empirically derived confounders that examined perinatal and

environmental factors were included in the multivariate analyses. The results indicated that after adjustment for the confounding variables, there were no significant exposure-group differences on measures of cognitive, academic or behavior problems. Females had higher scores on overall IQ, higher reading achievement scores and fewer caregiver-reported attention and aggression problems. This gender difference was evident regardless of PDE status. The children who participated in this study were from low income families and scores obtained were well below normative expectations. Future studies examining the effects of prenatal exposure to drugs need to be aware of the influence that poverty has on cognitive and behavioral development of children so that attributions to PDE are accurate. Nair, P., Black, M., Ackerman, J., Schuler, M., and Keane, V. Children's Cognitive-Behavioral Functioning at Age 6 and 7: Prenatal Drug Exposure and Caregiving Environment. Ambulatory Pediatrics, 8(3), pp. 154-162, 2008.

### Prenatal Cocaine Exposure: Drug and Environmental Effects at 9 Years

Dr. Sonia Minnes and her colleagues investigated the effects of prenatal cocaine exposure (CE) in a large sample of children with a high follow-up rate, controlling for a number of confounding variables such as polydrug exposure, blood lead levels, iron-deficiency anemia (IDA), quality of caregiving environment and foster/adoptive care. Three hundred and seventy one children in a longitudinal, prospective study from birth were assessed for IQ and school achievement at 9 years of age (192 cocaine exposure; 179 non-cocaine exposure). No effects were seen in school achievement measures. Poorer perceptual reasoning IQ was seen in CE children; the degree of impairment was linearly related to a cocaine metabolite. Effects were mediated by smaller birth head circumference, indicating a relationship with fetal brain growth. Positive effects of the home environment and negative effects of alcohol, lead, and marijuana exposure were additive. The most pervasive negative effects were associated with lead exposure, underscoring the need for stronger public health efforts. Lower lead levels and better home environments were seen in those CE children who were placed in foster/adoptive care. This study shows the importance of documenting environmental factors in behavioral teratology studies. Singer, L., Nelson, S., Short, E., Min, M., Lewis, B., Russ, S., and Minnes, S. Prenatal Cocaine Exposure: Drug and Environmental Effects at 9 years. Journal of Pediatrics, 153(1), pp. 105-111, 2008.

### The Development of Corpus Callosum Microstructure and Associations with Bimanual Task Performance in Healthy Adolescents

Studies utilizing conventional magnetic resonance imaging studies have provided important information regarding the development of the corpus callosum (CC). This study used diffusion tensor imaging to examine the relationship of fine motor skills with white matter microstructural development of the CC in healthy children, adolescents, and young adults (ages 9 - 24 years). Fractional anisotropy (FA), which is a measure of white matter's structural organization, was the primary DTI variable. An alternating finger tapping test was used to assess interhemispheric transfer and motor speed. Relationships between behavioral performance on the tapping task and white matter microstructure, age, and gender were examined. Younger subjects performed the unilateral and bimanual finger tapping task significantly slower. Improved motor performance was correlated with increased white matter integrity in the splenium. The splenium of the CC is believed to be primarily involved in the transmission of interhemispheric signals from the posterior cortical regions. Gender differences were also noted in that males outperformed females. Decreases in alternating finger tapping time and increases in FA likely reflect increased myelination in the CC and more efficient

neuronal signal transmission. The data from this study suggest that white matter integrity continues to develop until 18 years of age, which is consistent with findings from conventional MRI studies that show similar age related changes in splenium white matter volume. This study has expanded the utility of diffusion tensor imaging by using this method to demonstrate relationships between fine motor skills and underlying white matter microstructure in childhood and adolescence. Muetzel, R., Collins, P., Mueller, B., Schissel, A., Lim, K., and Luciana, M. The Development of Corpus Callosum Microstructure and Associations with Bimanual Task Performance in Healthy Adolescents. Neuroimage, 39(4), pp. 1918-1925, 2008.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2008

## Research Findings - Clinical Neuroscience Research

### Brain Monoamine Oxidase A (MAO A) Activity Predicts Trait Aggression

A group of scientists at Brookhaven National Laboratory used PET to determine the activity of MAO A in the brain of healthy, male non-smokers. The study was based on reports in the literature that a gene variant resulting in reduced expression of MAO A was associated with increased aggression. The PET method using a radioligand specific for MAO A allowed direct evidence of MAO A activity in the brain. Personality traits were assessed with a questionnaire. Results demonstrated a significant negative correlation between reported aggression tendencies and MAO A activity; greater aggression was associated with lower activity. This was true throughout the brain and only for the aggression trait (and not others) as assessed by the questionnaire. The reduced activity was about 15% for the increased aggression which accounted for more than 30% of the variance. However, the result was found for those who carried the allele for low MAO A expression as was as for high, suggesting there was some other factor--likely environmental influences during development--that was affecting the results in the studies which measured only the genetic differences (coupled with environment). These directly measured results provide a better intermediate (or endo-) phenotype for aggressive tendencies which are also risk factors for drug abuse. Alia-Klein, N., Goldstein, R.Z., Kriplani, A., Logan, J., Tomasi, D., Williams, B., Telang, F., Sumay, E., Biegon, A., Craig, I.W., Henn, F., Wang, G.-J., Volkow, N.D., and Fowler, J.S. Brain Monoamine A Oxidase A Activity Predicts Trait Aggression. J. Neurosci., 28(19), pp. 5099-5104, 2008.

### Heritability of Evoked Potential Components during an Action Monitoring Task

Anokhin and colleagues at Washington University used a visually-presented task to assess the heritability of evoked potentials in a task where twin subjects could monitor their success. That is, the task was simple (responding rapidly to a central letter where the distracters that flanked the letter were either the same or different) so that an error of commission was immediately recognized. An error produced a negative-going peak within the first 100 msec and a positivity at about 250 msec. A correct response produced a negative peak after 300 msec. The study was motivated from synthesis of the literature that a reduced error-related negativity is associated with less controlled, disinhibited, and reckless behaviors which are risk factors for drug-taking. If it could be demonstrated that these electrical measures are genetically-determined, the ERPs could provide an endophenotype to associated psychopathologies including drug abuse. By using MZ and DZ twins it was demonstrated that all three responses were 40%-60% heritable and there were

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correlations among them suggesting some common genetic bases. The authors state that this is the first study to provide evidence for heritable individual differences in the neural substrates of action monitoring suggesting that the three cortical electrical responses could be endophenotypes. Anokhin, A., Golosheykin, S., and Heath, A.C. Heritability of Frontal Brain Function to Action Monitoring. Psychophysiol., 45, pp. 524-534, 2008.

### A Risk Allele for Nicotine Dependence in CHRNA5 is a Protective Allele for Cocaine Dependence

In a highly collaborative study led by L. Bierut at Washington University, a gene that codes the alpha-5 subunit of the nicotinic acetylcholine receptor which had shown to be associated with nicotine dependence has now been found to be associated with cocaine dependence but as a protective factor--i.e., the opposite as that found for nicotine dependence. This unexpected conclusion was reached after extensive statistical analysis and replication in an independent sample including smokers/non-smokers and cocaine-dependent/non-dependent users. The postulated explanation involves the effect on specific nicotine receptor function which may act differently for the effects of nicotine as compared to cocaine. Grucza, R.A., Wang, J.C., Stitzel, J.A., Hinrichs, A.L., Saccone, S.F., Saccone, N.L., Bucholz, K.K., Cloninger, C.R., Neuman, R.J., Budde, J.P., Fox, L., Bertelsen, S., Kramer, J., Hesselbrock, V., Tischfield, J., Nurnberger, Jr., J.I., Almasy, L., Goate, A.M., and Bierut, L.J. A Risk Allele for Nicotine Dependence in CHRNA5 is a Protective Allele for Cocaine Dependence. Biol. Psychiat., (doi:10.1016), 2008.

### Reduced White Matter Integrity in Smokers as Assessed by Diffusion Tensor Imaging

In a multi-site, international study the integrity of white matter of the corpus callosum was assessed by diffusion tensor imaging. Comparing smokers with non-smokers as well as smokers with low and high (Faegerstrom) smoking scores, the data suggest that smoking reduces the integrity of the white matter in the corpus callosum. Paul, R.H., Grieve, S.M., Niaura, R., David, S.P., Laidlaw, D.H., Cohen, R., Swet, L., Taylor, G., Clark, C.R., Pogun, S., and Gordon, E. Chronic Cigarette Smoking and the Microstructural Integrity of White Matter in Healthy Adults: A Diffusion Tensor Imaging Study. Nicotine & Tobacco Res., 10(1), pp. 137-147, 2008.

### The Effect of Sleep Disturbances on Cognitive Function in Abstinent Cocaine Users

Peter Morgan in Robert Malison's laboratory assessed changes in the sleep architecture and sleep-associated learning in the two weeks of abstinence following binge cocaine ingestion. In the first 9 days of abstinence REM sleep significantly increased while REM latency decreased compared to immediate post-drug days and longer abstinence periods. Accordingly, slow-wave sleep was reduced. A visual texture discrimination task has been shown in healthy subjects to be sleep-stage dependent as was shown in this study for cocaine subjects. However, those subjects whose sleep architecture was disrupted showed deficits in this task. These results suggest that disturbances in sleep in cocaine use (and abstinence) could be directly related to some cognitive deficits. Thus treatment strategies should consider the effects on sleep quality. Morgan, P.T., Pace-Schott, E.F., Sahul, Z.H., Coric, V., Stickgold, R., and Malison, R.T. Sleep Architecture, Cocaine, and Visual Learning. Addiction, 103, pp. 1344-1352, 2008.

### A Review of the Abuse and Dependence Liability of

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### Benzodiazepine-type Drugs

Stephanie Licata and her colleague at the McLean Hospital/Harvard Medical School have provided this review of the literature on the increasingly important issue of the abuse potential of benzodiazepine-type drugs. Over the past several decades, benzodiazepines and the newer non-benzodiazepines have become the anxiolytic/hypnotics of choice over the more readily abused barbiturates. While all drugs from this class act at the GABA(A) receptor, benzodiazepine-type drugs offer the advantage of being safer and better tolerated. However, there is still potential for these drugs to be abused, and significant evidence exists to suggest that this is a growing problem. This review examines the behavioral determinants of the abuse and dependence liability of benzodiazepine-type drugs. Moreover, the pharmacological and putative biochemical basis of the abuse-related behavior is discussed. Licata, S.C., and Rowlett, J.K. Abuse and Dependence Liability of Benzodiazepine-Type Drugs: GABA(A) Receptor Modulation and Beyond. Pharmacology, Biochemistry and Behavior, 90(1), pp. 74-89, 2008.

### A New Approach to Understanding the Impact of Circadian Disruption on Human Health

Mark Rea and colleagues at Rensselaer Polytechnic Institute conducted this study to examine the relationship between circadian disruption and health outcomes. Light and dark patterns are the major synchronizer of circadian rhythms to the 24-hour solar day. Disruption of circadian rhythms has been associated with a variety of maladies. Ecological studies of human exposures to light are very few, making it difficult to determine if light-induced circadian disruption directly affects human health. A newly developed field measurement device recorded circadian light exposures and activity from day-shift and rotating-shift nurses. Circadian disruption also was determined for rats subjected to a consistent 12-hour light/12-hour dark pattern (12L:12D) and ones subjected to a "jet-lagged" schedule. Humans and rats exposed to the consistent light-dark pattern exhibited pronounced similarities in their circular cross-correlation functions and 24-hour phasor representations except for an approximate 12-hour phase difference between species. The phase difference reflects the diurnal versus nocturnal behavior of humans versus rodents. Individuals that worked a rotating shift and rats subjected to the "jet-lagged" schedule exhibited significant reductions in phasor magnitudes compared to the 12L:12D rats and workers on a day shift. The reductions in the 24-hour phasor magnitudes indicate a loss of behavioral entrainment compared to both humans and rats with regular light-dark exposure patterns. This paper provides a quantitative foundation for systematically studying the impact of light-induced circadian disruption in humans and in animal models. Moreover, it should now be possible to bridge ecological studies of circadian disruption in humans to parametric studies of the relationships between circadian disruption and health outcomes using animal models. Rea, M.S., Bierman, A., Figueiro, M.G., and Bullough, J.D. A New Approach to Understanding the Impact of Circadian Disruption on Human Health. Journal of Circadian Rhythms, 6:7, doi:10.1186/1740-3391-6-7, 2008.

### Assessment of Forebrain-Dependent Trace Eyeblink Conditioning in Chronic Cannabis Users

Patrick Skosnik and colleagues at the Indiana University used a forebrain-dependent trace eyeblink conditioning procedure in humans to compare results with known results from similar studies in CB1 knockout mice. While CB1 knockout mice exhibit striking impairments on a cerebellar-dependent task called delay eyeblink conditioning (dEBC), these animals demonstrate intact trace EBC (tEBC). Although heavy human cannabis users also show impaired

delay EBC, their performance on tEBC is currently unknown. Therefore, 13 heavy cannabis users and 13 cannabis naive controls completed a tEBC procedure. The cannabis group exhibited similar rates of conditioned responding compared to controls in the acquisition and extinction phase. Consistent with reports of overt attentional abnormalities, the cannabis group exhibited decreased N100 ERP amplitudes to the tone CS that were unrelated to mean levels of conditioning across blocks during the acquisition phase. The lack of a significant effect of heavy cannabis use on tEBC reported here, combined with the previous report of impaired dEBC in such users, mirrors the findings observed in CB1 knockout mice, and suggests that the cannabinoid system differentially mediates forebrain- and cerebellar-dependent learning processes in both humans and animals. Edwards, C.R., Skosnik, P.D., Steinmetz, A.B., Vollmer, J.M., O'Donnell, B.F., and Hetrick, W.P. Assessment of Forebrain-Dependent Trace Eyeblink Conditioning in Chronic Cannabis Users. Neuroscience Letters, 439(3), pp. 264-268, 2008.

### Evidence for Cannabinoid Modulation of Cerebellar-dependent Learning

Patrick Skosnik and colleagues at the Indiana University examined the effect of chronic cannabis use on classical eyeblink conditioning (EBC), a cerebellar-mediated task which has been shown to be disrupted in CB1 knockout mice. While the cerebellum contains the highest density of cannabinoid receptor (CB1) in the brain, no studies have assessed the effect of exogenous cannabinoids on cerebellar-dependent learning in humans. Chronic cannabis users were evaluated. A delay EBC task was utilized, in which a conditioned stimulus (CS; 400 ms tone) co-terminated with a corneal air puff unconditioned stimulus (US; 50 ms), thus eliciting a conditioned blink response (CR). The cannabis group exhibited markedly fewer, and more poorly timed CRs as compared to drug-naive controls. There were no differences between the groups in either the unconditioned response (UR) or an EEG measure of selective attention to the CS (N100 auditory ERP), indicating that the disruption observed in the cannabis group was specific to CR acquisition. These results suggest that cannabis use is associated with functional deficits in the cerebellar circuitry underlying EBC, a finding that corroborates the recent work in CB1 knockout mice. Skosnik, P.D., Edwards, C.R., O'Donnell, B.F., Steffen, A., Steinmetz, J.E., and Hetrick, W.P. Cannabis Use Disrupts Eyeblink Conditioning: Evidence for Cannabinoid Modulation Of Cerebellar-Dependent Learning. Neuropsychopharmacology. 33(6), pp.1432-1440, 2008.

### Quantification of Drug Choice with the Generalized Matching Law in Rhesus Monkeys

Mikhail Koffarnus at the University of Michigan conducted this study to examine rhesus monkeys' drug self-administration choices between identical drug doses, different doses, different drugs (cocaine, remifentanil, and methohexital), and between drug and drug-paired stimuli. The generalized matching law provides precise descriptions of choice, but has not been used to characterize choice between different doses of drugs or different classes of drugs. The bias parameter of the generalized matching law was used to quantify preference for one reinforcer over another. Choice between identical drug doses yielded undermatching. Choice was relatively insensitive to differences in random interval schedule value when one reinforcer was replaced with drug-paired stimulus presentations. These findings suggest the bias parameter may be useful in quantitatively measuring level of preference, which would be an advantage over concurrent FR procedures that often result in exclusive choice. Koffarnus, M.N., and Woods, J.H. Quantification of Drug Choice with the Generalized Matching Law in Rhesus Monkeys. Journal of the Experimental Analysis of Behavior, 89(2), pp. 209-224, 2008.

### Antidepressant-Like Effects of Intracerebroventricular FGF2 in Rats

Cortney Turner and her colleagues tested whether administering agents that act on fibroblast growth factor (FGF) receptors would have antidepressant-like effects in rodents. The FGF system is altered in post-mortem brains of individuals with major depressive disorder (MDD), but the functional relevance of this observation remains to be elucidated. They microinjected either FGF2 (200 ng, i.c.v.) or the FG loop (FGL) of neural cell adhesion molecule (NCAM) (5 mug, i.c.v.) into the lateral ventricle of rats and tested them on the forced swim test. Activating FGF receptors acutely had an antidepressant-like effect in the forced swim test. Furthermore, chronic FGF2 decreased depression-like behavior as assessed by two independent tests. Finally, the FGF system itself was altered after FGF2 administration (showing an increase in FGFR1 mRNA in the dentate gyrus 24 h post-FGF2), suggesting the potential for self-amplification of the initial signal. These results support the potential therapeutic use of FGF2 or related molecules in the treatment of MDD and point to alternate mechanisms of neuronal remodeling that may be critical in this treatment. Turner, C.A., Gula, E.L., Taylor, L.P., Watson, S.J., and Akil, H. Antidepressant-Like Effects of Intracerebroventricular FGF2 in Rats. Brain Research, 1224, pp. 63-68, 2008.

### Valence and Salience Contribute To Nucleus Accumbens Activation

Knutson and colleagues at Stanford University used fMRI to determine the psychological properties of stimuli that activate the nucleus accumbens. Different accounts of nucleus accumbens (NAcc) function have emphasized its role in representing either valence or salience during incentive anticipation. Using an event-related fMRI paradigm, they independently manipulated valence and salience by cuing participants (healthy subjects) to anticipate certain and uncertain monetary gains and losses. NAcc activation correlated with both valence and salience. On trials with certain outcomes, NAcc activation increased for anticipated gains and decreased for anticipated losses. On trials with uncertain outcomes, NAcc activation increased for both anticipated gains and losses but did not differ between them. These findings suggest that NAcc activation separately represents both valence and salience, consistent with its hypothesized role in appetitive motivation. Knowing what properties of environmental stimuli activate the nucleus accumbens contributes to our understanding of how this brain area is involved in the rewarding properties of drugs of abuse. Cooper, J. C., and Knutson, B. Valence and Salience Contribute To Nucleus Accumbens Activation. Neuroimage 39(1), pp.538-47, 2008.

### How Subjective Valuation Contributes to Approach and Avoidance During Decision Making

Bechara and colleagues at the University of Southern California investigated whether approach and avoidance motivations influence decision making through the process of subjective valuation. Studies using the Iowa Gambling Task have revealed individual differences in performance on the task. They examined the implications of a high sensitivity to gains or losses from two perspectives which we labeled scalar multiplication and valuation by feeling. Using two versions of the Iowa Gambling Task, the evidence supported the view that asymmetry in the systems regulating approach and avoidance leads to systematic biases that translate to differences in performance. Specifically, high sensitivity in the Behavioral Activation System (BAS) translated to valuation by feeling and insensitivity to scope in the domain of gains, while high sensitivity in the Behavioral Inhibition System (BIS) translates to valuation by feeling and insensitivity to scope in the domain of losses. These

results provide a new perspective in the interpretation of impaired performance on the Iowa Gambling Task exhibited by substance abusers. Desmeules, R., Bechara, A., and Dube, L. Subjective Valuation and Asymmetrical Motivational Systems: Implications of Scope Insensitivity for Decision Making. Journal of Behavioral Decision Making, 21(2), pp. 211-224, 2008.

### Effects of Haloperidol on Delta-9-Tetrahydrocannabinol Effects in Humans

D'Souza and colleagues at Yale School of Medicine investigated the extent to which dopaminergic (DA) systems contribute to the effects of Delta-9-tetrahydrocannabinol (Delta-9-THC), by testing how pretreatment with a dopamine receptor antagonist altered the effects of Delta-9-THC in humans. A 2-test-day double-blind study was conducted in both healthy subjects (n=17) and frequent users of cannabis (n=11). The participants were administered active (0.057 mg/kg) or placebo oral haloperidol in random order followed 90 and 215 min later by fixed order intravenous administration of placebo (vehicle) and active (0.0286 mg/kg) Delta-9-THC, respectively. Consistent with previous reports, intravenous Delta-9-THC produced psychotomimetic effects, perceptual alterations, and subjective effects including "high." Delta-9-THC also impaired verbal recall and attention. Contrary to the initial hypothesis, haloperidol pretreatment did not reduce any of the behavioral effects of Delta-9-THC. In fact, haloperidol worsened the immediate free and delayed free and cued recall deficits produced by Delta-9-THC. In addition, Haloperidol and Delta-9-THC worsened distractibility and vigilance. Neither drug impaired performance on a motor screening task, the Stockings of Cambridge task, or the delayed match to sample task. Frequent users had lower baseline plasma prolactin levels and blunted Delta-9-THC induced memory impairments. Although the results are consistent with the preclinical literature in suggesting crosstalk between DA-ergic and cannabinoid systems, the results indicate that DA D-2 receptor mechanisms play a major role in mediating the psychotomimetic and perceptual altering effects of Delta-9-THC. D'Souza, D. Braley, G., Blaise, R., Vendetti, M. Oliver, S., Pittman, B, Ranganathan, M., Bhakta, S., Zimolo, Z., Cooper, T., and Perry E. Effects of Haloperidol on the Behavioral, Subjective, Cognitive, Motor, and Neuroendocrine Effects of Delta-9-Tetrahydrocannabinol in Humans. Psychopharmacology, 198(4), pp. 587-603, 2008.

### Error And Post-Error Neural Activity Associated With Adaptive Post-Error Behavior Change

Garavan and colleagues at Trinity College used fMRI to examine how neural activity during and after error commission contributes sustained post-error behavior changes and performance improvements in future trials in healthy participants. Activation of the medial frontal cortex (pMFC) activity during commission of an error has been shown previously to relate to adaptive post-error changes in response behavior on the immediately following trial. In the present study, a modification was made to a standard task that required participants to inhibit a prepotent motor response during infrequent lure trials, which were randomly interspersed among numerous go trials. Post-error behavior was manipulated by introducing a dynamic condition, in which an error on a lure trial ensured that the next lure would appear within two to seven go trials. Behavioral data indicated significantly higher levels of post-error slowing and accuracy during the dynamic condition, as well as fewer consecutive lure errors. Bilateral prefrontal cortex (PFC) and pMFC activity during the post-error period, but not during commission of the error itself, was associated with increased post-error slowing. Activity within two of these regions (right PFC and pMFC) also predicted success on the next lure trial. The findings support a relationship between pMFC/PFC activity and adaptive post-error behavior change, and lay the foundation for investigating neuronal

dysfunction that may underlie the failure of drug abusers to correct their behavior after commission errors. Hester, R., Barre, N., Mattingley, J., Foxe, J., and Garavan, H. Avoiding Another Mistake: Error and Post-Error Neural Activity Associated with Adaptive Post-Error Behavior Change. Cognitive Affective & Behavioral Neuroscience, 7(4), pp. 317-326, 2008.

### Propranolol Improves Cognitive Flexibility and Memory in Acute Cocaine Withdrawal

Beversdorf and colleagues at Ohio State University determined the effect of beta-adrenergic antagonists on cognitive performance in acute cocaine withdrawal. Their previous work revealed impaired cognitive flexibility in acute cocaine withdrawal, a cognitive domain that appears to be modulated by noradrenergic activity. Eleven subjects acutely withdrawing from cocaine were tested on tasks of cognitive flexibility as well as word fluency, attention, verbal memory, and spatial memory, off and on propranolol in a double-blinded manner. Propranolol significantly benefited certain aspects of cognitive flexibility in acute cocaine withdrawal, and improved some measures of verbal fluency and verbal recall. These results suggest that propranolol or other beta adrenergic agents may help treat cognitive impairment during cocaine withdrawal. Kelley, B., Yeager, K., Pepper, T., Bornstein, R., and Beversdorf, D. The Effect of Propranolol on Cognitive Flexibility and Memory in Acute Cocaine Withdrawal. Neurocase, 13(5-6), pp. 320-327, 2008.

### Nucleus Accumbens Mediates Effect of Reward Cues on Financial Risk Taking

Incidental reward cues that activate the nucleus accumbens (NAcc) can influence subsequent financial risk taking. Prior studies have shown that nucleus accumbens (NAcc) activation spontaneously increases before financial risk taking. As predicted, anticipation of viewing rewarding stimuli (erotic pictures in 15 healthy, heterosexual men) increased financial risk taking, and this effect was partially mediated by increases in NAcc activation. These results identify a brain process that may underlie how environmental stimuli associated with drug use not only can lead to subjective craving, but more importantly can lead to increased risk taking. Knutson, B., Wimmer, G., Kuhnen, C., and Winkielman, P. Nucleus Accumbens Activation Mediates the Influence of Reward Cues on Financial Risk Taking. Neuroreport, 19(5), pp. 509-513, 2008.

### Brain Mechanisms Leading to Over Valuing Things You Already Own

Knutson and colleagues at Stanford University used fMRI to investigate brain processes that underlie the "endowment effect", which is the tendency to place greater value on items that one owns. The "endowment effect" is of interest because it is an anomaly that violates the reference-independence assumption of rational choice theories. Healthy participants were scanned while considering six products paired with 18 different prices under buying, choosing, or selling conditions. Subjects showed greater nucleus accumbens (NAcc) activation for preferred products across buy and sell conditions combined, but greater medial prefrontal cortex (MPFC) activation in response to low prices when buying versus selling. During selling, right insular activation for preferred products predicted individual differences in susceptibility to the endowment effect. These findings are consistent with a reference-dependent account in which ownership increases value by enhancing the salience of the possible loss of preferred products. In other words, how the brain becomes "attached" to external objects by over estimating the value of those objects. It is notable that these areas of the brain are known to be dysfunctional in substance abusers. These

results provide a novel perspective on why drug abusers overvalue drugs and thereby find it difficult to give up drug use. Knutson, B., Wimmer, G., Rick, S., Hollon, N., Prelec, D., and Loewenstein, G. Neural Antecedents of the Endowment Effect. Neuron, 58(5), pp. 814-822, 2008.

### Neural Correlates of Impulse Control in Cocaine Abusers

Li and colleagues at Yale University used fMRI to study altered impulse control dysfunction in cocaine abusers. Impulse control was assessed using the stop signal task (SST) which measures the ability to inhibit an action once it has started. Previous studies employing the SST have provided ample evidence indicating the importance of the medial cortical brain regions in conflict/error processing and postconflict/error behavioral adjustment. The SST was modified in order to elicit errors in approximately half of the stop trials despite constant behavioral adjustment of the observers. Prefrontal loci including the ventrolateral prefrontal cortex were found to be involved in post-error slowing in reaction time in a sample of cocaine dependent men. These results add to the accumulating evidence that dysfunction of ventrolateral prefrontal cortex may contribute to impaired inhibitory control in cocaine abusers. Li, C. R., Huang, C., Yan, P., Bhagwagar, Z., Milivojevic, V., and Sinha, R. Neural Correlates of Impulse Control During Stop Signal Inhibition in Cocaine-Dependent Men. Neuropsychopharmacology, 33(8), pp. 1798-806, 2008.

### Brain Regions Mediating Post-Error Slowing During A Stop Signal Task

Li and colleagues at Yale University used fMRI to study the neural correlates of behavioral adjustments to impulsive errors in abstinent male patients with cocaine dependence (CD) and healthy controls (HC) subjects. The Stop Signal Task was modified to permit trial-by-trial evaluation of response inhibition co-varying for stop success rate, task-related frustration rating, and post-error slowing, allowing the neural substrates of response inhibition to be isolated independent of attentional monitoring (of the stop signal) and post-response processes including affective responses and error monitoring. No differences were seen in between HC and CD who were matched in stop signal performance in the pre-supplementary motor area (pre-SMA) previously shown to be associated with SSRT. However, compared with HC, CD demonstrated less activation of the rostral anterior cingulate cortex (rACC), an area thought to be involved in the control of stop signal inhibition. The magnitude of rACC activation also correlated negatively with the total score and the impulse control subscore of the Difficulty in Emotion Regulation Scale in PCD. This study thus identified the neural correlates of altered impulse control in CD independent of other cognitive processes that may influence stop signal performance. Relative hypoactivation of the rACC during response inhibition may represent a useful neural marker of difficulties in impulse control in abstinent cocaine-dependent men who are at risk of relapse. Li, C.R., Huang, C., Yan, P., Paliwal, P., Constable, R.T., and Sinha, R. Neural Correlates of Post-Error Slowing During A Stop Signal Task: A Functional Magnetic Resonance Imaging Study. Journal of Cognitive Neuroscience, 20(6), pp. 1021-1029.

### Individual Differences in Nicotine Dependence, Withdrawal Symptoms, and Sex Predict Brain Responses to Smoking Cues

McClernon and colleagues at Duke University used fMRI to study the influence of individual difference factors and withdrawal symptoms on brain cue reactivity. Multiple regression analysis was used to evaluate relations between individual difference factors and withdrawal symptoms and event-related fMRI responses to visual smoking cues in a sample of 30 smokers. Predictors were

self-report nicotine dependence (Fagerstroem test of nicotine dependence, FTND), prescan withdrawal symptoms (craving and negative affect), and sex. The unique variance of each predictor was examined after controlling for each of the others. Positive associations were observed between FTND and reactivity to cues in right anterior cingulate and orbitofrontal cortex (OFC) whereas negative associations were observed between prescan craving and reactivity in ventral striatum. Higher negative affect or being male was associated with greater reactivity in left hippocampus and left OFC. Women exhibited greater cue reactivity than men in regions including the cuneus and left superior temporal gyrus. Individual difference factors and withdrawal symptoms were uniquely associated with brain reactivity to smoking cues in regions subserving reward, affect, attention, motivation, and memory. These findings provide further evidence that reactivity to conditioned drug cues is multiply determined and suggest that smoking cessation treatments designed to reduce cue reactivity focus on each of these variables. McClernon, F.J., Kozink, R.V., and Rose, J.E. Individual Differences in Nicotine Dependence, Withdrawal Symptoms, and Sex Predict Transient fMRI-BOLD Responses to Smoking Cues. Neuropsychopharmacology, 33(9), pp. 2148-2157, 2008.

### Neuronal Basis of Learning and Memory Deficits in Human Cannabis Users

Garavan and colleagues at Trinity College used fMRI to test the hypothesis that impairments in learning and memory in chronic cannabis users is due to alterations in hippocampal functioning. In the first part of the study, 35 current users of cannabis and 38 matched controls were administered a face-name task, which has been shown previously to activate the hippocampal region. Cannabis users were significantly worse on this task with respect to learning, short and long-term memory performance. Based on the behavioral results, a subsequent study used a modified version of the face-name task during fMRI scanning, to examine cortical and (para) hippocampal activity during learning and recall in 14 current users of cannabis and 14 controls. Despite non-significant differences in learning and memory performance, cannabis users had significantly lower levels of BOLD activity in the right superior temporal gyrus, right superior frontal gyrus, right middle frontal gyrus and left superior frontal gyrus compared to controls during learning. In addition, cannabis users had significantly higher BOLD activity in the right parahippocampal gyrus during learning. These results indicate that hypoactivity in frontal and temporal cortices, and relative hyperactivity in the para-hippocampus are involved in functional deficits and compensatory processes in cannabis users. Nestor, L., Roberts, G., Garavan, H., and Hester, R. Deficits in Learning and Memory: Parahippocampal Hyperactivity and Frontocortical Hypoactivity in Cannabis Users. Neuroimage, 40(3), pp. 1328-1339, 2008.

### Reduced Behavioral and Neural Activation in Stimulant Users To Different Error Rates During Decision Making

Paulus and colleagues at the University of California, San Diego used fMRI to test the hypothesis that stimulant-using subjects fail to adjust decision-making less as a function of errors, and that this failure is accompanied by reduced neural activation patterns. Twelve young adults who had used stimulants were compared with 12 education-matched, stimulant-naive comparison subjects. Subjects completed the two-choice prediction task with three fixed error-rate conditions (20%, 50%, or 80% errors) during fMRI scanning. Stimulant users relative to comparison subjects showed less strategy adjustment to different error rates. For example, they were less likely to stay with winning responses (win-stay) and to shift away from losing responses (lose-shift). These subjects also showed different activation patterns as a function of error rate in the left insular and bilateral dorsolateral prefrontal cortex but not anterior cingulate. The degree to which individuals adjusted switching rate, or win-stay/lose-shift

consistent responses, as a function of errors was correlated with the difference in insular cortex activation differences between high and low error rates. These results indicate that the behavior of stimulant users is less adaptive to the frequency of errors made and fewer brain processing resources are deployed during decision making to anticipate erroneous performance. These findings could be markers for the predisposition of drug taking; however, their relevance for development of drug dependence requires further study. Paulus, M., Lovero, K., Wittmann, M., and Leland, D. Reduced Behavioral and Neural Activation in Stimulant Users to Different Error Rates During Decision Making. Biological Psychiatry, 63(11), pp. 1054-1060, 2008.

### A Novel PET Ligand for Imaging Muscarinic M2 Receptors: C-11-Labeled TZTP

Ding and colleagues at Yale University and Brookhaven National Laboratories studied the pharmacokinetics of a novel series of C-11 labeled PET tracers for muscarinic M2 receptors based on an existing F18 labeled ligand: 3-(3-{3-[F-18]fluoropropyl)thio}-1,2,5 -thiadiazol-4-yl)-1,2,5,6-tetrahydro-1-methylpyridine) ([F-18]FP-TZTP). They compared the effect of small structural changes on tracer pharmacokinetics (PK) in brain and peripheral organs for 3 analogs (3, 6, and 10). Values for log D, PPB and affinity constants were similar for the 3 analogs. The fraction of parent radiotracer in the plasma was higher and the AUC lower for the 10 analog than for 3 and 6 analogs. Time Activity Curves for brain regions were similar for 3 and 6, which showed PK similar to the 18F tracer, while 10 showed slower uptake and little clearance over 90 min. Distribution volumes for 3 and 6 were similar to the F-18 tracer but higher for 10. Uptake of the three tracers was significantly reduced by coinjection of unlabeled 3 and 6. These studies indicate that small structural variations on the TZTP structure greatly altered the PK in brain and behavior in blood with little change in the log D, PPB or affinity. The study suggests that C-11-radiolabeled 3 will be a suitable alternative to [F-18]FP-TZTP for translational studies in humans. Reid, A., Ding, Y., Eckelman, W., Logan, J., Alexoff, D., Shea, C., Xu, Y., and Fowler, J. Comparison of the Pharmacokinetics of Different Analogs of C-11-Labeled TZTP for Imaging Muscarinic M2 Receptors With PET. Nuclear Medicine and Biology, 35(3), pp. 287-298, 2008.

### Preserved Implicit Attention In Methamphetamine Dependent Subjects

Salo and colleagues at University of California, Davis studied whether methamphetamine abuse leads to deficits in implicit measures of attention, in addition to the known wide range of deficits on explicit tasks of selective attention. A computerized spatial priming task was used to assess implicit attentional processes in 54 methamphetamine (MA) dependent subjects and 32 healthy controls. The MA dependent subjects had been drug-abstinent a minimum of 3 weeks with a mean duration of MA use of 13.27+/-7.75 years. The MA dependent subjects did not differ significantly from controls on either inhibitory priming or facilitory priming. This result is consistent with earlier findings of intact object-based priming in MA dependent individuals and suggests that cortical brain systems typically supporting implicit attentional functioning are relatively intact in long-term MA dependent individuals in contrast to dysfunctions in brain systems supporting explicit attentional processes. Salo, R., Leamon, M. H., Natsuaki, Y., Moore, C., Waters, C., and Nordahl, T. E. Findings of Preserved Implicit Attention in Methamphetamine Dependent Subjects. Prog. Neuropsychopharmacol. Biol. Psychiatry, 32(1), pp. 217-223, 2008.

### Behavioral Predictors of Recurrent Methamphetamine-Induced

### Psychosis

Salo and colleagues at University of California, Davis studied currently drug-abstinent methamphetamine (MA)-dependent subjects (n=39) who experienced psychotic symptoms associated with MA abuse. All participants completed the Wender Utah Rating Scale (WURS), which retrospectively assesses Attention Deficit Hyperactivity Disorder-relevant childhood behaviors. The results suggest the existence of an early cognitive vulnerability to the development of frequent MA-induced psychotic symptoms as well as increased vulnerability associated with a family history of psychiatric illness. Salo, R., Nordahl, T. E., Leamon, M. H., Natsuaki, Y., Moore, C. D., Waters, C., and Carter, C. S. Preliminary Evidence of Behavioral Predictors of Recurrent Drug-Induced Psychosis in Methamphetamine Abuse. Psychiatry Res., 157(1-3), pp. 273-247, 2008.

### Individual Differences in Insular Sensitivity During Loss Anticipation Predict Avoidance Learning

Knutson and colleagues at Stanford University used fMRI to study whether individual differences in insular sensitivity would predict learning to avoid aversive stimuli. The anterior insula has been implicated in both the experience and the anticipation of negative outcomes. Insular sensitivity was assessed as participants anticipated monetary losses while undergoing fMRI scanning. Insular responsiveness to anticipated losses predicted participants' ability to learn to avoid losses (but not to approach gains) in a behavioral test several months later. These findings suggest heightened insular sensitivity may promote learning to avoid loss. Dysfunction of the insula may therefore impair the ability of individuals to learn from the adverse consequences of drug use. Samanez-Larkin, G.R., Hollon, N.G., Carstensen, L.L., and Knutson, B. Individual Differences in Insular Sensitivity During Loss Anticipation Predict Avoidance Learning. Psychological Science, 19(4), pp. 320-323, 2008.

### Smoking Opportunity Affects Striatal Responses to Monetary Gain and Loss

Delgado and colleagues at Rutgers University and University of Pittsburgh used fMRI to examine the effects of smoking opportunity on neural responses to monetary outcomes in nicotine-deprived cigarette smokers. Participants who were told that they would be able to smoke during the study exhibited smaller responses to monetary gains and losses in the caudate nucleus than did those who anticipated having to wait several hours before having the opportunity to smoke. These findings highlight the importance of investigating the effects of perceived drug use opportunity on motivational processing in addicted populations. Wilson, S., Sayette, M., Delgado, M., and Fiez, J. Effect of Smoking Opportunity on Responses to Monetary Gain and Loss in the Caudate Nucleus. Journal of Abnormal Psychology, 117(2), pp. 428-434, 2008.

### Cortical Sources and Targets of Attentional Modulation

Yantis reviewed current findings regarding how the brain implements selective attention. Selective attention is an intrinsic component of perceptual representation in a visual system that is hierarchically organized. Modulatory signals originate in brain regions that represent behavioral goals. These signals specify which perceptual objects are to be represented by sensory neurons that are subject to contextual modulation. Attention can be deployed to spatial locations, features, or objects, and corresponding modulatory signals must be targeted within these domains. Open questions include how nonspatial perceptual domains are modulated by attention and how abstract goals are transformed into targeted modulatory signals. Since drug abuses exhibit a bias

to selectively attend to drug-related stimuli, understanding of the brain mechanisms of selective attention will aid in the understanding of cue-related craving and relapse. Yantis, S. The Neural Basis of Selective Attention: Cortical Sources and Targets of Attentional Modulation. Current Directions in Psychological Science, 17(2), pp. 86-90, 2008.

### Interpersonal Nature of Empathic Accuracy

Ochsner and colleagues at Columbia University tested the prediction that empathic accuracy may depend on both targets' tendency to express emotion and perceivers' tendency to empathically share that emotion. Although current theories suggest that affective empathy (perceivers' experience of social targets' emotions) should contribute to empathic accuracy (perceivers' ability to accurately assess targets' emotions), extant research has failed to consistently demonstrate a correspondence between them. This group reasoned that prior null findings may be attributable to a failure to account for the fundamentally interpersonal nature of empathy. Using a continuous affect-rating paradigm, they found that perceivers' trait affective empathy was unrelated to empathic accuracy unless targets' trait expressivity was taken into account. Perceivers' trait affective empathy predicted accuracy only for expressive targets. These data suggest that perceivers' self-reported affective empathy can indeed predict their empathic accuracy, but only when targets' expressivity allows their thoughts and feelings to be read. These results may provide a foundation for improving empathic therapeutic relationships in the treatment of substance abusers. Zaki, J., Bolger, N., and Ochsner, K. It Takes Two: The Interpersonal Nature of Empathic Accuracy. Psychological Science, 19(4), pp. 399-404, 2008.

### Impaired Visuomotor Performance in Smokers More Related to Addiction Severity as an Individual Difference than to Abstinence/Satiety State

Edythe London and colleagues at UCLA demonstrated that among smokers, performance on the d2 Test of Attention and the Digit Symbol Test Acute did not appreciably differ between overnight abstinence versus ad libitum smoking conditions. Rather, performance under both conditions correlated negatively with measures of addiction severity, where smokers with high nicotine dependence performed more slowly on both tests than less dependent smokers or nonsmokers. The findings suggest that severity of nicotine dependence and slowness in perceptual-motor tasks of attention share an underlying basis. Azizian, A., Monterosso, J.R., Brody, A.L., Simon, S.L., and London, E.D. Severity of Nicotine Dependence Moderates Performance on Perceptual-Motor Tests of Attention. Nicotine and Tobacco Research, 10(4), pp. 599-606, 2008.

### Pharmacologic Mechanisms of Methamphetamine

Stephen Kish from the University of Toronto reviewed the pharmacologic mechanisms of crystal methamphetamine. Crystal meth is a form of the stimulant drug methamphetamine that, when smoked, can rapidly achieve high concentrations in the brain. Methamphetamine causes the release of the neurotransmitters dopamine, norepinephrine and serotonin and activates the cardiovascular and central nervous systems. The levels of dopamine are low in the brain of some drug users, but whether this represents neuronal loss is uncertain. The areas of the brain involved in methamphetamine addiction are unknown but probably include the dopamine-rich striatum and regions that interact with the striatum. There is no medication approved for the treatment of relapses of methamphetamine addiction; however, potential therapeutic agents targeted to dopamine and non-dopamine (e.g., opioid) systems are in clinical testing. Kish, S.J. Pharmacologic Mechanisms of Crystal Meth. Canadian

Medical Association Journal, 178(13), pp. 167-1682, 2008.

### Methamphetamine-Dependent Subjects Show Altered Cortical Recruitment when Evaluating Faces

Predoctoral (F31) fellow Doris Payer and colleagues at UCLA exposed MA-dependent and healthy comparison participants to fearful and angry faces while they performed an affect matching task during fMRI. Although the groups did not differ in task performance, the healthy participants showed more task-related activity than the MA-dependent participants in ventrolateral prefrontal cortex (VLPFC), temporoparietal junction (TPJ), anterior and posterior temporal cortex, and fusiform gyrus in the right hemisphere, and the cuneus in the left hemisphere. In contrast, the MA-dependent participants showed more task-related activity than the healthy participants in the dorsal anterior cingulate cortex (dACC). Dorsal ACC hyperactivity, along with high ratings of hostility in facial stimuli by the MA-dependent group, suggest a hyper-sensitivity to socially threatening cues in the MA-dependent participants, while lower VLPFC activation could point to a deficit in integrating socio-emotional information and/or regulating this limbic hyperactivity. Differences In Cortical Activity Between Methamphetamine-Dependent and Healthy Individuals Performing a Facial Affect Matching Task. Payer, D.E., Lieberman, M.D., Monterosso, J.R., Xu, J., Fong, T.W., and London, E.D. Drug and Alcohol Dependence, 93(1-2), pp. 93-102, 2008.

### Cognitive Stress Demands More Brain Reserve Capacity and Uncovers Attention Deficits and is Exacerbated by Antiretroviral Medications in Neuroasymptomatic HIV+ Individuals

Drs. Linda Chang and Thomas Ernest tested whether fMRI could be used as a reasonably sensitive measurement of brain reserve capacity in HIV+ patients . While antiretroviral (ARV) medications successfully lower viral load and improve immune deficit, they may have detrimental effects on brain function in HIV-infected patients. Subtle neuronal dysfunction associated with minor neuronal damage has higher prevalence in otherwise asymptomatic HIV+ individuals. However, no clinical assessment of the minor neurodegenerative damage is currently available. The study was based upon the observation that performance accuracy in response to steps of increasing difficulty of visual attention (cognitive load), and diminished brain function can be detected in HIV+ people who were otherwise neurologically asymptomatic. BOLD signals in frontal regions of normal subjects during visually tracking balls on screen normally decreases across repeated trials even when difficulties in attention level (number of balls) progressively increases. While HIV+ patients also exhibit repetitive adaptation when the requirement of attention level was low, they failed to exhibit adaptation with difficult visual challenges. In contrast to normal subjects, HIV+ patients exhibited load-dependent increases in brain activation. Standard, long-term use of ARV exacerbated the problem, leading to even greater load-dependent BOLD activations in the bilateral superior frontal regions, along with diminished accuracy of visual attention performance. In other words, HIV+ subjects on ARV may demand greater usage of the brain attention network to maintain performance. Since the study controlled for baseline disease stage and medical variables associated with HIV infection, it suggests that the HIV infection could impair plasticity of the brain and lower the compensatory strength of endogenous regulatory system and intrinsic resilience. Therefore, HIV+ARV subjects and HIV+ subjects under stress or influence of drugs may exhibit functional discompensation and declined behavioral performance. Chang, L., Yakupov, R., Nakama, H., Stokes, B., and Ernst, T. Antiretroviral Treatment is Associated with Increased Attentional Load-Dependent Brain Activation in HIV Patients, Journal of Neuroimmunology and Pharmacology, 3, pp. 95-104, 2008.

### Individual Differences in Responses to Opioid Analgesic Medications

Dr. James P. Zacny and colleagues investigated how two opioid analgesics containing a common antipyretic agent (cacetaminophen) at typically prescribed doses differed in subjective, psychomotor, and physiological effects within the same healthy individuals. The study was carried out in a randomized, placebo-controlled, double-blind, crossover trial consisting of six sessions. Higher dosage of the drug combinations produced a significant, wider spectrum of subject effects, and impaired psychomotor performance including cognitive abilities in some subjects. Those included substantially increased ratings of "drug high" and "dizzy" and decreased ratings of "in control of body" and "in control of thoughts". Some subjects displayed increased ratings in such measures as "drug liking" and "wanting to take drug again". These results emphasize the need for individualized assessment of subject effects and remediation for chronic pain patients under medications that have addiction potential. Given the diverse individual sensitivity to the drug combination physicians and pharmacists need to discuss safety concerns with their patients on an individualized basis. Zacny, J.P., and Gutierrez, S. Subjective, Psychomotor, and Physiological Effects Profile of Hydrocodone/Acetaminophen and Oxycodone/Acetaminophen Combination Products. Pain Medicine, 9(4), pp. 433-443, 2008.

### Capacity of "Remembering to Remember" as a Predictor for Adherence to Antiretroviral Medications

Dr. Igor Grant and colleagues at the University of San Diego investigated whether HIV-associated impairment of prospective memory had predictive value for adherence to antiretroviral medications. Prospective memory represented the ability to encode and execute a future intention, such as remembering to take a medication at a specific time. Optimal adherence to antiretroviral medications is critical to the effective long-term management of HIV+ individuals who often have cognitive deficits and impaired everyday functioning. The results showed a strong association between impaired prospective memory and self-reported medication management in HIV+ persons currently prescribed antiretroviral medications. Specifically, poorer performance in prospective memory tasks correlated well to more frequent complaints on remembering to remember projected events and to poorer self-reported medication management. Analyses revealed that HIV-associated impairment of prospective memory accounted for a significant amount of variance in self-reported medication management, more than that could be explained by other factors known to predict nonadherence, such as mood disorders, psychosocial variables, environmental structure and deficits on a traditional battery of neuropsychological tests. It suggests that an early assessment of the capacity of "remembering to remember" will help medical professionals to better predict their patients' ability in everyday function and their adherence to antiviral medications. It will also be informative for a strategy of individualized remediation. Woods, S.P., Moran, L.M., Carey, C.L., Dawson, M.S., Iudicello, J.E., Gibson, S., Grant, I., Atkinson, J.H., and HIV Neurobehavioral Research Center Group. Prospective memory in HIV infection: is "Remembering to Remember" a Unique Predictor of Self-Reported Medication Management? Archive of Clinical Neuropsychology, 23(3), pp. 257-270, 2008.

### Risk Factors Contributing to Major Depressive Episodes in HIV+ Persons

Dr. Igor Grant and colleagues at the University of California, San Diego, carried out a 2-year prospective study to determine risk factors contributing to major depressive episodes in HIV+ persons. When factors like baseline disease stage

and medical variables associated with HIV infection were carefully controlled, they found that more severe immune deficit and more rapid progression of HIV infection correlated with higher morbidity of the disease. The two-year cumulative rate of a major depressive episode ranged from 40% in those with stable symptomatic-advanced illness to about 20% in asymptomatic individuals and in controls. Those with symptomatic HIV disease were at significant higher risk by the second year than were people in earlier stage HIV disease and uninfected controls. A history of major depression or of psychiatric comorbidity (two or more psychiatric disorders) strongly predicted subsequent major depressive episode. The rate of first onset and recurrent expression was similar. The likelihood of first onset of depression in symptomatic patients was 50% higher than that in seronegative controls, raising the question of whether HIV infection triggers episodes in individuals previously resistant to mood disorder. This paper also discussed factors that might have an impact on the observation that impaired performance on neuropsychological testing and abnormal neuroimaging did not predict a later depressive episode in this study. Atkinson, J.H., Heaton, R.K., Patterson, T.L., Wolfson, T., Deutsch, R., Brown, S.J., Summers, J., Sciolla, A., Gutierrez, R., Ellis, R.J., Abramson, I., Hesselink, J.R., McCutchan, J.A., Grant, I., and The HNRC Group. Two-year Prospective Study of Major Depressive Disorder in HIV-Infected Men. Journal of Affective Disorders, 108, pp. 225-234, 2008.

### Attentional Deficits in Cocaine-Dependent Patients: Converging Behavioral and Electro-physiological Evidence

Boutros and colleagues at Wayne State University used evoked potentials to investigate altered brain activity related to deficits in attention in cocaine abusers. Cocaine-dependent patients (n=14) were examined and compared with healthy control individuals (n=15) on two sustained attention tasks; an auditory oddball event-related task and a Continuous Performance Test (CPT, Identical Pairs version). The cocaine-dependent group displayed P300 amplitude reduction compared to controls, but there were no significant group differences in P300 response latency. On the CPT, 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 electrophysio-logical 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.

### Tobacco / Nicotine and Endogenous Brain Opioids

Dr. Edward Domino and his colleague at the University of Michigan reviewed the limited knowledge regarding the contribution of the endogenous opioid system to the complex effects of nicotine/tobacco smoking. Standard medications to assist in smoking cessation, such as nicotine replacement therapies and bupropion, are ineffective in many smokers who attempt to quit. Recent developments in the neurobiology of nicotine dependence have identified several neurotransmitter systems that may contribute to the process of smoking maintenance and relapse. These include, especially, dopamine, but also norepinephrine, 5-hydroxytryptamine, acetylcholine, endogenous opioids, gamma-aminobutyric acid (GABA), glutamate, and endocannabinoids. Xue, Y., and Domino, E.F. Tobacco/Nicotine and Endogenous Brain Opioids. Progress in Neuropsychopharmacology & Biological Psychiatry, 32(5), pp. 1131-1138, 2008.

### Evidence Against a "Prototypical" Pattern of Neuropsychological

### Impairment in HIV+ Patients

Dr. Igor Grant and colleagues, at the University of California San Diego, investigated the existence of a "prototypical pattern" of neuropsychological results with HIV infection. Previous studies by others have led to the proposal that HIV infection is characterized by a specific neuropsychological pattern consisting of impaired executive functioning, motor skills, speed of information processing, and learning. On the other hand, memory retention, most language skills, and visuospatial functioning were intact. Using factor analysis of a relatively comprehensive neuropsychological battery from 553 HIV+ adults, 6 component factors were found: verbal memory (VeM), visual memory (ViM), processing speed (PS), attention/working memory (A/WM), executive function (EF), and motor (M). These factor scores were then submitted to a hierarchical cluster analysis followed by a K-means analysis. A 6-cluster solution was found to best fit the data. The definitions of the clusters indicate the relative performance strengths and weaknesses (independent of overall level of performance): Cluster 1: strong EF; Cluster 2: strong M, weak VeM and EF; Cluster 3: strong PS, weak ViM and EF; Cluster 4: strong VeM, weak M; Cluster 5: strong A/WM; Cluster 6: strong VeM, weak EF. Neuropsychological-impairment rates differed across clusters, but all 6 clusters contained substantial numbers of impaired and unimpaired individuals. Cluster membership was not explained by demographic variables or psychiatric or neuromedical confounds. Thus, there does not appear to be a single, prototypical pattern of neuropsychological impairment associated with HIV infection for this battery of representative neuropsychological tests. Dawes, S., Suarez, P., Casey, C.Y., Cherner, M., Marcotte, T.D., Letendre, S., Grant, I., Heaton, R.K.; and HNRC Group. Collaborators (39): Grant, I., Atkinson, J.H., Ellis, R.J., McCutchan, J.A., Marcotte, T.D., Hale, B.R., Ellis, R.J., McCutchan, J.A., Letendre, S., Capparelli, E., Schrier, R., Heaton, R.K., Cherner, M., Woods, S.P., Dawes, S., Jernigan, T., Fennema-Notestine, C., Archibald, S.L., Hesselink, J., Annese, J., Taylor, M.J., Schweinsburg, B., Masliah, E., Everall, I., Langford, T.D., Richman, D., Smith, D.M., McCutchan, J.A., Everall, I., Lipton, S., Atkinson, J.H., von Jaeger, R., Gamst, A.C., Cushman, C., Frybarger, M., Masys, D.R., Abramson, I., Ake, C., and Lazzaretto, D. Variable Patterns of Neuropsychological Performance in HIV-1 Infection. Journal of Clinical and Experimental Neuropsychology, 30(6), pp. 613-626, 2008.

### Increased Dynorphin Concentrations in Striatum and Ventral Pallidum in Human Chronic Cocaine Users

Dr. Stephen Kish and colleagues, at the University of Utah examined alterations in neuropeptide levels using radioimmunoassays in post-mortem brains of cocaine abusers. Several brain neuropeptide systems have been proposed as targets for medication development for treatment of cocaine addiction (e.g., kappa opioid agonists) based on animal data showing interactions between the neuropeptides, brain dopamine, and cocaine. Increased dynorphin and other neuropeptides (e.g., metenkephalin, neurotensin and substance P) levels were found in the dopamine-rich caudate, putamen, and nucleus accumbens of human chronic cocaine users (n=12) compared to matched control subjects (n=17). The most marked changes were increased dynorphin immunoreactivity in the ventral pallidum (+346%), caudate (+92%), and decreased neurotensin in the caudate (-49%). There was also a trend for increased dynorphin (+75%) in the putamen. Dynorphin levels were normal in other examined subcortical/cerebral cortical area. In contrast cerebral cortical metenkephalin levels were generally decreased and neurotensin variably changed. The human dynorphin observations parallel well animal findings and suggest that the dynorphin system is upregulated, manifested as elevated neuropeptide levels, after chronic drug exposure in striatum and ventral pallidum. However, the other striatal neuropeptides were not consistent with animal data, but this could be due to differences in patterns

between human drug users and the animal models. Nonetheless, the postmortem brain data support the testing of new dynorphin-related therapeutics for the treatment of cocaine addiction. Frankel, P.S., Alburges, M.E., Bush, L., Hanson, G.R., and Kish, S.J. Striatal and Ventral Pallidum Dynorphin Concentrations are Markedly Increased in Human Chronic Cocaine Users. Neuropharmacology, 55(1), pp. 41-46, 2008.

### Improved PET Dopamine Receptor Quantification with an Automated Partial Volume Correction

Dr. Dean Wong and colleagues at the Johns Hopkins University tested a new algorithm for partial volume correction (PVC) using an automatized atlas-based analysis to define 3-dimensional regions of interest (ROIs). This new analysis method was evaluated on PET dopamine receptor ligand binding in the normal human brain striatum, without and with PVC. Healthy volunteers received a single injection of (11)C-raclopride, and automatic segmentation of concomitant structural MR images was performed using a maximum-probability atlas in combination with a trained neural network. The results were comparable with those obtained with a manual method currently in use in their laboratory. However, dopamine receptor binding potential appeared less heterogeneous in the normal human striatum after PVC than they did without PVC. Thus, the new algorithm allows for traditional PET data extraction and PVC in an entirely automatic fashion, thus avoiding labor-intensive analyses and potential intra- or interobserver variability. Rousset, O.G., Collins, D.L., Rahmim, A., and Wong, D.F. Design and Implementation of an Automated Partial Volume Correction in PET: Application to Dopamine Receptor Quantification in the Normal Human Striatum. J Nuclear Medicine, 49(7), pp. 1097-1106, 2008.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2008

## Research Findings - Epidemiology and Etiology Research

### Substance Use Among ADHD Adults

Diagnosing ADHD in adults is difficult when the diagnostician cannot establish an onset prior to the DSM-IV criterion of age seven or if the number of symptoms does not achieve the DSM threshold for diagnosis. These diagnostic issues are an even larger concern for clinicians faced with adults with substance use disorders (SUD). The present study compared four groups of adults: full ADHD subjects who met all DSM-IV criteria for childhood onset ADHD (n=127), late onset ADHD subjects who met all criteria except the age at onset criterion (79), subthreshold ADHD subjects who did not meet full symptom criteria (41), and non-ADHD subjects who did not meet any of the above criteria (123). Subjects were between the ages of 18 and 55, and were recruited from psychiatric clinic referrals and advertisements. Diagnoses were by the Structured Clinical Interview for DSM-IV, and the Drug Use Severity Index (DUSI) was used for self-report of substance use. The authors found that cigarette and marijuana use was significantly greater in all ADHD groups relative to non-ADHD controls. Although usage rates of other drugs failed to reach significance, the ADHD groups were more likely to have used each drug (except alcohol) compared with the non-ADHD group. The late onset and full ADHD groups were more likely to have endorsed ever having a problem due to use of cigarettes, alcohol, or marijuana and reported more trouble resisting use of drugs or alcohol. The full ADHD group was more likely than the other groups to have reported 'getting high' as their reason for using their preferred drug. The authors conclude that adults with ADHD have elevated rates of substance use and related impairment, and that their data about late onset ADHD provides further support for the idea that the DSM-IV age at onset criterion is too stringent. In contrast, they surmised that subthreshold ADHD seems to be a milder form of the disorder, or perhaps a heterogeneous group of true ADHD cases and false positives. Faraone, S., Wilens, T., Petty, C., Antshel, K., Spencer, T., and Biederman, J. Substance Use among ADHD Adults: Implications of Late Onset and Subthreshold Diagnoses. Am. J. Addict., 16 Suppl 1, pp. 24-34, 2007.

### Developmental Trajectories of Young Adult Poly-Substance Use

Despite the prominence of comorbidity among substances and the recent attention focused on trajectory-based approaches to characterizing developmental change, little research in the substance use field has simultaneously considered both course and comorbidity. Using nationally representative panel data from the Monitoring the Future Project (MTF; n = 32,087; 56% female; 82% Caucasian), authors identified developmental courses of heavy drinking, smoking, and marijuana use using 4 waves of data spanning ages 18 to 26 in a multi-cohort young adult sample. Comorbidity was

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examined by cross-classifying group membership in substance use trajectories. Finally, the extent to which risk factors (sex, race, alcohol expectancies, delinquency, sensation seeking, depressive affect, religiosity, academic achievement, and parent education) accounted for combinations of comorbidity that occurred at a rate greater than chance was examined. For each substance, authors identified 4 courses of substance use that were largely consistent with those found in the literature (chronic high use, late-onset use, developmentally limited use, and low-use), with a fifth moderate smoking group. Heavy drinking, smoking, and marijuana use were each highly associated, and distinct patterns of comorbidity were evident, with greatest agreement along the diagonal. All risk factors explained comorbidity to some degree, with delinquency, sensation seeking, alcohol expectancies, and religion in particular predicting combinations of comorbidity that were characterized by early onset and chronic high use. Cross-substance trajectory concordance was high, with parallel changes in substance use over emerging adulthood. This suggests similar developmental timing of use, perhaps due to the experience of developmental transitions that have a common influence on use of different substances. Prediction of combinations of comorbidity characterized by early onset and persistently high use suggests that to some extent, individuals use multiple substances because of a common vulnerability to each, rather than directional relations among substances (e.g., cross-tolerance, cueing). Jackson, K., Sher, K., and Schulenberg, J., Conjoint Developmental Trajectories of Young Adult Substance use. Alcohol Clin. Exp. Res., 32(5), pp. 723-737, 2008.

### High School Drinking Mediates the Relationship Between Parental Monitoring and College Drinking

This study examined whether parental monitoring indirectly exerts a protective effect on college drinking by reducing high school alcohol consumption. A longitudinal cohort of 1,253 male and female students, ages 17 to 19, attending a large, public, mid-Atlantic university was studied at two time points. First, data on high school parental monitoring and alcohol consumption were gathered via questionnaire during the summer prior to college entry. Second, during the first year of college, past-year alcohol consumption was measured via a personal interview. Multiple regression models tested the relationship between parental monitoring and past year alcohol use (i.e., number of drinks per drinking day). Holding constant demographics, SAT score, and religiosity, parental monitoring had a significant protective effect on both high school and college drinking level. However, the association between parental monitoring and college drinking level became non-significant once high school drinking level was held constant. While parental monitoring did not directly influence college alcohol consumption, evidence for mediation was observed, whereby parental monitoring had an indirect influence on college drinking through reductions in high school drinking. The authors conclude that initiatives that promote effective parenting might be an important strategy to curb high-risk drinking among older adolescents. Arria, A., Kuhn, V., Caldeira, K., O'Grady, K., Vincent, K., Wish, E., and Wish, E. High School Drinking Mediates the Relationship Between Parental Monitoring and College Drinking: A Longitudinal Analysis. Subst. Abuse Treat. Prev. Policy, 3, pp. 6, 2008.

### Genetic and Environmental Influences on Substance Use over Development

The authors sought to expand our understanding of the changing roles of environmental and genetic influences on psychoactive substance use (PSU) through development from early adolescence through middle adulthood. Data were gathered using a retrospective assessment by life history calendar, from a total of 1796 members of male-male pairs from the population-based Virginia Adult Twin Study of Psychiatric and Substance Use Disorder, interviewed

between 1998 and 2004, when the twins were ages 24 to 62 years old. Data were analyzed with univariate and bivariate structural modeling. Levels of use of alcohol, caffeine, cannabis, and nicotine were recorded for every year of the respondent''s life. For nicotine, alcohol, and cannabis, modeling found that familial environmental factors were critical in influencing use in early adolescence and gradually declined in importance through young adulthood. Genetic factors, by contrast, had little or no influence on PSU in early adolescence and gradually increased in their effect with increasing age. The sources of individual differences in caffeine use changed much more modestly over time. Substantial correlations were seen among levels of cannabis, nicotine, and alcohol use and specifically between caffeine and nicotine. In adolescence, those correlations were strongly influenced by shared effects from the familial environment. However, as individuals aged, more and more of the correlation in PSU resulted from genetic factors that influenced use of both substances. The authors conclude that these results support an etiologic model for individual differences in PSU in which initiation and early patterns of use are strongly influenced by social and familial environmental factors while later levels of use are strongly influenced by genetic factors. The substantial correlations seen in levels of PSU across substances are largely the result of social environmental factors in adolescence, with genetic factors becoming progressively more important through early and middle adulthood. Kendler, K., Schmitt, E., Aggen, S., and Prescott, C., Genetic and Environmental Influences on Alcohol, Caffeine, Cannabis, and Nicotine Use from Early Adolescence to Middle Adulthood. Arch. Gen. Psychiatry, 65(6), pp. 674-682, 2008.

### Drugs and Driving by American High School Seniors

The aim of this study was to report trends from 2001 to 2006 in the percentage of all high school seniors who drive after using marijuana, other illicit drugs, or alcohol or who are exposed as passengers to such behaviors. A second objective is to examine demographic and psychosocial correlates of these behaviors. The data were obtained from the Monitoring the Future study, in which nationally representative samples of high school seniors have been surveyed annually since 1975 (approximately 14,000-16,000 seniors per year between 2001-2006). In 2006, 30% of high school seniors reported exposure to a drugged or drinking driver in the past 2 weeks, down from 35% in 2001. Exposure was demonstrated to be widespread as defined by demographic characteristics (population density, region of the country, socioeconomic status, race/ethnicity, and family structure). Individual lifestyle factors (religiosity, grade point average, truancy, frequency of evenings out for fun, and hours of work) showed considerable association with the outcome behaviors. O'Malley, P., and Johnston, L. Drugs and Driving by American High School Seniors, 2001-2006. J. Stud. Alcohol Drugs, 68(6), pp. 834-842, 2007.

### Neighborhood Effects on Smoking Moderated by Prosocial Activities

Investigators examined the association between neighborhood characteristics and cigarette use among 824 ninth graders and explored the protective effects of participation in prosocial activities to better understand strengths in adolescents' lives and help identify protective factors for the prevention of adolescent smoking. Investigators interviewed ninth graders who had grade point averages of 3.0 or lower and who were not developmentally disabled. Participants' addresses were geocoded so that interview data could be linked to 1990 US census data on neighborhood characteris-tics. Neighborhood disadvantage and the percentage of Black residents in a neighborhood had different effects on cigarette smoking among Black and White adolescents. Living in a neighborhood with a high percentage of Black residents had favorable effects for Blacks but not for Whites. For both groups, a low percentage of Black residents was a risk factor for cigarette use, and risk

effects were higher in the more disadvantaged neighborhoods. Involvement in prosocial activities moderated neighborhood risks. Neighborhood effects on adolescent cigarette use were contingent upon both contextual and individual characteristics. Participation in prosocial activities had a protective effect among adolescents in high-risk neighborhoods. Engaging adolescents in such activities may help offset the adverse effects of living in a disadvantaged neighborhood. Xue, Y., Zimmerman, M., and Caldwell, C. Neighborhood Residence and Cigarette Smoking among Urban Youths: The Protective Role of Prosocial Activities. Am. J. Public Health, 97(10), pp. 1865-1872, 2007.

### Predictors of the Degree of Drug Treatment Coverage for Injection Drug Users in 94 Metropolitan Areas in the United States

Researchers conducted a secondary analysis of drug treatment data, including estimated numbers of injection drug users in treatment, for 94 large metropolitan statistical areas (MSAs) in the United States. Treatment coverage for IDU varied from 1.1 to 39.3 percent, and only nine MSAs provided coverage greater than 20 percent. In multiple regression analysis, one general resource (lower long term debt per capital) was weakly related to treatment coverage. A lower percentage of drug users in treatment who are non-injectors and a greater percentage of the non-Hispanic White population strongly predicted treatment coverage for IDU (standardized beta>.20). These findings suggest that, in conditions of scarce treatment coverage for drug injectors, an indicator of epidemiologic need (such as per capita extent of AIDS among IDU) is not likely to predict treatment coverage. Competition for treatment slots by non-injectors may reduce injectors' access to treatment, however. Metropolitan finances, as well as social, structural, political, and other budgetary factors may also interact as potential barriers to expanding drug treatment for drug injectors. Friedman, S., Tempalski, B., Brady, J., Friedman, J., Cooper, H., Flom, P., McGrath, M., Gostnell, K., and Des Jarlais, D. Predictors of the Degree of Drug Treatment Coverage for Injection Drug Users in 94 Metropolitan Areas in the United States. Int. J. Drug Policy, 18(6), pp. 475-485, 2007.

### School Truancy Predicts Drug Use

This study examined the relationship between truancy and the onset of drug use in a cohort of 304 youth ages 12-15 participating in the Denver Youth Survey, a longitudinal sample of 1528 youth who grew up in socially disorganized neighborhoods of Denver, CO. The DYS was conducted from 1988 to 1992. This cohort, born in 1976, was one of five cohorts participating in the DYS, and the only one assessed each year between ages 12 and 15, the time that adolescents are legally required to be in school. The study used discrete time survival analysis to assess the effect of truancy on initiation of drug use after adjusting for several potential confounders. Results indicated that in this population, truancy was a significant predictor of initiation of alcohol, tobacco, and marijuana use. The robust effect of truancy persisted after controlling for potential confounders, including school performance, school isolation, association with delinquent peers, personal delinquent values, parental monitoring, and family attachment. Although this study cannot point to a causal relationship, the effect may be at least in part due to the unsupervised, unmonitored time with peers that truancy affords a young person. The findings suggest that keeping youth in school every day is likely to have many beneficial effects. Effective truancy prevention efforts may also help to prevent or delay the onset of drug use among adolescents. Henry, K., and Huizinga, D. Truancy's, Effect on the Onset of Drug use Among Urban Adolescents Placed at Risk. J. Adolesc. Health, 40(4), pp. 358e9-358e17, 2007.

### Association Between Psychiatric Disorders and Smoking Stages

Investigators examined the prevalence of smoking behaviors and their association with specific psychiatric disorders in a representative sample of 8,568 youth from behavioral health clinics in Puerto Rico. A complex sampling design was used to select the sample, and analyses were conducted to account for the unequal selection probability, stratification, and clustering. All analyses were weighted back to the clinical population from which they were drawn. Psychiatric and substance use disorders were assessed using the parent and youth versions of the Diagnostic Interview Schedule for Children, Version 4.0. More than one third of the sample reported experience with cigarette smoking, and approximately one quarter reported smoking at least once per week (23.4%). As expected, the alcohol and drug use disorders demonstrated some of the strongest associations with individual smoking stages. These were the only disorders that remained significantly associated with nicotine dependence after controlling for comorbidity. The findings confirm the need for screening of smoking behavior and nicotine dependence in treatment settings and the integration of psychiatric/substance use treatments with smoking cessation. Dierker, L., Sledjeski, E., Botello-Harbaum, M., Ramirez, R., Chavez, L., and Canino, G. Association between Psychiatric Disorders and Smoking Stages within a Representative Clinic Sample of Puerto Rican Adolescents. Compr. Psychiatry, 48(3), pp. 237-244, 2007.

### Social Networks, Norms, and 12-Step Group Participation

Researchers assessed associations among frequency of attending a 12-step program, perceived social norms, and social network structure among 931 heroin and cocaine users from March 2004 to March 2006. They classified 197 (21%) as Frequent Attenders (FA), 229 (25% as Infrequent Attenders (IA), and 505 (54%) as Non-Attenders (NA). Significant differences were found among the 3 groups: Participants who reported that most or all of their drug partners attended 12-step groups were > 10 times more likely to be frequent attenders compared to individuals who did not go to Narcotics Anonymous (NA). Frequent Attenders also had the highest average total network size of 9.3 individuals while Non-Attenders had the lowest (8.1 individuals). Those who perceived that their drug-using 'buddies' went to Narcotics Anonymous were more likely to attend a 12-step program; this association held regardless of attendance level and after adjusting for social network structure. These findings highlight the effectiveness of 12-step programs for developing more social relationships, which then lead to more frequent attendance. Individuals who are trying to control their drug use should be encouraged to affiliate with others in recovery or attending a 12-step program. Davey-Rothwell, M., Kuramoto, S., and Latkin, C. Social Networks, Norms, and 12-Step Group Participation. Am. J. Drug Alc. Abuse, 34(2), pp. 185-193, 2008.

### Social Context of Drinking and Alcohol Problems Among College Students

This study examined how social contexts of drinking are related to alcohol use disorders, other alcohol-related problems, and depression among college students. Data were analyzed from a longitudinal cohort of 1,253 undergraduate students attending a University in the mid-Atlantic region. Logistic regression models controlling for drinking frequency measured the association between social context and problems among the 728 current drinkers (students who had consumed alcoholic beverages on 5 or more days during the past 12 months) in the cohort. Drinking for social facilitation was associated with drinking and driving and housing violations. Drinking in the context of motor vehicles was associated with alcohol abuse/ dependence. Drinking in a context of emotional pain was associated with clinical depression. The authors conclude that alcohol-free programming that fulfills needs for conviviality and addresses early signs of depression might reduce alcohol problems among college students. Beck, K., Arria, A., Caldeira, K., Vincent, K.,

O 'Grady, K., and Wish, E. Social Context of Drinking and Alcohol Problems Among College Students. Am. J. Health Behav., 32(4), pp. 420-430, 2008.

### Long-term Trends in Adolescent and Young Adult Smoking in the US

The authors sought to describe long-term adolescent and young adult smoking trends and patterns by analyzing adolescent data from Monitoring the Future, 1976 to 2005, and young adult (aged 18-24 years, roughly 16,000 students per year) data from the National Health Interview Survey, 1974 to 2005 (n~1800-5600), overall and in subpopulations to identify trends in current cigarette smoking prevalence. Five metapatterns emerged (1) a large increase and subsequent decrease in overall smoking over the past 15 years, (2) a steep decline in smoking among Blacks through the early 1990s, (3) a gender gap reversal among older adolescents and young adults who smoked over the past 15 years, (4) similar trends in smoking for most subgroups since the early 1990s, and (5) a large decline in smoking among young adults with less than a high school education. Long-term patterns for adolescent and young adult cigarette smoking were decidedly nonlinear, and the authors found evidence of a cohort effect among young adults. Continued strong efforts and a long-term societal commitment to tobacco use prevention are needed, given these unprecedented declines in smoking among most subpopulations since the mid- to late 1990s. Nelson, D., Mowery, P., Asman, K., Pederson, L., O 'Malley, P., Malarcher, A., Maibach, E., and Pechacek, T. Long-Term Trends in Adolescent and Young Adult Smoking in the United States: Metapatterns and Implications. Am. J. Public Health, 98(5), pp. 905-915, 2008.

### Associations between Adolescent Bipolar Disorder and Substance Use Disorders

This study used a case-control design to evaluate the risk for substance use disorders and cigarette smoking associated with bipolar disorder in adolescents. Subjects included adolescents with bipolar disorder (n=105, age 13.6+/-2.5 years [mean]; 70% male) and without bipolar disorder ('controls'; n=98, age 13.7+/-2.1 years; 60% male). Rates of substance use and other disorders were assessed with structured interviews (KSADS-E for subjects younger than 18, SCID for 18-year-old subjects). The authors found that bipolar disorder was associated with a significant age-adjusted risk for any substance use disorder, alcohol abuse, drug abuse and dependence, and cigarette smoking, independent of attention deficit/hyperactivity disorder, multiple anxiety, and conduct disorder (CD). The primary predictor of substance use disorders in bipolar youth was older age. They conclude that adolescent bipolar disorder is a significant risk factor for substance use disorders and cigarette smoking, independent of psychiatric comorbidity, and recommend that clinicians should carefully screen adolescents with bipolar disorder for substance and cigarette use. Wilens, T., Biederman, J., Adamson, J., Henin, A., Sgambati, S., Gignac, M., Sawtelle, R., Santry, A., and Monuteaux, M., Further Evidence of an Association between Adolescent Bipolar Disorder with Smoking and Substance Use Disorders: A Controlled Study. Drug Alcohol Depend., 95(3), pp. 188-198, 2008.

### Factors Associated with HIV Viral Load in a Respondent Driven Sample in Los Angeles

This study used a modified version of the Behavioral Model for Vulnerable Populations to examine the predisposing, enabling, and need factors associated with detectable viral load (VL) among HIV positive persons participating in NIDA's Sexual Acquisition and Transmission of HIV Cooperative Agreement Program (SATHCAP) at the Los Angeles, California research site. HIV status

was measured using saliva and confirmed by blood. Of 797 persons enrolled, 193 were HIV positive and provided VL counts. A hierarchical multivariate logistic regression approach was used to demonstrate that homelessness and recent substance abuse, particularly methamphetamine abuse, were negatively associated with VL. The negative association of homelessness on VL was weakened, however, when participants were able to access and use HIV medication. Mediation analysis showed that methamphetamine use was a significant predictor of detectable viral load, regardless of having access to HIV medication, underscoring the importance of addressing substance abuse among those who are HIV positive is needed to improve biological outcomes. King, Larkins, Hucks-Ortiz, Wang, Gorbach, Veniegas, and Shoptaw. Factors Associated with HIV Viral Load in a Respondent Driven Sample in Los Angeles. AIDS Behav., E-pub, pp. 1-9, 2007.

### Greater Drug Injecting Risk for HIV, HBV, and HCV Infection in a City Where Syringe Exchange and Pharmacy Syringe Distribution are Illegal

Researchers compared drug-injecting risk for HIV, hepatitis B, and hepatitis C among IDU in Newark, NJ and New York City to assess the efficacy of legalizing sterile syringe distribution as a structural intervention to prevent HIV and other parenterally transmitted infections among IDUs. Over the period of data collection (2004-2006), syringe distribution programs were illegal in Newark and legal in NYC. IDU were recruited in both cities, serotested, and interviewed about syringe sources and injecting risk behaviors (prior 30 days). In multivariate logistic regression, adjusted odds ratios (AOR) and 95% confidence intervals (95% CI) for city differences were estimated controlling for potential city confounders. IDUs in Newark (n = 214) vs. NYC (n = 312) were more likely to test seropositive for HIV (26% vs. 5%; AOR = 3.2; 95% CI = 1.6, 6.1), antibody to the HBV core antigen (70% vs. 27%; AOR = 4.4; 95% CI = 2.8, 6.9), and antibody to HCV (82% vs. 53%; AOR = 3.0; 95% CI = 1.8, 4.9), were less likely to obtain syringes from syringe exchange programs or pharmacies (AOR = 0.004; 95% CI = 0.001, 0.01), and were more likely to obtain syringes from street sellers (AOR = 74.0; 95% CI = 29.9, 183.2), to inject with another IDU''s used syringe (AOR = 2.3; 95% CI = 1.1, 5.0), and to reuse syringes (AOR = 2.99; 95% CI = 1.63, 5.50). These findings demonstrate that IDUs are more likely to obtain syringes from unsafe sources and to engage in injecting risk behaviors in localities where syringe distribution programs are illegal. When these programs are legal and accessible, however, IDUs who are not in drug treatment will access them to reduce their risks of parenterally acquiring or transmitting HIV, HBV, and HCV. Neaigus, A., Zhao, M., Gyarmathy, V., Cisek, L., Friedman, S., and Baxter, R. Greater Drug Injecting Risk for HIV, HBV, and HCV Infection in a City Where Syringe Exchange and Pharmacy Syringe Distribution are Illegal. J. Urban Health, 85(3), pp. 309-322, 2008.

### Individual, Social, and Environmental Influences Associated with HIV Infection Among Injection Drug Users in Tijuana, Mexico

Researchers examined correlates of HIV infection among injection drug users (IDUs) in Tijuana, Mexico, a city bordering the United States, which is situated on major migration and drug trafficking routes. IDUs aged > or =18 years were recruited using respondent-driven sampling. Participants underwent antibody testing for HIV and syphilis and structured interviews. Weighted logistic regression identified correlates of HIV infection. Of 1056 IDUs, the median age was 37 years, 86% were male, and 76% were migrants. HIV prevalence was higher in female participants than in male participants (8% vs. 3%; P = 0.01). Most IDUs testing HIV-positive were previously unaware of their serostatus (93%). IDUs reported injecting with a median of 2 people in the prior 6 months and had been arrested for having injection stigmata (ie,

'track-marks') a median of 3 times. Factors independently associated with HIV infection were being female, syphilis titers consistent with active infection, larger numbers of recent injection partners, living in Tijuana for a shorter duration, and being arrested for having track-marks. These findings reveal the range of individual, social, and environmental factors that are independently associated with HIV infection among IDUs in Tijuana. They point to the need to intervene not solely on individual risk behaviors but on social processes that drive these behaviors, including problematic policing practices. Strathdee, S., Lozada, R., Pollini, R., Brouwer, K., Mantsios, A., Abramovitz, D., Rhodes, T., Latkin, C., Loza, O., Alvelais, J., Magis-Rodriguez, C., and Patterson, T. Individual, Social, and Environmental Influences Associated with HIV Infection among Injection Drug Users in Tijuana, Mexico. J Acquir Immune Defic Syndr, 47(3), pp. 369-376, 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. 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.

### Circumstances of First Crystal Methamphetamine Use and Initiation of Injection Drug Use Among High-Risk Youth

Despite the widely noted increases in crystal methamphetamine (CM) use, there are few studies on circumstances of first CM use or correlates of use among high-risk populations (e.g. street-involved youth). Street-involved youth in Vancouver, Canada, were enrolled in a study called the At-Risk Youth Study (ARYS) prospective cohort. Extensive outreach produced a representative sample of Vancouver street youth who use illicit drugs. Researchers examined circumstances of first CM use and factors associated with CM use among the cohort. They found that, among 478 participants, 339 (70.9%) had used CM previously. Despite intensive covariate adjustment, a history of CM use was associated independently with having initiated injection drug use [OR = 3.15 (95% CI: 1.89-5.2); $p < 0.001$]. Among those who had used CM, route of first administration included: 11 (3.2%) oral ingestion; 25 (7.4%) injected; 105 (31.0%) snorted; 231 (68.1%) smoked. The proportion of respondents reporting current CM injection was significantly greater than the proportion reporting injection as the route for first CM use (18.3% vs. 7.4%; McNemar's test $p < 0.001$). Ability to obtain CM the first time was reported as

'very easy' or 'easy ' by 93.5% and 5.3% of participants, respectively. These findings indicate that crystal methamphetamine use was independently associated with injection drug use, and that significant increases in injecting as the primary mode of administration were observed when patterns of use were considered longitudinally. The easy accessibility of CM and its common use during transition into injection drug use demonstrate the need for innovative drug policy to address this growing concern. Wood, E., Stoltz, J., Zhang, R., Strathdee, S., Montaner, J., and Kerr, T. Circumstances of First Crystal Methamphetamine Use and Initiation of Injection Drug Use among High-Risk Youth. Drug Alcohol Rev, 27(3), pp. 270-276, 2008.

### Predicting Hospitalization among HIV-Infected Antiretroviral Naive Patients Starting HAART: Determining Clinical Markers and Exploring Social Pathways

In the era of highly active antiretroviral therapy (HAART), hospitalization as a measure of morbidity has become of increasing interest. The objectives of this study were to determine clinical predictors of hospitalization among HIV-infected persons initiating HAART and to explore the impact of gender and drug use on hospitalization. The analysis was based on a cohort of HIV-positive individuals initiating HAART between 1996 and 2001. Information on hospitalizations was obtained through data linkage with the BC Ministry of Health. Cox-proportional hazard models were used to assess variables associated with time to hospitalization. A total of 1,605 people were eligible and 672 (42%) were hospitalized for one or more days. The final multivariate model indicated that there was an increased risk of hospitalization among those with high baseline HIV RNA (HR for > 100,000 copies/mL: 1.26; 95%CI: 1.16-1.59) or low CD4 cell counts (HR [95% CI] compared to > or = 200 cells/mm3: 1.62 [1.28-2.06] and 1.29 [1.07-1.56] for < 50 and 50-199 cells/mm(3), respectively). Other factors, including adherence, previous hospitalization, gender and injection drug use remained predictive of hospitalization. These findings highlight the importance of closely monitoring patients starting therapy with low CD4 cell counts in order to mediate or prevent outcomes requiring hospitalization. Fielden, S., Rusch, M., Levy, A., Yip, B., Wood, E., Harrigan, R., Goldstone, I., Guillemi, S., Montaner, J., and Hogg, R. Predicting Hospitalization among HIV-Infected Antiretroviral Naive Patients Starting HAART: Determining Clinical Markers and Exploring Social Pathways. AIDS Care, 20(3), pp. 297-303, 2008.

### Patterns of Opioid Analgesic Dependence Symptoms

This study examined symptoms of dependence related to the extramedical use of opioid analgesic medications. The 2002-2003 public data-files of the National Survey on Drug Use and Health were used to identify 7810 extramedical opioid analgesic users in the past-year. Latent Class Analysis was used to empirically define classes of past-year extramedical opioid analgesic users based on observed clustering of DSM-IV defined clinical dependence features; multinomial logistic regression was used to describe differences across these groups. The best-fitting four-class model identified classes that differed quantitatively and qualitatively, with 2% of the users in Class 4 (most severe) and 84% in Class 1 (least severe). Classes 2 and 3 had parallel symptom profiles, but those in Class 3 reported additional problems. Adolescents (12-17 year olds) were at higher odds of being in Class 3 versus older age groups; females were two times as likely to be in Classes 2 and 4, and those with mental health problems were at higher odds of belonging to the more severe classes. Differences by type of past year opioid users were also detected. This study sheds light on the classification and distribution of extramedical opioid analgesic dependence symptoms in the US general population and identifies significant subgroups. Ghandour, L., Martins, S., and Chilcoat, H. Understanding the Patterns and Distribution of Opioid Analgesic Dependence

Symptoms Using a Latent Empirical Approach. Int. J. Methods Psychiatr. Res., 17(2), pp. 89-103, 2008.

### Neurosyphilis in a Clinical Cohort of HIV-1-Infected Patients

Researchers sought to describe the risk factors, clinical presentation, and long-term follow up of patients enrolled in a clinical cohort of HIV-infected patients who were diagnosed and treated for neurosyphilis. They collected comprehensive demographic, clinical, and therapeutic data from all patients between 1990 and 2006. Patients were diagnosed with neurosyphilis if they had positive syphilis serologies and any of the following: (a) one or more cerebrospinal fluid abnormalities on lumbar puncture [white blood cells >10/microl; protein >50 mg/dl; reactive venereal diseases research laboratory], or (b) an otherwise unexplained neurological finding. Of the 231 newly diagnosed syphilis cases, 41 neurosyphilis cases met entry criteria. Their median age was 38.6 years, 79.1% were male, 90% African American, 42% IDU, 48% heterosexual, and 51% had prior history of syphilis). Risk factors for neurosyphilis included a CD4 cell count of less than 350 cells/ml at the time of syphilis diagnosis (odds ratio: 2.87; 95% confidence interval: 1.18-7.02), a rapid plasma regain titer >1: 128 (2.83; 1.11-7.26), and male sex (2.46; 1.06-5.70). Use of any highly active antiretroviral therapy before syphilis infection reduced the odds of neurosyphilis by 65% (0.35; 0.14-0.91). Sixty-three percent of cases presented with early neurosyphilis and the median time to neurosyphilis diagnosis was 9 months. Symptomatic patients had more cerebrospinal fluid abnormalities on initial lumbar puncture than asymptomatic patients (P = 0.01). Follow-up lumbar puncture within 12 months revealed that only 38% had resolution of all cerebrospinal fluid abnormalities. At 1 year, 38% had persistence of their major symptom despite adequate treatment for neurosyphilis. Twelve of 41 (29%) patients were retreated for syphilis. This study found that early neurosyphilis was common in this cohort. Highly active antiretroviral therapy to reverse immunosuppression may help mitigate neurological complications of syphilis. Ghanem, K., Moore, R., Rompalo, A., Erbelding, E., Zenilman, J., and Gebo, K. Neurosyphilis in a Clinical Cohort of HIV-1-Infected Patients. AIDS, 22(10), pp. 1145-1151, 2008.

### Peer Environment Mediates Parental History and Individual Risk in the Etiology of Cannabis Use Disorder in Boys

Previous research has shown that a trait termed neurobehavior disinhibition (ND) measured in childhood predicts substance use disorder by young adulthood. The present investigation extends these findings by determining the degree to which peer environment mediates the association between ND and development of cannabis use disorder (CUD). ND was measured in a sample of 216 boys 10-12 years of age. The peer environment was assessed at age 16. Current CUD was determined at age 22. Paternal and maternal SUD predicted son's ND which, in turn, predicted son's peer environment and, subsequently, son's cannabis use frequency and CUD. Peer environment mediated the association between ND and cannabis use and ND and CUD. Maternal and paternal SUD predicted the peer environment. Parental SUD, son's ND, and son's peer environment predicted CUD at age 22 with 84% accuracy. Feske, U., Tarter, R., Kirisci, L., Gao, Z., Reynolds, M. and Vanyukov, M. Peer Environment Mediates Parental History and Individual Risk in the Etiology of Cannabis Use Disorder in Boys: A 10-Year Prospective Study. Am. J. Drug Alc. Abuse, 34(3), pp. 307-320, 2008.

### Substance Use among Asian Americans and Pacific Islanders Sexual Minority Adolescents: Findings from the National Longitudinal Study of Adolescent Health

Researchers assessed the prevalence, incidence, and correlates of substance use among Asian American individuals transitioning from adolescence to young adulthood. Data were obtained from the National Longitudinal Study of Adolescent Health, Wave II (1996) and Wave III (2001). Information on substance use was abstracted from a nationally representative sample of 1108 Asian Americans and Pacific Islanders (AAPIs) from both Waves. Weighted prevalence, incidence, and patterns of smoking, binge drinking, marijuana use, and other drug use were analyzed by sexual orientation and gender. Multiple logistic regression analyses were conducted to investigate the unique contribution of being a sexual minority in relation to four types of substance use by gender. A link between sexual orientation and substance use behaviors among AAPIs did not emerge until young adulthood. Significant increases in the incidence and prevalence of all four types of substance use (tobacco, binge drinking, marijuana, and other drugs) were found among sexual minority AAPIs. Specifically being an AAPI sexual minority young woman, compared with being a heterosexual young woman, a heterosexual young man, or a sexual minority young man, was significantly associated with substance use after controlling for demographic characteristics, problem behaviors, and substance use during adolescence. The highest prevalence of substance use was found among AAPI sexual minority women. These findings bring new light to the importance of sexual orientation in the design of substance abuse programs. Hahm, H., Wong, F., Huang, Z., Ozonoff, A., and Lee, J. Substance Use among Asian Americans and Pacific Islanders Sexual Minority Adolescents: Findings from the National Longitudinal Study of Adolescent Health. J. Adolesc. Health, 42(3), pp. 275-283, 2008.

### Smoking Tobacco Along with Marijuana Increases Symptoms of Cannabis Dependence

User practices/rituals that involve concurrent use of tobacco and marijuana - smoking blunts and 'chasing' marijuana with tobacco - are hypothesized to increase cannabis dependence symptoms. For this project, ethnographers administered group surveys to a diverse, purposive sample of marijuana users who appeared to be 17-35 years old. The setting in which the study took place was New York City, including non-impoverished areas of Manhattan, the transitional area of East Village/Lower East Side, low-income areas of northern Manhattan and South Bronx, and diverse areas of Brooklyn and Queens. Participants were 481 marijuana users ages 14-35, 57% male, 43% female; 27% White, 30% Black, 19% Latino, 5% Asian, 20% of other/multiple race. Among many other topics, group surveys measured cannabis dependence symptoms; frequencies of chasing, blunt smoking, joint/pipe smoking, using marijuana while alone, and general tobacco use; and demographic factors. Authors found blunt smoking and chasing marijuana with tobacco were each uniquely associated with five of the seven cannabis dependence symptoms. Across symptoms, predicted odds were 2.4-4.1 times greater for participants who smoked blunts on all 30 of the past 30 days than for participants who did not smoke blunts in the past 30 days. Significant increases in odds over the whole range of the five-point chasing frequency measure (from never to always) ranged from 3.4 times to 5.1 times. Using tobacco with marijuana contributes to cannabis dependence symptoms. Treatment for cannabis dependence may be more effective if it addresses the issue of concurrent tobacco use. Ream, G., Benoit, E., Johnson, B., and Dunlap, E. Smoking Tobacco along with Marijuana Increases Symptoms of Cannabis Dependence. Drug Alcohol Depend., 95(3), pp. 199-208, 2008.

### Prescription Opioid Use, Misuse, and Diversion Among Street Drug Users in New York City

This study documents patterns of prescription opioid (PO) use, misuse, and diversion among street drug users, and begins to indicate how drug culture

practices interact with the legitimate therapeutic goals of PO prescriptions (e.g. pain management). The authors completed interviews inquiring about the reasons for use of POs and illicit drugs with 586 street drug users. Ethnographers wrote extensive field notes about subjects' complex patterns of PO use. Methadone was used (71.9%) and sold (64.7%) at a higher level than OxyContin, Vicodin, and Percocet, used by between 34% and 38% of the users and sold by between 28% and 41% of the sellers. Recent PO use is associated with the recency of using heroin and cocaine ($p<.001$). Half of the heroin/cocaine sellers sold POs, and one quarter of the PO sellers only sold POs. Subjects were classified into four groups by whether they diverted POs or used POs to relieve pain or withdrawal rather than for euphoria. This classification was associated with frequency of PO use, whether POs were obtained from doctors/pharmacies or from drug dealers and family members, and those mostly likely to use POs for pain and withdrawal. POs are an important component of street drug users '' drug-taking regimes, especially those who are Physically Ill Chemical Abusers (PICA). Future research is needed to model PO use, misuse, and diversion among this population. Davis, W. and Johnson, B. Prescription Opioid Use, Misuse, and Diversion among Street Drug Users in New York City. Drug Alcohol Depend., 92(1-3), pp. 267-276, 2008.

### Assessment of Risk for Substance Use Disorder Consequent to Consumption of Illegal Drugs

Previous research has shown that the trait neurobehavior disinhibition (ND), which consists of affect, behavior, and cognitive indicators of self-regulation, is a significant predictor of substance use disorder (SUD) between childhood and young adulthood. The authors evaluated the psychometric properties of the ND trait in 278 boys evaluated at ages 10-12 and 16 years. ND scores significantly predicted SUD and outcomes that commonly manifest in tandem with SUD by age 19, such as violence, arrests, committing crime while intoxicated, and concussion injury. In addition to predictive validity, the ND trait was found to have good construct, discriminative, and concurrent validity, as well as good test-retest and internal reliability. The ND trait may be useful for detecting youths at high risk for developing SUD and related outcomes. Mezzich, A., Tarter, R., Feske, U., Kirisci, L., McNamee, R. and Day, B. Assessment of Risk for Substance Use Disorder Consequent to Consumption of Illegal Drugs: Psychometric Validation of the Neurobehavior Disinhibition Trait. Psych. Addict. Behav. 21(4), pp. 508-515, 2007.

### The Role of Gender and Family on Long-Term Patterns of Drug Use among an Urban African-American Cohort

The current study uses longitudinal data from a community cohort of African-American inner-city males and females followed from first grade through mid-adulthood (n=1242 at baseline). It identifies the substance use patterns through mid-adulthood, including lifetime prevalence, age of onset and termination, and sequencing of substance classes, as well as the risk of initiation of substance use changes over the life course using survival analysis. It also investigates whether early family structure and process play a role in drug use initiation throughout the life course, and whether the relationship between family factors and drug initiation differs by gender. Overall, among the general trends of use, the authors find a considerable amount of abstention with over 40% of the participants never using illegal drugs by mid-adulthood, over 70% never using cocaine, and over 90% never using heroin. With respect to onset, the authors find a long-term influence of early family factors on substance use, particularly for females. Family discipline in childhood and family cohesion and parental rule setting during adolescence seem to be key factors in predicting later substance use for females. The implica-tions of these findings for future research and policy are discussed. Doherty, E., Green, K.,

Reisinger, H., and Ensminger, M. Long-Term Patterns of Drug Use among an Urban African-American Cohort: the Role of Gender and Family. J. Urban Health, 85(2), pp. 250-267, 2008.

### Factors Related to Correctional Facility Incarceration Among Active Injection Drug Users in Baltimore

The authors investigated the moderating effect of impulse control on the association between drug use and incarceration among active injection drug users (IDU). The study sample consisted of 282 IDUs aged 15-50 years from the Baltimore metropolitan region who reported injection drug use within the past 6 months and indicated that heroin or speedball was their drug of choice. Impulse control was measured using commission error standardized scores from the Test of Variables of Attention (TOVA). Incarceration was obtained using self-reported lifetime history of incarceration in correctional facilities. Findings indicated that impulse control moderated the association between years of injection drug use and incarceration in correctional facilities adjusting for ethnicity, gender, estimated pre-morbid intelligence, and age of first injection use. Specifically, among individuals who were intact in impulse control, four or more years of injection drug use was associated with incarceration (AOR=4.97, 95% CI: 2.02-12.23). This finding was not observed among individuals with impaired impulse control (AOR=0.57, 95% CI: 0.10-3.23). Furthermore, impulse control moderated the association between regular cocaine use and incarceration. Among individuals who had a history of cocaine use, individuals with low impulse control but not impaired were more likely to have reported time in a correctional facility (AOR=6.28, 95% CI: 1.68-23.60). There was no association among individuals with impaired or intact impulse control. Results highlight the importance of considering cognitive measures of impulse control in addressing negative outcomes associated with drug use. Severtson, S., and Latimer, W. Factors Related to Correctional Facility Incarceration among Active Injection Drug Users in Baltimore, MD. Drug Alcohol Depend., 94(1-3), pp. 73-81, 2008.

### Investigating the Long-Term Influence of Adolescent Delinquency on Drug Use Initiation

Prior research has found a positive relationship between delinquency and early onset of drug use. However, little is known about the influence of delinquency on drug initiation through mid-adulthood. This paper investigates the long-term relationship between serious adolescent delinquency and the onset of marijuana and cocaine use among an epidemiologically defined community sample of African American males and females followed from first grade (n=1242) through age 42 (n=833). Using propensity score methods authors match individuals on several etiological variables that may explain both delinquency and drug use in an attempt to examine the extent to which there may be a causal link between delinquency and drug use initiation. Through a comparison of survival curves on the unmatched and matched samples of serious delinquents and non-serious delinquents, authors found evidence that serious adolescent delinquency has at least some causal influence on drug use initiation that extends into mid-life. These findings suggest that the prevention of delinquency in adolescence should be included in behavioral interventions and other approaches to reduce and prevent substance use. Doherty, E., Green, K., and Ensminger, M. Investigating the Long-term Influence of Adolescent Delinquency on Drug Use Initiation. Drug Alcohol Depend., 93(1-2), pp. 72-84, 2008.

### The MAOA Promoter Polymorphism, Disruptive Behavior Disorders, and Early Onset Substance Use Disorder: Gene-Environment Interaction

Conduct, oppositional defiant, and attention deficit hyperactivity disorders, reflecting early antisociality and behavior dysregulation, are predictive of substance use disorders. Liabilities to these disorders share genetic and environmental variance. Parenting characteristics have been shown to influence development of antisociality, moderated by variation at the MAOA gene, which has also been associated with the risk for substance use disorders. To extend these findings, the authors tested the relationships between the MAOA promoter polymorphism (variable number tandem repeat), indices of child's perception of paternal and maternal parenting, and disruptive behavior disorders and substance use disorders. A sample of 148 European-American males was assessed prospectively at ages from 10-12 to 18-19 years and genotyped for the monoamine oxidase A variable number tandem repeat. The Diagnostic and Statistical Manual of mental disorders-III-R diagnoses were obtained using standard methodology. Parenting was assessed using a scale summarizing the child's evaluation of the parenting style (parent's behavior toward him, parental emotional distance and involvement). Correlation, logistic regression, and Cox proportional hazard regression analysis were used to determine the relationships between the variables. The strength of association between parenting index and conduct and attention deficit hyperactivity disorders depended on the MAOA genotype. Unlike earlier findings, the parenting-risk relationships were observed in the 'high' rather than 'low-activity' genotypes. The strength and direction of relationships depended on the parental sex. The MAOA polymorphism's association with the risk for substance use disorders was detected when parenting was controlled for. The results are consistent with the contribution of the MAOA gene, parenting style, and their interactions to variation in the risk for early onset behavior disorders and liability to substance use disorders. Vanyukov, M., Maher, B., Devlin, B., Kirillova, G., Kirisci, L., Yu, L., and Ferrell, R. The MAOA Promoter Polymorphism, Disruptive Behavior Disorders, and Early Onset Substance Use Disorder: Gene-Environment Interaction. Psychiatr. Genet., 17(6), pp. 323-332, 2007.

### Differences in Attitudes Towards Drugs Between Adolescent Ecstasy Users Compared to Marijuana Users

Perceived risk and attitudes about the consequences of drug use, perceptions of others expectations and self-efficacy influence the intent to try drugs and continue drug use once use has started. The authors examine associations between adolescents' attitudes and beliefs towards ecstasy use. Because most ecstasy users have a history of marijuana use, the association was estimated for three groups of adolescents: non-marijuana/ecstasy users, marijuana users (used marijuana at least once but never used ecstasy) and ecstasy users (used ecstasy at least once). Data come from 5049 adolescents aged 12-18 years old who had complete weighted data information in Round 2 of the Restricted Use Files (RUF) of the National Survey of Parents and Youth (NSPY). Data were analyzed using jackknife weighted multinomial logistic regression models. Adolescent marijuana and ecstasy users were more likely to approve of marijuana and ecstasy use as compared to non-drug using youth. Adolescent marijuana and ecstasy users were more likely to have close friends who approved of ecstasy as compared to non-drug using youth. The magnitudes of these two associations were stronger for ecstasy use than for marijuana use in the final adjusted model. The authors' final adjusted model shows that approval of marijuana and ecstasy use was more strongly associated with marijuana and ecstasy use in adolescence than perceived risk in using both drugs. Information about the risks and consequences of ecstasy use need to be presented to adolescents in order to attempt to reduce adolescents' approval of ecstasy use as well as ecstasy experimentation. Martins, S., Storr, C., Alexandre, P., and Chilcoat, H. Do Adolescent Ecstasy Users have Different Attitudes towards Drugs when Compared to Marijuana Users? Drug Alcohol Depend., 94(1-3), pp. 63-72, 2008.

### Physical Maturation, Peer Environment, and the Ontogenesis of Substance Use Disorders

The risk for substance use disorders (SUD) is transmissible between generations via both genetic and environmental mechanisms. One path that is hypothesized to mediate this transmission and include both types of mechanisms is through faster physiological maturation, leading to sub-optimal self-regulation, affiliation with deviant peers, and higher risk for conduct disorder (CD). Extending prior research, this hypothesis was tested in a longitudinal sample of 478 males whose fathers were affected with SUD or psychiatrically normal was assessed prospectively at ages from 9-13 to 17-20. The DSM-III-R diagnoses were obtained using standard methodology. Blood testosterone was assayed by radioimmunoassay, and Tanner staging was used to evaluate sexual maturation. Peer deviance was evaluated by the Peer Delinquency Scale. Correlation and path analysis, Cox proportional hazard regression, and growth curve modeling were used to determine the relationships between the variables. The data support the hypothesis that parental SUD liability influences the rate of physiological maturation in offspring, which in turn is related to affiliation with deviant peers and an elevated rate of the development of CD and SUD. Kirillova, G., Vanyukov, M., Kirisci, L., and Reynolds, M. Physical Maturation, Peer Environ-ment, and the Ontogenesis of Substance Use Disorders. Psych.Res. 158(1), pp. 43-53, 2008.

### Reciprocal Influence of Parent Discipline and Child 's Behavior on Risk for Substance Use Disorder

This study aimed at determining the association of father's and mother's (parental) substance use disorder (SUD) and discipline styles and son's neurobehavioral disinhibition (ND) with son's SUD from childhood (age 10-12) to young adulthood (age 19). It was hypothesized that (1) parental discipline styles and son's ND mediate the association between parental SUD and son's SUD, (2) son's ND mediates the association between parental discipline styles and son's SUD, and (3) parental discipline styles mediate the association between ND and SUD in the son. Two-hundred-sixty-three families including a 10-12 year-old son and both parents participated in the study. The authors found that mother's discipline styles predicted father's discipline styles, son's ND predicted mother's instilling guilt positively and father's punishment negatively, son's ND mediated the association between father's SUD and punishment and son's SUD, and mother's SUD predicted son's ND and SUD. The reciprocal prediction between son's ND and father's punishment and prediction of father's punishment by mother's punishment point to the need for family-based interventions that take into account the quality of specific dyadic interactions pertaining to discipline behaviors that amplify the risk for SUD in male children. Mezzich, A., Tarter, R., Kirisci, L., Feske, U., Day, B., and Gao, Z. Reciprocal Influence of Parent Discipline and Child's Behavior on Risk for Substance Use Disorder: a Nine-Year Prospective Study. Am. J. Drug Alcohol Abuse, 33(6), pp. 851-867, 2007.

### Premature Mortality among Males with Substance Use Disorders

The objective of this study was to assess whether the presence of substance use disorder (SUD) or antisocial personality disorder (ASP) is associated with early mortality among males (fathers) in a predominantly community sample, using a 15-year prospective longitudinal study design. The authors conducted a prospective longitudinal study of adolescents and their fathers. The adolescent subjects were recruited at age 10-12 years, with follow-up evaluations at ages 14, 16, 19, 22, and 25. Questions were asked about paternal mortality during each of those visits. The study sample for this study was the 769 fathers of the

adolescent subjects, who included N=341 fathers with a DSM-III-R diagnosis of SUD and N=428 control fathers without a SUD. 89% of these fathers were recruited from the community, and 11% were recruited from clinical sources. Comorbidity patterns were described. A multivariate Cox regression analysis was performed with the father's age at death or last assessment as the dependent variable, and education, SUD, and ASP as the independent variables. Lower education level, the presence of a substance use disorder, and the presence of antisocial personality disorder were significantly associated with earlier mortality. Most subjects died from medical illnesses, as opposed to drug overdoses or accidents, which is different from the pattern often noted in clinical samples. The results of this study demonstrate that the presence of SUD, the presence of ASP, and a lower education level were associated with early mortality in this primarily community-based sample, which extends previous reports of similar findings in clinical samples. The magnitude of the prematurity of the deaths was less than that generally noted in previous studies involving clinical samples, and the causes of death were also somewhat different from those noted in clinical samples. The majority of cases of mortality in the SUD sample resulted from medical illnesses rather than from accidents or overdoses. Cornelius, J., Reynolds, M., Martz, B., Clark, D., Kirisci, L., and Tarter, R. Premature Mortality among Males with Substance Use Disorders. Addict. Behav., 33(1), pp. 156-160, 2008.

### Relationship Between Newspaper Coverage of Tobacco Issues and Smoking Attitudes and Behavior among American Teens

Geographic variation in youth smoking prevalence suggests that community-level factors influence risk of tobacco use. Authors examined the extent to which newspaper coverage of tobacco issues is related to youth smoking attitudes and behaviors. Authors conducted a content analysis of 8390 newspaper articles on tobacco issues from 386 daily newspapers circulating at 5% or more in 2001-3 Monitoring the Future (MTF) survey communities. This resulted in the creation of community level measures of news volume, content and valence. Associations between news and youth outcomes were assessed using logistic regression analyses adjusting for individual, geographic and tobacco policy factors linked to youth smoking and attitudes. The sample consisted of 98,747 youth participating in the nationally representative school-based MTF annual surveys between 2001 and 2003. Main outcomes included perceived harm of smoking, perceived peer smoking, disapproval of smoking, smoking within the past 30 days, daily cigarette consumption. In the five months preceding survey administration, newspapers in MTF communities published an average of 11.9 tobacco related articles (range 0-55.7). Each 10-article increase in newspaper volume over the five-month period was associated with increased odds of perceiving great harm from smoking (OR = 1.04, $p<0.01$) and disapproving of smoking (OR = 1.04, $p<0.05$) and decreased odds of perceiving most or all friends smoke (0.94, $p<0.01$) and smoking in the past 30 days (OR = 0.93, $p<0.001$). No consistent association was found between the content or valence of coverage and youth smoking outcomes. Findings support gaining and keeping tobacco on the media agenda as an important tool for tackling youth smoking. Smith, K., Wakefield, M., Terry-McElrath, Y., Chaloupka, F., Flay, B., Johnston, L., Saba, A., and Siebel, C., Relation between Newspaper Coverage of Tobacco Issues and Smoking Attitudes and Behavior among American Teens. Tob. Control, 17(1), pp. 17-24, 2008.

### Sex Work and HIV Status among Transgender Women: Systematic Review and Meta-Analysis

Transgender women are a key risk group for HIV, and epidemiologic studies have attributed high rates of HIV infection to behaviors associated with sex work in this population. This systematic review compared HIV prevalence

among transgender female sex workers (TFSWs) with prevalence among transgender women who do not engage in sex work, male sex workers, and biologically female sex workers. The researchers conducted systematic searches of six electronic databases. They extracted data, appraised methodologic quality, assessed hetero-geneity, and organized meta-analyses by comparison groups. They identified 25 studies among 6405 participants recruited from 14 countries. The overall crude HIV prevalence was 27.3% in TFSWs, 14.7% in transgender women not engaging in sex work, 15.1% in male sex workers, and 4.5% in female sex workers. Meta-analysis indicated that TFSWs experienced significantly higher risk for HIV infection in comparison to all other groups, and particularly in comparison to female sex workers. Significant heterogeneity was found among the included studies, along with methodologic limitations and imprecise definitions of sex work and gender. This study suggests that TFSWs could benefit from targeted HIV prevention interventions, HIV testing, and interventions to help reduce the risk of contracting or transmitting HIV. Operario, D., Soma, T., and Underhill, K. Sex Work and HIV Status among Transgender Women: Systematic Review and Meta-Analysis. J. Acquir. Imm. Defic. Syndr., 48(1), pp. 97-103, 2008.

### Positive Deviance Control-Case Life History: A Method to Develop Grounded Hypotheses about Successful Long-Term Avoidance of Infection

Prevalence rates for long-term injection drug users in some localities surpass 60% for HIV and 80% for HCV. Researchers conducting a project called 'Staying Safe' sought to develop grounded hypotheses on why some injectors avoid infection with either virus. They recruited 25 drug injectors who have injected drugs 8 - 15 years in New York City, of whom 17 have remained without antibody to either HIV or HCV; 3 are double-positives; and 5 are positive for HCV but not HIV. They then compared serostatus groups using detailed biographical timelines and narratives; information on how subjects maintain access to physical resources and social support; their strategies and tactics to remain safe; how they handle problems of addiction and demands by drug dealers and other drug users; and how their behaviors and strategies do or do not become socially-embedded practices. These grounded theory and life-history analysis techniques allow for comparisons among injectors who are doubly-uninfected with those infected with both viruses or only with HCV. Two emerging themes and initial hypotheses seem most salient for further study and potential use in improving preventive interventions: 1) Staying uninfected is not simply a question of social structure or social position. It involves agency by drug injectors, including sustained hard work and adaptation to changing circumstances. 2) Multiple intentionalities contribute to remaining uninfected, including balancing addiction, income, withdrawal, other drug users who want to share drugs, and knowing the risks for HIV (and perhaps HCV) infection. Focusing on a single goal in prevention might be sub-optimal when other (competing) needs and intentionalities are at play. This study has begun the work of identifying strategies and tactics that some doubly-uninfected, long-term IDUs have developed to avoid infection. The methods developed and used for the study lend themselves to refinement and testing through, e.g., cohort studies on behavioral change, risk reduction, prevention, and treatment among IDU. The grounded hypotheses methodology used in the study, a positive deviance control-case life history method, might also be useful to identify other strategies to avoid infections, such as like genital herpes among sex workers. Friedman, S., Mateu-Gelabert, P., Sandoval, M., Hagan, H., and Des Jarlais, D. Positive Deviance Control-Case Life History: A Method to Develop Grounded Hypotheses about Successful Long-Term Avoidance of Infection. BMC Public Health, 8, pp. 94-104, 2008.

### Pathways to Depression: The Impact of Neighborhood Violent Crime on Inner-City Residents in Baltimore, Maryland, USA

Crime and neighborhood disorder may negatively impact the health of urban residents. Neighborhoods with high levels of violent crime may also increase residents' risk of experiencing violence. Most studies supporting the assertion that neighborhood disorder impacts mental health have used residents' own ratings of their neighborhoods. The present study examines the relationships among block-group level crime, perceived neighborhood disorder, violence experienced in the neighborhood, and depression. The sample comprising the current and former drug users (n=786) nested in 270 block groups within Baltimore, Maryland. Using path analysis, researchers tested the hypothesis that neighborhood violent crime has a direct impact on experiences of violence. They also hypothesized that neighborhood violence had a direct and indirect impact on depressive symptoms. Results support a model in which violence is associated with psychological distress through perceptions of neighborhood disorder, and through experiences of violence. They conclude that community and structural level interventions are needed to decrease neighborhood crime and improve residents' perception of their neighborhood. Curry, A., Latkin, C., and Davey-Rothwell, M. Pathways to Depression: The Impact of Neighborhood Violent Crime on Inner-City Residents in Baltimore, Maryland, USA. Soc. Sci. Med., 67(1), pp. 23-30, 2008.

### Improved Injection Network Ascertainment with Supplementary Elicitation Techniques

Prior research indicates that injection drug users forget substantial proportions of their injection partners when asked to recall them. Such under-reporting hampers ascertainment of the injection networks that underlie transmission of blood-borne pathogens as well as contact-tracing efforts for disease control. In this study, researchers evaluated supplementary elicitation techniques--a set of prompting strategies and recall cues--for use in contacting injection partners. Sixty-one index drug injectors in Seattle participated in the study. The supplementary partner elicitation techniques enhanced recall of injection partners substantially and identified persons relevant to transmission of blood-borne pathogens. As a set, the supplementary techniques elicited additional partners from 70% of injectors, and the additional partners elicited represent a 75% increase on average. Drug injectors who recalled many partners before administration of the supplementary techniques tended to report more additional partners in response to the supple-mentary techniques than injectors who freely recalled few partners. In addition, partners elicited by the supplementary techniques were as likely as freely recalled partners to test positive for hepatitis C virus antibody and engage in risk behavior with indexes. Furthermore, the supple-mentary techniques were found effective for enhancing connectivity in the observed injection network. Brewer, D., Hagan, H., and Hough, E. Improved Injection Network Ascertainment with Supplementary Elicitation Techniques. Int. J. STD AIDS, 19(3), pp. 188-191, 2008.

### Exploring Drug Users' Attitudes and Decisions Regarding Hepatitis C (HCV) Treatment in the U.S.

Individuals with a history of injecting drugs are at the highest risk of becoming infected with the hepatitis C virus (HCV), with studies of patients in methadone maintenance treatment programmes (MMTPs) reporting that 60-90 percent of intravenous drug users (IDUs) have the virus. Fortunately, HCV therapy has been shown to be effective in 42-82 percent of all patients with chronic HCV infection, including IDUs. While the decision to start HCV therapy requires significant consideration, little research exists that explores the attitudes of drug users toward HCV therapy. This paper examines how drug users perceive the treatment, as well as the processes by which HCV-positive individuals weigh the advantages and disadvantages of starting the HCV medications.

Interviews were conducted with 164 patients from 14 drug treatment programmes throughout the United States. Both uninfected and HCV-positive drug users described a pipeline of communication among their peers that conveys largely negative messages about the medications that are available to treat HCV. Although many of the HCV-positive individuals said that these messages heightened their anxiety about the side effects and difficulties of treatment, some patients said that their peers helped them to consider, initiate HCV treatment, or both. Gaining a better understanding of drug users perceptions of HCV treatment is important, because so many of them, particularly IDUs, are already infected with HCV and may benefit from support in addressing their HCV treatment needs. In addition, currently uninfected drug users will likely remain at high risk for contracting HCV and may need to make decisions about whether or not to start the HCV medical regimen in the future. Munoz-Plaza, C., Strauss, S., Astone-Twerell, J., Jarlais, D., Gwadz, M., Hagan, H., Osborne, A., and Rosenblum, A. Exploring Drug Users' Attitudes and Decisions Regarding Hepatitis C (HCV) Treatment in the U.S. Int. J. Drug Policy, 19(1), pp. 71-78, 2008.

### Stimulant Use and Sexual Risk Behaviors for HIV in Rural North Carolina

While literature exists on sexual risks for HIV among rural populations, the specific role of stimulants in increasing these risks has primarily been studied in the context of a single drug and/or racial group. This study explores the use of multiple stimulants and sexual risk behaviors among individuals of different races and sexual identities in rural North Carolina. In-depth interviews were conducted with 41 individuals (40% female, 54% African America, 44% White, 40% younger than 34 years and 30% 45 years of age or older) in 3 rural North Carolina counties between June 2004 and December 2005. Data were transcribed and imported for analysis using the software system, AskSam. With marijuana, stimulants, including powder cocaine, crack, and methamphetamine were the most frequently used illicit drugs in these counties. Powder cocaine use was more closely associated with White participants, crack with African Americans, and both were more commonly used by female participants. Participants reported 3 overlapping behaviors involving stimulant use that may be associated with increased risk of HIV infection: engaging in sex while using drugs, sex trading, and group sex. Nearly half of participants reported engaging in group sex activity. HIV risk through injection appears to be low in these rural counties. However, nearly all study participants reported some form of sexual risk behavior that may increase transmission of HIV and other sexually transmitted infections, indicating the clear nexus between substance abuse and risky sexual behaviors. Zule, W., Costenbader, E., Coomes, C., Meyer, W., Riehman, K., Poehlman, J., and Wechsberg, W. Stimulant Use and Sexual Risk Behaviors for HIV in Rural North Carolina. J. Rural Health, 23 Suppl, pp. 73-78, 2007.

### HIV Risks Associated with Incarceration among Injection Drug Users: Implications for Prison-Based Public Health Strategies

Recent policy announcements in Canada and the United States may potentially affect the risk environment for HIV transmission among incarcerated injection drug users (IDU). Researchers sought to evaluate the potential impact of incarceration on HIV risk behavior among the IDU enrolled in a prospective cohort study. They examined patterns of incarceration among 1247 IDU participants enrolled in a 6-year prospective cohort study in Vancouver, Canada, and tested for potential associations between HIV risk behavior and incarceration. Correlates of incarceration were identified using generalized estimating equations (GEE). At baseline, factors significantly associated with incarceration included daily injection heroin and injection cocaine use and inconsistent condom use with casual sexual partners. In a GEE analysis, factors

independently associated with incarceration included: used syringe borrowing (adjusted odds ratio [AOR] = 1.36; [95% CI: 1.16-1.60]), used syringe lending (AOR = 1.31; [95% CI: 1.12-1.55]) and inconsistent condom use with casual sexual partners (AOR = 1.16; [1.02-1.33]). All variables P < 0.05. Incarceration was independently associated with HIV transmission and acquisition behaviors. These findings suggest that increased rates of incarceration of IDU may be associated with increased HIV transmission among this group. Werb, D., Kerr, T., Small, W., Li, K., Montaner, J., and Wood, E. HIV Risks Associated with Incarceration among Injection Drug Users: Implications for Prison-Based Public Health Strategies. J. Public Health (Oxf), 30(2), pp. 126-132, 2008.

### Associations Between Outpatient and Inpatient Service Use Among Persons with HIV Infection: A Positive or Negative Relationship?

This observational study sought to examine the prospective association between frequency of outpatient visits and subsequent inpatient admissions. It used medical record data on 13,942 patients with HIV infection seen in 10 HIV specialty care sites across the United States, following a cohort of HIV-infected patients who were in care in the first half of 2001. Numbers of inpatient admissions and outpatient visits were calculated for each patient for each 3-month period, from 2001 through 2004. Negative binomial and logistic regression analyses using random-effects models examined the effects of inpatient admissions and outpatient visits in the previous period on inpatient and outpatient service utilization, controlling for background characteristics and HIV disease stage. The study found that, for 3-month periods, between 5 and 9 percent of patients had an inpatient admission. The linear association between number of outpatient visits and any inpatient admission in the subsequent period was positive (adjusted odds ratio=1.05; 95 percent confidence interval [CI]=1.04, 1.06). However, patients with no prior outpatient visits had significantly greater admission rates than those with one prior visit. Hospitalization rates were also higher among those with a prior hospitalization and those with more advanced HIV disease. These results suggest a J-shaped relationship between outpatient use and inpatient use among persons with HIV disease. Those in worse health have greater utilization of both inpatient and outpatient care. However, having no outpatient visits may also increase the likelihood of subsequent hospitalization. Although outpatient care cannot be justified as a cost-saving mechanism, maintaining regular clinical monitoring of patients is important. Fleishman, J., Moore, R., Conviser, R., Lawrence, P., Korthuis, P., and Gebo, K. Associations Between Outpatient and Inpatient Service Use among Persons with HIV Infection: A Positive or Negative Relationship? Health Serv. Res., 43(1 Pt 1), pp. 76-95, 2008.

### Methamphetamine and Poly-Substance Use among Gym-Attending Men who have Sex with Men in New York City

The aim of this study is to describe patterns of methamphetamine and other drug use and to delineate psychosocial and demographic factors associated with use in a sample of MSM attending gyms in New York City. Active recruitment strategies were used to sample 311 MSM. Participants completed a one-time survey regarding health risks and health promotion. Methamphetamine use in the last 6 months was reported by 23.8% of men. Inhalation and smoking were the most common modes of administration, and 84% of men reported more than one mode of use. Study participants indicated a variety of other substances used, including but not limited to alcohol, inhalant nitrates, and 3,4 methylenedioxymethamphetamine (MDMA). Compared to nonusers, methamphetamine users were more likely to report being black or Latino, depressed, HIV-positive, perceiving more benefits of unprotected sex, and understanding masculinity in sexual terms. These data

suggest that health-risk behaviors are common among MSM who are regularly using a gym and are indicative of the complexities of health issues for this segment of the population. Halkitis, P., Moeller, R., Siconolfi, D., Jerome, R., Rogers, M., and Schillinger, J. Methamphetamine and Poly-Substance Use among Gym-Attending Men who have Sex with Men in New York City. Ann. Behav. Med., 35(1), pp. 41-48, 2008.

### Analysis of HIV Medication Adherence in Relation to Person and Treatment Character-istics Using Hierarchical Linear Modeling

This study examined person characteristics, treatment level variables, and illicit drug use to help explain HIV antiviral adherence patterns in a community-based, non-drug-treatment-seeking sample of men who have sex with men (MSM). Adherence data were gathered for 300 MSM (diverse in age and race/ethnicity) eight times over the course of 1 year using electronic monitoring. Treatment and person level characteristics were assessed at baseline using computer-administered surveys, and drug usage was established using a diagnostic inventory. Longitudinal data were analyzed with Hierarchical Linear Modeling. Over the year in which participants were assessed, adherence rates were relatively stable and high (means: 82% to 90%) at each time point. Lower adherence rates were evident among those who were drug users, black identified, older, and by pill burden. Individuals on HIV antiretroviral therapy demonstrated consistent although not optimal adherence rates. In this study, adherence to treatment appears to be impacted by the circumstances that the individual brings to the treatment behavior, suggesting that interventions should address life social and intrapersonal circumstances that may interfere with adherence behaviors. Halkitis, P., Palamar, J., and Mukherjee, P. Analysis of HIV Medication Adherence in Relation to Person and Treatment Characteristics Using Hierarchical Linear Modeling. AIDS Patient Care STDS, 22(4), pp. 323-335, 2008.

### Peer Norms and Sharing of Injection Paraphernalia among Puerto Rican Injection Drug Users in New York and Puerto Rico

This study examines the influence of peer norms on sharing of injection paraphernalia (e.g., indirect sharing behaviors, including sharing of cookers, cotton, rinse water and back/front loading) among Puerto Rican injection drug users (IDUs) in Bayamon, Puerto Rico, and East Harlem, New York City. Data were collected from 873 Puerto Rican IDUs recruited in the two locations by outreach workers. Multiple logistic regression was conducted using sociodemographic and other control variables (e.g., education, frequency of injection, pooling money to buy drugs, use of needle exchange program, injection in galleries and syringe sharing behaviors) and two types of norms related to sharing of injection paraphernalia-encouraging risk norms (what others approve) and objecting to risk norms (what others disapprove). One type of norms, encouraging or approval norms, was associated with indirect sharing in New York but not in Puerto Rico. Pooling money to buy drugs, use of shooting galleries and syringe sharing were associated with indirect sharing in both locations. These findings suggest that prevention programs to reduce indirect sharing behaviors should take into consideration different types of risk norms in order to reduce indirect sharing risk behaviors. Andia, J., Deren, S., Robles, R., Kang, S., and Colon, H. Peer Norms and Sharing of Injection Paraphernalia among Puerto Rican Injection Drug Users in New York and Puerto Rico. AIDS Educ. Prev., 20(3), pp. 249-257, 2008.

### Self-Reported HIV Testing Behaviors among a Sample of Southeast Asians in an Urban Setting in the United States

Given the growing HIV/AIDS epidemic in Asia, there has been concern in recent

years over the HIV/AIDS risks of Asian and Pacific Islander (AAPI) migrating populations to the United States. Little is known, however, about existing HIV risks among non-MSM AAPIs. This study examined self-reported HIV testing behaviors and their correlates among a sample of 604 Southeast Asians adults living in a U.S. urban setting. The HIV testing rate among the sample was 30.8%, lower than the median HIV testing rate in the U.S. adult population by state and in the AAPI MSM population. A low sexually transmitted infection (STI) testing rate as a proxy for low perceived sexual risks and a dearth of HIV knowledge were associated with the low HIV testing rate. Traditional health care access measures, such as availability of medical insurance and a personal doctor, did not explain the low HIV testing rate in this predominantly immigrant population. Culturally and linguistically appropriate HIV prevention campaigns may help to increase awareness of HIV/STI risk and improve the HIV testing HIV rate in this AAPI population. Huang, Z., Wong, F., De Leon, J., and Park, R. Self-Reported HIV Testing Behaviors among a Sample of Southeast Asians in an Urban Setting in the United States. AIDS Educ. Prev., 20(1), pp. 65-77, 2008.

### Risk Factors for Distress in the Adolescent Children of HIV-Positive and HIV-Negative Drug-Abusing Fathers

Researchers examined comorbid drug addiction and HIV infection in the father as related to his adolescent child's psychological distress. Individual structured interviews were administered to 505 HIV-positive and HIV-negative drug-abusing fathers (mean age 42; 76% lifetime IDU; 42% HIV positive) and one of their children, aged 12-20 (54% male; 50% African American; 37% Latino). Structural equation modeling tested an hypothesized model linking paternal latent variables, ecological factors and adolescent substance use to adolescent distress. Results demonstrated a direct pathway between paternal distress and adolescent distress, as well as an indirect pathway; namely, paternal distress was linked with impaired paternal teaching of coping skills to the child, which in turn was related to adolescent substance use and, ultimately, to the adolescent's distress. There was an additional association between paternal drug addiction/HIV and adolescent distress, which was mediated by both ecological factors and adolescent substance use. The direct effect of paternal drug addiction/HIV on the child's substance use may suggest the adolescent's role modeling of the father's risk behaviors and/or a genetic diathesis for substance use, shared by father and child. Findings suggest an increased risk of distress in the adolescent children of fathers with comorbid drug addiction and HIV/AIDS, which may be further complicated by paternal distress. Brook, D., Brook, J., Rubenstone, E., Zhang, C., Castro, F., and Tiburcio, N. Risk Factors for Distress in the Adolescent Children of HIV-Positive and HIV-Negative Drug-Abusing Fathers. AIDS Care, 20(1), pp. 93-100, 2008.

### Pooling Data From Multiple Longitudinal Studies: The Role of Item Response Theory in Integrative Data Analysis

There are a number of significant challenges researchers encounter when studying development over an extended period of time, including subject attrition, the changing of measurement structures across groups and developmental periods, and the need to invest substantial time and money. Integrative data analysis is an emerging set of methodologies that allows researchers to overcome many of the challenges of single-sample designs through the pooling of data drawn from multiple existing developmental studies. This approach is characterized by a host of advantages, but this also introduces several new complexities that must be addressed prior to broad adoption by developmental researchers. In this article, the authors focus on methods for fitting measurement models and creating scale scores using data drawn from multiple longitudinal studies. The authors performed an analysis of repeated measures of internalizing symptomatology that were pooled from

three existing developmental studies. The sample was pooled from the Michigan Longitudinal Study (n=512 ages 10-17), the Adolescent/Adult Family Development Project (n=830, ages 10-33), and the Alcohol and Health Behavior Project (n=485, ages 17-23) for a total sample of 1827 participants who were each assessed between 1-5 times, resulting in a total of 7377 person-by-time observations. The authors conclude that the simultaneous integration of multiple developmental data sets is recommended and should be considered for testing a broad range of theoretically derived research hypotheses. Advantages include increases in power, greater heterogeneity in participant demographics, broader psychometric assessment of theoretical constructs, longer longitudinal windows, opportunity to test hypotheses not originally considered, and cost/time effectiveness. Curran, P., Hussong, A., Cai, L., Huang, W., Chassin, L., Sher, K., and Zucker, R. Pooling Data from Multiple Longitudinal Studies: The Role of Item Response Theory in Integrative Data Analysis. Dev. Psychol., 44(2), pp. 365-380, 2008.

### Defining Risk Heterogeneity for Internalizing Symptoms Among Children of Alcoholic Parents

Adopting a developmental epidemiology perspective, the current study examines sources of risk heterogeneity for internalizing symptomatology among children of alcoholic parents (COAs). Parent-based factors, including comorbid diagnoses and the number of alcoholic parents in the family, as well as child-based factors, namely child gender, formed the indicators of heterogeneity. Following a novel approach to cross-study methods, the authors present a three-stage analysis involving measurement development using item response theory, examination of study effects on latent trajectories over time using latent curve modeling, and prediction of these latent trajectories testing our theoretically derived hypotheses in two longitudinal investigations across both mother- and self-reported symptomatology. Data used were the Michigan Longitudinal Study (596 children from 338 families ) and the Adolescent/Adult Family Development Project (454 adolescents and their families). Authors replicated previous findings that parent alcoholism has a unique effect on child internalizing symptoms, above and beyond those of both parent depression and antisocial personality disorder. However, they also found important subgroup differences, explaining heterogeneity within COAs risk profile in terms of the number of alcoholic parents in the family, comorbid diagnoses for the alcoholic parent and, for self-reported symptoms, child gender. Such factors serve to refine the definition of risk among COAs, suggesting a more severely impaired target group for preventive interventions, identifying the significance of familial alcoholism in individual differences underlying internalizing symptoms over time, and further specifying the distal risk matrix for an internalizing pathway to alcohol involvement. Hussong, A., Flora, D., Curran, P., Chassin, L., and Zucker, R. Defining Risk Heterogeneity for Internalizing Symptoms among Children of Alcoholic Parents. Dev. Psychopathol., 20(1), pp. 165-193, 2008.

### Disaggregating the Distal, Proximal, and Time-Varying Effects of Parent Alcoholism on Children's Internalizing Symptoms

The authors tested whether children show greater internalizing symptoms when their parents are actively abusing alcohol by combining observations over ages 2 through 17 from two longitudinal studies of children of alcoholic parents and matched controls recruited from the community. This integrative analysis included data from the Michigan Longitudinal Study (n=596 children from 338 families) and the Adolescent/Adult Family Development Project (454 adolescents and their parents). Using a mixed modeling approach, investigators tested whether children showed elevated mother- and child-reported internalizing symptoms (a) at the same time that parents showed alcohol-related consequences (time-varying effects), (b) if parents showed greater alcohol-related consequences during the study period (proximal

effects), and (c) if parents had a lifetime diagnosis of alcoholism that predated the study period (distal effects). No support for time-varying effects was found; proximal effects of mothers' alcohol-related consequences on child-reported internalizing symptoms were found and distal effects of mother and father alcoholism predicted greater internalizing symptoms among children of alcoholic parents. Hussong, A., Cai, L., Curran, P., Flora, D., Chassin, L., and Zucker, R. Disaggregating the Distal, Proximal, and Time-Varying Effects of Parent Alcoholism on Children's Internalizing Symptoms. J. Abnorm. Child Psychol., 36(3), pp. 335-346, 2008.

### The Relationship Among Cardiovascular Risk Factors, Diet Patterns, Alcohol Consumption, and Ethnicity Among Women Aged 50 Years and Older

This study used cluster analysis to examine diet patterns and the association between diet patterns and the presence of major cardiovascular disease (CVD) risk factors among women over 50 years of age. Data from the cross-sectional National Health and Nutrition Examination Survey (NHANES) 2001-2002 were used. Women 50 years and older were included (n=1,313), and the following major CVD risk factors were examined: being overweight or obese (body mass index >24.9), having elevated systolic blood pressure (>120 mm Hg), and having low levels of high-density lipoprotein cholesterol (<50 mg/dL [<1.30 mmol/L]). Dietary patterns were derived by cluster analysis using data from a 24-hour dietary recall. Odds Ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression to determine the probability of having a risk factor according to diet pattern while accounting for race/ethnicity, physical activity, age, and smoking. Cluster analysis generated six nonoverlapping diet patterns labeled: Pasta and Yellow Vegetables; Sweets; Beef, Starches, Fruits, and Milk; Frozen Meals, Burritos, and Pizza; Meat Dishes; and Soft Drinks and Poultry. The majority of the women were grouped in the Sweets diet pattern. Factors associated with adequate levels of high-density lipoprotein cholesterol included being non-Hispanic African American (OR 0.59, 95% CI 0.44 to 0.81; P<0.0001), alcohol consumption (OR 0.76, 95% CI 0.69 to 0.84; P<0.0001), and being assigned to the Sweets diet pattern (OR 0.27, 95% CI 0.14 to 0.50; P<0.0001) or Meat dishes diet pattern (OR 0.94, 95% CI 0.54 to 1.65; P<0.0075). The Sweets pattern was also associated with having normal systolic blood pressure levels (OR 0.51, 95% CI 0.34 to 0.76; P<0.0001). Individuals grouped in the Beef, Starches, and Milk diet pattern were more likely to have an adequate body mass index (OR 0.42, 95% CI 0.23 to 0.77; P<0.0032). Significant associations between dietary patterns and major CVD risk factors were observed. Food and nutrition professionals can use this information to assess unhealthful food choices observed in the dietary patterns to guide nutrition recommendations and help reduce the incidence of CVD risk factors. Future research should aim to evaluate dietary intake via complementary methods (ie, dietary patterns and nutrient assessment) to better understand diet-disease relationships. Lopez, E., Rice, C., Weddle, D., and Rahill, G. The Relationship among Cardiovascular Risk Factors, Diet Patterns, Alcohol Consumption, and Ethnicity among Women Aged 50 Years and Older. J. Am. Diet. Assoc., 108(2), pp. 248-256, 2008.

### Prevalence of Smoking and Drinking among Older Adults in Seven Urban Cities in Latin America and the Caribbean

In 2000, a representative sample of the elderly population (60 years or older) was selected from seven urban cities in Latin America and the Caribbean: Buenos Aires (Argentina), Mexico City (Mexico), Santiago (Chile), Havana (Cuba), Montevideo (Uruguay), Bridgetown (Barbados), and Sao Paulo (Brazil) to examine the prevalence of smoking and drinking in this population. A face-to-face interview was uniformly administered in the respective official languages. A total of 10,577 older adults were included in this study. The

elderly in Havana had the highest prevalence of smoking (46.5% of men and 21.5% women). The highest prevalence of daily drinking was in Buenos Aires (19%). In contrast, only 1.5% of respondents in Mexico City and 2.3% of respondents in Havana consumed alcohol daily. Smoking and daily drinking were highly prevalent among older adults. As the older adult population grows steeply, the health behavior of this population starts carrying important implications for health care systems. Kim, S., De La Rosa, M., Rice, C., and Delva, J. Prevalence of Smoking and Drinking among Older Adults in Seven Urban Cities in Latin America and the Caribbean. Subst. Use Misuse, 42(9), pp. 1455-1475, 2007.

### Substance Use in Marital Dyads: Premarital Assortment and Change Over Time

The purpose of this study was to examine change in substance use with marriage, premarriage similarity in substance use between spouses, and the role of spouse use in predicting changes in use with marriage. Nationally representative samples of high school seniors were followed longitudinally through age 35. The sample consisted of 2,169 adults from eight senior-year cohorts (1977-1984) from the Monitoring the Future study who completed a questionnaire at least once before their first marriage and at 2-year intervals at four consecutive points in time after marriage. Results indicate significant reductions in use with marriage for cigarette smoking, heavy drinking, and marijuana use. Both men and women reported reductions in all three substances following marriage. Changes in women's use followed a linear pattern. Although men's decreases in cigarette smoking and heavy drinking were initially rapid and then decelerated, their decrease in marijuana use accelerated over time. Declines in use for both genders were associated with getting married to individuals who also decreased their use. Those with higher premarriage levels of substance use experienced greater reductions in use. A significant association between respondent and spouse premarital use suggests assortative mating takes place for all three substances. This study affirms and further qualifies the presence of a marriage effect on substance use using multiwave and multicohort national data. Results suggest that the effects of marriage on smoking, heavy drinking, and marijuana use are related to one's own initial levels of use and the direction of change in the spouse's use. These findings have important implications for life span theoretical advances as well as interventions aimed at the marital dyad. Merline, A., Schulenberg, J., O'Malley, P., Bachman, J., and Johnston, L. Substance Use in Marital Dyads: Premarital Assortment and Change Over Time. J. Stud. Alcohol Drugs, 69(3), pp. 352-361, 2008.

### Adolescent Ecstasy and Other Drug Use in the National Survey of Parents and Youth: The Role of Sensation-Seeking, Parental Monitoring and Peer's Drug Use

The association between high sensation-seeking, close friends' drug use and low parental monitoring with ecstasy (MDMA) use in adolescence was examined in a sample of US household-dwelling adolescents aged 12-18 years (N=5049). The authors also tested whether associations were of stronger magnitude than associations between these correlates and marijuana or alcohol/tobacco use in adolescence. Data from Round 2 of the National Survey of Parents and Youth (NSPY) Restricted Use Files (RUF) was analyzed via Jackknife weighted multinomial logistic regression models. High sensation-seekers were more likely to be ecstasy, marijuana, and alcohol/tobacco users, respectively, as compared to low sensation-seekers. High sensation-seeking and close friends' drug use were more strongly associated with ecstasy as compared to marijuana and alcohol/tobacco use. Low parental monitoring was associated with marijuana use and alcohol/tobacco use and there was a trend for it to be associated with ecstasy use. Ecstasy use is strongly associated with peer drug

use and more modestly associated with high sensation-seeking. School prevention programs should target high-sensation-seeking adolescents and also encourage them to affiliate with non-drug using peers. Martins, S., Storr, C., Alexandre, P., and Chilcoat, H. Adolescent Ecstasy and Other Drug Use in the National Survey of Parents and Youth: The Role of Sensation-Seeking, Parental Monitoring and Peer's Drug Use. Addict. Behav., 33(7), pp. 919-933, 2008.

### Movie Smoking Exposure and Smoking Onset: A Longitudinal Study of Mediation Processes in a Representative Sample of U.S. Adolescents

The authors tested 2 mechanisms for the relation of movie smoking exposure with onset of cigarette smoking in adolescence. Longitudinal data with 8-month follow-up were obtained from a representative sample of 6,522 U.S. adolescents, ages 10-14 years. Structural modeling analysis based on initial nonsmokers, which controlled for 10 covariates associated with movie exposure, showed that viewing more smoking in movies was related to increases in positive expectancies about smoking and increases in affiliation with smoking peers, and these variables were both related to smoking onset. A direct effect of movie exposure on smoking onset was also noted. Mediation findings were replicated across cross-sectional and longitudinal analyses. Tests for gender differences indicated that girls showed larger effects of movie exposure for some variables. Wills, T., Sargent, J., Stoolmiller, M., Gibbons, F., and Gerrard, M. Movie Smoking Exposure and Smoking Onset: A Longitudinal Study of Mediation Processes in a Representative Sample of U.S. Adolescents. Psychol. Addict. Behav., 22(2), pp. 269-277, 2008.

### The Effect of Early Cognitions on Cigarette and Alcohol Use During Adolescence

This study predicts cigarette and alcohol use in adolescence from the development of children's cognitions in the elementary years. Using latent growth modeling, the authors examined a model using data from 712 participants in the Oregon Youth Substance Use Project, who were in the 2nd through 5th grade at the 1st assessment and followed for 6 annual or semiannual assessments over 7 years. Growth in children's prototypes and subjective norms in the elementary years (Times 1 through 4) were related to their substance use in adolescence (Time 6) through their willingness and intentions (Time 5) to smoke and drink. Across the sample, for both substances, the intercept and slope of prototypes were either indirectly related to use through willingness or directly related to use. Both the intercept and slope of subjective norms were indirectly related to use of both substances through both willingness and intentions and directly related to cigarette use. Results suggest that elementary children have measurable cognitions regarding substance use that develop during the elementary years and predict use later in adolescence. These findings emphasize the need for prevention programs targeted at changing children's social images of substance users and encouraging more accurate perceptions of peers' use. Andrews, J., Hampson, S., Barckley, M., Gerrard, M., and Gibbons, F. The Effect of Early Cognitions on Cigarette and Alcohol Use during Adolescence. Psychol. Addict. Behav., 22(1), pp. 96-106, 2008.

### Suicidal Ideation Among Juvenile Detainees

This study examined suicidal ideation, suicide attempts, lethality of suicide attempts and the relationship between psychiatric disorder and recent attempts in newly detained juveniles. The sample included 1,829 juveniles, ages 10 to 18 years, sampled after intake to a detention center in Chicago, IL.

Interviewers administered the Diagnostic Interview Schedule for Children to assess for thoughts of death, suicidal ideation, suicide plans, lifetime suicide attempts, number of attempts, age at first attempt, attempts within the past 6 months, method of suicide attempts and psychiatric disorder. Data indicated that more than one third of juvenile detainees and nearly half of females had felt hopeless or thought about death in the 6 months before detention. Approximately 1 in 10 (10.3%, 95% confidence interval: 7.7%-12.8%) juvenile detainees had thought about committing suicide in the past 6 months, and 1 in 10 (11.0%, 95% confidence interval: 8.3%-13.7%) had ever attempted suicide. Recent suicide attempts were most prevalent in females and youths with major depression and generalized anxiety disorder. Fewer than half of detainees with recent thoughts of suicide had told anyone about their ideation. Identifying youths at risk for suicide, especially those suffering from depressive and anxiety disorders, is a crucial step in preventing suicide. Abram, K., Choe, J., Washburn, J., Teplin, L., King, D., and Dulcan, M. Suicidal. Ideation and Behaviors among Youths in Juvenile Detention. J. Am. Acad. Child. Adolesc. Psych., 47(3), pp. 291-300, 2008.

### The Drinking Culture of Alcohol Use

Binge drinking is a substantial health problem. Community norms about drinking may influence individual drinking problems. This study examined the relation between aspects of the neighborhood drinking culture and individual alcohol use by using data from the New York Social Environment Study conducted in 2005. The sample consisted of 4,000 New York City residents greater than 18 year of age. Methods to address social stratification and social selection, both of which are challenges to interpreting neighborhood research were applied. In adjusted models, permissive neighborhood drinking norms were associated with moderate drinking (odds ratio (OR) = 1.28, 95% confidence interval (CI): 1.05, 1.55) but not binge drinking; however, social network and individual drinking norms accounted for this association. By contrast, permissive neighborhood drunkenness norms were associated with more moderate drinking (OR = 1.20, 95% CI: 1.03, 1.39) and binge drinking (OR = 1.92, 95% CI: 1.44, 2.56); the binge drinking association remained after adjustment for social network and individual drunkenness norms (OR = 1.58, 95% CI: 1.20, 2.08). Drunkenness norms were more strongly associated with binge drinking for women than for men (p(interaction) = 0.006). Propensity distributions and adjustment for drinking history suggested that social stratification and social selection, respectively, were not plausible explanations for the observed results. Results suggest that further epidemiologic studies investigating the social and structural factors that shape harmful drinking may inform efforts targeting the problematic aspects of alcohol consumption. Ahern, J., Galea, S., Hubbard, A., Midanik, L., and Syme, S. Culture of Drinking and Individual Problems with Alcohol Use. Am. J. Epidemiol., 167(9), pp. 1041-1049, 2008.

### Prevalence of Recent Illicit Substance Use and Reporting Bias among MSM and Other Urban Males

This study explores whether the high rates of self-reported substance use among men who have sex with men (MSM) when compared to other males may be an artifact of reporting bias. The reported past month prevalence rates of marijuana, cocaine, heroin, methamphetamine, Ecstasy, and Ketamine use were compared between a sample of MSM (n=216) and a general household sample of men (n=241). Participants were all between 18 to 55 years old, and all resided in Chicago. The researchers compared rates of self-reported use, and test-corrected rates based on the results of drug testing using urine and oral fluid tests. While MSM over 30 years old were significantly more likely than other men in this age group to report past month use of cocaine, test-corrected rates of use were equivalent. On the other hand, test-corrected estimates

confirmed elevated rates of Ketamine and Ecstasy use in the MSM sample. Differential disclosure of substance use between MSM and other males may in some cases lead to distorted conclusions about differences in substance use between these groups. The researchers suggest that the use of biological testing in epidemiological studies of substance use can reduce the uncertainty of such comparisons. Mackesy-Amiti, M., Fendrich, M., and Johnson, T.P. Prevalence of Recent Illicit Substance Use and Reporting Bias among MSM and Other Urban Males. Addict. Behav., 33, pp. 1055-1060, 2008.

### Vicarious Exposure to Terrorist Attacks and Substance Use: Results from an Urban Household Survey

Traumatic events and exposure to disasters can have profound effects upon mental health, including posttraumatic stress disorder (PTSD) and drug and alcohol use. This study investigated the impact of the 9/11 attacks on substance use among a sample of 627 participants between the ages of 18 and 40 years in Chicago, Illinois. The study design utilized a cross-sectional, audio-computer-assisted self-interview survey conducted in 2001 and 2002. Biological samples, including samples of saliva and urine, were also collected for drug toxicological analyses. Compared to pre-9/11 interviewees, post-9/11 interviewees showed significantly less self-reported marijuana use, marijuana use per test results, and cocaine use per test results. This study contributes to a better understanding of the relationship between exposure to trauma and substance use and highlights the need for additional subsequent research to elucidate further the nature of this relationship. Lippert, A., Fendrich, M., and Johnson, T. Vicarious Exposure to Terrorist Attacks and Substance Use: Results from an Urban Household Survey. J. Urban Health, 85(3), pp. 411-427, 2008.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2008

## Research Findings - Prevention Research

### Universal Childhood Prevention Effects Developmental Course of Antisocial Personality Disorder and Violent and Criminal Behavior

Antisocial personality disorder (ASPD), violent and criminal behavior, and drug abuse disorders often share the common antecedent of early aggressive, disruptive behavior. In the 1985-1986 school year teachers implemented the Good Behavior Game (GBG), a classroom behavior management strategy targeting aggressive, disruptive behavior and socializing children to the student role. From first through seventh grade the developmental trajectories of 2311 students from 19 Baltimore City Public Schools were examined. GBG impact on these trajectories and ASPD and violent and criminal behavior by age 19-21 is reported. In five urban, poor to lower middle class predominately African-American areas, three to four schools were matched and within each set randomly assigned to one of three conditions: (1) GBG, (2) a reading achievement program, or (3) the standard program. Classrooms and teachers were randomly assigned to intervention or control. Measures at 19-21 included self reports and juvenile court and adult incarceration records. GBG impact was assessed via General Growth Mixture Modeling based on repeated measures of aggressive, disruptive behavior. Three trajectories of aggressive, disruptive behavior were identified. By young adulthood, GBG significantly reduced the rates of ASPD and violent and criminal behavior among males in the persistent high aggressive, disruptive trajectory. A replication was implemented with the following cohort of first-grade children using the same teachers, but with diminished mentoring and monitoring. Beneficial impact was found among persistent high males through seventh grade. By young adulthood GBG effects on ASPD and violent and criminal behavior were non-significant, but generally in the hypothesized direction. This study demonstrated strongest effects on high risk males, suggesting the need to understand the shared and non-shared developmental processes within and across genders. Petras, H., Kellam, S.G., Brown, C.H., Muthen, B., Ialongo, N., and Poduska, J. Developmental Epidemiological Courses Leading to Antisocial Personality Disorder and Violent and Criminal Behavior: Effects By Young Adulthood of a Universal Preventive Intervention in First- and Second-Grade Classrooms. Drug Alcohol Depend., 95S1 pp. S45-S59, 2008.

### Universal Classroom-Based Preventive Intervention Impacts Young Adult Service Use for Drugs, Alcohol and Other Problem Behaviors

The Good Behavior Game (GBG) is a classroom behavior management strategy focused on socializing children to the role of student and aimed at reducing early aggressive, disruptive behavior, a confirmed antecedent to service use. The GBG was tested in a randomized field trial in 19 elementary schools with

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two cohorts of children as they attended first and second grades. This article reports on the impact of the GBG on service use through young adulthood. Three or four schools in each of five urban areas were matched and randomly assigned to one of three conditions: (1) GBG, (2) an intervention aimed at academic achievement, or (3) the standard program of the school system. Children were assigned to classrooms to ensure balance, and teachers and classrooms were randomly assigned to intervention conditions. A positive impact of the universal preventive intervention on later service use for problems with emotions, behavior, or drugs or alcohol was found for males, but not females. For both cohorts, males in GBG classrooms who had been rated as highly aggressive, disruptive by their teachers in the fall of first grade had a lower rate of school-based service use than their counterparts in control classrooms. The design employed two cohorts of students. Although both first- and second-grade teachers received less training and support with the second cohorts of students than with the first cohort, the impact of GBG was similar across both cohorts. Poduska, J., Kellam, S.G., Wang, W., Brown, C.H., Ialongo, N., and Toyinbo, P. Impact of the Good Behavior Game, a Universal Classroom-Based Behavior Intervention, on Young Adult Service Use for Problems with Emotions, Behavior, or Drugs or Alcohol. Drug Alcohol Depend., 95S1 pp. S29-S44, 2008.

### Prevention of Behavior Problems for Children in Foster Care: Outcomes and Mediation Effects

Parent training for foster parents is mandated by federal law and supported by state statues in nearly all states; however, little is known about the efficacy of that training, and recent reviews underscore that the most widely used curricula in the child welfare system (CWS) have virtually no empirical support. On the other hand, numerous theoretically based, developmentally sensitive parent training interventions have been found to be effective in experimental clinical and prevention intervention trials. One of these, Multidimensional Treatment Foster Care (MTFC) has been used with foster parents of youth referred from juvenile justice. The effectiveness of a universal intervention, KEEP (Keeping Foster Parents Trained and Supported) based on MTFC (but less intensive) was tested in a universal randomized trial with 700 foster and kinship parents in the San Diego County CWS. The goal of the intervention was to reduce child problem behaviors through strengthening foster parents' skills. The trial was designed to examine effects on both child behavior and parenting practices, allowing for specific assessment of the extent to which improvements in child behavior were mediated by the parenting practices targeted in the intervention. Child behavior problems were reduced significantly more in the intervention condition than in the control condition, and specific parenting practices were found to mediate these reductions, especially for high-risk children in foster families reporting more than six behavior problems per day at baseline. Chamberlain, P., Price, J., Leve, L., Laurent, H., Landsverk, J., and Reid, J. Prevention of Behavior Problems for Children in Foster Care: Outcomes and Mediation Effects. Prev. Sci., 9(1), pp. 17-27, 2008.

### A Randomized Evaluation of Multidimensional Treatment Foster Care: Effects on School Attendance and Homework Completion in Juvenile Justice Girls

Despite growing evidence that child welfare youth are at increased risk for juvenile delinquency, little is known about gender-specific processes and effective treatment programs for girls. Multidimensional Treatment Foster Care (MTFC), an empirically validated intervention for child welfare and juvenile justice populations, has demonstrated efficacy in reducing arrest rates in delinquent boys and girls. In this study, the efficacy of MTFC on school attendance and homework completion was examined in juvenile justice girls

who were referred to out-of-home care (N = 81). Results from this randomized intervention trial suggest that MTFC was more effective than group care in increasing girls' school attendance and homework completion while in treatment and at 12 months post baseline. In addition, the previously reported effect of MTFC on reducing girls' days in locked settings was mediated by homework completion while girls were enrolled in the intervention setting. Implications for policy and practice are described. Leve, L.D., and Chamberlain, P.A Randomized Evaluation of Multidimensional Treatment Foster Care: Effects on School Attendance and Homework Completion in Juvenile Justice Girls. Res. Soc. Work Pract., 17(6), pp. 657-663, 2007.

### Impact of First and Second Grade Universal Prevention on Young Adult Behavioral, Psychiatric and Social Outcomes

The Good Behavior Game (GBG), a method of classroom behavior management used by teachers, was tested in first- and second-grade classrooms in 19 Baltimore City Public Schools beginning in the 1985-1986 school year. The intervention was directed at the classroom as a whole to socialize children to the student role and reduce aggressive, disruptive behaviors, confirmed antecedents of later substance abuse and dependence disorders, smoking, and antisocial personality disorder. This article reports on impact to ages 19-21. In five poor to lower-middle class, mainly African American urban areas, three or four schools were matched and within each set randomly assigned to one of three conditions: (1) GBG, (2) a curriculum-and-instruction program directed at reading achievement, or (3) the standard program. Balanced assignment of children to classrooms was made, and then, within intervention schools, classrooms and teachers were randomly assigned to intervention or control. By young adulthood significant impact was found among males, particularly those in first grade who were more aggressive, disruptive, in reduced drug and alcohol abuse/dependence disorders, regular smoking, and antisocial personality disorder. These results underline the value of a first-grade universal prevention intervention. A replication was implemented with the next cohort of first-grade children with the same teachers during the following school year, but with diminished mentoring and monitoring of teachers. The results showed significant GBG impact for males on drug abuse/dependence disorders with some variation. For other outcomes the effects were generally smaller but in the predicted direction. Kellam, S., Brown, C., Poduska, J., Ialongo, N., Wang, W., Toyinbo, P., Petras, H., Ford, C., Windham, A., and Wilcox, H. Effects of a Universal Classroom Behavior Management Program in First and Second Grades on Young Adult Behavioral, Psychiatric, and Social Outcomes. Drug Alcohol Depend., 95 Suppl 1 pp. S05-S28, 2008.

### Impact of Two Universal School-Based Preventive Interventions On Young Adult Suicide Ideation and Attempts

This paper reports the impact of two first- and second-grade classroom based universal preventive interventions on the risk of Suicide Ideation (SI) and Suicide Attempts (SA) by young adulthood. The Good Behavior Game (GBG) was directed at socializing children for the student role and reducing aggressive, disruptive behavior. Mastery Learning (ML) was aimed at improving academic achievement. Both were implemented by the teacher. The design was epidemiologically based, with randomization at the school and classroom levels and balancing of children across classrooms. The trial involved a cohort of first-grade children in 19 schools and 41 classrooms with intervention at first and second grades. A replication was implemented with the next cohort of first grade children with the same teachers but with little mentoring or monitoring. In the first cohort, there was consistent and robust GBG-associated reduction of risk for suicide ideation by age 19-21 years compared to youths in standard setting (control) classrooms regardless of any type of covariate adjustment. A GBG-associated reduced risk for suicide attempt was found, though in some

covariate-adjusted models the effect was not statistically robust. No statistically significant impact on these outcomes was found for ML. The impact of the GBG on suicide ideation and attempts was greatly reduced in the replication trial involving the second cohort. In conclusion, a universal preventive intervention directed at socializing children and classroom behavior management to reduce aggressive, disruptive behavior may delay or prevent onset of suicide ideation and attempts. The GBG must be implemented with precision and continuing support of teachers. Wilcox, H.C., Kellam, S.G., Brown, C.H., Poduska, J., Ialongo, N., Wang, W., and Anthony, J.C. The Impact of Two Universal Randomized First-And Second-Grade Classroom Interventions on Young Adult Suicide Ideation and Attempts. Drug Alcohol Depend., 95S pp. S60-S73, 2008.

### Efficacy of the Parents Who Care Prevention Program at 24 Month Follow-Up

This study was designed to test the efficacy of Parents Who Care (PWC), a seven-session universal prevention program which includes parenting, youth, and family components designed to prevent substance use and other problem behaviors. Using an intent-to-treat experimental design, this study tests the program efficacy across race within a balanced sample of European American and African American youth and their parents (n = 331). Families were recruited and randomly assigned to three conditions: a) group-administered intervention (PA), b) self-administered intervention with telephone support (SA), and c) no-treatment control. The intervention was administered when the adolescents were in the eighth grade. The investigators examined the 24-month impact of the intervention on perceptions of drug use harm, favorable attitudes about drug use, delinquent and violent behavior, and initiation into cigarette, alcohol, other drug use, or sexual activity. Regression analyses with multiple imputations for missing data detected group differences in means at 24-month follow-up. Both program formats reduced favorable attitudes toward drug use among youth (SA d = 0.39, PA d = 0.22); and African American youth in the self-administered intervention reported significantly less violent behavior than their control counterparts (d = 0.45). No effects were found for drug use harm or delinquency. Finally, logistic regression predicting a combined outcome measure of initiation of alcohol, tobacco, drug use, and/or sexual activity found African American youth in both the group- and self-administered intervention conditions significantly less likely to initiate substance use and/or sexual activity than those in the control condition. Odds ratios indicated the chances of initiating sex or substance use were reduced by almost 70% (OR = 0.31) for African American teens in the SA condition compared to controls, and 75% (OR = 0.25) for the African American teens in the PA compared to controls. Haggerty, K., Skinner, M., Mackenzie, E., and Catalano, R. A Randomized Trial of Parents Who Care: Effects on Key Outcomes at 24-Month Follow-up. Prev. Sci., 8(4), pp. 249-260, 2007.

### Engagement in Family-Centered Intervention Reduces Problem Behaviors

This research extends previous research on the efficacious Adolescent Transitions Program family prevention program to examine the effects of the program through adolescence and to study the process of treatment engagement and the impact of treatment engagement on adolescent problem behavior. For these analyses the investigator used Complier Average Causal Effect analysis techniques (CACE; see G. Imbens & D. Rubin, 1997) to examine program effects on rates of substance use and antisocial behavior among students ages 11-17. Students were randomly assigned to a family-centered intervention (N = 998) in 6th grade and offered a multilevel intervention that included (as needed) (a) a universal classroom-based intervention, (b) a selective intervention, the Family Check-Up and (c) indicated family

management treatment. All services were voluntary, and approximately 25% of the families engaged in the selected and indicated levels. Participation in the Family Check-Up was significantly related to the likelihood of biological fathers being absent from the home, youth reports of elevated family conflict, and teacher reports of elevated risk behaviors at school, suggesting that highly vulnerable families were likely to agree to participate in the intervention. Relative to randomized matched controls, adolescents whose parents engaged in the Family Check-Up exhibited less growth in alcohol, tobacco, and marijuana use and problem behavior during ages 11 through 17, along with decreased risk for substance use diagnoses and police records of arrests by age 18. Connell, A., Dishion, T., Yasui, M., and Kavanagh, K. An Adaptive Approach to Family Intervention: Linking Engagement in Family-Centered Intervention to Reductions in Adolescent Problem Behavior. J. Consult. Clin. Psychol., 75(4), pp. 568-579, 2007.

### Therapeutic Interactive Voice Response for Chronic Pain Reduction and Relapse Prevention

Therapeutic Interactive Voice Response (TIVR) is an automated, telephone-based tool for maintenance enhancement following group cognitive-behavioral therapy for chronic pain. TIVR has four components: a daily self-monitoring questionnaire, a didactic review of coping skills, pre-recorded behavioral rehearsals of coping skills, and monthly personalized feedback messages from the cognitive behavioral therapy provider based on a review of the patient's daily reports. The first three components are pre-recorded and all four can be accessed remotely by patients via touch-tone telephone on demand. Following 11 weeks of group therapy, 51 subjects with chronic musculoskeletal pain were randomized to one of two study groups. Twenty-six subjects participated in 4 months of TIVR, while a control group of 25 subjects received standard care only. The TIVR group showed significant improvement ($p<.001$) over baseline at the 8-month follow-up for seven of the eight outcome measures. Between group analysis of covariance revealed significantly greater improvement for the experimental group at both 4- and 8-month follow ups for most outcomes. Results demonstrate that TIVR can be used to decrease pain, improve coping, and decrease likelihood of relapse into pain behavior. Preliminary analysis of medication usage suggests that the superior outcome of the TIVR group was unlikely to be a consequence of differential medication use. Naylor, M.R., Keefe, F.J., Brigidi, B., Naud, S., and Helzer, J.E. Therapeutic Interactive Voice Response for Chronic Pain Reduction and Relapse Prevention. Pain, 134(3), pp. 335-345, 2008.

### Differences in Marijuana and Alcohol Use Trajectories Between Rural and Urban Youth

This study investigated differences in the development of heavy drinking and marijuana use among students in urban and rural areas and assessed whether any such differences can be accounted for by locality differences in racial/ethnic makeup, social disorganization/low social bonding, feelings of despondency and escapism, and the availability of drugs. Drawn from 62 South Dakota middle schools involved in a drug prevention field trial, participating students were assigned to a locality category based on the location of their seventh-grade school. Schools in metropolitan areas were distinguished from schools in nonmetropolitan areas. Schools in nonmetropolitan areas were further distinguished into those in micropolitan (medium and large towns) and noncore (rural areas without towns and with small towns) areas. Latent growth curve analysis was used to model the influence of locality on the development of heavy drinking and marijuana use from ages 13 to 19 and to determine whether differences in development across locality were attributable to location-based differences in race/ethnicity, social disorganization/ bonding, feelings of despondency and escapism, and alcohol and marijuana availability.

Heavy drinking increased at a faster rate among youth living in micropolitan areas compared with youth living in metropolitan areas. Marijuana use increased at a faster rate among youth living in metropolitan and micropolitan areas compared with youth living in noncore areas. Differences in the rate of change in heavy drinking were attributable to differences in the racial/ethnic composition of metropolitan and micropolitan areas. Differences in the rate of change in marijuana use were attributable to differences in residential instability and marijuana availability. This study underscores the diversity of drug use within rural communities, suggesting that living in a very rural area is protective against some forms of drug use but that living in a rural area that includes a medium or large town is not. Martino, S., Ellickson, P., and McCaffrey, D. Developmental Trajectories of Substance Use from Early to Late Adolescence: A Comparison of Rural and Urban Youth. J. Stud. Alcohol Drugs, 69(3), pp. 430-440, 2008.

### Media Resistance Skills Related to Reduced Alcohol Use Among Inner-City Adolescents

This longitudinal study examined the impact of media resistance skills on subsequent drinking among adolescents residing in inner-city regions of New York City. The study also tested whether drug skill refusal techniques (knowing how to say no to alcohol and other drugs) mediated the relationship between media resistance skills and adolescent drinking. A panel sample of baseline, one-year and two-year follow-ups (N = 1318) from the control group of a longitudinal drug abuse prevention trial participated. A series of structural equations models showed that media resistance skills directly negatively predicted alcohol use 2 years later and that drug skill refusal techniques mediated this effect. Baseline media resistance skills were associated with one-year drug skill refusal techniques, which in turn negatively predicted two-year alcohol use. These findings provide empirical support for including media resistance skills and drug skill refusal techniques in alcohol prevention programs. Epstein, J., and Botvin, G. Media Resistance Skills And Drug Skill Refusal Techniques: What Is Their Relationship With Alcohol Use Among Inner-City Adolescents? Addict. Behav., 33 pp. 528-537, 2008.

### Random Drug Testing in US Public High Schools

This study of random drug testing in high schools was conducted within a larger study of the diffusion of evidence-based drug prevention programs in US middle schools. Estimates of the proportion of the nation's public school districts that have high school grades in which random drug testing is conducted were generated. Data were collected in the spring of 2005 from 1343 drug prevention coordinators in a nationally representative sample of school districts with schools that have high school grades. Of these districts, 14% conducted random drug testing. Almost all districts randomly tested athletes, and 65% randomly tested other students engaged in extracurricular activities; 28% randomly tested all students. Ringwalt, C., Vincus, A., Ennett, S., Hanley, S., Bowling, J., Yacoubian, G., and Rohrbach, L. Random Drug Testing in US Public School Districts. Am. J. Public Health, 98(5), pp. 826-828, 2008.

### Sexual Risk Behavior in College and Non-College Youth

This study examined sexual risk behavior among a community sample of youth in the fall after their senior year of high school. The primary goal was to examine associations between college and residential status and 3 behaviors: casual sex, inconsistent condom use, and high-risk sex. Data were from 834 participants in the Raising Healthy Children project who were surveyed annually during high school and in the fall of the post-high school year. Thirty

percent of participants reported inconsistent condom use, 23% reported casual sex, and 11% reported high-risk sex in the fall after high school. Youth in college were less likely than non-college youth to report sexual risk behavior. The protective association between college attendance on one hand and casual sex and intermittent condom use on the other was fully explained by high school substance use, risky sex, and academic performance. The protective effect of college attendance on high-risk sex was partly explained by high school predictors. Living with parents at age 18-19 years was not related to sexual risk behavior. Results from this study indicate that the higher prevalence of sexual risk behavior among non-college youth is largely a continuation of patterns of higher risk behavior and lower academic performance during high school. Findings suggest that human immunodeficiency virus and sexually transmitted infection prevention efforts are needed among young adults who are not attending college and among high school students who have earned poor grades, used drugs, or engaged in sexual risk behavior. Bailey, J., Fleming, C., Henson, J., Catalano, R., and Haggerty, K. Sexual Risk Behavior 6 Months Post-High School: Associations with College Attendance, Living with a Parent, and Prior Risk Behavior. J. Adolesc. Health, 42(6), pp. 573-579, 2008.

### Factors Affecting the Implementation of an Indicated School-Based Prevention Program for Adolescents

This paper presents the organizational factors and program characteristics that promote or hinder the implementation of a school-based drug prevention program, Reconnecting Youth, designed to address academic, substance use and mood management goals among adolescents at risk of dropping out of high school. A randomized controlled effectiveness trial was conducted in 10 schools in two school districts in the United States. Data were collected using surveys and interviews from teachers and school and district staff who participated in the implementation of the program in the study schools. Results suggest that certain program characteristics made it difficult to implement. Small class size, resource-intensive procedures for student selection and recruitment and special training, qualities and skills needed to be an effective Reconnecting Youth teacher meant that schools had to significantly change their usual practices to implement the program. Organization barriers included a lack of financial resources and leadership support for program implementation. Thaker, S., Steckler, A., Sanchez, V., Khatapoush, S., Rose, J., and Hallfors, D.D. Program Characteristics and Organizational Factors Affecting the Implementation of a School-Based Indicated Prevention Program. Health Educ. Res., 23(2), pp. 238-248, 2008.

### Self-Regulation Moderates the Association Between Peer Deviance and Antisocial Behavior

This study tests the hypothesis that self-regulation serves as a resiliency factor in buffering youth from negative influences of peer deviance in middle to late adolescence. The interactive effects between peer deviance and self-regulation were investigated on change in antisocial behavior from age 17 to 19 years in an ethnically diverse sample of adolescents recruited for a prevention trial. The current analysis includes data from 655 youth. A multi-agent construct was created using adolescent, parent, and teacher reports of self-regulation and peer deviance. Antisocial behavior was assessed through a 9 item self-report measure of problem behaviors reported in the month prior to the interview. Results indicated that self-regulation shows convergent validity and covaries as expected with developmental patterns of adolescent antisocial behavior. Self-regulation moderated the association of peer deviance with later self-reported adolescent antisocial behavior after controlling for prior levels of antisocial behavior. Gardner, T., Dishion, T., and Connell, A. Adolescent Self-Regulation as Resilience: Resistance to Antisocial Behavior within the Deviant Peer

Context. J Abnorm Child Psychol., 36(2), pp. 273-284, 2008.

### Defining the At-risk Adolescent Marijuana Nonuser

This research expands the user/nonuser dichotomy commonly used in research on marijuana. By conceptualizing nonusers as homogeneous, vital nuances in susceptibility to risk and protective factors may be overlooked. Research operations tested the predictive validity of a brief measure that divided nonusers into resolute and vulnerable subcategories; determined whether variables that distinguished nonusers and users were more informative when a tripartite classification was used; and with an eye on future prevention, examined variables on which resolute nonusers were similar to vulnerable nonusers or users, and on which they differed from both. A nationally representative sample of respondents (N = 2,111; ages 12-16 years) from the National Survey of Parents and Youth was used in this secondary analysis. Panel data gathered yearly over four rounds included information on intentions and use of marijuana and other illicit substances, along with social, demographic, intrapersonal, and parental variables. The three groups differed significantly on associates' marijuana use, participants' approval of others' use, and cigarette and alcohol use. Resolute nonusers differed from vulnerable nonusers and users alike on religiosity, delinquency (self and friends'), refusal strength, sensation seeking, parental monitoring and warmth, and adult supervision. Results support the utility of distinguishing vulnerable from resolute nonusers, counsel against considering nonusers as a homogeneous group, and provide insight into variables that might prove useful in future prevention efforts. Crano, W., Siegel, J., Alvaro, E., Lac, A., and Hemovich, V. The At-risk Adolescent Marijuana Nonuser: Expanding the Standard Distinction. Prev. Sci., 9(2), pp. 129-137, 2008.

### Methods For Integrating Person, Place and Time in Randomized Prevention Trials

Randomized trials in real world settings provide unique opportunities to examine effectiveness and to test and extend both theory of etiology and theory of intervention. These trials are designed not only to test for overall intervention impact but also to examine how impact varies as a function of individual level characteristics, context, and across time. Examination of such variation in impact requires analytical methods that take into account the trial's multiple nested structure and the evolving changes in outcomes over time. The models described in this paper merge multilevel modeling with growth modeling, allowing for variation in impact to be represented through discrete mixtures-growth mixture models-and nonparametric smooth functions-generalized additive mixed models. These methods are part of an emerging class of multilevel growth mixture models, and are illustrated with models that examine overall impact and variation in impact. Intent-to-treat analyses in group-randomized multilevel field trials are defined and appropriate ways to identify, examine, and test for variation in impact without inflating the Type I error rate are discussed. Descriptions are provided for how to make causal inferences more robust to misspecification of covariates in such analyses and how to summarize and present these interactive intervention effects clearly. Practical strategies for reducing model complexity, checking model fit, and handling missing data are discussed using six randomized field trials to show how these methods may be used across trials randomized at different levels. Brown, C.H., Wang, W., Kellam, S.G., Muthen, B., Petras, H., Toyinbo, P., Poduska, J., Ialongo, N., Wyman, P., Chamberlain, P., Sloboda, Z., Mackinnon, D.P., and Windham, A. Methods for Testing Theory and Evaluating Impact in Randomized Field Trials: Intent-To-Treat Analyses for Integrating the Perspectives of Person, Place, and Time. Drug Alcohol Depend., 95S1 pp. 74-104, 2008.

### After-School Activities May Predict Delinquency in Youth

The social development model hypothesizes that antisocial behavior in one developmental time period leads to less involvement in activities and interactions that have positive socializing influence in the subsequent developmental period. As a test of the model, analyses were conducted on data from 776 students who participated in the Raising Healthy Children study. Annual survey data from sixth through ninth grade were used to study the relationships among after-school activities, misbehavior in school, and delinquency. Overall correlations between structured activities and both misbehavior in school and delinquency did not suggest a strong protective effect of structured activities. However, results from a cross-lagged model adjusting for prior activity and behavior patterns supported the hypothesis. Consistent with prior research, unstructured activity involvement and delinquent behavior in the first year of high school were positively correlated. These findings point to the beginning of middle school as a crucial time when prior patterns of behavior predict levels of involvement in activities that in turn predict behavioral outcomes. Fleming, C.B., Catalano, R.F., Mazza, J.J., Brown, E.C., Haggerty, K P., and Harachi, T.W. After-School Activities, Misbehavior in School, and Delinquency from the End of Elementary School Through the Beginning of High School. J. of Early Adoles., 28(2), pp. 277-303, 2008.

### Enhancing Prediction of Inhalant Abuse Risk Among Adolescents

The theory of reasoned action (TRA) was used to estimate adolescents' vulnerability to inhalant abuse, operationalized by intentions to use or avoid inhalants. The sample consisted of 596 6th and 7th grade children from southwest Arizona. It was drawn from a larger group of 4th through 12th grade schoolchildren that was the basis of Ramirez et al.'s (2004) earlier research on inhalant and marijuana use. Only 6th and 7th graders are included in the present study, as the goal was to identify predictive features of drug use for early adolescents. The gender breakdown was relatively even: 304 (51%) males and 292 (49%) females. Forty two percent of the sample was 6th graders. Most respondents described themselves as White (62.4%), followed by Hispanic (18.8%). The remaining 18.8% reported their ethnicity as Black, Asian, American Indian, or "other." The model correctly differentiated 78% of all respondents (N=596). A second analysis highlighted variables that discriminated properly identified from misclassified youth. False positives, those defined as being at-risk, but who repudiated inhalants, were significantly less likely than their at-risk peers to have used inhalants; they used inhalants and marijuana less frequently; were monitored more closely by parents; and were less rebellious (all $p<.05$). False negatives, defined as not at-risk, but who had not unequivocally rejected inhalants, were significantly more likely than their similarly classed peers to have used inhalants and marijuana, and to have used both more frequently; also, they were less highly acculturated. This study reaffirmed the utility of the TRA and underscored factors that might improve classification accuracy. This approach may facilitate prevention efforts, and may be extrapolated to any context in which risk categorization is used as a basis for prevention or amelioration. Crano, W., Gilbert, C., Alvaro, E., and Siegel, J. Enhancing Prediction of Inhalant Abuse Risk in Samples of Early Adolescents: A Secondary Analysis. Addict. Behav., 33(7), pp. 895-905, 2008.

### Family Functioning and Identity Confusion Affect Substance Use and Sexual Behavior of Hispanic Adolescents

This study examined adolescent-reported family functioning and identity confusion as they relate to onset of substance use and sexual behavior in a sample of 250 Hispanic adolescents from immigrant families ranging in age between 12 and 16 years. Participants were part of a family-centered adolescent HIV prevention trial and completed assessments at baseline, 6

months, 1 year, 2 years, and 3 years. The sample for this study came from families who provided data during at least two of the five time points. Results indicated that adolescents whose identity confusion scores increased over time were most likely to initiate cigarette use, alcohol use, and sexual behavior during the course of the study. Adolescents whose identity confusion scores remained stable over time were less likely to initiate, and adolescents whose identity confusion scores decreased over time were least likely to initiate. Thus, increases in identity confusion during early and middle adolescence may place youth at risk for substance use and sexual risk behavior. In these analyses, family functioning predicted identity confusion and also predicted substance use and sexual behavior initiation. Schwartz, S.J., Mason, C.A., Pantin, H., and Szapocznik, J. Effects of Family Functioning and Identity Confusion on Substance Use and Sexual Behavior in Hispanic Immigrant Early Adolescents. Identity: An International Journal of Theory and Research, 8, pp. 107-124, 2008.

### A New Statistical Procedure to Examine Behavioral Transitions

The set of statistical methods available to researchers is continually being expanded, allowing for questions about change over time to be addressed in new, informative ways. Indeed, new developments in methods to model change over time create the possibility for new research questions to be posed. Latent transition analysis, a longitudinal extension of latent class analysis, is a method that can be used to model development in discrete latent variables, for example, stage processes, over 2 or more times. The current article illustrates this approach using a new SAS procedure, PROC LTA, to model change over time in adolescent and young adult dating and sexual risk behavior. Gender differences are examined, and substance use behaviors are included as predictors of initial status in dating and sexual risk behavior and transitions over time. Lanza, S., and Collins, L. A New SAS Procedure for Latent Transition Analysis: Transitions in Dating and Sexual Risk Behavior. Dev. Psychol., 44(2), pp. 446-456, 2008.

### Ten Year Follow Up of a Preventive Intervention: Locating Children of Drug Abusers

Longitudinal studies require high follow-up rates in order to maintain statistical power, reduce bias, and enhance the generalizability of results. This study reports on locating and survey completion for a 10-year follow-up of the Focus on Families project, an investigation of 130 families headed by parents who were enrolled in methadone treatment for opiate addiction. Despite having no contact with participants in the study for at least 10 years, the project successfully located nearly 99% of parent participants and 98% of their children. Twenty-four percent of the parents and one child had died before the follow-up. Of the surviving sample, 91% of parents and 86% of the children completed the follow-up interview. Multiple techniques were used to locate study participants, including internet searches, researching court and public records, collaborating with government and service agencies, and contacting family and social networks. For more than half of the sample, costly efforts were required to locate individual participants. Haggerty, K., Fleming, C., Catalano, R., Petrie, R., Rubin, R., and Grassley, M. Ten Years Later: Locating and Interviewing Children of Drug Abusers. Eval. Program Plann. 31(1), pp. 1-9, 2008.

### Substance Abuse is Associated with HCV Viremia and HCV Transmission Potential

Co-infection with hepatitis C virus (HCV) is common among HIV-infected women. To further the understanding of risk factors for HCV viremia and the

predictors of HCV viral load among women, sociodemographic, immunologic, and virologic factors associated with presence and level of HCV viremia were investigated among 1049 HCV-seropositive women, 882 of whom were HIV-infected and 167 HIV-uninfected at their entry into the Women's Interagency HIV Study. Plasma HCV RNA was detected in 852 (81%) of these 1049 women (range: 1.2-7.8 log(10)copies/ml). HCV-viremic women were more likely to have an HIV RNA level >100,000 copies/ml (p = 0.0004), to have reported smoking (p =0.01), or to be Black (p = 0.005). They were less likely to have current or resolved hepatitis B infection. HCV RNA levels were higher in women who were >35 years old, or HIV-infected. Current smoking and history of drug use (crack/freebase cocaine, marijuana, amphetamines, or heroin) were each associated with both presence and level of viremia. Substance abuse counseling aimed at eliminating ongoing use of illicit drugs and tobacco may reduce clinical progression, improve response to treatment, and decrease HCV transmission by lowering levels of HCV viremia in women. Operskalski, E., Mack, W., Strickler, H., French, A., Augenbraun, M., Tien, P., Villacres, M., Spencer, L., Degiacomo, M., and Kovacs, A. Factors Associated With Hepatitis C Viremia in a Large Cohort of HIV-Infected and -Uninfected Women. J. Clin. Virol., 41(4), pp. 255-263, 2008.

### Experienced Consequences of Drinking and Changes in Plans to Drink

This study examined experienced consequences of alcohol use and short-term changes in alcohol use plans and perceptions of the importance of alcohol-related consequences. Participants were 176 traditionally aged first-year university students who completed a 10-week telephone diary study (total weeks=1735). In multi-level models, men and students who experienced more positive and negative consequences on average planned to drink more and rated avoiding negative consequences as less important. Students who experienced more positive consequences rated them as more important (between-person analyses). Following weeks of experiencing relatively more positive drinking consequences, students planned to drink more and rated experiencing positive consequences as more important for the subsequent week (within-person analyses). Challenges for intervening in the ongoing formation of anticipatory cognitions regarding alcohol use are discussed. Patrick, M., and Maggs, J. Short-Term Changes in Plans to Drink and Importance of Positive and Negative Alcohol Consequences. J. Adolesc., 31(3), pp. 307-321, 2008.

### Modeling Confidence Intervals Without Distributional Assumptions

Confidence intervals for the intraclass correlation coefficient (ICC) have been proposed under the assumption of multivariate normality. In this study, confidence intervals which do not require distributional assumptions are proposed. A simulation study to assess the coverage rates of normal theory (NT) and asymptotically distribution free (ADF) intervals was performed and the results showed that ADF intervals performed better than NT intervals when kurtosis was greater than 4. When violations of distributional assumptions were not too severe, both the intervals performed about the same. The point estimate of the ICC was robust to distributional violations. Codes for computing the ADF confidence intervals for the ICC are provided. Coffman, D.L., Maydeu-Olivares, A., and Arnau, J. Asymptotic Distribution Free Estimation for an Intraclass Correlation Coefficient with Applications to Longitudinal Data. Methodology, 4(1), pp. 4-9, 2008.

### Engaging Communities to Prevent Youth Use of Harmful Legal Products

This study applied the Community Readiness Model (CRM) as part of a multi-stage community mobilization strategy to engage community leaders, retailers, parents, and school personnel in preventing youth use of inhalants and other harmful legal products in rural Alaska. The CRM is designed to assess readiness to address a single social problem, based on a limited set of key informant interviews. In this study, researchers conducted 32 baseline and 34 post-intervention community readiness assessment interviews in four rural Alaskan communities. The aggregate results were analyzed using hierarchical linear modeling (HLM), and the individual community scores were analyzed in the context of the overall study. Significant positive changes in community readiness were found across six readiness dimensions as well as for the overall readiness score. Variation in the degree of changes in readiness across the four communities is attributed to differences in the implementation of the intervention. The implications of these results include the potential for CRM assessments to serve as an integral component of a community mobilization strategy and also to offer meaningful feedback to communities participating in prevention research. Ogilvie, K., Moore, R., Ogilvie, D., Johnson, K., Collins, D., and Shamblen, S. Changing Community Readiness to Prevent the Abuse of Inhalants and Other Harmful Legal Products in Alaska. J. Community Health, 33(4), pp. 248-258, 2008.

### The Use of Harmful Legal Products among Pre-adolescent Alaskan Students

This study examined pre-adolescent use of harmful but legally obtainable products (HLPs) "in order to get high" in 4 communities in northwest and southeast Alaska. These products include inhalants, over-the-counter medications, prescription medications taken without a doctor ''s prescription and common household products. A student survey was administered to the 447 students whose parents consented and who agreed to participate. The lifetime overall use of HLPs among fifth, sixth and seventh grade students in 4 Alaskan communities was 17.4%. The lifetime use of inhalants (6.8%) and prescription medications taken without a doctor's prescription (8.0%) appear to be comparable to use rates from other studies. The use of over-the-counter medications (5.7%) appears to be slightly higher than in other U.S. surveys. The use of common household products was 6.1%. No significant differences in the lifetime or 30-day use were found correlated to region, gender, and ethnicity or student grade. There was a strong association between 30-day or lifetime use of some HLPs and the (30-day or lifetime) use of alcohol, cigarettes and smokeless tobacco. The use of harmful everyday legal products by fifth, sixth and seventh graders in Alaska appears to be similar to data collected in other parts of the country. The possibility that there may be a link between the use of available legal substances and alcohol, tobacco and marijuana deserves additional attention. Saylor, B., Fair, M., Deike-Sims, S., Johnson, K., Ogilvie, K., and Collins, D. The Use of Harmful Legal Products among Pre-Adolescent Alaskan Students. Int. J. Circumpolar Health, 66(5), pp. 425-436, 2007.

### HIV Disclosure Among Adults Living with HIV

Research on disclosure among heterosexual adult person(s) living with HIV (PLH) was reviewed, omitting disclosure of parental HIV to children. Disclosure has been studied within five additional relational contexts: with partners, family members, friends, healthcare professionals and in work settings. Disclosure is higher among women than men, among Latino and white compared to African-American families, and among younger compared to older HIV-positive adults. Most PLH disclose to their sexual partners and family members, yet there is a significant minority who do not disclose. Similarly, rates of disclosure to employers range from 27-68%, suggesting broad variability in perceived

consequences of employment disclosures. Of concern, 40% of PLH do not consistently disclose to their healthcare professionals. Rather than examine HIV disclosures in the context of relationships, it is possible to understand disclosures around personal identity. Disclosure decisions are often made to tell everyone (making HIV status a central attribute of one's identity), no one (requiring strategies for securing social support while remaining anonymous) or some people (requiring strategic decisions based on context). Given that disclosure decisions are central to personal identity, future data on disclosure and interventions designed to increase disclosure or comfort with disclosure must focus on communication strategies adopted by PLH to present a coherent identity. Arnold, E.M., Arnold, E.M.E.R., Flannery, D., and Rotheram-Borus, M.J. HIV Disclosure Among Adults Living with HIV. AIDS Care, 20(1), pp. 80-92, 2008.

### Tobacco Use Among Indian Students Attending Government Schools Versus Private Schools

This study examined whether the distribution of tobacco use and related psychosocial risk factors among youth in urban India vary by socioeconomic status (SES). Data were derived from a cross-sectional survey of students enrolled in the 6th and 8th grades in 32 schools in Delhi and Chennai (N = 11,642). The survey was conducted in 2004. Mixed-effect regression models were used (a) to determine the prevalence of tobacco use among private (higher SES) and government (lower SES) school students, (b) to investigate whether certain psychosocial factors were associated with increased tobacco use, and (c) to determine how these factors varied by school type. Ever-use of multiple forms of tobacco (e.g., gutkha, bidis, and cigarettes) was more prevalent among government school students than private school students. After adjusting for city, gender, grade, and age, the authors found the prevalence rate for ever-use of any tobacco product to be 18.9% for government school students, compared with 12.2% for private school students ($p<.01$). Students in government schools scored lower than private school students on most psychosocial risk factors for tobacco use studied here, indicating higher risk. Government school students scored the lowest for refusal skills, self-efficacy, and reasons not to use tobacco. Social susceptibility to chewing tobacco and social susceptibility to smoking were strong correlates of current tobacco use among government school students. Exposure to tobacco advertising was also a strong correlate of current tobacco use for government school students but not private school students. In two large cities of India, the psychosocial risk profile of government school students suggests they are more vulnerable to initiation and use and to outside influences that encourage use. Mathur, C., Stigler, M., Perry, C., Arora, M., and Reddy, K. Differences in Prevalence of Tobacco Use Among Indian Urban Youth: The Role of Socioeconomic Status. Nicotine Tob. Res., 10(1), pp. 109-116, 2008.

### The Association of Tobacco Marketing to Tobacco Use Among Urban Youth in India

This study examined whether receptivity and exposure to tobacco marketing were correlated with tobacco use and psychosocial risk factors for tobacco use among a sample of urban Indian youth. In 2004, sixth and eighth graders (n = 11,642) in 32 schools in Delhi and Chennai, completed a cross-sectional survey from Project MYTRI, a group randomized intervention trial. Analyses indicated that exposure to tobacco advertisements and receptivity to tobacco marketing was significantly related to increased tobacco use among students. This association suggests the need to strengthen policy and program-based interventions in India to reduce the influence of such exposures. Arora, M., Reddy, K., Stigler, M., and Perry, C. Associations Between Tobacco Marketing and Use Among Urban Youth in India. Am. J. Health Behav, 32(3), pp. 283-294, 2008.

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# Director's Report to the National Advisory Council on Drug Abuse - September, 2008

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

### Cognitive Deficits in Marijuana Users: Effects on Motivational Enhancement Therapy Plus Cognitive Behavioral Therapy Treatment Outcome

The clinical variables that affect treatment outcome for marijuana-dependent individuals are not yet well understood, including the effects of cognitive functioning. Dr. Aharonovich and colleagues from Columbia University did a study to address this by investigating the level of cognitive functioning and treatment outcome. At the beginning of treatment, 20 marijuana-dependent outpatients were given a series of tests that measure psychological functioning known to be linked to particular brain structures or pathways. All patients received 12 weekly individual sessions of combined motivational enhancement therapy and cognitive behavioral therapy. Cognitive functioning test scores were compared between those who completed and those who dropped out of treatment. Also, the proportion of urine samples that were negative for marijuana was compared between those with higher and lower scores on the cognitive tests. Marijuana abstinence was unrelated to cognitive functioning, however, dropouts scored significantly lower than completers on measures of abstract reasoning and processing accuracy. These results provide initial evidence that cognitive functioning plays a role in retaining adult marijuana-dependent patients in treatment. If supported by further studies, the findings may help inform the development of interventions made specifically for cognitively impaired marijuana-dependent patients. Aharonovich, E., Brooks, A., Nunes, E., and Hasin, D. Cognitive Deficits in Marijuana Users: Effects on Motivational Enhancement Therapy plus Cognitive Behavioral Therapy Treatment Outcome. Drug. Alcohol Depend., 95(3), pp. 279-283, 2008.

### Menstrual Phase Effects on Smoking Relapse

The research on smoking cessation suggests that women have a more difficult time quitting than do men, although the reasons for this are not well understood. Some studies have found that smoking behavior fluctuates with the menstrual phase cycle, where smoking and craving is higher in the luteal than the follicular phase, making it more difficult to quit during that phase. To test this, Dr. Allen and colleagues from the University of Minnesota conducted a study to examine if menstrual phase affects relapse in 202 women who were attempting to quit smoking. The women were assigned to quit smoking in either the follicular (F) or luteal (L) menstrual phase and were followed for up to 26 weeks. They measured how many days before relapse and relapse phase to determine if those who begin a quit attempt during the F phase were more successful than those who begin during the L phase. The mean number of days to relapse after a period of continuous abstinence for the F group was 13.9

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versus 21.5 days for the L group. Relapse from prolonged abstinence for the F group was 20.6 versus 39.2 days for the L group. At 14 days, 84% of the F group had relapsed compared with 65% of the L group. At 30 days, 86% of the F group relapsed, compared with 66% of the L group. These results suggest that women attempting to quit smoking in the F phase had less favorable outcomes than those attempting to quit in the L phase. This could relate to ovarian hormones, which may play a role in smoking cessation for women. Allen, S.S., Bade, T., Center, B., Finstad, D., and Hatsukami, D. Menstrual Phase Effects on Smoking Relapse. Addiction, 103(5), pp. 809-821, 2008.

### Distress Tolerance Treatment for Early-Lapse Smokers: Rationale, Program Description, and Preliminary Findings

A significant percentage of individuals attempting to quit smoking have a cigarette within a matter of days, and very few are able to recover to achieve long-term abstinence. This observation suggests that many smokers may have a history exclusively of quitting only to return to smoking very soon after. Recent evidence suggests that certain individuals' reactions to, and the inability to tolerate, withdrawal symptoms (rather than withdrawal severity itself), may represent an important treatment target for developing new behavioral interventions for these individuals. In this article, Dr. Brown and colleagues from Brown Medical School describe a novel, multi-component distress-tolerance treatment for smokers who repeatedly return to smoking shortly after quit attempts that incorporates behavioral and pharmacological elements of standard smoking-cessation treatment. The theoretical rationale for the treatment is presented, drawing distress-tolerance elements from exposure-based and Acceptance and Commitment Therapy-based treatment approaches. The article also presents preliminary data from a pilot study (N = 16) and discusses the clinical implications of this approach. Brown, R., Palm, K., Strong, D., Lejuez, C., Kahler, C., Zvolensky, M., Hayes, S., Wilson, K., and Gifford, E. Distress Tolerance Treatment for Early-Lapse Smokers: Rationale, Program Description, and Preliminary Findings. Behav. Modif., 32(3), pp. 302-332, 2008.

### Behavioral Drug and HIV Risk Reduction Counseling (BDRC) with Abstinence-Contingent Take-Home Buprenorphine: A Pilot Randomized Clinical Trial

Office-based buprenorphine maintenance treatment (BMT) is usually provided with limited counseling or oversight of medication adherence. Dr. Chawarski and colleagues from Yale University evaluated whether the efficacy of BMT is improved by adding individual drug counseling and take-home doses of buprenorphine that are given contingent on being drug-free. After a 2-week buprenorphine and stabilization period, heroin dependent individuals (n=24) in Muar, Malaysia were randomly assigned to Standard Services BMT (physician administered advice and support, and weekly, non-contingent medication pick-up) or Enhanced Services (nurse-delivered manual-guided behavioral drug and HIV risk reduction counseling (BDRC) and abstinence-contingent take-home buprenorphine (ACB), 7 day supply maximum). Outcomes included retention, proportion of opioid-negative urine tests, self-reported drug use, and self-reported HIV risk behaviors. 12/12 (100%) of Enhanced Services and 11/12 (92%) of Standard Services participants completed the entire study. The proportion of opioid-negative urine tests increased significantly over time for both groups, and the reductions were significantly greater in the Enhanced Services group. Enhanced Services group gave significantly higher overall proportions of opiate negative urine tests (87% vs. 69%), and tended to have longer periods of consecutive abstinence from opiates (10.3 weeks vs. 7.8 weeks). Both groups significantly reduced HIV risk behaviors to a similar degree during treatment (26% vs. 17% reductions from the baseline levels for

Enhanced and Standard Services, respectively). These results suggest that manual-guided behavioral drug and HIV risk reduction counseling and abstinence-contingent take-home buprenorphine may improve office-based BMT provided with limited drug counseling and medication oversight. Chawarski, M., Mazlan, M., and Schottenfeld, R. Behavioral Drug and HIV Risk Reduction Counseling (Bdrc) with Abstinence-Contingent Take-Home Buprenorphine: A Pilot Randomized Clinical Trial Drug. Alcohol Depend, 94(1-3), pp. 281-284, 2008.

### Evaluation of Ongoing Oxycodone Abuse among Methadone-Maintained Patients

Prevalence of prescription opioid abuse has increased dramatically in recent years in the United States generally, and a similar pattern of increasing prescription opioid use has also been noted among patients seeking treatment for opioid dependence. Drs. Dunn and Higgins and colleagues from the University of Vermont evaluated 100 patients in outpatient methadone maintenance (MM) treatment and examined the extent of ongoing oxycodone abuse that might be going undetected with current urinalysis-testing methods. Urine samples were collected from these patients over a 6-week period and analyzed using the clinic's usual enzyme multiplied immunoassay test (EMIT) opiate assay (300 ng/ml opiate cutpoint), and a supplemental oxycodone test strip (100 ng/ml oxycodone cutpoint). The EMIT assay identified only 6% (20/437) of samples as positive for oxycodone, whereas the oxycodone test strip indicated that 19% (83/437) tested positive for recent oxycodone use. Oxycodone users were more likely to report a prescription opioid as their primary drug at intake, be in MM treatment for a significantly shorter duration, and provide significantly more opioid- and cocaine-positive urine samples. Overall, these data illustrate the potential importance of monitoring for ongoing oxycodone use in MM clinics. Although future efforts should examine this question using more rigorous experimental methods, findings from this initial project have implications for clinical issues such as evaluating patient stability in treatment, making medication-dosing decisions, and determining patient eligibility for methadone take-home privileges. Dunn, K., Sigmon, S., McGee, M., Heil, S., and Higgins, S. Evaluation of Ongoing Oxycodone Abuse among Methadone-Maintained Patients. J. Subst. Abuse Treat., 2008 Feb 21 [E-pub ahead of print].

### Latinos and HIV/AIDS: Examining Factors Related to Disparity and Identifying Opportunities for Psychosocial Intervention Research

Latinos maintain an AIDS case rate more than 3 times higher than whites, a greater rate of progression to AIDS, and a higher rate of HIV/AIDS-related deaths. Dr. Gonzalez and colleagues from Massachusetts General Hospital reviewed three broad areas related to these disparities: (1) relevant demographic, socioeconomic, and socio-cultural factors among Latinos; (2) drug abuse and mental health problems in Latinos relevant to HIV/AIDS outcomes; and (3) opportunities for psychosocial intervention. Latinos living with HIV are a rapidly growing group, are more severely impacted by HIV than whites, and confront unique challenges in coping with HIV/AIDS. A body of research suggests that depression, substance abuse, treatment adherence, health literacy, and access to healthcare may be fruitful targets for intervention research in this population. Though limited, the current literature suggests that psychosocial interventions that target these factors could help reduce HIV/AIDS disparities between Latinos and whites and could have important public health value. Gonzalez, J., Hendriksen, E., Collins, E., Duran, R., and Safren, S. Latinos and HIV/AIDS: Examining Factors Related to Disparity and Identifying Opportunities for Psychosocial Intervention Research. AIDS Behav., 2008 [E-pub ahead of print].

### Therapeutic Education System (TES) to Augment Office Based Buprenorphine

Office based buprenorphine offers a novel way to treat opioid abuse which may reduce barriers to care because patients can receive opioid maintenance pharmacotherapy via a physician without having to attend treatment at a methadone clinic. Drs. Bickel, Marsch, and colleagues have developed a web based computerized therapeutic education system (TES) based on a promising behavioral treatment called the Community Reinforcement Approach (CRA) to provide skills training and psycho-education and abstinence reinforcement which are not typically a focus of physician training but which are thought to influence pharmacotherapy outcomes. Researchers conducted a randomized clinical trial of buprenorphine maintained patients comparing opioid and cocaine using patients randomized to (1) TES plus Voucher Reinforcement plus in person therapy every other week vs. (2) Completely in-person therapist delivered CRA treatment plus Voucher Reinforcement therapy, vs. (3) Standard Treatment (buprenorphine alone). Both the computerized augmented treatment plus Vouchers and the therapist delivered CRA plus Vouchers conditions produced more weeks of cocaine and opioid abstinence than usual care indicating the novel behavioral treatments did indeed augment the pharmacotherapy. Additionally, although durations of abstinence were similar in the computer augmented and therapist only delivered conditions, participants in the computer augmented conditions spent 934 minutes less on average with their therapists than did those in the non-computerized condition. Results suggest that computer augmented treatment may be a useful way to reduce staff and patient time for behavioral treatment while still improving treatment over standard medication alone. Further studies are needed to examine what effect the TES contributes beyond the Abstinent Contingent Voucher Component of the behavioral treatment. Bickel, W., Marsch, L., Buchhalter, A., and Badger, G. Computerized Behavior Therapy for Opioid-dependent Outpatients: A Randomized Controlled Trial. Exp. Clin. Psychopharm., 16(2), pp.132-143, 2008.

### Predictors of Dropout from Group Therapy among Patients with Bipolar and Substance Use Disorders

Bipolar and substance use disorders frequently occur together. Group therapies that integrate treatment for both disorders can effectively reduce substance use, but no study has examined factors related to early drop out from integrated group therapy. Dr. Weiss and colleagues from Harvard Medical School identified baseline demographic and clinical characteristics that predict treatment dropout among patients with co-occurring bipolar and substance use disorders. Baseline data were analyzed from patients who took part in a randomized controlled trial of integrated group therapy for bipolar and substance use disorders. Cigarette smoking, recent mood episode, and lack of a college education were strong predictors of dropout. This was the case even after possible associations with other demographic and substance use variables were taken into account. These results suggest that, given the strength of smoking as a predictor of dropout as well as the high rate of smoking among this population, a greater focus on the relationship between smoking and bipolar disorder may be needed to potentially reduce the rate of early dropout from integrated treatment. Graff, F., Griffin, M., and Weiss, R. Predictors of Dropout from Group Therapy among Patients with Bipolar and Substance Use Disorders. Drug Alcohol Depend., 94(1-3), pp. 272-275, 2008.

### Effects of Voucher-Based Incentives on Abstinence from Cigarette Smoking and Fetal Growth among Pregnant Women

Drs. Heil and Higgins and colleagues from the University of Vermont examined whether vouchers that are given contingent upon smoking abstinence during pregnancy are an effective way to decrease maternal smoking and improve fetal growth. A total of 82 smokers entering prenatal care were randomly assigned to either contingent or non-contingent voucher conditions. Vouchers exchangeable for retail items were available during pregnancy and for 12 weeks postpartum. In the contingent condition, vouchers were earned for biochemically verified smoking abstinence; in the non-contingent condition, vouchers were earned independent of smoking status. Smoking outcomes were evaluated using urine-toxicology testing and self-report. Fetal growth outcomes were evaluated using serial ultrasound examinations performed during the third trimester. Contingent vouchers significantly increased abstinence at the end-of-pregnancy (41% versus 10%) and at the 12-week postpartum point (24% versus 3%). There was significantly greater fetal growth with the contingent condition in terms of estimated weight, femur length and abdominal circumference. These results provide further evidence that abstinent-contingent vouchers can substantially decrease maternal smoking during pregnancy, and provide new evidence of positive effects on fetal health. Heil, S., Higgins, S., Bernstein, I., Solomon, L., Rogers, R., Thomas, C., Badger, and G. Lynch, M. Effects of Voucher-Based Incentives on Abstinence from Cigarette Smoking and Fetal Growth among Pregnant Women. Addiction, 103(6), pp. 1009-1018, 2008.

### Attempts to Stop or Reduce Marijuana Use in Non-Treatment Seekers

Dr. Hughes and colleagues at the University of Vermont examined the short-term outcomes of individuals who intended to quit or reduce their marijuana use on their own, without seeking treatment. Daily marijuana smokers (n=19) called a phone each night for 28 nights to report marijuana use and reported intentions to change at the end of each week. Outcomes did not differ between those who initially planned to reduce vs. quit in the next month. Participants averaged three attempts to reduce and one attempt to quit during the 28 days. Participants reduced marijuana use on 11% and abstained from marijuana on 14% of days. Most were successful in reducing or abstaining on half or more of the days they attempted; however, only four participants (21%) reduced 50% or more for at least 7 consecutive days, and only two (10%) abstained for that long. Abstinence or reduction did not appear to change alcohol or caffeine use. The authors concluded that: (a) initial intentions are poor predictors of outcomes, (b) most users make multiple, short-lived attempts to change, (c) reduction was as common as abstinence, (d) many attempts to change are initially successful but few persist, and (e) other drug use does not appear to worsen with marijuana reduction or abstinence. Hughes, J., Peters, E., Callas, P., Budney, A., and Livingston, A. Attempts to Stop or Reduce Marijuana Use in Non-Treatment Seekers. Drug Alcohol Depend., 97(1-2), pp. 180-184, 2008.

### Exercise as an Adjunct to Nicotine Gum in Treating Tobacco Dependence among Women

The acute effects of exercise on reducing withdrawal from and craving for cigarettes has suggested that exercise may be a useful adjunct for smoking cessation treatment. Dr. Kinnunen and colleagues from Harvard conducted the first randomized controlled trial assessing the efficacy of an exercise intervention as an adjunct to nicotine gum therapy. They compared the exercise intervention with both an equal contact control and a standard care control condition. Sedentary female smokers (N = 182) aged 18-55 years were provided with nicotine gum treatment along with brief behavioral counseling and were randomized into one of these three behavioral adjunct conditions. At the end of treatment and at 1-year follow-up, there were clear trends showing that both the exercise and equal contact control conditions had higher rates of

abstinence than the standard care control, although the effect was not statistically significant. However, the equal contact condition had a significantly lower likelihood of relapse after 1 week compared with the standard care condition and there was a near significant trend in which exercise offered an advantage over standard care as well. While these findings suggest a slightly improved likelihood of abstinence with exercise compared with standard care, exercise did not differ from equal contact control in its efficacy. Potential explanations for these equivalent levels of efficacy and implications for the findings are discussed. Kinnunen, T., Leeman, R., Korhonen, T., Quiles, Z., Terwal, D., Garvey, A., and Hartley, H. Exercise as an Adjunct to Nicotine Gum in Treating Tobacco Dependence among Women. Nicotine Tob. Res., 10(4), pp. 689-703, 2008.

### Smoking in Help-Seeking Veterans with PTSD Returning from Afghanistan and Iraq

Past research has shown that veterans and individuals with posttraumatic stress disorder (PTSD) have increased rates of smoking. However, the rates of smoking in younger help-seeking veterans returning from Afghanistan and Iraq, and possible correlates of smoking among this population are unknown. In this study, Dr. Kirby and colleagues from Duke University evaluated the rate of lifetime and current smoking among a sample of 90 returning male veterans diagnosed with PTSD. Fifty-nine percent reported a lifetime history of smoking including 32% that were current smokers. Current smokers were significantly younger than non-smokers. Current smokers (mean age=31) reported a mean age of smoking onset as 15.86 with a history of smoking a pack per day of 8.89 years. These smokers reported on average five previous quit attempts. According to a stages of change model, which characterizes individuals' readiness to quit, one-half of the smokers were in the contemplation phase of stopping smoking (50%), 29% were in the pre-contemplation phase and 21% were in the preparation phase. The results are placed in the context of non-psychiatric and psychiatric smokers. Kirby, A., Hertzberg, B., Collie, C., Yeatts, B., Dennis, M., McDonald, S., Calhoun, P., and Beckham, J. Smoking in Help-Seeking Veterans with PTSD Returning from Afghanistan and Iraq. Addict. Behav., 2008 [E-pub ahead of print].

### A Randomized Clinical Trial of Community-Based Directly Observed Therapy as an Adherence Intervention for HAART among Substance Users

Interventions aimed to improve adherence to highly active antiretroviral therapy (HAART) can impact challenging populations, such as active substance users. Dr. Macalino and colleagues from Brown University evaluated a promising community-based approach called modified directly observed therapy (MDOT). HIV seropositive substance users were randomized to either standard of care (SOC) or MDOT (experience with HAART was taken into account during random assignment procedures). All participants were placed on a once-daily regimen and were met by an outreach worker for all 7 days during the first 3 months. They evaluated differences in viral load suppression [> 2 log drop in plasma viral load (PVL) or PVL < 50] and changes in PVL and CD4 cell count from baseline to 3 months. A total of 87 participants were enrolled (43 in SOC, 44 in MDOT). MDOT participants were more than twice as likely to achieve PVL suppression. This effect was more dramatic among those who were HAART-experienced; they were almost three times more likely to achieve PVL suppression. CD4 cell count was also significantly higher in the MDOT group. The rates of undetectable PVL did not differ between the groups. This study provides evidence that MDOT is an effective strategy to reduce viral load and increase CD4 cell counts in HAART experienced substance users. MDOT should be included in the spectrum of options to enhance adherence in this population. Macalino, G.E., Hogan, J.W., Mitty, J.A., Bazerman, L.B.,

Delong, A.K., Loewenthal, H., Caliendo, A.M., and Flanigan, T.P. A Randomized Clinical Trial of Community-Based Directly Observed Therapy as an Adherence Intervention for HAART among Substance Users. AIDS, 21(11), pp. 1473-1477, 2007.

### HIV Risk Behavior among Patients with Co-Occurring Bipolar and Substance Use Disorders: Associations with Mania and Drug Abuse

Bipolar and substance use disorders frequently occur together, and both are associated with impulsivity, impaired judgment, and risk-taking. Dr Weiss and colleagues from Harvard conducted this study to: (1) describe the rates of HIV sexual and drug risk behaviors among patients with co-occurring bipolar and substance use disorders, (2) test whether acute mania, psychiatric severity, and drug severity independently predict HIV risk, and (3) examine the relationship between specific substance dependencies and sexual risk behaviors. Participants (N=101) were assessed for psychiatric diagnoses, substance abuse, and HIV risk behavior using structured clinical interviews and self-report questionnaires. The majority (75%) were sexually active in the past 6 months and reported high rates of sexual risk behaviors, including unprotected intercourse (69%), multiple partners (39%), sex with prostitutes (24%, men only), and sex trading (10%). Recent manic episode, lower psychiatric severity, and greater drug severity were independent predictors of total HIV risk. Cocaine dependence was associated with increased risk of sex trading. These results suggest an important need for HIV prevention interventions for this population. Meade, C.S., Graff, F.S., Griffin, M.L., and Weiss, R.D. HIV Risk Behavior among Patients with Co-Occurring Bipolar and Substance Use Disorders: Associations with Mania and Drug Abuse. Drug Alcohol Depend., 92(1-3), pp. 296-300, 2008.

### A Randomized Trial of Brief Interventions for Problem and Pathological Gamblers

Limited research exists on best methods for reducing problem gambling. Dr. Petry and colleagues from the University of Connecticut randomly assigned problem gamblers (N = 180) to an assessment only control condition, 10 min of brief advice, 1 session of motivational enhancement therapy (MET), or 1 session of MET plus 3 sessions of cognitive-behavioral therapy. Gambling was assessed at baseline, at 6 weeks, and at a 9-month follow-up. Relative to assessment only, brief advice was the only condition that significantly decreased gambling between baseline and Week 6, and it was associated with clinically significant reductions in gambling at Month 9. Between Week 6 and Month 9, MET plus cognitive-behavioral therapy significantly reduced scores on the gambling section of the Addiction Severity Index (which measures dollars wagered and days gambled in the previous month), compared with the control condition. These results suggest that a very brief intervention can reduce gambling among problem and pathological gamblers who are not actively seeking gambling treatment. Petry, N.M., Weinstock, J., Ledgerwood, D.M., and Morasco, B. A Randomized Trial of Brief Interventions for Problem and Pathological Gamblers. J. Consult. Clin. Psychol., 76(2), pp. 318-328, 2008.

### When the Levee Breaks: Treating Adolescents and Families in the Aftermath of Hurricane Katrina

Hurricane Katrina brought to the surface serious questions about the capacity of the public health system to respond to community-wide disaster. The storm and its aftermath severed developmentally protective family and community ties; thus its consequences are expected to be particularly acute for vulnerable adolescents. Research confirms that teens are at risk for a range of negative

outcomes under conditions of life stress and family disorganization. Specifically, the multiple interacting risk factors for substance abuse in adolescence may be compounded when families and communities have experienced a major trauma. Further, existing service structures and treatments for working with young disaster victims may not address their risk for co-occurring substance abuse and traumatic stress reactions because they tend to be individually or peer group focused, and fail to consider the multi-systemic aspects of disaster recovery. This article proposes an innovative family-based intervention for young disaster victims, based on a model for adolescent substance abuse that has demonstrated effects, Multidimensional Family Therapy (MDFT; Liddle, 2002). The mechanisms and outcomes of the model are being investigated in a randomized clinical trial with clinically referred substance-abusing teens in a New Orleans area community impacted by Hurricane Katrina. Rowe, C.L., and Liddle, H.A. When the Levee Breaks: Treating Adolescents and Families in the Aftermath of Hurricane Katrina. J. Marital Fam. Ther., 34(2), pp. 132-48, 2008.

### Is Attention Deficit Hyperactivity Disorder (ADHD) Symptom Severity Associated with Tobacco Use?

Several studies report a strong link between ADHD and tobacco use; however, the nature of this relationship is not entirely clear. Drs. Upadhyaya and Carpenter from the Medical University of South Carolina examined the relationship between attention deficit hyperactivity disorder (ADHD) symptoms and tobacco use within a sample of college students. Although tobacco use was the main focus, they also examined alcohol and marijuana use. They examined the association between the number of ADHD symptoms endorsed (severity), and tobacco, alcohol, and marijuana use in a convenience sample of 334 college students in the southeastern United States. Survey data were based on the annual Core Alcohol and Drug Survey for substance use, and the Current Symptom Scale (CSS) for ADHD, conduct disorder (CD), and antisocial personality disorder (ASPD) symptoms. Among those who had ever used a substance, the number (severity) of current ADHD symptoms, including inattentive and hyperactive symptoms, was significantly associated with the frequency of tobacco and marijuana use in the past month and past year, as well as to the frequency of alcohol use in the past month. The results suggest that the number of ADHD symptoms is proportionally associated with tobacco, alcohol, and marijuana use, and may have implications for clinical treatment. Upadhyaya, H.P., and Carpenter, M.J. Is Attention Deficit Hyperactivity Disorder (ADHD) Symptom Severity Associated with Tobacco Use? Am. J. Addict., 17(3), pp. 195-198, 2008.

### Use of Brief Interventions for Drug Abusing Teenagers within a Middle and High School Setting

Promising and encouraging results have been recently reported on the use of briefer interventions for adolescent drug abusers. Because middle- and high-school-based drug abuse intervention programs have grown in popularity over the past several decades, the use of brief interventions (BIs) in school settings needs further consideration. Dr. Winters and colleagues from the University of Minnesota reviewed several clinical and school contextual issues pertaining to the scientific efficacy, feasibility, and application of BIs for students who are abusing drugs. Several advantages for employing BIs in a school setting are identified, including the relatively high base rate of students with mild-to-moderate drug involvement and the likelihood that school counselors can readily learn BI techniques. The authors describe practical, systemic, and clinical barriers that need consideration before implementing BIs. Despite these concerns, they conclude that schools are a viable setting in which to screen youth for drug abuse problems and to conduct a BI. Winters, K.C., Leitten, W., Wagner, E., and O'Leary Tevyaw, T. Use of Brief Interventions for Drug Abusing Teenagers within a Middle and High School Setting. J. Sch. Health,

77(4), pp. 196-206, 2007.

### The Impact of Managed Care on Drug-Dependent Pregnant Women and their Children

Using archival data, this study examined the effects of managed care (MC) on a population of drug-dependent women and their children in a multidisciplinary, comprehensive care substance user treatment facility in pre- (1995, n=132) and post (2000, n=108)-managed care conditions. The two groups had similar birth parameters, but the MC group had more fetal and infant deaths, decreased immunization rates, and greater incidence of social services intervention. While these data are correlational and need to be interpreted with caution, they suggest that the shift from fee-for-service to managed care (MC) has resulted in poorer outcomes for drug-exposed children under MC. Jansson, L.M., Svikis, D.S., Velez, M., Fitzgerald, E., and Jones, H.E. The Impact of Managed Care on Drug-Dependent Pregnant and Postpartum Women and their Children. Subst. Use Misuse, 42(6), pp. 961-974, 2007.

### Higher Relapse Rate for Drug-Dependent Pregnant Women with Mood Disorders

The purpose of this study was to examine the potential treatment impact of co-occurring Axis I disorders in a sample of opiate-dependent pregnant women receiving methadone treatment. Participants were categorized into three groups according to their primary current SCID diagnosis: (1) absence of any current mood/anxiety disorder (ND, n = 29), (2) primary mood disorder (MD, n = 39), and (3) primary anxiety disorder (AD, n = 38). Demographically, the groups were similar. The MD group was significantly more likely to be positive for drugs while in treatment compared with both the ND and AD groups. The MD and AD groups had more psychosocial impairment and higher incidence of suicidal ideation compared with the ND group. Interestingly, the AD group spent more days in treatment compared with the ND or MD group. The authors conclude that the poor treatment outcomes in the MD group suggest the need for treatment that specifically targets the mood disorder in addition to the substance use disorder. While enhanced treatment resources for all substance-abusing pregnant patients with co-occurring disorders would be ideal, it may be possible to achieve improvement in treatment outcomes by recognizing the particular needs of different substance-abusing subpopulations and by tailoring treatments both at the programmatic and individual level to specifically address those needs. Fitzsimons, H.E., Tuten, M., Vaidya, V., and Jones, H.E. Mood Disorders Affect Drug Treatment Success of Drug-Dependent Pregnant Women. J. Subst. Abuse Treat., 32(1), pp. 19-25, 2007.

### Secondary Family Effects of Treating Paternal Alcoholism with Learning Sobriety Together

This study examined whether Learning Sobriety Together, a treatment for substance abuse that combines behavioral couples therapy and individual counseling, had comparable secondary benefits on the internalizing and externalizing behaviors of adolescent versus preadolescent siblings living in homes with their alcoholic fathers (N = 131) and their non-substance-abusing mothers. During a 17-month assessment period, the association between parents' functioning (i.e., fathers' drinking as determined by percentage of days abstinent and parents' dyadic adjustment) and children's adjustment (as rated by mothers, fathers, and children's teachers) was stronger for preadolescents than for their adolescent siblings, particularly in terms of children's externalizing behaviors. It appears that preadolescents are at a point developmentally where their behavior is more influenced by the familial environment than by their adolescent counterparts. Furthermore, the finding

that teachers reported the same patterns suggests that changes in the home environment were related to the externalizing behavior of preadolescent children in an important out-of-home context (i.e., school). In conclusion, interventions designed to reduce paternal drinking and improve couple functioning may be viable preventative interventions for preadolescents in these homes and a way to benefit children without identifying or treating children directly. Kelley, M.L., and Fals-Stewart, W. Treating Paternal Alcoholism with Learning Sobriety Together: Effects on Adolescents versus Preadolescents. J. Fam. Psychol., 21(3), pp. 435-444, 2007.

### Fathering Among Drug-Dependent Men Receiving Methadone Maintenance Treatment

Using a structured research interview, this pilot study was designed to examine patterns of fathering among 50 men enrolled in methadone maintenance treatment. The men in this study reported attempts to conceive and parent children in socially responsible ways. However, their involvement in the children's lives, their relationships with the children's mothers, and their ability to provide financial support deteriorated over time as their drug abuse continued. The investigators also found that the men seemed even less involved in the lives of their non-biological children. The authors conclude that the drug abuse treatment system could provide better support for drug-abusing men interested in being effective parents. McMahon, T.J., Winkel, J.D., Suchman, N.E., and Rounsaville, B.J. Drug-Abusing Fathers: Patterns of Pair Bonding, Reproduction, and Paternal Involvement. J. Subst. Abuse Treat., 33(3), pp. 295-302, 2007.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2008

## Research Findings - Research on Pharmacotherapies for Drug Abuse

### Oral Oxycodone, Hydrocodone and Hydromorphone Exhibit Similar Abuse Liabilities, Despite Dissimilar Analgesic Potencies

Abuse of prescription opioids has risen precipitously in the United States. Few controlled comparisons of the abuse liability of the most commonly abused opioids have been conducted. This outpatient study employed a double-blind, randomized, within-subject, placebo-controlled design to examine the relative abuse potential and potency of oral oxycodone (10, 20 and 40mg), hydrocodone (15, 30 and 45mg), hydromorphone (10, 17.5 and 25mg) and placebo. Healthy adult volunteers (n=9) with sporadic prescription opioid abuse participated in 11 experimental sessions (6.5h in duration) conducted in a hospital setting. All three opioids produced a typical mu opioid agonist profile of subjective (increased ratings of liking, good effects, high and opiate symptoms), observer-rated, and physiological effects (miosis, modest respiratory depression, exophoria and decrements in visual threshold discrimination) that were generally dose-related. Valid relative potency assays revealed that oxycodone was roughly equipotent to or slightly more potent than hydrocodone. Hydromorphone was only modestly more potent (less than two-fold) than either hydrocodone or oxycodone, which is inconsistent with prior estimates arising from analgesic studies. These data suggest that the abuse liability profile and relative potency of these three commonly used opioids do not differ substantially from one another and suggest that analgesic potencies may not accurately reflect relative differences in abuse liability of prescription opioids. Walsh, S.L., Nuzzo, P.A., Lofwall, M.R., and Holtman, J.R., Jr. The Relative Abuse Liability of Oral Oxycodone, Hydrocodone and Hydromorphone Assessed in Prescription Opioid Abusers. Drug Alcohol Depend., 2008, Jul 5. E-pub ahead of print.

### A Review of Drug Self-administration Paradigms That Have Been Employed to Assess the Abuse Liability of Substances During Processes Drug Development

The purpose of this review is to illustrate the utility and value of employing human self-administration procedures in medication development, including abuse liability assessments of novel medications and evaluation of potential pharmacotherapies for substance use disorders. Traditionally, human abuse liability testing has relied primarily on subjective reports describing drug action by use of questionnaires; similarly, drug interactions between putative treatment agents and the drugs of abuse have relied on these measures. Subjective reports are highly valued because they provide qualitative and quantitative information about the characteristics of central and peripheral pharmacodynamic effects as well as safety and tolerability. However, self-

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administration procedures directly examine the behavior of interest - that is, drug taking. The present paper (1) reviews the most commonly used human self-administration procedures, (2) discusses the concordance of subjective reports and self-administration within the context of medications development for substance use disorders, focusing primarily on illustrative examples from development efforts with opioid and cocaine dependence, and (3) explores the utility of applying self-administration procedures to assess the abuse liability of novel compounds, including "abuse-deterrent" formulations (ADFs). The review will focus on opioid and cocaine dependence because a rich database from both clinical laboratory and clinical trial research exists for these two drug classes. The data reviewed suggest that drug-induced changes in self-administration and subjective effects are not always concordant. Therefore, assessment of self-administration in combination with subjective effects provides a more comprehensive picture that may have improved predictive validity for translating to the clinical setting. Comer, S.D., Ashworth, J.B., Foltin, R.W., Johanson, C.E., Zacny, J.P., and Walsh, S.L. The Role of Human Drug Self-administration Procedures in the Development of Medications. Drug Alcohol Depend. 96(1-2), pp. 1-15, 2008.

### Oral Bupropion Does Not Increase Abstinence from Tobacco, Opioids, or Cocaine in Buprenorphine-stabilized (Opioid-dependent) Individuals, but Significantly Increases Treatment Non-compliance

In this double-blind, placebo-controlled trial, bupropion (BUPRO, 300 mg/day) was compared to placebo (PBO) for the concurrent treatment of opioid and tobacco addiction in 40 opioid-dependent smokers stabilized on buprenorphine (BUPRE, 24 mg/day). Participants received contingent, monetary reinforcement for abstinence from smoking, illicit opioids, and cocaine. Significant differences in treatment retention were observed (BUPRE+BUPRO, 58%; BUPRE+PBO, 90%). BUPRO treatment was not more effective than placebo for abstinence from tobacco, opioids, or cocaine in BUPRE-stabilized patients. These preliminary findings do not support the efficacy of BUPRO, in combination with BUPRE, for the concurrent treatment of opioid and tobacco addiction. Mooney, M.E., Poling, J., Gonzalez, G., Gonsai, K., Kosten, T., and Sofuoglu, M. Preliminary Study of Buprenorphine and Bupropion for Opioid-dependent Smokers. Am. J. Addict., 17(4), pp. 287-292, 2008.

### Rural Opioid-using Pregnant Women Appear to Have Some Characteristics Associated With Better Treatment Outcomes

Historically, research on opioid use during pregnancy has occurred in urban settings and it is unclear how urban and rural populations compare. This study examined socio-demographic and other variables in opioid-using pregnant women seeking treatment and screened for participation in a multi-site randomized controlled trial. Women screened in rural Burlington, Vermont (n=54), were compared to those screened in urban Baltimore, Maryland (n=305). Rural opioid-using pregnant women appear to have some characteristics associated with better treatment outcomes (e.g., less severe drug use, greater employment). However, they may face additional barriers in accessing treatment (e.g., greater distance from treatment clinic). Heil, S.H., Sigmon, S.C., Jones, H.E., and Wagner, M. Comparison of Characteristics of Opioid-using Pregnant Women in Rural and Urban Settings. Am. J. Drug Alcohol Abuse, 34(4), pp. 463-471, 2008.

### Disulfiram Enhances Both the Rewarding- and Aversive Subjective Effects of Acute Dextroamphetamine in Normal Subjects, Without Significantly Increasing Heart Rate or Blood Pressure

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., and Kosten, T. Disulfiram Enhances Subjective Effects of Dextroamphetamine in Humans. Pharmacol. Biochem. Behav. 90(3), pp. 394-398, 2008.

### Bupropion Hydrochloride versus Placebo, in Combination with Cognitive Behavioral Therapy, for the Treatment of Cocaine Abuse/Dependence

This article describes a randomized, double-blind, placebo controlled trial comparing outpatient treatment with bupropion (N=37) and placebo (N=33) in combination with standard cognitive behavioral therapy (CBT) in cocaine dependent subjects. Bupropion was tested because it is a dopamine and norepinephrine reuptake inhibitor, and might have potential as an effective treatment for cocaine dependence due to its ability to reverse deficits in dopaminergic functioning that occur in chronic cocaine users. There were no statistically significant differences between bupropion and placebo in treatment outcomes, including measures of urine drug screen results (Joint Probability Index at 16 weeks: 0.43 for bupropion and 0.38 for placebo), treatment retention, cocaine craving ratings, and assessments of depressive symptoms. The results of this study suggest that further testing of bupropion for the treatment of cocaine dependence is not warranted. Shoptaw, S., Heinzerling, K.G., Rotherham-Fuller, E., Kao, U.H., Wang, P.C., Bholat, M.A., and Ling, W. Bupropion Hydrochloride versus Placebo, in Combination with Cognitive Behavioral Therapy, for the Treatment of Cocaine Abuse/Dependence. J. Addict. Dis., 27(1), pp. 13-23, 2008.

### A Double-blind, Placebo-controlled Trial That Combines Disulfiram and Naltrexone for Treating Co-occurring Cocaine and Alcohol Dependence

This is a double blind, placebo-controlled trial that evaluated the efficacy of disulfiram, naltrexone and their combination in patients with co-occurring cocaine and alcohol dependence. 208 patients were randomized to disulfiram (250 mg/day), naltrexone (100 mg/day), the combination, or placebo for 11 weeks. Outcomes were in-trial abstinence from cocaine and/or alcohol. Few safety concerns were reported, although medication adherence was low in a number of patients for both medications, alone or in combination. In the primary analyses (GEE modeling), abstinence from cocaine as measured by cocaine-negative urines and days of self-reported abstinence from cocaine or alcohol did not differ between placebo and any of the medication groups. However, patients taking disulfiram (alone or in combination) were most likely

to achieve combined abstinence from cocaine and alcohol. Secondary analyses revealed that patients taking the disulfiram-naltrexone combination were most likely to achieve 3 consecutive weeks of abstinence from cocaine and alcohol. There was an association between disulfiram treatment and abstinence from cocaine and alcohol. More patients taking the disulfiram-naltrexone combination achieved 3 consecutive weeks of abstinence in treatment than placebo-treated patients. Pettinati, H.M., Kampman, K.M., Lynch, K.G., Xie, H., Dackis, C., Rabinowitz, A.R., and O'Brien, C.P. A Double Blind, Placebo-Controlled Trial that Combines Disulfiram and Naltrexone for Treating Co-occurring Cocaine and Alcohol Dependence. Addict. Behav., 33, pp. 651-667, 2008.

### Agonist-replacement Therapies May Have Implications as Treatments for Stimulant Dependence

Two experiments were conducted to determine whether methylphenidate or modafinil, two potential pharmacotherapies for stimulant dependence, would impair inhibitory behavior in cocaine users. Eleven cocaine abusers were administered methylphenidate (0, 15, 30, and 45 mg) or modafinil (0, 150, 300, and 450 mg) across four experimental sessions. A cued go-no-go task was used to measure response execution and inhibition. Subjective and cardiovascular measures were collected. Neither methylphenidate nor modafinil impaired inhibitory control, but produced prototypical subject-rated and cardiovascular effects. The results of these studies may have implications for the use of these drugs as agonist-replacement therapies for stimulant dependence. Vansickel, A.R., Fillmorex, M.T., Hays, L.R., and Rush, C.R. Effects of Potential Agonist-replacement Therapies for Stimulant Dependence on Inhibitory Control in Ccaine Ausers. Am. J. Drug Alcohol Abuse, 34(3), pp. 293-305, 2008.

### Gender Differences With High-dose Naltrexone in Patients With Co-occurring Cocaine and Alcohol Dependence

This is a randomized, double-blind, placebo-controlled clinical trial that evaluated the efficacy of a higher-than-typical daily dose of naltrexone (150 mg/day), taken for 12 weeks, in 164 patients (n = 116 men and n = 48 women) with co-occurring cocaine and alcohol dependence. Patients were stratified by gender and then randomly assigned to either naltrexone or placebo, and to either cognitive-behavioral therapy or a type of medical management. The two primary outcomes were cocaine use and alcohol use. Significant Gender x Medication interactions were found for cocaine use via urine drug screens (three way, with time) and self-reports (two way) for drug severity (two way) and alcohol use (two way). The type of psychosocial treatment did not affect outcomes. Thus, 150 mg/day naltrexone added to a psychosocial treatment resulted in reductions in cocaine and alcohol use and drug severity in men, compared to higher rates of cocaine and alcohol use and drug severity in women. Pettinati, H.M., Kampman, K.M., Lynch, K.G., Suh, J.J., Dackis, C.A., Oslin, D.W., and O'Brien, C.P. Gender Differences with High-dose Naltrexone in Patients with Co-occurring Cocaine and Alcohol Dependence. J. Subst. Abuse Treat., 34, pp. 378-390, 2008.

### Randomized, Placebo-controlled Trial of Bupropion for the Treatment of Methampheta-mine Dependence

This study compared bupropion to placebo for reducing methamphetamine use, increasing retention, and reducing the severity of depressive symptoms and methamphetamine cravings in 73 treatment-seeking methamphetamine dependent participants, with a secondary objective of comparing bupropion to placebo for reducing cigarette smoking among study participants. Participants

were randomly assigned to bupropion SR (150 mg twice daily, N=36) or placebo (twice daily, N=37) for 12 weeks under double-blind conditions. Participants attended clinic thrice weekly to provide urine samples, complete research measures and assessments, and to receive contingency management and weekly cognitive behavioral therapy sessions. Results of this study showed that there were no statistically significant effects for bupropion relative to placebo on methamphetamine use, for reducing the severity of depressive symptoms or methamphetamine cravings, or on study retention. In a post hoc analysis, there was a statistically significant effect of bupropion treatment on methamphetamine use among participants with lighter (0-2 methamphetamine positive urines but not heavier (3 - 6 methamphetamine positive urines) during baseline. Bupropion treatment was associated with significantly reduced cigarette smoking. The post hoc findings of an effect for bupropion among baseline light, but not heavy, methamphetamine users suggests further evaluation of bupropion for light methamphetamine users is warranted. Shoptaw, S., Heinzerling, K.G., Rotherham-Fuller, E., Steward, T., Wang, J., Swanson, A-N., De La Garza, R., Newton, T., and Ling, W. Randomized, Placebo-controlled Trial of Bupropion for the Treatment of Methamphetamine Dependence. Drug and Alc. Dep., 96, pp. 222-232, 2008.

### Predictors of Cardiovascular Response to Methamphetamine Administration in Methamphetamine-dependent Individuals May Help in the Prevention and Treatment of Cardiovascular Events in a Population at High Risk

The goal of this study was to determine predictors of cardiovascular response to methamphetamine administrated in the laboratory. Heart rate (HR) and blood pressure (BP) were measured at baseline and at several time points following the administration of methamphetamine or saline placebo. One-way ANOVA was used to determine the differences between female and male subjects in their cardiovascular response. In male subjects, linear regression and one-way ANOVA were used to determine the influence of potential predictors on cardiovascular response, including age, weight, drug use indicators, concurrent use of other substances, route of administration, and race. Methamphetamine administration provoked significant increases in HR and BP, as compared to placebo. Female gender was associated with larger peak change in diastolic BP following administration. Baseline HR and BP were found to be strong predictors of cardiovascular response to methamphetamine administration in male subjects. Lifetime use and recent use of methamphetamine and nicotine did not predict cardiovascular response to methamphetamine. Recent alcohol use was associated with increased peak change in diastolic BP. Also, current use of cannabis was negatively correlated with peak HR change. Male cannabis users show lower peak change in HR as compared to non-cannabis users. As compared to methamphetamine smokers, intravenous users demonstrated higher peak change in diastolic BP following drug administration. Race did not have a significant effect on cardiovascular response. Taken together, these findings may help in the prevention and treatment of cardiovascular events in a population at high risk of premature morbidity and mortality. Fleury, G., DeLaGarza, R., Mahoney, J.J., Evans, S.E., and Newton, T.F. Predictors of Cardiovascular Response to Methamphetamine Administration in Methamphetamine-dependent Individuals. Am. J. Addict. Mar-Apr;17(2) pp. 103-110, 2008.

### Pharmacological Manipulations That Enhance Brain ACh Warrant Continued Investigation as Potential Treatments for Methamphetamine Addiction

Acetylcholine (ACh) has been implicated in the reinforcing and locomotor-activating effects produced by methamphetamine (Meth). Of interest, recent

data suggest that acetylcholinesterase (AChE) inhibitors attenuate Meth-seeking behaviour in rats. This study was conducted in order to determine the safety (adverse events, mood changes, cardiovascular effects) and preliminary efficacy (subjective effects) of the AChE inhibitor rivastigmine (Riv) when tested in combination with Meth. Twenty-three non-treatment-seeking Meth-dependent participants resided in an in-patient unit at UCLA for 2 wk, and completed this double-blind, between-subjects, placebo-controlled study. The data analyses compared across-study measures of adverse events and mood, and a post-randomization analysis of cardiovascular and subjective effects (on day 11). The data reveal that rivastigmine was not associated with increased adverse events or alterations in mood. As expected, acute Meth exposure (30 mg i.v.) increased heart rate and blood pressure, as well as several positive subjective effects, Addiction Research Center Inventory (ARCI) ratings, and reported monetary value ($p<0.05$). The data indicated that Riv, at 3 mg, significantly attenuated Meth-induced increases in diastolic blood pressure, and self-reports of 'anxious' and 'desire' ($p<0.05$). Taken together, the findings in the current report suggest that pharmacological manipulations that enhance brain ACh warrant continued investigation as potential treatments for Meth addiction. DeLaGarza, R., Shoptaw, S. and Newton, T.F. Evaluation of the Cardiovascular and Subjective Effects of Rivastigmine in Combination with Methamphetamine in Methamphet-amine-dependent Human Volunteers. Int. J. Neuropsychopharm. Feb 4, pp. 1-13, 2008.

### The Prevalence of Antisocial Behaviors Syndromes is Similar Within Either Cannabis- or Cocaine-dependent Populations of Patients

Antisocial personality disorder (ASPD) is highly associated with substance use disorders (SUD). In addition to the full ASPD syndrome, which requires both childhood conduct disorder and the adult features, other antisocial behavioral syndromes, including conduct disorder (CD) alone without the adult syndrome, and the adult antisocial behavioral syndrome without childhood CD (AABS) are also frequently diagnosed in patients with SUD. The aim of this study was to compare the rates of these various ASPD syndromes between cocaine- and cannabis-dependent individuals seeking treatment. A structured interview for ASPD excluding symptoms that occurred solely in the context of substance use was conducted in 241 outpatients (cocaine dependence, n = 111; cannabis dependence, n = 130). Overall, the proportion of substance-dependent individuals in this study with AABS was significantly larger than the proportion with ASPD (30.9% vs. 17.3%). A diagnosis of CD-only, where CD did not progress to ASPD, was uncommon. No significant differences in the prevalence of antisocial behavioral syndrome diagnoses were found between cocaine- and cannabis-dependent patients. Antisocial behavioral syndrome diagnosis did not influence treatment retention. Antisocial behavioral syndromes are commonly diagnosed in patients with SUD and future research should evaluate prognostic implications of AABS compared to ASPD in a variety of clinical treatment settings. Mariani, J.J., Horey, J., Bisaga, A., Aharonovich, E., Raby, W., Cheng, W.Y., Nunes, E., and Levin, F.R. Antisocial Behavioral Syndromes in Cocaine and Cannabis Dependence. Am. J. Drug Alcohol Abuse, 34(4), pp. 405-414, 2008.

### Cannabis Reinforcement and Dependence: Role of the Cannabinoid CB1 Receptor

Awareness of cannabis dependence as a clinically relevant issue has grown in recent years. Clinical and laboratory studies demonstrate that chronic marijuana smokers can experience withdrawal symptoms upon cessation of marijuana smoking and have difficulty abstaining from marijuana use. This paper reviews data implicating the cannabinoid CB1 receptor in regulating the behavioral effects of Delta(9)-tetrahydrocannobinol (THC), the primary

psychoactive component of cannabis, across a range of species. The behavioral effects discussed included those that directly contribute to the maintenance of chronic marijuana smoking, such as reward, subjective effects, and the positive and negative reinforcing effects of marijuana, THC and synthetic cannabinoids. The role of the CB1 receptor in the development of marijuana dependence and expression of withdrawal was also discussed. Lastly, treatment options that may alleviate withdrawal symptoms and promote marijuana abstinence will be considered. Cooper, Z.D. and Haney, M.. Cannabis Reinforcement and Dependence: Role of the Cannabinoid CB1 Receptor. Addict. Biol., 13, pp. 188-195, 2008.

### Under Certain Conditions, Psychostimulants May be a Pharmacologic Option in the Treatment of Patients With Co-morbid ADHD and SUD

This review addresses the relationship between attention-deficit/hyperactivity disorder (ADHD) and substance use disorders (SUDs), with an emphasis on factors that determine the potential for psychostimulant abuse. Strategies for identification and treatment of patients with ADHD who are at risk for, or have, co-morbid SUD are also addressed. The article was based on a qualitative review of current literature addressing co-morbid ADHD and SUD. Adolescent and adult patients with ADHD are at increased risk for SUD, as well as a number of other psychiatric disorders. Psychostimulant agents like methylphenidate (MPH) and mixed amphetamine salts (MAS) are effective first-line pharmacotherapies for ADHD; however, they are Schedule II controlled substances with a potential for abuse. Evidence suggests that treatment of ADHD during childhood with stimulant agents may reduce the risk of developing SUD later on. Factors associated with the highest risk of SUD in patients with ADHD include co-morbid antisocial personality disorder, bipolar disorder, an eating disorder, severe ADHD and/or antisocial behavior symptoms, and dropping out of school. Treatment initiation during adolescence or young adulthood also has been linked to increased risk of polydrug use and non-medical stimulant use, a pattern of behavior consistent with a risk of SUD development. Treatment plans for patients with ADHD and co-morbid SUD should include behavioral interventions, careful monitoring, and when appropriate, pharmacotherapy. When oral formulations of psychostimulants are used at recommended doses and frequencies, they are unlikely to yield effects consistent with abuse potential in patients with ADHD. Long-acting stimulant formulations and non-stimulants, like atomoxetine or bupropion, have a lower potential for abuse, and provide several safe and effective treatment options for the development of a comprehensive management plan for patients with co-morbid ADHD and SUD. Patients with ADHD are at increased risk for SUD. Under certain conditions, psychostimulants may be a pharmacologic option in the treatment of patients with co-morbid ADHD and SUD. However, clinicians should be mindful of the risks and benefits of this treatment approach in a high-risk population and should also bear in mind the labeling guidelines when working with this co-morbidity. Kollins, S.H. A Qualitative Review of Issues Arising in the Use of Psycho-stimulant Medications in Patients with ADHD and Co-morbid Substance Use Disorders. Curr. Med. Res. Opin. 24(5) pp. 1345-1357. E-pub 2008 Apr 1.

### Sex and Opioid Maintenance Dose Influence Response to Naloxone in Opioid-dependent Humans

Pooled self-report and physiological data from 32 male and 15 female methadone or 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 minutes 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 analysis,

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 subscales of the Adjective Rating Scale, and the LSD sub-scale of the Addiction Research Center Inventory at 20 minutes 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 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 long 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. Pharm. Biochem. Behav., 2008 (E-pub ahead of print).

### Buprenorphine for Opioid-dependent Patients in Office Practice

The profile of opioid dependence in the United States is changing. Abuse of prescription opioids is more common than that of illicit opioids: Recent data indicate that approximately 1.6 million persons abuse or are dependent on prescription opioids, whereas 323,000 abuse or are dependent on heroin. Despite this prevalence, nearly 80% of opioid-dependent persons remain untreated. One option for expanding treatment is the use of buprenorphine and the buprenorphine-naloxone combination. Buprenorphine is a partial opioid agonist that can be prescribed by trained physicians and dispensed at pharmacies. This article addresses the clinical presentation of a patient with opioid dependence and describes the relatively new practice of office-based treatment with buprenorphine-naloxone. The different components of treatment; the role of the physician who provides this treatment; and the logistics of treating this growing, multifaceted patient population are also examined. Sullivan, LE. and Fiellin, D.A. Narrative Review: Buprenorphine for Opioid-dependent Patients in Office Practice. Ann. Intern. Med., 148, pp. 662-670, 2008.

### Pharmacogenetic Treatments for Drug Addiction: Alcohol and Opiates

Psychiatric pharmacogenetics involves the use of genetic tests that can predict the effectiveness of treatments for individual patients with mental illness such as drug dependence. This review article covers the developments in the pharmacotherapy of alcohol and opiates, addictive drugs for which the majority of FDA-approved pharmacotherapies exists. The results of an extensive literature review conclude that alcohol's physiological and subjective effects are associated with enhanced ss-endorphin release. Naltrexone increases baseline ss-endorphin release blocking further release by alcohol. Naltrexone's action as an alcohol pharmacotherapy is facilitated by a putative functional single nucleotide polymorphism (SNP) in the opioid mu receptor gene (A118G) which alters receptor function. Patients with this SNP have significantly lower relapse rates to alcoholism when treated with naltrexone. Caucasians with various forms of the CYP2D6 enzyme results in a 'poor metabolizer' phenotype and appear to be protected from developing opioid dependence. Others with a 'ultra-rapid metabolizer' phenotype do poorly on methadone maintenance and have frequent withdrawal symptoms. These patients can do well using buprenorphine because it is not significantly metabolized by CYP2D6. The authors conclude that pharmacogenetics has a great potential for improving treatment outcome as gene variants are identified that affect pharmacodynamic and pharmacokinetic factors. These mutations guide pharmacotherapeutic agent choice for optimum treatment of alcohol and opiate abuse and subsequent relapse. Haile, C., Kosten, T.A., and Kosten, T.R. Pharmacogenetic Treatments for Drug Addiction: Alcohol and Opiates. Am. J.

Drug Alcohol Abuse, 34, pp. 355-381, 2008.

### Impact of a Brief Training on Medical Resident Screening for Alcohol Misuse and Illicit Drug Use

Educational initiatives are needed to improve primary care substance use screening. This study assesses the impact on 24 medical residents of a 2.5-day curriculum combining experiential and manual-based training on screening for alcohol misuse and illicit drug use. A retrospective chart review of new primary care outpatients demonstrated that nearly all were asked about current alcohol use before and after curriculum participation. Adherence to national screening guidelines on quantification of alcohol consumption modestly improved ($p < .05$), as did inquiry about current illicit drug use ($p < .05$). Continued efforts are needed to enhance educational initiatives for primary care physicians. Gunderson, E.W., Levin, F.R., and Owen, P. Impact of a Brief Training on Medical Resident Screening for Alcohol Misuse and Illicit Drug Use. Am. J. Addict., 17, pp. 149-154, 2008.

### A Placebo-controlled Randomized Clinical Trial of Naltrexone in the Context of Different Levels of Psychosocial Intervention

Naltrexone is approved for the treatment of alcohol dependence when used in conjunction with a psychosocial intervention. This study was undertaken to examine the impact of 3 types of psychosocial treatment combined with either naltrexone or placebo treatment on alcohol dependency over 24 weeks of treatment: (1) Cognitive-Behavioral Therapy (CBT) + medication clinic, (2) BRENDA (an intervention promoting pharmacotherapy) + medication clinic, and (3) a medication clinic model with limited therapeutic content. Two hundred and forty alcohol-dependent subjects were enrolled in a 24-week double-blind placebo-controlled study of naltrexone (100 mg/d). Subjects were also randomly assigned to 1 of 3 psychosocial interventions. All patients were assessed for alcohol use, medication adherence, and adverse events at regularly scheduled research visits. There was a modest main treatment effect for the psychosocial condition favoring those subjects randomized to CBT. Intent-to-treat analyses suggested that there was no overall efficacy of naltrexone and no medication by psychosocial intervention interaction. There was a relatively low level of medication adherence (50% adhered) across conditions, and this was associated with poor outcome. Results from this 24-week treatment study demonstrate the importance of the psychosocial component in the treatment of alcohol dependence. Moreover, results demonstrate a substantial association between medication adherence and treatment outcomes. The findings suggest that further research is needed to determine the appropriate use of pharmacotherapy in maximizing treatment response. Oslin, D.W., Lynch, K.G., Pettinati, H.M., Kampman, K.M., Gariti, P., Gelfand, L., Ten Have, T., Wortman, S., Dundon, W., Dackis, C., Volpicelli, J.R., and O'Brien, C.P. A Placebo-controlled Randomized Clinical Trial of Naltrexone in the Context of Different Levels of Psychosocial Intervention. Alcohol Clin. Exp. Res., 32, pp. 1299-1308, 2008.

### Stability of the Nicotine Metabolite Ratio in Ad Libitum and Reducing Smokers

The ratio of two nicotine metabolites, cotinine and trans-3'-hydroxycotinine (3-HC), has been validated as a method of phenotyping the activity of the liver enzyme cytochrome P450 (CYP) 2A6 and, thus, the rate of nicotine metabolism. The objective of this study was to evaluate the correlates and stability of the 3-HC to cotinine ratio in ad libitum and reducing smokers, using nicotine replacement therapy (NRT), over a period of months. Smokers ($n = 123$, 94% Caucasian) participated in a smoking reduction study, where one-

third of the sample smoked ad libitum for 8 weeks (Waitlist phase), before joining the rest of the participants for 12 weeks of cigarette reduction (Reduction phase) using NRT. Urinary nicotine, cotinine, and 3-HC were measured at each visit. The baseline 3-HC to cotinine ratio was significantly but weakly correlated with cigarettes per day (r = 0.19), BMI (r = -0.27), and waking at night to smoke (r = 0.23). As assessed by repeated measure ANOVA, the 3-HC to cotinine ratio was stable in the Waitlist phase [coefficient of variation for 3 to 4 measurements, 38% (range, 5-110%)], whereas minor variation was noted in the Reduction phase [coefficient of variation for 3-5 measurements, 35% (range, 10-107%)]. In nonreducing ad libitum smokers, the 3-HC to cotinine ratio was generally stable, whereas during smoking reduction using NRT, some small variation was detected. Although the current findings are suggestive of the stability of the 3-HC to cotinine ratio in a predominantly Caucasian sample smoking freely or reducing smoking with NRT, additional research is needed in more diverse populations. Mooney, M.E., Li, Z.Z., Murphy, S.E., Pentel, P.R., Le, C., and Hatsukami, D.K. Stability of the Nicotine Metabolite Ratio in ad libitum and Reducing Smokers. Cancer Epidemiol. Biomarkers Prev., 17, pp. 1396-1400, 2008.

### Exposure to Nicotine and a Tobacco-specific Carcinogen Increase With Duration of Use of Smokeless Tobacco

Smokeless tobacco is an efficient delivery vehicle for nicotine and can contain significant amounts of carcinogens. However, few studies have examined factors that might moderate levels of nicotine or carcinogen exposure. The purpose of this study was to determine the effect of duration of smokeless tobacco use on the uptake of nicotine and a tobacco-specific carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Questionnaires on use of smokeless tobacco were administered, and urine samples from 212 smokeless tobacco users were analysed for biomarkers of uptake of nicotine and NNK. The biomarkers were cotinine and total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL). Male smokeless tobacco users were recruited for studies designed to investigate methods of reducing smokeless tobacco use. The questionnaire and biomarker data were obtained at baseline, prior to reduction. Levels of cotinine ($p<0.001$) and total NNAL ($p<0.001$) were significantly correlated with duration (in years) of use of smokeless tobacco products. Median cotinine and total NNAL were 2.4 and 2.1 times higher, respectively, in the > or = 21 years of use than in the 0-5 years of use category. Smokeless tobacco users adjust their intensity of use with experience in order to increase their nicotine dose, resulting in a corresponding increase in exposure to NNK, a powerful carcinogen. These results indicate the importance of educating smokeless tobacco users about the effects of prolonged use of these products. Hecht, S.S., Carmella, S.G., Edmonds, A., Murphy, S.E., Stepanov, I., Luo, X., and Hatsukami, D.K. Exposure to Nicotine and a Tobacco-specific Carcinogen Increase with Duration of Use of Smokeless Tobacco. Tob. Control, 17, pp. 128-131, 2008.

### Combined Active and Passive Immunization Enhances the Efficacy of Immunotherapy Against Nicotine in Rats

Vaccination against nicotine reduces the behavioral effects of nicotine in rats, and it is under clinical evaluation as a treatment for tobacco addiction. Efficacy is limited by the need for high serum nicotine-specific antibody (NicAb) levels, and currently available nicotine vaccines do not uniformly generate the required NicAb levels. Passive immunization with a nicotine-specific monoclonal antibody (Nic311) has also shown efficacy in rats. The principal aim of this study was to determine whether the combined use of vaccination and passive immunization would produce greater effects than vaccination alone on nicotine pharmacokinetics and locomotor sensitization (LMS) to nicotine. Rats were treated with vaccination alone, Nic311 alone, both, or neither, and then they

were administered 10 daily injections of 0.3 mg/kg nicotine s.c. Treatment with Nic311 or vaccination alone increased the binding of nicotine in serum, reduced the unbound serum nicotine concentration and nicotine distribution to brain, and attenuated the development of LMS. Combined use of vaccination and passive immunization produced higher total serum NicAb levels, greater changes in nicotine pharmacokinetics, and a greater attenuation of LMS than either treatment alone. The total serum NicAb concentration was significantly correlated with brain nicotine levels and locomotor activity. These data indicate that providing higher serum NicAb concentrations improves the efficacy of immunotherapy against nicotine and that supplementing vaccination with passive immunization is a potential strategy to accomplish this. Roiko, S.A., Harris, A.C., Keyler, D.E., LeSage, M.G., Zhang, Y., and Pentel, P.R.. Combined Active and Passive Immunization Enhances the Efficacy of Immunotherapy Against Nicotine in Rats. J. Pharmacol. Exp. Ther., 325, pp. 985-993, 2008.

### Prelude to Passion: Limbic Activation By "Unseen" Drug and Sexual Cues

The human brain responds to recognizable signals for sex and for rewarding drugs of abuse by activation of limbic reward circuitry. Does the brain respond in similar way to such reward signals even when they are "unseen", i.e., presented in a way that prevents their conscious recognition? Can the brain response to "unseen" reward cues predict the future affective response to recognizable versions of such cues, revealing a link between affective/motivational processes inside and outside awareness? The investigators exploited the fast temporal resolution of event-related functional magnetic resonance imaging (fMRI) to test the brain response to "unseen" (backward-masked) cocaine, sexual, aversive and neutral cues of 33 milliseconds duration in male cocaine patients (n = 22). Two days after scanning, the affective valence for visible versions of each cue type was determined using an affective bias (priming) task. They demonstrated, for the first time, limbic brain activation by "unseen" drug and sexual cues of only 33 msec duration. Importantly, increased activity in a large interconnected ventral pallidum/amygdala cluster to the "unseen" cocaine cues strongly predicted future positive affect to visible versions of the same cues in subsequent off-magnet testing, pointing both to the functional significance of the rapid brain response, and to shared brain substrates for appetitive motivation within and outside awareness. These findings represent the first evidence that brain reward circuitry responds to drug and sexual cues presented outside awareness. The results underscore the sensitivity of the brain to "unseen" reward signals and may represent the brain's primordial signature for desire. The limbic brain response to reward cues outside awareness may represent a potential vulnerability in disorders (e.g., the addictions) for whom poorly-controlled appetitive motivation is a central feature. Childress, A.R., Ehrman, R.N., Wang, Z., Li, Y., Sciortino, N., Hakun, J., Jens, W., Suh, J., Listerud, J., Marquez, K., Franklin, T., Langleben, D., Detre, J., and O'Brien, C.P. Prelude to Passion: Limbic Activation by "Unseen" Drug and Sexual Cues. PLoS.ONE., 3, e1506, 2008.

### Changes in Mood, Cognitive Performance and Appetite in the Late Luteal and Follicular Phases of the Menstrual Cycle in Women With and Without PMDD (Premenstrual Dysphoric Disorder)

Although it's been reported that women with premenstrual dysphoric disorder (PMDD) have increased negative mood, appetite (food cravings and food intake), alcohol intake and cognitive deficits premenstrually, few studies have examined these changes concurrently within the same group of women or compared to women without PMDD. Thus, to date, there is not a clear understanding of the full range of PMDD symptoms. The present study concurrently assessed mood and performance tasks in 29 normally cycling

women (14 women who met DSM-IV criteria for PMDD and 15 women without PMDD). Women had a total of ten sessions: two practice sessions, 4 sessions during the follicular phase and 4 sessions during the late luteal phase of the menstrual cycle. Each session, participants completed mood and food-related questionnaires, a motor coordination task, performed various cognitive tasks and ate lunch. There was a significant increase in dysphoric mood during the luteal phase in women with PMDD compared to their follicular phase and compared to Control women. Further, during the luteal phase, women with PMDD showed impaired performance on the Immediate and Delayed Word Recall Task, the Immeate and Delayed Digit Recall Task and the Digit Symbol Substitution Test compared to Control women. Women with PMDD, but not Control women, also showed increased desire for food items high in fat during the luteal phase compared to the follicular phase and correspondingly, women with PMDD consumed more calories during the luteal phase (mostly derived from fat) compared to the follicular phase. In summary, women with PMDD experience dysphoric mood, a greater desire and actual intake of certain foods and show impaired cognitive performance during the luteal phase. An altered serotonergic system in women with PMDD may be the underlying mechanism for the observed symptoms; correspondingly, treatment with specific serotonin reuptake inhibitors (SSRIs) remains the preferred treatment at this time. Reed, S.C., Levin, F.R., and Evans, S.M. Changes in Mood, Cognitive Performance and Appetite in the Late Luteal and Follicular Phases of the Menstrual Cycle in Women With and Without PMDD (Premenstrual Dysphoric Disorder). Horm. Behav., 54, pp. 185-193, 2008.

### A Cocaine Hydrolase Engineered from Human Butyrylcholinesterase Selectively Blocks Cocaine Toxicity and Reinstatement of Drug Seeking in Rats

In this report, the authors describe the effectiveness of engineered cocaine hydrolase from human butyrylcholinesterase in rats and its potential clinical application in humans. Successive rational mutations of human butyrylcholinesterase (BChE) followed by fusion to human serum albumin have yielded an efficient hydrolase that offers realistic options for therapy of cocaine overdose and abuse. This albumin-BChE prevented seizures in rats given a normally lethal cocaine injection (100 mg/kg, i.p.), lowered brain cocaine levels even when administered after the drug, and provided rescue after convulsions commenced. Moreover, it selectively blocked cocaine-induced reinstatement of drug seeking in rats that had previously self-administered cocaine. The enzyme treatment was well tolerated and may be worth exploring for clinical application in humans. Brimijoin, S., Gao, Y., Anker, J.J., Gliddon, L.A., LaFleur, D., Shah, R., Zhao, Q., Singh, M. and Carrol, M.E. Neuropsychopharmacology, advance online publication, 16 Jan. 2008.

### Rational Design of an Enzyme Mutant for Anti-cocaine Therapeutics

This article described the computational design of high-activity mutants of human butyrylcholinesterase (BChE) against (-)-cocaine. The computational design of BChE mutants have been based on not only the structure of the enzyme, but also the detailed catalytic mechanisms for BChE-catalyzed hydrolysis of (-)-cocaine and (+)-cocaine. By using the computational insights into the catalytic mechanisms, a unique design strategy based on the simulation of the rate-determining transition state has led to the exciting discovery of BChE mutants with a considerably improved catalytic efficiency against (-)-cocaine. One of the discovered BChE mutants has an approximately 456-fold improved catalytic efficiency against (-)-cocaine. The encouraging outcome demonstrates that the computational design approach based on the transition-state simulation is promising for rational enzyme redesign and drug discovery. Zheng, F., and Zhan, C.G. J. Comput. Aided Mol. Des. Nov 8, 2007.

### A Neutral CB1 Receptor Antagonist Reduces Weight Gain in Rat

This study examined the effect of a neutral CB1 antagonist, AM4113, on food intake, weight gain, and emesis. The Ki value of AM4113 was 100-fold more selective for CB1 over CB2 receptors. AM4113 significantly reduced food intake and weight gain in rat. Compared with AM251, higher doses of AM4113 were needed to produce similar effects on food intake and body weight. Unlike AM251, a highly anorectic dose of AM4113 did not significantly potentiate emesis. The results show that a centrally active neutral CB1 receptor antagonist shares the appetite suppressant and weight loss effects of inverse agonists. They could be developed into a new class of antiobesity agents. Chambers, A.P., Vemuri, V.K., Peng, Y., Wood, J.T., Olszewska, T., Pittman, Q.J., Makriyannis, A., and Sharkey, K.A. Am. J. Physiol. Regul. Integr. Comp. Physiol. 293(6), pp. R2185-R2193, 2007.

### Antidepressant-like Effects of the Novel Kappa Opioid Antagonist MCL-144B in the Forced-swim Test

Previous studies have demonstrated that kappa opioid receptor (KOR) antagonists reduce stress- and depression-like behaviors. The authors hypothesized that administration of a novel opioid mixed agonist/antagonist capable of antagonist activity at the KOR would attenuate forced-swim stress (FSS)-induced immobility, an animal model of depression-like behavior. Mice were exposed to repeated FSS after pretreatment with a graded dose of a novel bivalent morphinan compound, MCL-144B. In support of the hypothesis, pretreatment with MCL-144B dose-dependently attenuated stress-induced antinociception and immobility in the forced-swim test. Reindl, J.D., Rowan, K., Carey, A.N., Peng, X., Neumeyer, J.L., and McLaughlin, J.P. Pharmacology, 81(3), pp. 229-235, 2008.

### Novel Sigma Receptor Agonists Produce Antidepressant-like Effects in Mice

In this study, two novel sigma receptor agonists (UMB23, UMB82) were evaluated for antidepressant-like activity in mice. First, radioligand binding studies confirmed that the novel compounds had preferential affinity for sigma receptors. Second, the forced swim test, a well established animal model for screening potential antidepressant drugs, showed that both compounds dose-dependently reduced immobility time. The sigma receptor antagonist BD1047 attenuated the antidepressant-like effects of UMB23 and UMB82. Third, locomotor activity suggested that the effects of UMB23 and UMB82 in the forced swim test were not due to non-specific motor activating effects. Together, the data provide further evidence that sigma receptor agonists represent a possible new class of antidepressant medication. Wang, J., Mack, A.L., Coop, A., and Matsumoto, R.R. Eur. Neuropsychopharmacol. 17(11), pp. 708-716, 2007.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2008

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

### HIV/AIDS

### Early Retinal Vascular Abnormalities in African-American Cocaine Users

The purpose of this study was to investigate whether cocaine use is associated with early retinal vascular abnormalities. The design used was a population-based cross-sectional study. The study setting comprised inner-city neighborhoods in Baltimore, Maryland. Sixty-eight participants were recruited from an ongoing observational study, investigating cardiovascular complications of human immunodeficiency virus (HIV) infection and cocaine use in African Americans aged between 25 and 54 years. Those with hypertension and known cardiovascular/cerebrovascular diseases were excluded. Ophthalmoscopic examinations and fundus photography of the retinas of these subjects were performed after papillary dilation. The largest angle of arterial bifurcation (LAAB), central retinal artery equivalent (CRAE), and central retinal vein equivalent (CRVE) were measured by single-masked fundus image examiners. Main outcome measures studied were: LAAB, CRAE, and CRVE. Among the 68 study subjects, 52 (76.5%) were chronic cocaine users and 16 (23.5%) were non-cocaine users. Univariate and multivariate analyses indicated that the LAAB was associated with age and duration of cocaine use of more than 10 years. The LAAB was also inversely associated with very low-density lipoproteins levels. Multivariate analysis indicated a positive association between CRVE and cocaine use. CRAE was also associated with intravenous injection. The authors confirmed that CRAE was inversely associated with age. HIV infection was not found to be associated with any retinal vascular parameters. The authors concluded that cocaine use is associated with increased retinal arterial branching angle and venular caliber. The retinal vascular changes provided the first evidence that cocaine use has an effect on the retinal vascular system. Leung, I.Y., Lai, S., Ren, S., Kempen, J., Klein, R., Tso, M.O., and Lai, H.C. Am. J. Ophthalmol. Jul 26, 2008.

### C-reactive Protein: A Poor Marker of Cardiovascular Disease Risk in HIV+ Populations with a High Prevalence of Elevated Serum Transaminases

Blood lipids and high-sensitivity C-reactive protein (hsCRP) are used to assess cardiovascular disease (CVD) risk. The authors evaluated in a cross-sectional design the relationship of hsCRP to markers of liver function (aspartate and alanine transaminases [AST and ALT, respectively]), CVD risk factors and HIV-disease progression markers in 226 HIV-1 sero-positive drug users. hsCRP showed a significant inverse relationship with ALT and high-density lipoprotein,

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independent of age, gender, viral load, CD4 cell-count and antiretroviral (ARV) use, and was not significantly associated with HIV-disease progression markers. Serum markers of liver damage, AST and ALT, were associated with lower hsCRP, total cholesterol, low-density lipoproteins and triglycerides. Elevated liver enzymes (> or =40 IU/L) were predictive of hsCRP levels that are considered a low risk for CVD. In conclusion, hsCRP may not be a reliable marker of CVD risk in populations with HIV at-risk for elevated liver enzymes due to high hepatitis B virus/hepatitis C virus prevalence and ARV use. Baum, M.K., Rafie, C., Sales, S., Lai, S., Duan, R., Jayaweera, D.T., Page, J.B., Campa, A. Int. J. STD AIDS. 19(6), pp. 410-413, 2008.

### A Pilot Survey of Attitudes and Knowledge about Opioid Substitution Therapy for HIV-Infected Prisoners

A majority of inmates in the state of Connecticut Department of Corrections use opioids or are opioid dependent before incarceration. None of the state's prisons offer opioid substitution therapy other than for detoxification or maintenance therapy for women during pregnancy. On release to the community, most prisoners relapse to drug use and this has been associated with higher recidivism rates, and less adherence to antiretroviral medications for HIV-infected persons. Nationally and internationally, methadone (METH) and buprenorphine (BUP) have been found to decrease relapse to drug use, decrease recidivism rates, improve adherence to antiretroviral medications, decrease HIV-risk taking behaviors, and improve mortality. However, the general knowledge about opioid substitution therapy among correctional facility staff has been reported as substandard. This pilot study compiled results of answers to anonymous surveys from 27 individuals who work directly with inmates in a patient-care capacity for the Connecticut Department of Corrections (CT DOC) and CT DOC case-management referral program (Project TLC) in the year 2006. The surveys included questions regarding current attitudes and knowledge about opioid substitution therapy for prisoners. A minority of respondents refer released prisoners with a history of opioid dependency to METH or BUP treatment. The majority of correctional workers and case-management referral workers did not have knowledge about BUP or METH's ability to improve health and decrease HIV risk taking behaviors. This study found that more education of individuals treating and caring for HIV-infected opioid dependent prisoners is needed. Springer, S.A., and Bruce, R.D. J. Opioid Manag. 4(2), pp. 81-86, 2008.

### Drug Use and Other Risk Factors Related to Lower Body Mass Index Among HIV-Infected Individuals

Malnutrition is associated with morbidity and mortality in HIV-infected individuals. Little research has been conducted to identify the roles that clinical, illicit drug use and socioeconomic characteristics play in the nutritional status of HIV-infected patients. This cross-sectional analysis included 562 HIV-infected participants enrolled in the Nutrition for Healthy Living study conducted in Boston, MA and Providence, RI. The relationship between body mass index (BMI) and several covariates (type of drug use, demographic, and clinical characteristics) were examined using linear regression. Overall, drug users had a lower BMI than non-drug users. The BMI of cocaine users was 1.4 kg/m(2) less than that of patients who did not use any drugs, after adjusting for other covariates (p=0.02). The BMI of participants who were over the age of 55 years was 2.0 kg/m(2) less than that of patients under the age of 35, and BMI increased by 0.3 kg/m(2) with each 100 cells/mm(3) increase in CD4 count. HAART use, adherence to HAART, energy intake, AIDS status, hepatitis B and hepatitis C co-infections, cigarette smoking and depression were not associated with BMI in the final model. In conclusion, BMI was lower in drug users than non-drug users, and was lowest in cocaine users. BMI was also

directly associated with CD4 count and inversely related to age more than 55 years old. HIV-infected cocaine users may be at higher risk of developing malnutrition, suggesting the need for anticipatory nutritional support. Quach, L.A., Wanke, C.A., Schmid, C.H., Gorbach, S.L., Mwamburi, D.M., Mayer, K.H., Spiegelman, D., and Tang, A.M. Drug Alcohol Depend. 95(1-2), pp. 30-36, 2008.

### Relationship between T cell Activation and CD4+ T cell Count in HIV-Seropositive Individuals with Undetectable Plasma HIV RNA Levels in the Absence of Therapy

Untreated human immunodeficiency virus (HIV)-infected patients maintaining undetectable plasma HIV RNA levels (elite controllers) have high HIV-specific immune responses; however it is unclear whether they experience abnormal levels of T cell activation, potentially contributing to immunodeficiency. The authors found that controllers had higher CD4(+) and CD8(+) cell activation levels ($P < .001$ for both) than HIV-negative subjects and higher CD8(+) cell activation levels than the antiretroviral therapy suppressed ($P = .048$). In controllers, higher CD4(+) and CD8(+) T cell activation was associated with lower CD4(+) cell counts ($P = .009$ and $P = .047$). These findings suggest that HIV controllers have abnormally high T cell activation levels, which may contribute to progressive CD4(+) T cell loss even without measurable viremia. Hunt, P.W., Brenchley, J., Sinclair, E., McCune, J.M., Roland, M., Page-Shafer, K., Hsue, P., Emu, B., Krone, M., Lampiris, H., Douek, D., Martin, J.N., and Deeks, S.G. J. Infect. Dis.197(1), pp. 126-133, 2008.

### Linkage to Treatment and Supportive Services among HIV-Positive Ex-Offenders in Project Bridge

Access to supportive services is important for HIV-positive inmates upon release to improve continuity of medical care. Through Project Bridge, a federally funded demonstration project,18 months of intensive case management by teams of a professional social worker and an outreach worker between May 2003 and December 2005 provided 12 weekly followed by at least monthly client contacts thereafter. Most clients (95%) received medical care throughout their enrollment. Of all clients, 45.8% secured housing, 71% were linked to mental health care, and 51% were linked to addiction services. Despite high levels of addiction (97%) and mental health disorders (34% on medication), ex-offenders were retained in health care for a year after being released from incarceration. Zaller, N.D., Holmes, L., Dyl, A.C., Mitty, J.A., Beckwith, C.G., Flanigan, T.P., and Rich J.D. J. Health Care Poor Underserved 19(2), pp. 522-531, 2008.

### Status Epilepticus Resulting from Severe Efavirenz Toxicity in an HIV-infected Patient

The case of an HIV-infected patient with cirrhosis in whom severe neuropsychiatric signs and symptoms developed with significantly elevated plasma efavirenz level. Although mild neuropsychiatric symptoms are a well-known adverse effect of this medication, this was a first reported status epilepticus with routine efavirenz dosing. The case raised several significant questions regarding adverse effects and dosing of the medication, including which patient characteristics predispose to efavirenz toxicity, the relevance of the CYP2B6 mutation, and indications for therapeutic drug monitoring. Nijhawan, A.E., Zachary, K.C., Kwara, A., and Venna, N. AIDS Read. 18(7), pp. 386-388, C3, 2008.

### HIV/HCV

### Human Immunodeficiency Virus-Related Microbial Translocation and Progression of Hepatitis C

Human immunodeficiency virus (HIV)-1 infection has been associated with enhanced microbial translocation, and microbial translocation is a mechanism through which alcohol and some enteric conditions cause liver disease. The authors hypothesized that HIV promotes liver disease by enhancing microbial translocation. They studied human cohorts in which hepatitis C virus (HCV) and HIV outcomes were carefully characterized. Results indicated that HIV-related CD4(+) lymphocyte depletion was strongly associated with microbial translocation as indicated by elevated levels of circulating lipopolysaccharide (LPS), LPS-binding protein, soluble CD14, and fucose-binding lectin (AAL) reactive to immunoglobulin G specific for the alpha-galactose epitope and suppressed levels of endotoxin core antibodies (EndoCAb IgM) in HIV-infected subjects compared with the same persons before they had HIV infection and compared with HIV-uninfected subjects. The same measures of microbial translocation were strongly associated with HCV-related liver disease progression (cirrhosis), e.g., LPS, odds ratio, 19.0 ($P = .002$); AAL, odds ratio, 27.8 ($P < .0001$); in addition, levels of LPS were elevated prior to recognition of cirrhosis. The authors conclude that microbial translocation may be a fundamental mechanism through which HIV accelerates progression of chronic liver disease. Balagopal, A., Philp, F.H., Astemborski, J., Block, T.M., Mehta, A., Long, R., Kirk, G.D., Mehta, S.H., Cox, A.L., Thomas, D.L., and Ray, S.C. Gastroenterology, 135(1), pp. 226-233, 2008.

### The Challenge of Hepatitis C in the HIV-Infected Person

Hepatitis C virus (HCV) coinfection occurs in an estimated one quarter of HIV-infected persons in Europe, Australia, and the United States. As use of highly active antiretroviral drugs has markedly reduced opportunistic infections, HCV-related liver disease has emerged as a leading cause of death. HIV infection adversely affects both the natural history and the treatment of hepatitis C. Because there are no experimental models of coinfection and because the pathogenesis of each infection is incompletely understood, how HIV infection alters hepatitis C is not clear. This review considers the epidemiology, natural history, treatment, and pathogenesis of hepatitis C in HIV-infected persons. Thomas, D.L. Ann. Rev. Med. 59, pp. 473-485, 2008.

### Comprehensive Genetic and Epigenetic Analysis of Occult Hepatitis B from Liver Tissue Samples

Occult infection with hepatitis B virus (HBV) is a type of chronic HBV infection that is characterized by the absence of a detectable hepatitis B surface antigen in the blood and by very low levels of HBV DNA in the blood and liver. The mechanisms leading to occult HBV infection remain poorly understood but include possible genetic mutations and deletions. Recently, it has been shown that HBV has CpG islands that are methylated, raising the possibility that epigenetic changes may also be important. The full-length genomes of isolates from 5 cases of occult HBV infection were cloned and analyzed for mutations and deletions. Additional studies were performed to examine for APOBEC3G (1 member of a family of deaminating proteins that are part of the innate immune system's defense against viral infection) hyperediting and methylation of viral DNA. Numerous mutations and deletions were found in the genomes of occult HBV. However, similar types and locations of polymorphisms were also noted in the genome sequences of HBV isolated from control liver tissue samples obtained from individuals with nonoccult HBV infection. Evidence of APOBEC3G hyperediting was found in 1 case of occult HBV infection, but hyperedited sequences made up only a small proportion of the viral sequences. Methylation of HBV CpG islands 1 and 2 was evident in both occult and nonoccult HBV

sequences, with island 2 more densely methylated in occult HBV sequences and island 1 more densely methylated in nonoccult HBV sequences. The authors conclude that deletions and mutations are common in occult HBV but are also found in control nonoccult HBV, and no unique genetic signature for occult HBV was found. Methylation patterns differ between cases of occult and nonoccult HBV infection, suggesting that epigenetic changes may be relevant to occult HBV. Together, these findings suggest that multiple mechanisms can contribute to occult HBV infection. Vivekanandan, P., Kannangai, R., Ray, S.C., Thomas, D.L., and Torbenson, M. Clin. Infect. Dis. 46(8), pp. 1227-1236, 2008.

### HCV

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

The authors 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. 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. The authors concluded that this behavioral intervention reduced unsafe injection practices that may propagate HCV among injection drug users. Latka, M.H., Hagan, H., Kapadia, F., Golub, E.T., Bonner, S., Campbell, J.V., Coady, M.H., Garfein, R.S., Pu, M., Thomas, D.L., Thiel, T.K., and Strathdee, S.A. Am. J. Public Health. 98(5), pp. 853-861, 2008.

### Limited Uptake of Hepatitis C Treatment among Injection Drug Users

Authors characterized hepatitis C virus (HCV) treatment knowledge, experience and barriers in a cohort of community-based injection drug users (IDUs) in Baltimore, MD. In 2005, a questionnaire on HCV treatment knowledge, experience and barriers was administered to HCV-infected IDUs. Self-reported treatment was confirmed from medical records. Of 597 participants, 71% were male, 95% African-American, 31% HIV co-infected and 94% were infected with HCV genotype 1; 70% were aware that treatment was available, but only 22% understood that HCV could be cured. Of 418 who had heard of treatment, 86 (21%) reported an evaluation by a provider that included a discussion of treatment of whom 30 refused treatment, 20 deferred and 36 reported initiating treatment (6% overall). The most common reasons for refusal were related to treatment-related perceptions and a low perceived need of treatment. Compared to those who had discussed treatment with their provider, those who had not were more likely to be injecting drugs, less likely to have health insurance, and less knowledgeable about treatment. Low HCV treatment effectiveness was observed in this IDU population. Comprehensive integrated care strategies that incorporate education, case-management and peer support are needed to improve care and treatment of HCV-infected IDUs.

Mehta, S.H., Genberg, B.L., Astemborski, J., Kavasery, R., Kirk, G.D., Vlahov, D., Strathdee, S.A., and Thomas, D.L. J Community Health. 33(3), pp. 126-133, 2008.

### Progression of Fibrosis during Chronic Hepatitis C is Associated with Rapid Virus Evolution

Hepatic fibrosis is the primary mediator of disease due to chronic infection with hepatitis C virus (HCV). HCV exists as a quasispecies in each infected individual, and longitudinal viral sequence changes may reveal viral dynamics and the selection pressures applied by the host immune system. Thus, the authors hypothesized that patterns of sequence change might reveal the immunopathogenesis of fibrosis progression. They tested this hypothesis by studying individuals enrolled in a prospective study of chronic HCV-related hepatic fibrosis with little or no fibrosis at first biopsy (stage 0 or 1) and a second planned liver biopsy sample obtained 4 years later. Serum was obtained from five individuals with fast progression (FP; defined as a >2-stage change between visits) and 10 carefully matched individuals with slow progression (SP; defined as a <2-stage change between visits). The authors sequenced multiple cloned hemigenomic cDNAs from each person spanning six genes (core through NS3). Phylogenetic analysis revealed temporal shifts in phylogenetic clustering over time, suggesting frequent quasispecies replacement rather than simple diversification. In addition, mixed infections were detected in three subjects, with coexistence in two subjects (one FP, one SP) of subtypes 1a and 1b throughout the 4-year biopsy interval. Subjects with FP had a higher rate of evolution than subjects with SP, with a preponderance of synonymous changes, suggesting purifying selection, except in hypervariable region 1, where positive selection pressure is frequently detected. Thus, in a small but carefully matched cohort the authors found evidence for rapid neutral evolution of HCV in persons with rapid progression of hepatic fibrosis, suggesting higher turnover of infected cells. Wang, X.H., Netski, D.M., Astemborski, J., Mehta, S.H., Torbenson, M.S., Thomas, D.L., and Ray, S.C. J. Virol. 81(12), pp. 6513-6522, 2007.

### Immune Responses during Acute and Chronic Infection with Hepatitis C Virus

Hepatitis C virus (HCV) induces persistent infection and causes chronic liver disease in most infected patients. Vigorous HCV-specific CD4+ and CD8+ T cell responses against HCV multiple epitopes are necessary for spontaneous viral clearance during the acute phase, but the virus appears to have multiple strategies to evade these defenses. There are relatively few studies on the role of immune responses during the chronic phase of infection. CD4+ T cell responses appear to protect against liver injury and may be important to clearance during interferon and ribavirin based therapy. Classic cytotoxic T cells (CTL) may primarily damage the liver in chronic HCV, but there may be subpopulations of T cells that protect against liver inflammation. Resolution of these outstanding questions is important to the development of a prophylactic vaccine as well as improving therapeutic options for those with chronic infection. Ishii, S., and Koziel, M.J. Clin. Immunol. 128(2), pp. 133-147, 2008.

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

T-cell responses to hepatitis C virus (HCV) antigens reported in high-risk HCV seronegative persons suggest 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. The authors therefore 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. Findings suggested that HCV-specific T-cell responses are common among high-risk, seronegative IDUs. Zeremski, M., Shu, M.A., Brown, Q., Wu, Y., Des Jarlais, D.C., Busch, M.P., Talal, A.H., and Edlin B.R. J. Viral Hepat. 2008 Jul 17.

### Hepatitis C Virus (HCV)-Specific Immune Responses of Long-Term Injection Drug Users Frequently Exposed to HCV

Successful clearance of hepatitis C virus (HCV) among IDUs is associated with a reduced risk of developing chronic reinfection, despite continuing exposure to the virus. Immunological correlates for this apparent protection were studied via 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. Findings suggest 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). They were also noted in 16 (62%) of 26 nonviremic EIA-negative IDUs. In contrast, 19 (90%) of 21 viremic IDUs displayed neutralizing antibodies, compared with 9 (56%) of 16 nonviremic EIA-positive IDUs. Overall, the reduced risk of HCV persistence in IDUs previously recovered from HCV infection correlated with T cell responses, and prolonged antigenic stimulation appeared to be required to maintain humoral responses. Mizukoshi, E., Eisenbach, C., Edlin, B.R., Newton, K.P., Raghuraman, S., Weiler-Normann, C., Tobler, 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.

### Testing Strategy to Identify Cases of Acute Hepatitis C Virus (HCV) Infection and to Project HCV Incidence Rates

Surveillance for hepatitis C virus (HCV) is limited by the challenge of differentiating between acute and chronic infections. This study identified a cross-sectional testing strategy to determine individuals with acute HCV infection and estimate HCV incidence. Anti-HCV-negative persons from four populations with various risks, i.e., blood donors, Veterans Administration (VA) patients, young injection drug users (IDU), and older IDU, were screened for HCV RNA by minipool or individual sample nucleic acid testing (NAT). The number of detected viremic seronegative infections was combined with the duration of the preseroconversion NAT-positive window period (derived from analysis of frequent serial samples from plasma donors followed from NAT detection to seroconversion) to estimate annual HCV incidence rates. Projected incidence rates were compared to observed incidence rates. Projected HCV incidence rates per 100 person-years were 0.0042 (95% confidence interval [95% CI], 0.0025 to 0.007) for blood donors, 0.86 (95% CI, 0.02 to 0.71) for VA patients, 39.8 (95% CI, 25.9 to 53.7) for young IDU, and 53.7 (95% CI, 23.4 to 108.8) for older IDU. Projected rates were most similar to observed incidence rates for young IDU (33.4; 95% CI, 28.0 to 39.9). This study demonstrates the value of applying a cross-sectional screening strategy to detect acute HCV infections and to estimate HCV incidence. Page-Shafer, K., Pappalardo, B.L., Tobler, L.H., Phelps, B.H., Edlin, B.R., Moss, A.R., Wright, T.L., Wright, D.J., O'Brien, T.R., Caglioti, S., and Busch, M.P. J. Clin. Microbiol. 46(2), pp. 499-506, 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. MBL2 variants were examined as to their influence on 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. 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, pp. 57, 2008.

### Management of Hepatic Complications in HIV-Infected Persons

Liver disease-related deaths mostly result from chronic infection with hepatitis B virus (HBV) and/or hepatitis C virus (HCV), and are the 2nd most common cause of death from HIV. Management issues among HIV-infected persons require careful consideration, balancing potential benefits of therapy with the potential for significant treatment-related adverse effects (HCV infection) and viral resistance and/or hepatitis flares (HBV infection). Several antiretroviral agents are active against HBV infection, including lamivudine, emtricitabine, tenofovir, and, more recently, entecavir. Despite the complexity and potential for antiretroviral-associated hepatotoxicity, ART usually is safe for patients with viral hepatitis coinfection, and, in some cases, treatment for HIV infection may be beneficial for the liver. Sulkowski, M.S. J. Infect. Dis. 197 Suppl 3:S279-293, 2008.

### Traveling Young Injection Drug Users at High Risk for Acquisition and Transmission of Viral Infections

A cross-sectional study of young highly mobile (under age 30) injection drug users (IDU) in San Francisco (2004-2006) were interviewed and tested for hepatitis B virus (HBV), hepatitis C virus (HCV) and HIV infection. Travel was independently associated with heavy alcohol consumption, drinking to blackout, poly-substance use, more sexual risk behaviors and injection partners and receptive needle/syringe sharing, backloading syringes and pooling money to buy drugs; and infection status, after adjusting for demographic characteristics and years injecting. Two-thirds (62%) reported past (3 months) travel outside of San Francisco (n=355). Travelers, as compared to non-travelers, were more likely to be under age 20, female, and planned to leave San Francisco in the coming months. In an analysis of interactions with travel, younger travelers were more likely to be HCV positive than younger non-travelers. Findings showed that traveling young IDU are at exceptionally high risk for acquiring and transmitting viral infections, while their mobility makes it challenging to effectively deliver interventions. Hahn, J.A., Page-Shafer, K., Ford, J., Paciorek, A., and Lum, P.J. Drug Alcohol Depend. 93(1-2), pp. 43-50, 2008. Epub 2007 Nov 5.

### Other Infections

### Risk Factors Associated with Life-Threatening Rickettsial Infections

The authors retrospectively analyzed 92 cases of severe rickettsial infections in patients (median age = 49 years, 57% male, 37.0% with scrub typhus) in Hong Kong. Immunofluorescence assay was used for diagnostic confirmation. Identification of > or = 1 diagnostic sign (exposure history, rash, or eschar) was possible in 94.6% of the cases. Multivariate analysis suggested that pulmonary infiltrates (odds ratio [OR] = 25.2, 95% confidence interval [CI] = 3.9-160.9, P = 0.001) and leukocytosis (OR = 1.3, 95% CI = 1.0-1.5 per unit increase, P = 0.033) were independent predictors of admission to an intensive care unit (14.1%). Delayed administration of doxycycline was independently associated with major organ dysfunction (23.9%; oxygen desaturation, renal failure, severe jaundice, encephalopathy, cardiac failure) (OR = 1.2, 95% CI = 1.0-1.5 per day delay, P = 0.046; adjusted for age and rickettsia biogroup) and prolonged hospitalization > 10 days (25%) (OR = 1.4, 95% CI = 1.1-1.9 per day delay, P = 0.014). Treatment with fluoroquinolone/clarithromycin did not correlate with clinical outcomes (P > 0.05). Early empirical doxycycline therapy should be considered if clinico-epidemiologic signs of rickettsial infections are present. Lee, N., Ip, M., Wong, B., Lui, G., Tsang, O.T., Lai, J.Y., Choi, K.W., Lam, R., Ng, T.K., Ho, J., Chan, Y.Y., Cockram, C.S., and Lai, S.T. Am. J. Trop. Med. Hyg. 78(6), pp. 973-997, 2008.

### Cytoplasmic Vacuolization Responses to Cytopathic Bovine Viral Diarrhoea Virus

Bovine Viral Diarrhea Virus (BVDV) is a positive sense, single-stranded RNA virus which exhibits two biotypes in standard cell culture systems. The cytopathic strains of this virus (cpBVDV) induce dramatic cytoplasmic vacuolization in cell cultures, while infection with the non-cytopathic (NCP-BVDV) strains produces no overt changes in the host cells. The authors results show that extensive cytoplasmic vacuolization is the earliest morphological change in response to cpBVDV infection in MDBK cells. Cells with extensive vacuolization showed no co-existing chromatin condensation, caspase activation, or loss of membrane integrity. In addition, the caspase inhibitor (zVAD-fmk), although improving cell viability of infected cells from 6.7+/-2.2% to 18.8+/-2.2%, did not prevent vacuolization. On the ultrastructural level, the virus-induced cytoplasmic vacuoles are single membrane structures containing organelles and cellular debris, which appear capable of fusing with other vacuoles and engulfing surrounding cytoplasmic materials. LysoTracker Red which marks lysosomes did not stain the virus-induced cytoplasmic vacuoles. In addition, this lysosomal dye could be observed in the cytoplasm of vacuolized cells, suggesting a lysosomal abnormality. These data demonstrate that cpBVDV induced a novel cell death pathway in MDBK cells that is primarily associated with lysosomal dysfunction and the formation of phagocytic cytoplasmic vacuoles, and this mode of cell death is different from apoptosis and necrosis. Birk, A.V., Dubovi, E.J., Cohen-Gould, L., Donis, R., and Szeto, H.H. Virus Res. 132(1-2), pp. 76-85, 2008.

### Antiviral Activity of Geneticin against Bovine Viral Diarrhoea Virus

Aminoglycoside G418 is commonly used to generate stable replicons for RNA viruses, such as hepatitis C virus, West Nile virus, and bovine viral diarrhoea virus (BVDV). This precludes testing 6418's own antiviral activities against those viruses. Here, the authors report antiviral activity of 6418 against BVDV. Cell viability and virus yield reduction assays were used to investigate antiviral effects of G418 against BVDV. The expression of viral proteins and RNA were determined by western blot and real-time quantitive PCR, respectively. The authors demonstrated that G418 (50% cytotoxicity concentration of 400

microg/ml) improved cell viability of Madin-Darby bovine kidney cells infected with a cytopathic strain of BVDV (NADL) in a dose-dependent manner with 50% effective concentration of 4 microg/ml. Interestingly, close structural analogues with known properties as translation inhibitors similar to G418 - kanamycin and gentamicin - had no antiviral activity against BVDV. In addition, 6418 inhibits virus yield of two different strains of BVDV (NADL and NY-1) without affecting viral RNA replication and translation or viral NS3 protein processing. The data indicate that antiviral activity of G418 could result from interference with either the assembly or release of active virus, rather than the regulation of viral translation and replication. Thus, the authors propose the use of chemical analogues of G418 as antiviral therapeutics for treatment of viral diseases associated with the Flaviviridae family, such as hepatitis C virus, dengue virus, yellow fever virus, West Nile virus and others. Birk, A.V., Dubovi, E.J., Zhang, X., Szeto, H.H. Antivir. Chem. Chemother. 19(1), pp. 33-40, 2008.

## Non-Infection Drug Abuse Medical Consequences

### 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., Sylla, L., Haddad, M.S., Kamarulzaman, A., and Altice, F.L. Am. J. Drug Alcohol Abuse. 34(4), pp. 511-517, 2008.

### Platelet Fragmentation Requires a Specific Structural Conformation of Human Monoclonal Antibody against Beta3 Integrin

The authors have described an autoantibody against beta3 (GPIIIa49-66), a region of platelet integrin alphaIIbbeta3 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, we 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. The authors 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 beta3 integrin

and subsequent antibody-induced platelet fragmentation and aggregate dissolution. Li, Z., Nardi, M.A., Wu, J., Pan, R., Zhang, W., and Karpatkin, S. J. Biol. Chem. 283(6), pp. 3224-3230, 2008.

### Barriers to Seeking Mental Health Care after Treatment for Orofacial Injury at a Large, Urban Medical Center: Concordance of Patient and Provider Perspectives

Patients with orofacial injury in a large, urban medical center meeting screening criteria for probable mental health disorder (n = 25) and trauma service providers (n = 35) were queried regarding psychosocial aftercare and identified factors that impeded or facilitated aftercare participation. Bivariate analyses and Fisher's exact tests were used to describe and compare patient and provider responses. Although patient participants expressed interest in receiving aftercare services for psychological problems; lack of information about services, financial cost, and availability of transportation emerged as the most salient barriers to care, indicating potentially substantial unmet psychosocial needs after facial trauma. Providers were not necessarily aware of either the extent of patient interest in psychosocial services or the nature of the barriers that would impede care utilization. Chandra, A., Marshall, G.N., Shetty, V., Paddock, S.M., Wong, E.C., Zatzick, D., Luo, G., and Yamashita, D.D. J. Trauma 65(1), pp. 196-202, 2008.

### Arrested on Heroin: A National Opportunity

Arrestee drug-testing data, total number of arrests, an estimate of the mean annual number of arrests in a drug-using population, estimates of arrestees incarcerated, and estimates of heroin use and addiction in the U.S. population were derived to determine potential impact of interventions designed to link heroin-using individuals to addiction treatment. The authors found that a conservative estimate of 24 to 36 percent of all heroin addicts pass through the corrections system each year, representing more than 200,000 individuals, and offering a public health opportunity for effective linkages to addiction treatment, health care, prevention of disease transmission, criminality and recidivism. Boutwell, A.E., Nijhawan, A., Zaller, N., and Rich, J.D. J. Opioid Manag. 3(6), pp. 328-332, 2007.

### Trends in Methamphetamine Use in Young Injection Drug Users in San Francisco from 1998 to 2004: the UFO Study

Secondary analysis of cross-sectional baseline data collected for a longitudinal study of young IDU from 1998 to 2004 were examined to describe temporal trends in methamphetamine use among young injection drug users (IDU) in San Francisco. Median age was 22 years [interquartile range (IQR) 20-25], 30.3% were women and median duration of injecting was 4.4 years (IQR 2-7). Prevalence of methamphetamine use was high, with 50.1% reporting recent injection, but overall there were no temporal increases in reported 'ever' injected use. Recent methamphetamine injection (past 30 days) increased significantly, and peaked at 60% in 2003. MSM-IDU had higher methamphetamine injection ever (92.3%) and recently (59.5%) compared to heterosexual male (non-MSM) IDU (81.6% and 47.3%, respectively) and to female IDU (78.4% and 46.1%, respectively). Findings disclosed that despite reports of ubiquitous increases in methamphetamine use, there were no significant increases in 6 years in ever injecting methamphetamine overall among young IDU. Further, the methamphetamine 'epidemic' appeared to have been under way among young IDU earlier than in other populations. Inglez-Dias, A., Hahn, J.A., Lum, P.J., Evans, J., Davidson, P., and Page-Shafer, K. Drug Alcohol Rev. 27(3), pp. 286-291, 2008.

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# Director's Report to the National Advisory Council on Drug Abuse - September, 2008

## Research Findings - Services Research

### Oxford House Post-Treatment Residency Increases Sobriety, Efficacy to Remain Abstinent, and Earned Income

Oxford Houses are recovery home residences for individuals with substance abuse and dependence problems who seek a supportive, democratic, mutual-help setting. A national US sample of Oxford House (OH) residents (n=897: 604 men, 293 women) were recruited and interviewed at an initial baseline phase and then re-interviewed at three subsequent 4-month intervals. Change in cumulative abstinence was predicted using latent growth modeling (LGM) by low support for alcohol use, abstinence self-efficacy, and length of residency in OH (i.e., less than versus >=6 months), even after controlling for initial time spent in OH (model X2 =179, df = 74; NFI=.98, RFI=.98, CFI=.99, RMSEA=.04). Average monthly income of $941.90 was significantly higher than $794 at baseline (p<.01). Results suggest that receiving abstinence support, guidance, and information from recovery home members committed to the goal of long-term sobriety can enhance abstinence self-efficacy and enable persons recovering from alcohol and other drug addiction to reduce the probability of a relapse. Jason, L., Davis, M., and Ferrari, J. R. The Need for Substance Abuse After-Care: Longitudinal Analysis of Oxford House. Addict. Behav., 32(4), pp. 803-818, 2007.

### Post-Treatment Recovery Management Check-ups Improve Patient Outcomes

This article examines the effectiveness of quarterly Recovery Management Checkups (RMCs) for people with substance use disorders by level of co-occurring mental disorders (34% none, 27% internalizing disorders, and 39% internalizing and externalizing) across two randomized experiments with 92% to 97% follow-up. The 865 participants are 82% African American, 53% female, and age 37 on average. RMC involves identification of those in need of treatment, motivational interviews, and treatment linkage assistance. Results show RMC is effective in linking participants in need to treatment, with equal or better outcomes among those with more mental disorders. The data support the utility of monitoring and re-intervention for clients with co-occurring disorders. Rush, B., Dennis, M., Scott, C., Castel, S., and Funk, R. The Interaction of Co-occurring Mental Disorders and Recovery Management Checkups on Substance Abuse Treatment Participation and Recovery. Eval. Rev., 32(1), pp. 7-38, 2008.

### A Study of Methadone Maintenance for Male Prisoners: 3-Month Post-Release Outcomes

## Index

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This study examined benefits of methadone maintenance among pre-release prison inmates. Incarcerated males with pre-incarceration heroin dependence (n = 197) were randomly assigned to (a) group educational counseling (counseling only); (b) counseling, with opportunity to begin methadone maintenance on release (counseling + transfer); or (c) counseling and methadone maintenance in prison, with opportunity to continue methadone maintenance on release (counseling + methadone). At 90-day follow-up, counseling + methadone participants were significantly more likely than counseling-only and counseling + transfer participants to attend drug treatment (p = .0001) and less likely to be re-incarcerated (p = .019). Counseling + methadone and counseling + transfer participants were significantly less likely (all ps < .05) to report heroin use, cocaine use, and criminal involvement than counseling-only participants. Kinlock, T., Gordon, M., Schwartz, R., and O'Grady, K. A Study of Methadone Maintenance for Male Prisoners: 3-Month Post Release Outcomes Crim. Justice Behav., 35(1), pp. 34-47, 2008.

### Psychiatric Severity Trajectories are Associated with Long-Term Chemical Dependency Treatment Outcomes

This study used a group-based modeling approach to classify 934 adult individuals who entered chemical dependency treatment in a private, managed care health plan to into distinct trajectories of psychiatric status. It then estimated the statistical association between membership in these trajectory groups and substance use (SU) outcomes over the 9 year follow up period. Four distinct groups are identified: Low severity, deteriorating, improving, and high severity. Results from multivariate logistic generalized estimating equation models reveal that psychiatric severity trajectory is associated with lower odds of being abstinent from drugs during the 9 year follow up period (OR deteriorating 0.61 (CI 0.42-0.87); improving 0.61 [CI 0.40-0.93], high severity 0.43 (CI 0.29-0.66). Associations with alcohol abstinence were not statistically significant. Chi, F., and Weisner, C. Nine-Year Psychiatric Trajectories and Substance Use Outcomes: An Application of the Group-Based Modeling Approach. Eval. Rev., 32(1), pp. 39-58, 2008.

### Smoking Trends May Underly Increasing Education Level Differences in Health Status Relying on Data from the Multiple Cause of Death File and the National Longitudinal Mortality Study

This study examines educational disparities in mortality and life expectancy among non-Hispanic blacks and whites in the 1980s and 1990s. Age-standardized death rates per 100,000 Americans were estimated by education, race, sex and cause between 1990 and 2000. Differences in life expectancies between those with a high school diploma and those with some college education were significant. In 2000, a 25 year old with a high-school diploma could expect to live less than 50 years, until age 75, while a 25 year old with some college could expect to live 7 years longer. This gap had increased by about 30 percent over the study time period. Lung cancer and COPD, two diseases attributable largely to tobacco use, accounted for 21 percent of this widening gap overall, and 25 percent of the gap for less-educated white women over the age of 45, who have shown more modest declines in smoking rates. The gaps are increasing because, for most groups, longevity for more highly-educated individuals is increasing while that for less-educated groups is remaining the same. Meara, E., Richards, S., and Cutler, D. The Gap Gets Bigger: Changes In Mortality and Life Expectancy By Education, 1981-2000. Health Aff (Millwood), 27(2), pp. 350-360, 2008.

### The Long-Term Impact of Drug Court on Recidivism

The current study examined the long-term impact of drug court participation compared to regular probation. In a quasi-experimental design, the recidivism was examined of 475 drug-involved offenders under supervision. The sampling frame consisted of adult offenders who entered community supervision on either felony probation or drug offender probation in Hillsborough County, FL, from Feb. through Sept. 2002, and were determined to be drug involved, had at most one prior prison commitment, at most two supervision terms. Analytic methods were also used to control for differences between the drug court and non drug court samples. Using a combination of self-reported data (collected through in-person interviews at baseline, i.e., the beginning of supervision) and administrative records, the study employed a repeated measures framework (examining five 6-month time periods from baseline to 30 months post-baseline) and used generalized estimating equations to compare the likelihood of being arrested between drug court participants and a matched sample of comparison offenders. The results indicate that participation in drug court was associated with a significant decrease in the likelihood of being arrested in the 12-18 months post-baseline time period. Although the drug court effect was somewhat delayed (it was not significant prior to 12 months) and short-lived (it was not significant after 18 months), the fact that significant program effects were observed during a time period that coincides with the conclusion of drug court participation for graduates and a time period well beyond initial program exposure, suggests that drug court participants are more likely than comparable offenders not exposed to drug court to remain arrest free when no longer under community supervision. Krebs, C., Lindquist, C., Koetse, W., and Lattimore, P. Assessing the Long-Term Impact of Drug Court Participation on Recidivism with Generalized Estimating Equations. Drug Alc. Depend., 91(1), pp. 57-68, 2007.

### Special Gender-Specific Addiction Treatment Programs Had Superior Outcomes to Mixed-Gender Progams

This quasi-experimental, retrospective study reports on the continuity of care for women with children who were admitted to long-term residential substance abuse treatment. Women were admitted to seven agencies offering specialized, women's only treatment (SP, n = 747) or to nine agencies that provided standard mixed-gender treatment (ST, n = 823). Client and treatment data were gathered from administrative sources. Multivariate analyses revealed that SP clients who completed treatment with longer stays were most likely to continue care. Women in SP programs (37%) were more likely than those in ST programs (14%) to continue care. The findings show that specialized treatment for women promotes continuing care and demonstrate the importance of treatment completion. Orwin, R., Claus, R., Kissin, W., Krupski, A., Campbell, K., and Stark, K. Does Gender-Specific Substance Abuse Treatment for Women Promote Continuity of Care? J. Subst. Abuse Treat., 32, pp. 27-39, 2007.

### Larger Methadone Maintenance Clinics May be More Efficient

Using data from 159 methadone treatment programs (MTPs') that participated in the Center for Substance Abuse Treatment's Evaluation of the Methadone/LAAM Treatment Program Accreditation Project, the authors estimated two modified translog cost functions (multivariate regression models that allow for nonlinear relationships by regressing log total costs on the logs of measures of outputs, outputs squared, input prices, facility and client characteristics) to determine the extent to which this industry experiences economies of scale and scope. The first cost function estimation, a single product cost function which used log of patient days as the output variable, revealed that a 10% increase in annual patient days evaluated at the mean is associated with an 8.2% increase in total cost, suggesting that these programs experience economics of scale (i.e. larger programs have lower average costs). As expected from economic theory, higher counselor wages in the program's

location were positively associated with higher total costs, although the effects of other input prices included in the model (nurses' wages and office space costs) were not significant. The second model estimated a multi-product cost function, using the logs of annual counseling hours, case management hours, intake hours, and medical hours, and their squares, as measure of output. A multi-product cost function provides estimates of economies of scope which occur when the average cost of producing one output decreases as the volume of another output increases. This second model revealed economies of scale in the production of each of these outputs separately but only weak evidence of economies of scope. Further research is needed to investigate the relationship between client characteristics and costs, as only rough measures of client severity were included in this analysis due to data limitations. Dunlap, L., Zarkin, G., and Cowell, A. Examining Variation in Treatment Costs: A Cost Function for Outpatient Methadone Treatment Programs. Health Serv. Res., 43(3), pp. 931-950, 2008.

### HIV Risk Behaviors Among Rural Stimulant Users: Variation by Gender and Race/Ethnicity

The researchers examined data from a community sample of rural stimulant users (n = 691) in three diverse states to identify gender and racial/ethnic differences in HIV risk behaviors. Bivariate and logistic regression analyses were conducted with six risk behaviors as dependent variables: injecting drugs, trading sex to obtain money or drugs, trading money or drugs to obtain sex, inconsistent condom use, multiple sex partners, and using drugs with sex. Controlling for state, income, age, heavy drinking, and type of stimulant used, men had lower odds than women for trading sex to obtain money or drugs (adjusted odds ratio [AOR] =0.4, confidence interval [CI] = 0.28-0.59; p < .0001), greater odds than women for trading money or drugs to obtain sex (AOR = 44.4, CI = 20.30-97.09; p < .0001), greater odds than women of injecting drugs (adjusted odds ratio (AOR =1.6, CI = 1.11-2.42; p = .01), and lower odds than women of using condoms inconsistently (AOR = 0.6, CI = 0.35-0.92; p = .02); African Americans had lower odds than Whites of injecting drugs (AOR = .08, CI = 0.04-0.16; p < .0001), greater odds than Whites for trading sex to obtain money or drugs (AOR = 1.7, CI = 1.01-2.85; p = .04) and for trading money or drugs to obtain sex (AOR = 2.9,CI = 1.53-5.59; p = .001), and greater odds than Whites of using drugs with sex (AOR = 3.9, CI = 1.47-10.09; p = .006). These findings indicate HIV prevention efforts should be tailored to address gender and racial/ethnic differences in risk behaviors among rural stimulant users. Wright, P., Stewart, K., Fischer, E., Carlson, R., Falck, R., Wang, J., Leukefeld, C., and Booth, B. HIV Risk Behaviors among Rural Stimulant Users: Variation by Gender and Race/Ethnicity. AIDS Educ. Prev., 19(2), pp. 137-150, 2007.

### Trial of Computerized Screening for Adolescent Behavioral Concerns

The primary causes of adolescent morbidity and deaths are: injury risk, depressive symptoms, and substance use. The goal of this randomized, controlled trial was to determine whether computerized screening with real-time printing of results for pediatricians increased the identification of these adolescent behavioral concerns. A total of 878 primary care patients 11 to 20 years of age participated in computerized behavioral screening (The Health eTouch System) in waiting rooms of 9 urban clinics. These clinics all served predominantly low-income patients. The clinics were randomly assigned to have pediatricians receive screening results either just before face-to-face encounters with patients (immediate-results condition) or 2 to 3 business days later (delayed-results condition). It was found that fifty-nine percent of Health eTouch respondents had positive results for at least one of the following behavioral concerns: injury risk behaviors, significant depressive symptoms, or

substance use. Sixty-eight percent of youths in the immediate-results condition who screened positive were identified as having a problem by their pediatrician. This was significantly higher than the recognition rate of 52% for youths in the delayed-results condition. This study shows that the immediate provision of an adolescent's self-report of behavioral concerns to pediatrician increased recognition of those problems, compared with the delayed provision of results. Stevens, J., Kelleher, K., Gardner, W., Chisolm, D., McGeehan, J., Pajer, K., and Buchanan, L. Trial of Computerized Screening for Adolescent Behavioral Concerns. Pediatrics, 121(6), pp. 1099-1105, 2008.

### Buprenorphine Can Be Successfully Integrated Within an Outpatient Agonist Treatment Facility

Buprenorphine may be used to treat opioid dependence in office-based settings, but treatment models are needed to ensure access to the psychosocial services needed by many patients. The authors describe a novel buprenorphine treatment program colocated with methadone maintenance and outpatient chemical dependency services. They conducted a retrospective chart review of the first 40 consecutive patients initiating buprenorphine treatment in this program to determine characteristics associated with treatment retention. Exclusion criteria were current alcohol or benzodiazepine dependence. Secondary drug users and patients who were psychiatrically or medically ill were included. At 6 months, 60% (n = 24) were retained, 13% (n = 5) tested positive for opiates, and 25% (n = 10) tested positive for secondary substances. Patients who were older (odds ratio [OR] per year of age = 1.1, confidence interval [CI] = 1.0-1.2) and those who were employed (OR = 9.8, CI = 1.8-53.1) were more likely to remain in treatment, but other variables were not associated with retention. The authors' experience demonstrates that buprenorphine can be successfully integrated into outpatient substance abuse treatment. Whitley, S., Kunins, H., Arnsten, J., and Gourevitch, M. Collocating Buprenorphine with Methadone Maintenance and Outpatient Chemical Dependency Services. J. Subst. Abuse Treat., 33(1), pp. 85-90, 2007.

### Water Pipe Tobacco Smoking on a U.S. College Campus: Prevalence and Correlates

Water pipe tobacco smoking is reported to be growing in popularity, particularly among college students. This study examined the prevalence of water pipe tobacco smoking and perceptions in a university-based population. This was a cross-sectional Internet-based survey of first-year university students, which examined water pipe tobacco smoking and other tobacco use, risk perceptions, influences, and perceived social acceptability. Water pipe tobacco smoking within the past 30 days was reported by 20% (151/744). Relative to never users, users were more likely to perceive water pipe tobacco smoking as less harmful than cigarette use. Because water pipe tobacco smoking is increasing in prevalence and because it can involve toxicant inhalation at even greater levels than with cigarette smoking, it represents a growing public health issue. Eissenberg, T., Ward, K., Smith-Simone, S., and Maziak, W. Water Pipe Tobacco Smoking on a U.S. College Campus: Prevalence and Correlates. J. Adolesc. Health, 42(5), pp. 526-529, 2008.

### Drug Users Attitudes and Decisions Regarding Hepatitis C (HCV) Treatment

Individuals with a history of injecting drugs are at the highest risk of becoming infected with the hepatitis C virus (HCV), with studies of patients in methadone maintenance treatment programs (MMTPs) reporting that 60-90 percent of intravenous drug users (IDUs) have the virus. Fortunately, HCV therapy has been shown to be effective in 42-82 percent of all patients with chronic HCV

infection, including IDUs. While the decision to start HCV therapy requires significant consideration, little research exists that explores the attitudes of drug users toward HCV therapy. Therefore, this paper examines how drug users perceive the treatment, as well as the processes by which HCV-positive individuals examined the advantages and disadvantages of starting the HCV medications. Interviews were conducted with 164 patients from 14 drug treatment programs throughout the United States, and both uninfected and HCV-positive drug users described a pipeline of communication among their peers that conveys largely negative messages about the medications that are available to treat HCV. Although many of the HCV-positive individuals said that these messages heightened their anxiety about the side effects and difficulties of treatment, some patients said that their peers helped them to consider, initiate HCV treatment or both. Gaining a better understanding of drug users' perceptions of HCV treatment is important, because so many of them, particularly IDUs, are already infected with HCV and may benefit from support in addressing their HCV treatment needs. In addition, currently uninfected drug users will likely remain at high risk for contracting HCV and may need to make decisions about whether or not to start the HCV medical regimen in the future. Munoz-Plaza, C., Strauss, S., Astone-Twerell, J., Des Jarlais, D., Gwadz, M., Hagan, H., Osborne, A., Rosenblum, A., and Rosenblum, A. Exploring Drug Users Attitudes and Decisions Regarding Hepatitis C (HCV) Treatment in the U.S. Int. J. Drug Policy, 19(1), pp. 71-78, 2008.

### Cocaine Use and Hypertensive Renal Changes in HIV Infected Individuals

Cocaine causes kidney damage, but data linking cocaine use to chronic kidney disease in HIV patients is not described. This study was conducted to evaluate the possible association of cocaine use and histopathologic findings on biopsy in this population. Kidney biopsies that were performed in HIV-infected patients during the course of 11 years were reviewed. Demographic and clinical data were collected. Hypertensive changes were defined on the basis of the Banff 97 classification. Criteria of both arterial intimal fibrosis and thickening and hyaline arteriolosclerosis were used and graded as absent (0), mild (1) moderate (2), and severe (3). Hypertensive renal changes were considered present when the combined pathology score was > or = 2. To minimize confounding, those with hypertension or diabetes were excluded. Of the 193 HIV patients who underwent kidney biopsy, 53 had no history of hypertension or diabetes with HIV infection. Of those, 29 (55%) had hypertensive renal changes on kidney biopsy. Cocaine use was present in 16 (55%) of 29 with hypertensive renal changes compared with six (25%) of 24 without hypertensive renal changes (odds ratio [OR] 3.7; 95% confidence interval [CI] 1.2 to 11.7). In the adjusted analyses, only age (/yr; OR 1.08; 95% CI 1.00 to 1.16) and cocaine use (OR 3.55; 95% CI 1.04 to 12.14) were significantly associated with hypertensive renal changes on renal biopsy. Cocaine use is associated with hypertensive renal changes in HIV-infected patients in the absence of hypertension and diabetes. Fine, D., Garg, N., Haas, M., Rahman, M., Lucas, G., Scheel, P., and Atta, M. Cocaine Use and Hypertensive Renal Changes in HIV Infected Individuals. Clin. J. Am. Soc. Nephrol., 2(6), pp. 1125-1130, 2007.

### Physical Health, Illicit Drug Use, and Demographic Characteristics in Rural Stimulant Users

There is growing concern about illicit rural stimulant use, especially regarding methamphetamine use and its health consequences. This study describes associations between aspects of stimulant use and illness experience in rural areas, with additional focus on the role of demographic characteristics in these associations. The research participants were 710 stimulant drug users who were recruited from rural areas of Arkansas, Kentucky, and Ohio using

Heckathorns' respondent-driven sampling method. Health was measured by self-reports of perceived health and extent of current, recent, and lifelong health problems. Drug use was measured with self-reports of type and frequency of use. Several associations were found between drug use and illness, controlling for demographics. Stimulant use pattern related significantly with the sum of health problems in the previous 6 months and the sum of lifetime illness diagnoses, after adjustment for demographic factors. Extent of illicit drug use in the past month and self-perceived drug and alcohol problems were associated with several measures of health. In this sample of stimulant users, methamphetamine use was associated with fewer recent medical problems than crack cocaine, combined crack and powder cocaine use, and use of all 3 of these stimulants. These results, across the 3 sites, suggest that prevalent assumptions about the methamphetamine 'plague' and its negative health consequences must be viewed cautiously and examined with additional research. Garrity, T., Leukefeld, C., Carlson, R., Falck, R., Wang, J., and Booth, B. Physical Health, Illicit Drug Use, and Demographic Characteristics in Rural Stimulant Users. J. Rural Health, 23(2), pp. 99-107, 2007.

### Impact of a Brief Training on Medical Resident Screening for Alcohol Misuse and Illicit Drug Use

Substance use screenings in primary-care medical settings require numerous initiatives including educational. This study assesses the impact on 24 medical residents of a 2.5-day curriculum combining experiential and manual-based training on screening for alcohol misuse and illicit drug use. A retrospective chart review of new primary care outpatients demonstrated that nearly all were asked about current alcohol use before and after curriculum participation. Adherence to national screening guidelines on quantification of alcohol consumption modestly improved ($p < .05$), as did inquiry about current illicit drug use ($p < .05$). Continued efforts are needed to enhance educational initiatives for primary care physicians. Gunderson, E., Levin, F., and Owen, P. Impact of a Brief Training on Medical Resident Screening for Alcohol Misuse and Illicit Drug Use. Am. J. Addict., 17(2), pp. 149-154, 2008.

### Nurse Case-Managed Intervention for Latent Tuberculosis Among the Homeless

The efficacy of a nurse case-managed intervention was evaluated in subsamples of participants with one of the following characteristics: female gender, African American ethnicity, recruited from a homeless shelter, a history of military service, lifetime injection drug use, daily alcohol and drug use, poor physical health, and a history of poor mental health. The purpose of the study was to determine whether a validated nurse case managed intervention with incentives and tracking would improve adherence to latent tuberculosis infection treatment in subsamples of homeless persons with characteristics previously identified in the literature as predictive of non-adherence. A prospective 2-group site-randomized design was conducted with 520 homeless adults residing in 12 homeless shelters and residential recovery sites in the Skid Row region of Los Angeles from 1998 to 2003. Results revealed that daily drug users, participants with a history of injection drug use, daily alcohol users, and persons who were not of African American race or ethnicity had particularly poor completion rates, even in the nurse case-managed intervention program (48%, 55%, 54%, and 50%, respectively). However, the intervention achieved a 91% completion rate for homeless shelter residents and significantly improved latent tuberculosis infection treatment adherence in 9 of 12 subgroups tested (odds ratios = 2.51-10.41), including daily alcohol and drug users, when potential confounders were controlled using logistic regression analysis. It is concluded that nurse case management with incentives appears to be a good foundation for increasing adherence to 6-month isoniazid treatment in a variety of homeless subgroups and, in particular, for sheltered

homeless populations. However, additional social-structural and environmental strategies are needed to address those at greatest risk of non-adherence. Nyamathi, A., Nahid, P., Berg , J., Burrage, J., Christiani, A., Aqtash, S., Morisky, D., and Leake, B. Efficacy of Nurse Case-Managed Intervention for Latent Tuberculosis Among Homeless Subsamples. Nurs. Res., 57(1), pp. 33-39, 2008.

### Self-Treatment of Opioid Withdrawal Using Kratom (Mitragynia Speciosa Korth)

Kratom (Mitragynia speciosa korth) is recognized increasingly as a remedy for opioid withdrawal by individuals who self-treat chronic pain. A case history was described of a patient who had abruptly ceased injection hydromorphone abuse; he self-managed opioid withdrawal and chronic pain using kratom. After co-administering the herb with modafinil he experienced a tonic-clonic seizure, but he reported only modest abstinence once kratom administration stopped. The identity of the plant matter he ingested was confirmed as kratom and no contaminants or adulterants were identified. High-throughput molecular screening and the binding affinity at mu, delta and kappa receptors of mitragynine was also performed. This is the first report of the self-treatment of chronic pain and opioid withdrawal with kratom. The predominant alkaloid of kratom, mitragynine, binds mu- and kappa-opioid receptors, but has additional receptor affinities that might augment its effectiveness at mitigating opioid withdrawal. The natural history of kratom use, including its clinical pharmacology and toxicology, are poorly understood. Boyer, E., Babu, K., Adkins, J., McCurdy, C., and Halpern, J. Self-Treatment of Opioid Withdrawal Using Kratom (Mitragynia Speciosa Korth). Addiction, 103(6), pp. 1048-1050, 2008.

### HIV Treatment Adherence Among IDUs and the Role of Opioid Substitution Treatment (OST)

In the era of highly effective anti-retroviral therapy (ART), data show a significant difference in treatment outcomes between injecting drug users (IDUs) and non-IDUs. Factors that may contribute to suboptimal treatment outcomes in IDUs include delayed access to ART, competing comorbid diseases, psychosocial barriers and poor long-term adherence to ART. This review describes and compares several studies on adherence to ART and its correlates in HIV-infected individuals in general, then IDUs and finally those IDUs on opioid substitution treatment (OST). It highlights how ongoing drug use or OST can modify the pattern of these correlates. The aim is to extend all the experience acquired from these studies in order to optimize both access to care and adherence in those countries where HIV infection is mainly driven by IDUs and where ART and OST are only starting to be scaled up. The role of OST in fostering access to care and adherence to ART together with the promising results achieved to date using modified directly observed therapy (DOT) programs for patients taking methadone, allow us to emphasize the efficacy of a comprehensive care model which integrates substance dependence treatment, psychiatric treatment, social services, and medical treatment. The review concludes by suggesting areas of future research targeted at improving the understanding of both the role of perceived toxicity and patient-provider relationship for patients on ART and OST. Spire, B., Lucas, G., and Carrieri, M. Adherence to HIV Treatment Among IDUs and the Role of Opioid Substitution Treatment (OST). Int. J. Drug Policy, 18(4), pp. 262-270, 2007.

### Improving Session Attendance in Mental Health and Substance Abuse Settings: A Review of Controlled Studies

Patient non-attendance to scheduled sessions results in excessive costs to

mental health and substance abuse providers and compromises the care of clients. This paper presents a comprehensive review of interventions that have been shown to increase session attendance rates in these settings. Unique to other review papers, reliability estimates were performed in the selection and evaluation of obtained studies. Reliability of article selection and evaluation strategies was excellent (.80 to .88). Study results indicate several attendance improvement methods appear to be particularly promising, such as scheduling appointments promptly, reminder letters and telephone calls, soliciting patient commitment, and helping to resolve obstacles to attending the session. The specific manner in which these interventions are implemented appears to influence session attendance rates. Moreover, some attendance improvement interventions are clearly effective in some settings, but not others. Specific recommendations are provided in light of the study findings. Lefforge, N., Donohue, B., and Strada, M. Improving Session Attendace in Metal Health and Substance Abuse Settings: A Review of Controlled Studies. Behav. Ther., 38(1), pp. 1-22, 2007.

### Small Changes in Treatment Processes Can Lead to Big Improvements in Treatment Retention

The Network for the Improvement of Addiction Treatment (NIATx) teaches participating treatment centers to use process improvement strategies. A cross-site evaluation monitored impacts on days between first contact and first treatment and percent of patients who started treatment and completed two, three and four units of care (i.e., one outpatient session, 1 day of intensive outpatient care, and 1 week of residential treatment). The analysis included 13 agencies that began participation in August 2003, submitted 10-15 months of data, and attempted improvements in outpatient (n=7), intensive outpatient (n=4) or residential treatment services (n=4) (two agencies provided data for two levels of care). Days to treatment declined 37% (from 19.6 to 12.4 days) across levels of care; the change was significant overall and for outpatient and intensive outpatient services. Significant overall improvement in retention in care was observed for the second unit of care (72-85%; 18% increase) and the third unit of care (62-73%; 17% increase); when level of care was assessed, a significant gain was found only for intensive outpatient services. Small incremental changes in treatment processes can lead to significant reductions in days to treatment and consistent gains in retention. McCarty, D., Gustafson, D., Wisdom, J., Ford, J., Choi, D., Molfenter, T., Capoccia, V., and Cotter, F. The Network for the Improvement of Addiction Treatment (NIATx): Enhancing Access and Retention. Drug Alcohol Depend., 88(2-3), pp. 138-145, 2007.

### Buprenorphine Found To Be Superior to Clonidine for Addiction Treatment

In June 2004, a community-based residential medical detoxification center switched from clonidine to buprenorphine treatment for all new and returning heroin clients. This study is a retrospective chart review of subject outcomes with clonidine (n = 100) versus buprenorphine (n = 100). Bivariate analysis suggested few cohort differences in pretreatment demographics and client characteristics. In contrast, buprenorphine was significantly associated with increased length of stay and treatment completion. The positive associations between buprenorphine and both treatment completion and length of stay persisted and were slightly enhanced after regression analysis adjusted for potential confounders. Additionally, clinical staff reported better subject engagement in treatment and psychosocial group sessions. This single-site study is an example of successful integration of an evidence-based treatment into community-based practice. Kovas, A., McFarland, B., McCarty, D., Boverman, J., and Thayer, J. Buprenorphine for Acute Heroin Detoxification: Diffusion of Research into Practice. J. Subst. Abuse Treat., 32(2), pp. 199-206, 2007.

### Emotions that Move People from Pre-Contemplation to Contemplation of Behavior Change

Motivation for change has historically been viewed as the crucial element affecting responsiveness to drug treatment. Various external pressures, such as legal coercion, may engender motivation in an individual previously resistant to change. Dramatic relief may be the change process that is most salient as individuals internalize such external pressures. This process involves emotional arousal about one's current behavior and the psychological relief that can come from changing from Pre-contemplation to Contemplation--it is a trigger that prompts people to acknowledge, at an emotional level, their problem behavior and its impact on those around them. Fear, inspiration, guilt, and hope, for example, are some of the emotions that can promote dramatic relief and move people from Pre-contemplation to Contemplation. Results of structural equation modeling on data from 465 drug users (58.9% male; 21.3% Black, 34.2% Hispanic/Latino, and 35.1% White) entering drug treatment indicated that internal motivation and external pressure significantly and positively predicted dramatic relief and that dramatic relief significantly predicted attitudes towards drug treatment: chi (2) = 142.20, df = 100, $p < 0.01$; Robust Comparative Fit Index = 0.97, Root Mean Squared Error of Approximation = 0.03. These results indicate that when external pressure and internal motivation are high, dramatic relief is also likely to be high. When dramatic relief is high, attitudes towards drug treatment are likely to be positive. The findings indicate that interventions to get individuals into drug treatment should include processes that promote Dramatic Relief. Conner, B. T., Longshore, D., and Anglin, M. Modeling Attitude towards Drug Treament: The Role of Internal Motivation, External Pressure, and Dramatic Relief. J. Behav. Health Serv. Res, Special Issue, pp. 1-9, 2008.

### Intensive Case Management Is Associated with Improved Outcomes For Women With Substance Use Disorders

The aim of this study is to identify factors that predict, mediate or moderate the effects of intensive case management (ICM) on longer-term drug abstinence outcomes in women on welfare. In a parent study women were assigned randomly to usual care (UC) or intensive case management (ICM). Treatment was provided for 12 weeks and follow-up continued for 15 months after study intake. A set of hypothesized mediators was assessed at month 3 and a rigorous four-step mediational model was tested using outcomes in months 4-15. Participants were 302 drug-dependent women applying and eligible for federal welfare and not currently in drug abuse treatment. The ICM intervention provided intensive treatment engagement including voucher incentives for treatment attendance and case management services; UC provided primarily referral to community treatment programs. Substance use outcomes were assessed using the time-line follow-back interview and confirmed using biological and collateral measures. The authors report that participants in ICM had more case manager contacts, better treatment engagement and more self-help attendance than did those in UC. Each of these variables predicted, and was shown to be a mediator of outcome, but case management contact was an especially robust mediator. Further, ICM effects were strongest for those who attended treatment least. Contrary to prediction, greater psychopathology and environmental stressors did not predict worse outcomes. Findings suggest that case management is an active intervention that may both facilitate and substitute for formal drug abuse treatment. Morgenstern, J., Blanchard, K., Kahler, C., Barbosa, K., McCrady, B., and McVeigh, K. Testing Mechanisms of Action for Intensive Case Management. Addiction, 103(3), pp. 469-477, 2008.

### Marijuana Co-Morbidity Associated with Higher Inpatient Hospital

### Costs Among Patients with Primary Alcohol Diagnoses

Data from the 1995-2000 Florida Hospital Discharge Data set were used to examine the incremental cost of marijuana co-morbidity among hospital inpatients with primary alcohol (n=2,130), mood (n=8,738), and thought disorder diagnoses (n=4,245). General linear modeling and propensity score methods were used to compare the hospital charges for these patients against patients with the same primary diagnoses but no marijuana co-morbidity (alcohol = 54,699, mood= 256,938, thought = 139,626 patients), holding other factors constant. Under the preferred specification, patients with both disorders incurred charges 7-8% higher per discharge than patients with the same primary diagnosis but no marijuana co-morbidity, for an incremental cost of $226 dollars on average. The estimates for mood and thought disorders were statistically insignificant. These results suggest that the healthcare costs of marijuana are not negligible and are worthy of further research. Pacula, R., Ringel, J., Dobkin, C., and Truong, K. The Incremental Inpatient Costs Associated with Marijuana Co-Morbidity Drug Alcohol Depend., 92(1-3), pp. 248-257, 2008.

### Alcohol, Cannabis, and Methamphetamine Use and Other Risk Behaviors Among Black and Colored South African Women

There is a pressing need for brief behavioral interventions to address the intersection of high HIV prevalence, increasing substance use, and high-risk sex practices among South African women. The primary aim of this pilot, randomized trial was to examine whether an adapted evidence-based intervention would be equally, more, or less effective at reducing HIV risk behaviors when delivered using an individual or group format. The secondary aim was to examine differences between Black and Colored South African women across pre- and post-intervention measures of alcohol and illicit drug use and sex risk behaviors. The Cape Town Women's Health Co-Op was adapted from an evidence-based intervention known as the Women's Co-Op. Study participants included Black (n=60) and Colored (n=52) women living in the township communities of Cape Town, South Africa, who reported using illicit drugs and alcohol. Colored women reported greater methamphetamine use (13 days in the past 30 days) and Black women reported mostly cannabis use (27 days in the past 30 days). Although both groups reported having unprotected sex under the influence of alcohol and/or other drugs, Black women reported greater condom use and having one partner; Colored women reported having more than one sex partner. One-month post-intervention assessments indicated significant reductions in substance use and sex risk behaviors. After controlling for baseline measures, there were no significant differences between the two intervention conditions. Significant differences in risk behaviors were observed between Black and Colored South African women. However, both ethnic groups were responsive to the adapted intervention and no differences were found by intervention assignment. These findings support the assertion that group interventions may be more cost-effective in reaching at-risk women in resource-scarce environments. Larger studies are needed to show efficacy and effectiveness of woman-focused group prevention interventions. Wechsberg, W., Luseno, W., Karg, R., Young, S., Rodman, N., Myers, B., and Parry, C. Alcohol, Cannabis, and Methamphetamine Use and Other Risk Behaviors among Black and Colored South African Women: A Small Randomized Trial in the Western Cape. Int. J. Drug Policy, 19(2), pp. 130-139, 2008.

### The Deleterious Effects of Changing Treatment Providers for In-Prison Therapeutic Communities

Corrections officials frequently use private contractors to operate in-prison,

therapeutic community (TC) treatment programs. However, the recurrent competitive bidding process inherent in state agencies contracting for services sometimes results in a treatment-provider change. Few studies have focused on whether this change leads to better or worse treatment motivation and engagement for clients and how it might be evaluated. Using data collected during the larger Criminal Justice Drug Abuse Treatment Studies Performance Indicators for Corrections study, quantitative assessments of client functioning were made at two points in time. Changing to new treatment providers in three in-prison TC treatment facilities caused significant disruptions, leading to decreased client-counselor rapport and peer support as well as lower levels of treatment readiness, participation, and satisfaction of clients. Qualitative client and staff interviews provided further insight relevant for correctional administrators and treatment providers who may be considering similar changes. General recommendations for provider transition planning are offered. Saum, C., O'Connell, D., Martin, S., Hiller, M., Bacon, G., and Simpson, D. Tempest in a TC: Changing Treatment Providers for In-Prison Therapeutic Communities: Criminal Justice and Behavior, 34(9), pp. 1168-1178, 2007.

### Meta-Analysis of Day Treatment and Contingency-Management Dismantling Research

Four successive randomized clinical trials studying contingency management (CM), involving various treatment arms of drug-abstinent housing and work therapy and day treatment (DT) with a behavioral component, were compared on common drug abstinence outcomes at two treatment completion points (2 and 6 months). The clinical trials were conducted from 1990 to 2006 in Birmingham, Alabama, with a total of 644 homeless persons with primary crack cocaine addiction. The meta-analysis utilized the weighted least squares approach to integrate data encompassing 9 different treatment arms to assess the effects of CM and DT (neither, DT only, CM only, and CM + DT) on a common estimate of prevalence of drug abstinence. Taken together, the results show much stronger benefits from CM + DT and from CM only than for DT alone. Throughout all of the Birmingham Homeless Cocaine Studies, the CM + DT consistently produced higher abstinence prevalence than did no CM. Schumacher, J., Milby, J., Wallace, D., Meehan, D., Kertesz, S., Vuchinich, R., Dunning, J., and Usdan, S. Meta-analysis of Day Treatment and Contingency-Management Dismantling Research: Birmingham Homeless Cocaine Studies (1990-2006). J. Consult. Clin. Psychol., 75(5), pp. 823-828, 2007.

### Principal Stratification Designs to Estimate Input Data Missing Due to Death

Studies of cohorts of individuals after a critical event, such as an injury, were considered with the following characteristics. First, the studies are designed to measure 'input' variables, which describe the period before the critical event, and to characterize the distribution of the input variables in the cohort. Second, the studies are designed to measure 'output' variables, primarily mortality after the critical event, and to characterize the predictive (conditional) distribution of mortality given the input variables in the cohort. Such studies often possess the complication that the input data are missing for those who die shortly after the critical event because the data collection takes place after the event. Standard methods of dealing with the missing inputs, such as imputation or weighting methods based on an assumption of ignorable missingness are known to be generally invalid when the missingness of inputs is non-ignorable, that is, when the distribution of the inputs is different between those who die and those who live. To address this issue, the researchers propose a novel design that obtains and uses information on an additional key variable -- a treatment or externally controlled variable, which if set at its 'effective' level, could have prevented the death of those who died. It is shown that the new

design can be used to draw valid inferences for the marginal distribution of inputs in the entire cohort, and for the conditional distribution of mortality given the inputs, also in the entire cohort, even under non-ignorable missingness. The crucial framework that was used is principal stratification based on the potential outcomes, here mortality under both levels of treatment. Using illustrative preliminary injury data, it is shown that this approach can reveal results that are more reasonable than the results of standard methods, in relatively dramatic ways. Thus, the current approach suggests that the routine collection of data on variables that could be used as possible treatments in such studies of inputs and mortality should become common. Frangakis, C., Rubin, D., An, M., and MacKenzie, E. Principal Stratification Designs to Estimate Input Data Missing Due to Death. Biometrics, 63(3), pp. 641-662, 2007.

### Smoking-Cessation Media Campaigns and their Effectiveness Among Socioeconomically Advantaged and Disadvantaged Populations

The authors examined whether the impact of televised smoking cessation ads differed by a population's education and income. Longitudinal data from the Wisconsin Behavioral Health Survey, a statewide sample of 452 adult smokers who were interviewed in 2003 to 2004 and followed up 1 year later was used. Logistic regression was used to assess whether baseline recall of secondhand smoke ads and 'keep trying to quit' ads was associated with quit attempts and smoking abstinence at 1 year. Interaction terms were used to assess whether these associations differed by the smokers' education and income levels. It was found that overall, neither keep-trying-to-quit nor secondhand smoke ad recall was associated with quit attempts or smoking abstinence. Keep-trying-to-quit ads were significantly more effective in promoting quit attempts among higher- versus lower-educated populations. No differences were observed for secondhand smoke ads by the smokers' education or income levels. This study shows that some media campaign messages appear less effective in promoting quit attempts among less-educated populations compared with those who have more education. There is a need to develop media campaigns that are more effective with less-educated smokers. Niederdeppe, J., Fiore, M., Baker, T., and Smith, S. Smoking-Cessation Media Campaigns and their Effectiveness Among Socioeconomically Advantaged and Disadvantaged Populations. Am. J. Public Health, 98(5), pp. 916-924, 2008.

### Factors Associated with Dual Disorder Adolescent's Utilization of Mental Health Services

This study examined the rates and correlates of self-reported receipt for mental health services among 1,190 adolescents, aged 12-19, who were admitted to community-based substance abuse outpatient clinics and had a co-occurring mental health problem. Utilization of mental health service was ascertained 3 months post-intake. About one third (35%) of adolescents with a co-occurring mental health problem identified at intake received mental health service in the 3 months after treatment entry. After holding other correlates constant, history of mental health treatment, suicidal behavior, family history of mental disorder and insurance coverage at intake were associated with mental health service utilization at the 3-month follow up. Predictors of service utilization varied by gender and racial/ethnic status. The authors discuss implications for integrated substance use and mental health services. They recommend, for example, that substance abuse treatment programs provide a prompt and adequate mental health assessment for adolescents to design a treatment plan based on individual needs. In addition, youth with substance use and mental disorders have various and complex treatment needs, but may need additional insight and motivational counseling to address them. The authors also state that special attention and case management (e.g., linkage, advocacy) may be

necessary for uninsured groups as they may be the least likely to obtain services without special assistance. Chan, Y., Godley, M., Godley, S., and Dennis, M. Utilization of Mental Health Services Among Adolescents in Community-Based Substance Abuse Outpatient Clinics. J. Behav. Health Serv. Res, 2007 Dec 21. E-pub ahead of print, (Special Issue), pp. 1-17, 2007.

### Screening, Assessment, and Referral Practices in Adult Correctional Settings: A National Perspective

A national survey of adult prisons, jails, and community correctional agencies was conducted to examine the practices used to place offenders in appropriate treatment services. 289 administrators of adult facilities completed the survey (34% from prisons, 14.2% from jails, 24.6% from state-run community correctional facilities, and 27.2% from locally-run community correctional facilities). 58.2% of survey respondents reported the use of a standardized substance abuse-screening tool, and 34.2% reported use of an actuarial risk tool. The provision of higher intensity treatment programs, the use of standardized risk tools, and the provision of more community referral services were all independently associated with the use of a standardized substance abuse-screening tool. Taxman, F., Cropsey, K., Young, D., and Wexler, H. Screening, Assessment, and Referral Practices in Adult Correctional Settings: A National Perspective. Criminal Justice and Behavior, 34(9), pp. 1216-1234, 2007.

### Review of Office-Based Maintenance Treatment of Opioid Dependence

The increasing global public health burden of heroin dependence and prescription opioid dependence warrants further expansion of treatment models. The most effective intervention for opioid dependence remains maintenance with methadone, a full mu-opioid receptor agonist, or buprenorphine, a partial mu-opioid receptor agonist. A growing body of evidence supports the use of opioid receptor agonist maintenance in office-based settings. Office-based opioid treatment (OBOT) can expand treatment access in a less stigmatized environment, which enables integrated care of co-morbid conditions. The authors discuss clinical and practical considerations when providing treatment for opioid dependence in traditional versus office-based settings include patient selection and monitoring, health economics, management of co-morbid conditions, and access to ancillary psychosocial treatment. OBOT provides an additional opportunity to help address the tremendous public health impact of opioid dependence. Gunderson, E. and Fiellin, D. Office-Based Maintenance Treatment of Opioid Dependence: How Does it Compare With Traditional Approaches? CNS Drugs, 22(2), pp. 99-111, 2008.

### Professional Peer Norms Affect Attitudes Toward Medication in Addiction

Treatment Attitudes, perceived social norms, and intentions were assessed for 376 counselors and 1083 clients from outpatient, methadone, and residential drug treatment programs regarding four medications used to treat opiate dependence: methadone, buprenorphine, clonidine, and ibogaine. Attitudes, social norms, and intentions to use varied by treatment modality. Methadone clients and counselors had more positive attitudes toward the use of methadone, whereas their counterparts in residential and outpatient settings had neutral or negative assessments. Across modalities, attitudes, perceived social norms, and intentions toward the use of buprenorphine were relatively neutral. Assessments of clonidine and ibogaine were negative for clients and counselors in all settings. Social normative influences were dominant across

settings and medications in determining counselor and client intentions to use medications, suggesting that perceptions about beliefs of peers may play a critical role in use of medications to treat opiate dependence. Rieckmann, T., Daley, M., Fuller, B., Thomas, C., and McCarty, D. Client and Counselor Attitudes Toward the Use of Medications for Treatment of Opioid Dependence. J. Subst. Abuse Treat., 32(2), pp. 207-215, 2007.

### Modified Therapeutic Community for Co-occurring Disorders: A Summary of Four Studies

This article summarizes results from four research studies (n = 902) that examined the effectiveness of the modified therapeutic community (MTC) for clients with co-occurring disorders (most with severe mental disorders). The study populations included homeless individuals in New York City; offenders in Pueblo, CO; outpatients in Philadelphia, and HIV+ individuals in Philadelphia, respectively. Across four experimental versus control comparisons, significantly better outcomes for MTC were found on 12 of 52 primary outcome measures of substance use, mental health, crime, HIV risk, employment, and housing. Study limitations included the potential for selection bias, limited measurement of program fidelity, and insufficient examination of the relationship between treatment dose and outcome. Future research should emphasize clinical trial replications, multiple outcome domains, and further development of continuing care models. Given the need for research-based approaches, the MTC warrants consideration when program and policy planners are designing programs for co-occurring disorders. Sacks, S., Banks, S., McKendrick, K., and Sacks, J. Modified Therapeutic Community for Co-occurring Disorders: a Summary of Four Studies. J. Subst. Abuse Treat., 34(1), pp. 112-122, 2008.

### Variations in Client Contact Levels Are Statistically Associated with Programs' External Environment

Data from a survey of 116 outpatient non-methadone treatment programs in four regions of the U.S. (Great Lakes, Gulf Coast, Northwest, and Southeast) were used to estimate statistical associations between three measures of client contact and various program-level characteristics. Separate multivariate regression analysis was used to examine the effect of internal and environmental characteristics on program level summary measures of the average number of hours a typical client spends in individual or group counseling, the average number of hours a typical client spends in case management, and the average counselor caseload. Results reveal that the average client in public programs received 4.64 more hours of counseling compared with private non-profit programs ($p<0.01$), and those in nationally accredited programs received 2.14 more hours than in programs without such accreditation ($p<0.05$), holding other factors constant. The average client in a Southeast program received 4 hours fewer ($p <0.01$) and Great Lakes almost 3 hours fewer ($p<0.05$) of counseling than those in Gulf Coast State programs. The average client in programs with a higher proportion of recently hired counselors likewise received fewer counseling hours (each 10% increase was associated with a decrease of 20 minutes, $p <0.01$). Not surprising programs offering intensive outpatient treatment provided more counseling hours to the average patient. Both public and private for-profit programs reported providing more case management time to the average client than did private non-profit programs (0.86, hours $p <0.05$; 0.61 hours $p< 0.05$) but fewer minutes about were provided in programs with a higher proportion of dually-diagnosed (DD) clients (-4.5 minutes for each 10% increase in the proportion DD). Higher caseloads were associated with location in the Southeast, Great Lakes, and Northwest regions (compared with the Gulf Cost region) and having a higher proportion of criminal justice clients. Lower average caseloads were associated with having received national accreditation, while higher caseloads were associated with having a higher monthly client census, a high proportion of CJ

clients, and location outside of the Gulf Cost region. Knight, D., Broome, K., Simpson, D., and Flynn, P. Program Structure and Counselor-Client Contact in Outpatient Substance Abuse Treatment. Health Serv. Res., 43(2), pp. 616-634, 2008.

### Prescription Drug Diversion and Pain Medication

Prescription drug diversion involves the unlawful channeling of regulated pharmaceuticals from legal sources to the illicit marketplace, and can occur along all points in the drug delivery process, from the original manufacturing site to the wholesale distributor, the physician's office, the retail pharmacy, or the patient. However, empirical data on diversion are limited. In an attempt to develop a better understanding of how specific drug-using populations are diverting prescription opioids' and other medications, or obtaining controlled drugs that have already been diverted, qualitative interviews and focus group data were collected on four separate populations of prescription drug abusers in Miami, Florida --club drug users, street-based illicit drug users, methadone maintenance patients, and HIV positive individuals who abuse and/or divert drugs. Sources of abused prescription drugs cited by focus group participants were extremely diverse, including their physicians and pharmacists; parents and relatives; 'doctor shopping'; leftover supplies following an illness or injury; personal visits to Mexico, South America and the Caribbean; prescriptions intended for the treatment of mental illness; direct sales on the street and in nightclubs; pharmacy and hospital theft; through friends or acquaintances; under-the-door apartment flyers advertising telephone numbers to call; and 'stealing from grandma's medicine cabinet'. While doctor shoppers, physicians and the Internet receive much of the attention regarding diversion, the data reported in this paper suggest that there are numerous active street markets involving patients, Medicaid recipients and pharmacies as well. In addition, there are other data which suggest that the contributions of residential burglaries, pharmacy robberies and thefts, and 'sneak thefts' to the diversion problem may be understated. Inciardi, J., Surratt, H., Kurtz, S., and Cicero, T. Mechanisms of Prescription Drug Diversion Among Drug-Involved Club- and Street-Based Populations. Pain Med., 8(2), pp. 171-183, 2007.

### A Survey of Self-Help Referral Practices Among Adolescent Substance Abuse Treatment Programs

Clinicians in adolescent substance abuse treatment programs often recommend attendance at 12-Step meetings; however, there has been no systematic study of their referral practices or possible influence on attendance rates. The authors of this study used quantitative and qualitative data to examine: (a) the self-help referral practices of clinicians employed in adolescent substance abuse treatment programs; and (b) the potential relationship between practices and self-help attendance. Data were analyzed from open-ended interviews with 28 clinicians at eight CSAT-funded SCY sites and from follow-up interviews with over 1,600 adolescents. Results indicated that clinicians referred adolescents almost exclusively to 12-Step groups. Various factors were considered when recommending attendance, including substance use severity and ability to grasp 12-Step concepts. Meeting age composition and availability were common influences when suggesting specific meetings. Clinicians who described their treatment programs as '12-Step based' and actively linked adolescents to groups tended to be employed at sites that had the highest overall rates of self-help attendance. The authors note that if clinicians want to facilitate self-help attendance, providers might assess the 'fit' between individual adolescents and particular meetings. Additionally, programs may want to develop and train staff in standardized referral procedures. Further research is needed to empirically test referral strategies with adolescents. Passetti, L., and Godley, S., Adolescent Substance Abuse Treatment Clinicians Self-Help Meeting Referral Practices and Adolescent Attendance Rates. J.

Psychoactive Drugs, 40(1), pp. 29-40, 2008.

### A Description of One-Year Treatment Patterns of Adolescents in Addiction Treatment

The American Society on Addiction Medicine's Patient Placement criteria are commonly used in adolescent treatment. However, the use of these criteria and how they affect the course of treatment and interact with adolescent change has not been examined. Twelve-month treatment patterns were examined for 176 adolescents who entered their first ever episode in a treatment system using these criteria. Forty-one percent of the adolescents received additional treatment after their initial outpatient episode with over 30 unique treatment sequences (i.e., various combinations of outpatient, intensive outpatient, and residential treatment). Significant differences in treatment patterns were found between the change trajectory groups. For example, adolescents who participated in only one outpatient treatment episode were more likely to be in the low alcohol and drug use (AOD) group and less likely to have high rates of time in a controlled environment or to report moderate AOD use. Over one-third of the adolescents participated in additional treatment and almost one-quarter of those who only participated in outpatient treatment had problematic use. These findings suggest the need for clinical monitoring protocols that can be used to identify adolescents needing additional treatment or recovery services. Godley, S., Passetti, L., Funk, R., Garner, B., and Godley, M. One-Year Treatment Patterns and Change Trajectories for Adolescents Participating in Outpatient Treatment For the First Time. J. Psychoactive Drugs, 40(1), pp. 17-28, 2008.

### Children and Adolescents Treated for General Delinquency Problems and Rated as Having Sexual Behavior Problems Respond Well to Intensive, Caregiver-Focused Treatment

The authors of this study compare children and adolescents treated for general delinquency problems and rated by caregivers as having sexual behavior problems (SBP; N = 696) with youth from the same sample with no sexual behavior problems (NSBP; N = 1,185). Treatment outcome through 12-months post-treatment and criminal offending through an average 48-month post-treatment were compared for both groups. The authors hypothesized that both groups would improve over time; however, the SBP group would evidence greater psychopathology at follow-up, and these hypotheses were supported. It was further hypothesized that youth with SBP would not differ from youth with NSBP in rates of future sexual or nonsexual offenses. These hypotheses were also supported. SBP group membership was not a significant predictive factor in analyses modeling future offending (any) or future person offenses. Few youth in either group had sexual offenses. These results demonstrate that though youth with SBP apparently represent a substantial minority of delinquent youth referred for treatment, these youths appear to respond well to intensive, caregiver-focused treatment and are no more likely to commit future sexual offenses than delinquent youth without SBP when effectively treated. Letourneau, E., Chapman, J., and Schoenwald, S. Treatment Outcome and Criminal Offending by Youth with Sexual Behavior Problems. Child Maltreat., 13(2), pp. 133-144, 2008.

### Concensus Among Patients About the Value of Abstinence Leads to Better Treatment Outcomes

Secondary analysis of data from a 'Beliefs about Abstinence Scale', used in the Drug Abuse Treatment Outcomes Study (DATOS), was conducted for 76 programs, including outpatient methadone treatment, outpatient drug-free, short-term inpatient, and long-term residential programs. Findings show that

higher levels of client consensus after 1 month of treatment were associated with less use of drugs and alcohol at 1-year follow-up, after controlling for the mean of the scale score, gender, and age, client substance use at baseline and treatment modality. The implications of the results for substance abuse treatment are discussed. Melnick, G., Wexler, H., and Cleland, C. Client Consensus on Beliefs about Abstinence: Effects on Substance Abuse Treatment Outcomes. Drug Alcohol Depend., 93(1-2), pp. 30-37, 2008.

### There Is a Successful Model To Help Substance Abuse Treatment Clinics Make a Smoke-Free Transition

This article describes the Addressing Tobacco through Organizational Change (ATTOC) model which has successfully helped many addiction treatment programs to more effectively address tobacco use. The article reviews the six core strategies used to implement the ATTOC intervention, the 12-Stage approach guiding the model, and describes a case study where the intervention was implemented in a clinic setting. Ziedonis, D., Zammarelli, L., Seward, G., Oliver, K., Guydish, J., Hobart, M., and Meltzer, B. Addressing Tobacco Use Through Organizational Change: A Case Study of an Addiction Treatment Organization. J. Psychoactive Drugs, 39(4), pp. 451-459, 2007.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2008

## Research Findings - CTN-Related Research

### 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 1 of the 2 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 (28 [9.6%] for the Seeking Safety group and 21[7.2%] for the Women's Health Education group). Implementing PTSD treatment in substance abuse treatment programs appears to be safe, with minimal impact on intervention-related adverse psychiatric and substance abuse symptoms. 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. J. Subst. Abuse Treat. 2008 Feb 20. [E-pub ahead of print].

### Using a Standardized Patient Walk-through to Improve Implementation of Clinical Trials

This report describes a standardized patient (SP) walk-through to facilitate implementation of a clinical trial within the National Drug Abuse Treatment Clinical Trials Network (CTN). SPs are actors trained to portray a set of symptoms consistently across interactions with multiple clinicians. The Oregon/Hawaii Node of the CTN employed one SP to pilot participant screening processes in a study testing a combined pharmacological and behavioral therapy for women and men dependent on prescription opioid analgesics. The SP mimicked an individual seeking treatment and "walked" through study intake processes. Findings such as study staff members' inadequacy in describing issues of patient confidentiality and problems explaining the Health Insurance Portability and Accountability Act led to modifications to the clinical implementation of the study. Research coordinators and the staff found the use of an SP to be highly effective. The node is now making routine use of SPs in the implementation of CTN protocols. Fussell, H.E., Kunkel, L.E., Lewy, C.S., McFarland, B.H., McCarty, D.. J. Subst. Abuse Treat. 2008 May 28. [E-pub

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ahead of print].

### States and Substance Abuse Treatment Programs: Funding and Guidelines for Infection-Related Services

Community-based substance abuse treatment programs provide HIV, hepatitis C virus, and sexually transmitted infection services. To explore how state funding and guidelines affect practice, the authors surveyed state agency administrators and substance abuse treatment program administrators and clinicians regarding 8 infection-related services. Although state funding for infection-related services is widely available, substance abuse treatment programs do not always access it. Substance abuse treatment program guidelines are clearer in states that have written guidelines. Improved communication between state agencies and substance abuse treatment programs may enhance service. Kritz, S., Brown, L.S. Jr, Goldsmith, R.J., Bini, E.J., Robinson, J., Alderson, D., Novo, P., and Rotrosen, J. States and Substance Abuse Treatment Programs: Funding and Guidelines for Infection-Related Services. Am. J. Public Health. 98(5), pp. 824-826, E-pub 2008 Apr 1, May 2008.

### Smoking Cessation Treatment in Community-based Substance Abuse Rehabilitation Programs

Nicotine dependence is highly prevalent among drug- and alcohol-dependent patients. A multisite clinical trial of smoking cessation (SC) treatment was performed at outpatient community-based substance abuse rehabilitation programs affiliated with the National Drug Abuse Treatment, Clinical Trials Network. Cigarette smokers (N=225) from five methadone maintenance programs and two drug and alcohol dependence treatment programs were randomly assigned in a 2:1 ratio to receive either (1) SC treatment as an adjunct to substance abuse treatment-as-usual (TAU) or (2) substance abuse TAU. Smoking cessation treatment consisted of 1 week of group counseling before the target quit date and 8 weeks of group counseling plus transdermal nicotine patch treatment (21 mg/day for Weeks 1-6 and 14 mg/day for Weeks 7 and 8) after the target quit date. Smoking abstinence rates in SC, 10%-11% during treatment and 5%-6% at the 13- and 26-week follow-up visits, were significantly better than those in TAU during treatment ($p < .01$). In addition, SC was associated with significantly greater reductions as compared with TAU in cigarettes smoked per day (75% reduction, $p < .001$), exhaled carbon monoxide levels ($p < .001$), cigarette craving ($p < .05$), and nicotine withdrawal ($p < .05$). Smoking cessation did not differ from TAU on rates of retention in substance abuse treatment, abstinence from primary substance of abuse, and craving for primary substance of abuse. Compliance with SC treatment, moderate at best, was positively associated with smoking abstinence rates. Smoking cessation treatment resulted in significant reductions in daily smoking and modest smoking abstinence rates without having an adverse impact on substance abuse rehabilitation when given concurrently with outpatient substance abuse treatment. Substance abuse treatment programs should not hesitate to implement SC for established patients. Reid, M.S., Fallon, B., Sonne, S., Flammino, F., Nunes, E.V., Jiang, H., Kourniotis, E., Lima, J., Brady, R., Burgess, C., Arfken, C., Pihlgren, E., Giordano, L., Starosta, A., Robinson, J., and Rotrosen, J. J. Subst. Abuse Treat. 35(1), pp. 68-77, E-pub 2007 Oct 24, July 2008.

### Infrequent Illicit Methadone Use Among Stimulant-using Patients in Methadone Maintenance Treatment Programs: A National Drug Abuse Treatment Clinical Trials Network Study

The authors sought to determine the prevalence, patterns, and correlates of

past-month illicit methadone use and history of regular illicit use among stimulant-using methadone maintenance treatment patients. They obtained self-reported information on illicit methadone use from 383 participants recruited from six community-based methadone maintenance programs. Overall, 1.6% of participants reported illicit use in the past month, and 4.7% reported a history of regular use. Younger age and history of outpatient psychological treatment were associated with increased odds of past-month illicit use. Illicit methadone use among patients in maintenance programs is infrequent; however, a number of factors may increase risk of illicit use. Wu, L.T., Blazer, D.G., Stitzer, M.L., Patkar, A.A., and Blaine, J.D. Am. J. Addict. 17(4), pp. 304-311, Jul-Aug 2008.

### Motivational Enhancement Therapy to Improve Treatment Utilization and Outcome in Pregnant Substance Users

Pregnant substance users can benefit significantly from substance abuse treatment, but treatment retention can be challenging. Two hundred pregnant substance users entering outpatient substance abuse treatment at one of four treatment programs were randomized to receive either three individual sessions of Motivational Enhancement Therapy for pregnant substance users (MET-PS) or the first three individual sessions normally provided by the program. All participants were encouraged to participate in all other treatment offered by the program. Outcome measures included treatment utilization according to clinic records, qualitative urine toxicology measures, and self-report of substance use. One hundred sixty-two (81%) participants completed the 1-month active phase. Participants attended 62% of scheduled treatment on average and reported decreased substance use during the first month of treatment, with no differences between MET-PS and treatment-as-usual (TAU) participants. There was some evidence that the efficacy of MET-PS varied between sites and that MET-PS might be more beneficial than TAU in decreasing substance use in minority participants. These results suggest that MET-PS is not more effective than TAU for pregnant substance users in general but that there might be particular subgroups or treatment programs for which MET-PS might be more or less effective than TAU. Winhusen, T., Kropp, F., Babcock, D., Hague, D., Erickson, S.J., Renz, C., Rau, L., Lewis, D., Leimberger, J., and Somoza, E.. J. Subst. Abuse Treat. 35(2), pp. 161-73, Epub 2008 Feb 20, September 2008.

### NIDA CTN Membership is Diverse, But Due to the Need For Large Samples, Over Represents Larger Facilities

Programs participating in the National Drug Abuse Treatment Clinical Trials Network (CTN) completed Organizational Surveys (n=106 of 112; 95% response rate) and Treatment Unit Surveys (n=348 of 384; 91% response rate) to describe the levels of care, ancillary services, patient demographics, patient drug use and co-occurring conditions. Analyses describe the corporations participating in the CTN and provide an exploratory assessment of variation in treatment philosophies. A diversity of treatment centers participates in the CTN; not for profit organizations with a primary mission of treating alcohol and drug disorders dominate. Compared to National Survey of Substance Abuse Treatment Services (N-SSATS), programs located in medical settings are over-represented and centers that are mental health clinics are under-represented. Outpatient, methadone, long-term residential and inpatient treatment units differed on patients served and services provided. Larger programs with higher counselor caseloads in residential settings reported more social model characteristics. Programs with higher social model scores were more likely to offer self-help meetings, vocational services and specialized services for women. Conversely, programs with accreditation had less social model influence. The CTN is an ambitious effort to engage community-based treatment organizations into research and more fully integrate research and

practice. McCarty, D., Fuller, B., Kaskutas, L., Wendt, W., Nunes, E., Miller, M., Forman, R., Magruder, K., Arfken, C., Copersino, M., Floyd, A., Sindelar, J., and Edmundson, E. Treatment Programs In the National Drug Abuse Treatment Clinical Trials Network. Drug Alcohol Depend., 92(1-3), pp. 200-207, 2008.

### Staff Perceptions of Need to Improve Treatment are More Open to Implementing New Practices

Program administrators and staff in 249 treatment programs participating in the National Drug Abuse Treatment Clinical Trials Network completed surveys (95% response rate) to characterize participating programs and practitioners. A two-level random-effects regression model assessed the influence of Organizational Readiness for Change (ORC) and organizational attributes on opinions toward the use of four evidence-based practices (manualized treatments, medication, integrated mental health services, and motivational incentives) and practices with less empirical support (confrontation and noncompliance discharge). The ORC scales suggested greater support for evidence-based practices in programs where staff perceived more program need for improvement, better Internet access, higher levels of peer influence, more opportunities for professional growth, a stronger sense of organizational mission, and more organizational stress. Support for confrontation and noncompliance discharge, in contrast, was strong when staff saw less opportunity for professional growth, weaker peer influence, less Internet access, and perceived less organizational stress. The analysis provides evidence of the ORC's utility in assessing agency strengths and needs during the implementation of evidence-based practices. Fuller, B., Rieckmann, T., Nunes, E., Miller, M., Arfken, C., Edmundson, E., and McCarty, D. Organizational Readiness for Change and Opinions Toward Treatment Innovations. J. Subst. Abuse Treat. 33(2), pp. 183-192, 2007.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2008

## Research Findings - International Program-Related Research

*Publications by Former NIDA INVEST Fellows*

**Behavioral Characterization of the mGlu Group II/III Receptor Antagonist, LY-341495, in Animal Models of Anxiety and Depression**
Bespalov, A.Y., van Gaalen, M.M., Sukhotina, I.A., Wicke, K., Mezler, M., Schoemaker, H., and Gross, G.
Eur. J. Pharmacol. 2008 Jul 2; [E-pub ahead of print]
INVEST Fellow: Anton Bespalov, Russia
There is a growing body of evidence indicating that stimulation of metabotropic glutamate type II receptors (mGlu(2/3)) reduces anxiety in laboratory animals and humans. Surprisingly, it was reported that mGlu(2/3) receptor antagonists have antidepressant- and anxiolytic-like activities in laboratory animal studies as well. The present study aimed to resolve this controversy by characterizing behavioral effects of a selective mGlu(2/3) receptor antagonist, LY-341495, in a variety of animal models sensitive to clinically used anxiolytic and antidepressant agents. In agreement with previous reports, LY-341495 (0.3-3 mg/kg, i.p.) reduced immobility in the mouse forced swim test. LY-341495 was also effective in the marble-burying test in mice, although similar effects were observed after administration of various drugs including methamphetamine. Further, LY-341495 had no effects in the elevated plus maze and stress-induced hyperthermia tests in mice, as well as on punished drinking (Geller-Seifter's test) and differential reinforcement of low rates of responding (DRL) in rats. It is concluded that the behavioral profile of mGlu(2/3) receptor antagonists as represented by LY-341495 is different from that of conventional anxiolytic and antidepressant drugs.
PMID: 18634781 [PubMed - as supplied by publisher]

*Publications by Former NIDA Hubert H. Humphrey Fellows*

**Key Findings from the WHO Collaborative Study on Substitution Therapy for Opioid Dependence and HIV/AIDS**
Lawrinson, P., Ali, R., Buavirat, A., Chiamwongpaet, S., Dvoryak, S., Habrat, B., Jie, S., Mardiati, R., Mokri, A., Moskalewicz, J., Newcombe, D., Poznyak, V., Subata, E., Uchtenhagen, A., Utami, D.S., Vial, R., and Zhao, C.
Addiction. 2008 Jul 10; [E-pub ahead of print]
HHH Fellow: Sergey Dvoryak, Ukraine
Opioid substitution treatment has been studied extensively in industrialized countries, but there are relatively few studies in developing/transitional countries. The aim of this study was to examine the effectiveness of opioid substitution treatment (OST) in less resourced countries. The design used was a longitudinal cohort study. The setting was purposively selected OST sites in Asia (China, Indonesia, Thailand), Eastern Europe (Lithuania, Poland, Ukraine), the Middle East (Iran) and Australia. Participants Seven hundred and twenty-six OST entrants served as participants. Participants were interviewed at

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treatment entry, 3 and 6 months. Standardized instruments assessed drug use, treatment history, physical and psychological health, quality of life, criminal involvement, blood-borne virus (BBV) risk behaviors and prevalence of human immunodeficiency virus (HIV) and hepatitis C. Findings showed that participants were predominantly male, aged in their early 30s and had attained similar levels of education. Seroprevalence rates for HIV were highest in Thailand (52%), followed by Indonesia (28%) and Iran (26%), and lowest in Australia (2.6%). Treatment retention at 6 months was uniformly high, averaging approximately 70%. All countries demonstrated significant and marked reductions in reported heroin and other illicit opioid use; HIV (and other BBV) exposure risk behaviors associated with injection drug users (IDU) and criminal activity, and demonstrated substantial improvement in their physical and mental health and general wellbeing over the course of the study. The authors concluded that OST can achieve similar outcomes consistently in a culturally diverse range of settings in low- and middle-income countries to those reported widely in high-income countries. It is associated with a substantial reduction in HIV exposure risk associated with IDU across nearly all the countries. Results support the expansion of opioid substitution treatment. PMID: 18636999 [PubMed - as supplied by publisher]

**Activities**

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# Director's Report to the National Advisory Council on Drug Abuse - September, 2008

## Research Findings - Intramural Research

### Molecular Neurobiology Research Branch

**Genetics of Ability to Quit Smoking**
Smoking remains a major public health problem. Twin studies indicate that the ability to quit smoking is substantially heritable, with genetics that overlap modestly with the genetics of vulnerability to dependence on addictive substances. The objectives of theis study were to identify replicated genes that facilitate smokers' abilities to achieve and sustain abstinence from smoking (hereinafter referred to as quit-success genes) found in more than 2 genome-wide association (GWA) studies of successful vs. unsuccessful abstainers, and, secondarily, to nominate genes for selective involvement in smoking cessation success with bupropion hydrochloride vs. nicotine replacement therapy (NRT). The GWA results in subjects from 3 centers, with secondary analyses of NRT vs. bupropion responders were used. The study setting was 3 outpatient smoking cessation centers. European American smokers who successfully vs. unsuccessfully abstain from smoking with biochemical confirmation in a smoking cessation trial using NRT, bupropion, or placebo (N=550) served as participants. Main outcome measures were: quit-success genes, reproducibly identified by clustered nominally positive single-nucleotide polymorphisms (SNPs) in more than 2 independent samples with significant P values based on Monte Carlo simulation trials. The NRT-selective genes were nominated by clustered SNPs that display much larger t values for NRT vs. placebo comparisons. The bupropion-selective genes were nominated by bupropion-selective results. Results: Variants in quit-success genes are likely to alter cell adhesion, enzymatic, transcriptional, structural, and DNA, RNA, and/or protein-handling functions. Quit success genes are identified by clustered nominally positive SNPs from more than 2 samples and are unlikely to represent chance observations (Monte Carlo P<.0003). These genes display modest overlap with genes identified in GWA studies of dependence on addictive substances and memory. These results support polygenic genetics for success in abstaining from smoking, overlap with genetics of substance dependence and memory, and nominate gene variants for selective influences on therapeutic responses to bupropion vs. NRT. Molecular genetics should help match the types and/or intensity of antismoking treatments with the smokers most likely to benefit from them. 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.

**Genetics of Vulnerability to Methamphetamine Dependence**
Understanding of human methamphetamine dependence, and possibly our abilities to prevent and treat this devastating disorder can be improved by identifying genes whose allelic variants predispose to methamphetamine dependence. The objective of this study was to find "methamphetamine dependence" genes identified by each of 2 genome-wide association (GWA)

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studies of independent samples of methamphetamine-dependent individuals and matched controls. The study involved replicated GWA results in each of 2 case control studies and took place in Japan and Taiwan. Individuals with methamphetamine dependence and matched control subjects free from psychiatric, substance abuse, or substance dependence diagnoses (N=580) served as subjects. Main outcome measures included "Methamphetamine dependence" genes that were reproducibly identified by clusters of nominally positive single-nucleotide polymorphisms (SNPs) in both samples in ways that were unlikely to represent chance observations, based on Monte Carlo simulations that corrected for multiple comparisons, and subsets of "methamphetamine dependence" genes that were also identified by GWA studies of dependence on other addictive substances, success in quitting smoking, and memory. Results indicated that genes identified by clustered nominally positive SNPs from both samples were unlikely to represent chance observations (Monte Carlo P.00001). Variants in these "methamphetamine dependence" genes are likely to alter cell adhesion, enzymatic functions, transcription, cell structure, and DNA, RNA, and/or protein handling or modification. Cell adhesion genes CSMD1 and CDH13 displayed the largest numbers of clustered nominally positive SNPs. "Methamphetamine dependence" genes overlapped, to extents much greater than chance, with genes identified in GWAs studies of dependence on other addictive substances, success in quitting smoking, and memory (Monte Carlo P range <.04 to <.00001). These data support polygenic contributions to methamphetamine dependence from genes that include those whose variants contribute to dependence on several addictive substances, success in quitting smoking, and mnemonic processes. 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., Lin. Arch. Gen. Psychiatry. 65(3), pp. 345-355, 2008.

## Office of the Scientific Director

### Exercise Stress Testing in Recently Abstinent Chronic Cocaine Abusers

Cocaine has well established acute effects on cardiac function, but less is known about effects of chronic use persisting during abstinence. IRP scientists evaluated this question by comparing the results of treadmill exercise stress testing (EST) in 28 medically screened, chronic cocaine users (abstinent for a mean of 6.2 days, range 1-32 days) with the cardiovascular effects of an intravenous cocaine challenge (25 mg or 50 mg) (9 subjects). All subjects had a clinically normal EST; all but one subject reached their predicted heart rate (i.e., was able to exercise to capacity). Only one subject had an exaggerated blood pressure response to exercise. EST produced significantly greater increases in heart rate and blood pressure than did the cocaine challenges. These findings suggest that EST may not add any additional cardiac diagnostic information in asymptomatic, recently abstinent chronic cocaine abusers who have already been medically screened as healthy, and that single low doses of cocaine may not generate substantial cardiac work (as indicated by heart rate and blood pressure) in carefully screened, otherwise healthy cocaine users. Kanneganti, P., Nelson, R.A., Boyd, S.J., Ziegelstein, R.C., and Gorelick, D.A. American Journal of Drug and Alcohol Abuse, 34, pp. 489-498, 2008.

## Development and Plasticity Section, Cellular Neurobiology Research Branch

### A Mechanism for the Inhibition of Neural Progenitor Cell Proliferation by Cocaine

Prenatal exposure of the developing brain to cocaine causes morphological and behavioral abnormalities, possibly caused by cocaine-induced proliferation inhibition and/or apoptosis in neural progenitor cells. IRP investigators

therefore determined the molecular mechanism responsible for mediating the effect of cocaine on cell cycle regulation. Microarray analysis followed by qRT-PCR was used to screen cocaine-responsive and cell cycle-related genes in a neural progenitor cell line. Cyclin A2, among genes related to the G1-to-S cell cycle transition, was most strongly down-regulated by cocaine. Down-regulation of cyclin A was also found in cocaine-treated human primary neural and A2B5+ progenitor cells, as well as in rat fetal brains exposed to cocaine in utero. Reversing cyclin A down-regulation by gene transfer counteracted the proliferation inhibition caused by cocaine. Further, the authors found that cocaine-induced accumulation of reactive oxygen species, which involves N-oxidation of cocaine via cytochrome P450, promotes cyclin A down-regulation by causing an ER stress response, as indicated by increased phosphorylation of eIF2alpha and expression of ATF4. In the developing rat brain, the P450 inhibitor cimetidine counteracted cocaine-induced inhibition of neural progenitor cell proliferation as well as down-regulation of cyclin A. Therefore, down-regulation of cyclin A underlies cocaine-induced proliferation inhibition in neural progenitors. The down-regulation of cyclin A is initiated by N-oxidative metabolism of cocaine and consequent ER stress. Inhibition of cocaine N-oxidative metabolism by P450 inhibitors may provide a preventive strategy for counteracting the adverse effects of cocaine on fetal brain development. Lee, C.T., Chen, J., Hayashi, T., Tsai, S.Y., Sanchez, J.F., Errico, S.L., Amable, R., Su, T.P., Lowe, R.H., Huestis, M.A., Shen, J., Becker, K.G., Geller, H.M., and Freed, W.J. Public Library of Science Medicine, 5(6), pp. e117, 2008.

**Benefits and Risks of Intranigral Transplantation of GABA-producing Cells Subsequent to the Establishment of Kindling-induced Seizures**

IRP scientists assessed the anticonvulsant efficacy and safety of bilateral allotransplantation of genetically engineered striatal GABAergic rat cell lines into the SNr. Rats with previously-established seizures, induced by amygdala kindling, were used as a model of temporal lobe epilepsy. Three cell lines were transplanted: immortalized GABAergic cells (M213-2O) derived from embryonic rat striatum; M213-2O cells (CL4) transfected with human GAD67 cDNA to obtain higher GABA synthesis than the parent cell line; and control cells (121-1I), also derived from embryonic rat striatum, but which did not show GAD expression. A second control group received injections of medium alone. Transplantation of M213-2O cells into the SNr of kindled rats resulted in significant but transient anticonvulsant effects. Neither control cells nor medium induced anticonvulsant effects. Strong tissue reactions were, however, induced in the host brain of kindled but not of non-kindled rats, and only in animals that received grafts of genetically modified CL4 cells. These tissue reactions included graft rejection, massive infiltration of inflammatory immune cells, and gliosis. The anticonvulsant effect of M213-2O cells emphasizes the feasibility of local manipulations of seizures by intranigral transplantation of GABA-producing cells. On the other hand, kindling-induced activation of microglia in the SNr combined with immunological stimulation by CL4 cells, transfected with a human cDNA, caused graft rejection. Thus, it appears that the condition of the host brain and the production of foreign proteins by transplanted cells have to be considered in estimating the risks of rejection of transplants into the brain. Nolte, M.W., Loescher, W., Herden, C., Freed, W.J., and Gernert, M. Neurobiology of Disease, July 14, 2008, [E-pub ahead of print].

**Intranigral Transplants of a GABAergic Cell Line Produce Long-term Alleviation of Established Motor Seizures**

IRP researchers have previously shown that intranigral transplants of immortalized GABAergic cells decrease the number of kainic acid-induced seizures in an animal model. In the present study, recurrent spontaneous behavioral seizures were established by repeated systemic injections of this excitotoxin into male Sprague-Dawley rats. After the seizures had been established, cells were transplanted into the substantia nigra. Animals with transplants of control cells (without hGAD67 expression) or with sham

transplants showed a death rate of more than 40% over the 12 weeks of observation, whereas in animals with M213-2O CL-4 transplants, the death rate was reduced to less than 20%. The M213-2O CL-4 transplants significantly reduced the percentage of animals showing behavioral seizures; animals with these transplants also showed a lower occurrence of stage V seizures than animals in the other groups. In vivo and in vitro analyses provided evidence that the GABAergic cells show sustained expression of both GAD67 and hGAD67 cDNA, as well as increased gamma-aminobutyric acid (GABA) levels in the ventral mesencephalon of transplanted animals. Therefore, transplantation of GABA-producing cells can produce long-term alleviation of behavioral seizures in an animal model. Castillo, C.G., Mendoza-Trejo, S., Aguilar, M.B., Freed, W.J., and Giordano. M. Behavioural Brain Research, May 4, 2008, [E-pub ahead of print].

**Assessment of Stromal-derived Inducing Activity in the Generation of Dopaminergic Neurons from Human Embryonic Stem Cells**

Producing dopaminergic (DA) neurons is a major goal of human embryonic stem cell (hESC) research. DA neurons can be differentiated from hESC by coculture with the mouse PA6 stromal cell line; this differentiation-inducing effect is termed stromal-derived inducing activity (SDIA). The molecular and biochemical nature of SDIA is, however, unknown. Various studies have suggested that SDIA involves either a fixation-resistant component located on the PA6 cell surface or factors secreted into the medium by PA6 cells. To address this question, hESC were cocultured with PA6 cells for 12 days and then further differentiated with sonic hedgehog homolog, fibroblast growth factor-8, and glial cell line-derived neurotrophic factor. After 18 days, 34% of cells were tyrosine hydroxylase (TH)+. When PA6 cells were fixed or irradiated, the number of TH+ cells was decreased by threefold, whereas mitomycin-c treatment of feeder cells decreased the number of TH+ cells by 32%. The neural-inducing effect of PA6 cells, as monitored by beta-III-tubulin expression, was minimally affected by mitomycin-c treatment or fixation but was decreased 50% by irradiation. Medium conditioned by PA6 cells was ineffective in differentiating TH+ cells when used alone. Conditioned medium combined with heparin and/or fixed PA6 cells produced TH+ cell differentiation, although less effectively than PA6 cell coculture. Thus, PA6 cell surface activity is required for neural differentiation of hESC, but secreted factors are required for the specific DA neuron-inducing effect. Vazin, T., Chen, J., Lee, C.T., Amable, R., and Freed, W.J. Stem Cells, 26(6), pp. 1517-1525, 2008.

## Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

**Gene Expression Patterns in Mouse Cortical Penumbra after Focal Ischemic Brain Injury and Reperfusion**

Ischemic stress in the brain causes acute and massive cell death in the targeted core area followed by a second phase of damage in the neighboring penumbra. The purpose of this study was to examine the global gene expression patterns in the penumbra, because the ischemic lesion in this region could be rescued by restoration of blood flow and other protective therapies. Adult C57Bl/6 mice were subjected to a 90-min middle cerebral artery occlusion (MCAO). Laser capture microdissection (LCM) was used for tissue dissection at 4 and 24 hr after reperfusion. Sham-operated animals were used as controls. Gene expression in the penumbra was examined by using microarray analysis and quantitative RT-PCR. In agreement with previous reports, most genes were down-regulated at 4 hr after the onset of reperfusion in the ischemic penumbra compared with controls. In contrast, at 24 hr after reperfusion, most genes were up-regulated in the ischemic penumbra. Several genes not previously reported to be associated with ischemia were found. The gene lists generated in this study will help us to understand better the spatial and temporal distribution of molecules involved in the ischemic cascade.

Sarabi, A.S., Shen, H., Wang, Y., Hoffer, B.J., and Baeckman. C.M. Journal of Neuroscience Research, May 27, 2008, [E-pub ahead of print].

## Electrophysiology Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

### Analogs of JHU75528, a PET Ligand for Imaging of Cerebral Cannabinoid Receptors (CB1): Development of Ligands with Optimized Lipophilicity and Binding Affinity

Cyano analogs of Rimonabant with high binding affinity for the cerebral cannabinoid receptor (CB1) and with optimized lipophilicity have been synthesized as potential positron emission tomography (PET) ligands. The best ligands of the series are optimal targets for the future radiolabeling with PET isotopes and in vivo evaluation as radioligands with enhanced properties for PET imaging of CB1 receptors in human subjects. Extracellular electrophysiological recordings in rodent brain slices demonstrated that JHU75528, 4, the lead compound of the new series, has functional CB antagonist properties that are consistent with its structural relationship to Rimonabant. Molecular modeling analysis revealed an important role of the binding of the cyano group with the CB1 binding pocket. Fan, H., Kotsikorou, E., Hoffman, A.F., Ravert, H.T., Holt, D., Hurst, D.P., Lupica, C.R., Reggio, P.H., Dannals, R.F., and Horti, A.G. European Journal of Medicinal Chemistry, April 18, 2008, [E-pub ahead of print].

### Discovery of (-)-7-methyl-2-exo-[3'-(6-[(18)F]fluoropyridin-2-yl)-5'-pyridinyl]-7-azabicyclo[2.2.1]heptane, A Radiolabeled Antagonist for Cerebral Nicotinic Acetylcholine Receptor (alpha4beta2-nAChR) with Optimal Positron Emission Tomography Imaging Properties

Several isomers of 7-methyl-2- exo-([(18)F]fluoropyridinyl-5'-pyridinyl)-7-azabicyclo[2.2.1]heptane have been developed as radioligands with optimized brain kinetics for PET imaging of nAChR. The binding assay demonstrated that all isomers are beta-nAChR selective ligands with Ki = 0.02-0.3 nM. The experimental lipophilicity values of all isomers were in the optimal range for the cerebral radioligands (log D 7.4= 0.67-0.99). The isomers with higher binding affinity manifested slow baboon brain kinetics, whereas the isomer with the lowest binding affinity (Ki = 0.3 nM)((-)-7-methyl-2- exo-[3'-(6-[(18)F]fluoropyridin-2-yl)-5'-pyridinyl]-7-azabicyclo[2.2.1]heptane, [(18)F](-)-6c) and greatest lipophilicity (log D 7.4 = 0.99) exhibited optimal brain kinetics. [(18)F](-)-6c manifests a unique combination of the optimally rapid brain kinetics, high BP and brain uptake, and favorable metabolic profile. Pharmacological studies showed that (-)-6c is an alpha4beta2-nAChR antagonist with low side effects in mice. This combination of imaging properties suggests that [(18)F]-(-)-6c is a potentially superior replacement for 2-[(18)F]fluoro-A-85380 and 6-[(18)F]fluoro-A-85380, the only available nAChR PET radioligands for humans. Gao Y., Kuwabara, H., Spivak, C.E., Xiao, Y., Kellar, K., Ravert, H.T., Kumar, A., Alexander, M., Hilton, J., Wong, D.F., Dannals, R.F., and Horti, A.G. Journal of Medicinal Chemistry, July 8, 2008, [E-pub ahead of print].

## Proteomics Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

### The Role of Phosphorylated Residues in Peptide-Peptide Noncovalent Complexes Formation

Electrospray mass spectrometry (ESI-MS) has become the tool of choice for the study of noncovalent complexes. Previous work by IRP researchers has highlighted the role of phosphorylated amino acid residues in the formation of noncovalent complexes through electrostatic interaction with arginine residues' guanidinium groups. In this study, the authors employ tandem mass spectrometry to investigate the gas-phase stability and dissociation pathways

of these noncovalent complexes. The only difference in the three phosphopeptides tested is the nature of the phosphorylated amino acid residue. In addition, the absence of acidic residues and an amidated carboxyl terminus insured that the only negative charge came from the phosphate, which allowed for the comparison of the noncovalent bond between arginine residues and each of the different phosphorylated residues. Dissociation curves were generated by plotting noncovalent complex ion intensities as a function of the nominal energy given to the noncovalent complex ion before entering the collision cell. These results showed that noncovalent complexes formed with phosphorylated tyrosine were the most stable, followed by serine and threonine, which had similar stability. Jackson, S.N., Moyer, S.C., and Woods, A.S. Journal of American Society for Mass Spectrometry, July 3, 2008, [E-pub ahead of print].

**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 D2 receptor third intracellular loop. This is the same epitope involved in adenosine A 2A-D2 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 D2 receptor Arg-rich epitope and several CaM acidic epitopes are mainly responsible for the D2 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 D2 but not to the A 2A receptor epitope, and CaM disrupted the electrostatic interactions between the D2 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 Proteome Research, July 1, 2008, [E-pub ahead of print].

**Amazing Stability of Phosphate-Quaternary Amine Interactions**

IRP scientists have previously used MALDI mass spectrometry to highlight ammonium- or guanidinium-aromatic interactions via cation-pi bonding and ammonium- or guanidinium-phosphate interactions through salt bridge formation. In the present work, the gas-phase stability and dissociation pathways of the interaction between phosphorylated peptides and compounds containing quaternary amines are demonstrated using electrospray ionization mass spectrometry. The presence of one quaternary amine in a compound is enough to form a noncovalent complex with a phosphorylated residue. However, if two quaternary amines are present in one molecule, the electrostatic interactions of the quaternary amines with the phosphate results in a "covalent-like" stability, and these bonds can withstand fragmentation by collision-induced dissociation at energies similar to those that fragment covalent bonds. Such interactions are important in accounting for physiological, pathophysiological, and pharmacological effects of many therapeutic compounds and small molecules containing quaternary amines or phosphates. Woods, A.S., Moyer, S.C., and Jackson, S.N. Journal of Proteome Research, June 26, 2008, [E-pub ahead of print].

## Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch

### 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., Franco, R. Journal of Biological Chemistry, July 25, 2008, E-pub 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 scientists 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., Franco, R. Neuropharmacology, May 16, 2008, E-pub 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 researchers 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 endocannabinoid 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 favor 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., Piomelli, D.. British Journal of Pharmacology, 154, pp. 369-83, 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., Lluis, C. Brain Research Review, June 20, 2008, E-pub ahead of print, PMID: 18620000.

**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 investigators 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.

## Nicotine Psychopharmacology Unit, Treatment Section, Clinical Pharmacology and Therapeutics Research Branch

**Reliability and Validity of the Tobacco Craving Questionnaire--Short Form**

The Tobacco Craving Questionnaire (TCQ) is a valid and reliable, 47-item self-report instrument that assesses tobacco craving in four dimensions: emotionality, expectancy, compulsivity, and purposefulness. For use in research and clinical settings, IRP scientists constructed a 12-item version of the TCQ by selecting three items from each of the four factors that exhibited optimal within-factor reliability (Cronbach's alpha coefficient) and inter-item correlation. Smokers (n=196) completed the TCQ-Short Form (TCQ-SF) after overnight tobacco deprivation and on a separate day during ad libitum smoking. Confirmatory factor analyses indicated acceptable model fit for a 4-factor model, with congruence coefficients suggesting high to very high similarity in factor patterns and magnitude of factor loadings between the TCQ and TCQ-SF in both conditions. Scores on each factor were significantly greater after tobacco deprivation than ad libitum smoking, were associated with measures of tobacco withdrawal, and varied with degree of nicotine dependence. Cronbach's alpha coefficients and average inter-item correlations were similar in both conditions and were consistent with reliability values obtained in the initial validation of the TCQ. Test-retest correlation coefficients were also similar to those found in a previous study. These findings suggest that the TCQ-SF is as valid and reliable as the 47-item TCQ in measuring tobacco craving. Heishman, S.J., Singleton, E.G., and Pickworth, W.B. Nicotine and Tobacco Research, 10, pp. 643-651, 2008.

## Chemical Biology Research Branch

## Clinical Psychopharmacology Section, Chemical Biology Research Branch

### Studies of the Biogenic Amine Transporters. 12. Identification of Novel Partial Inhibitors of Amphetamine-induced Dopamine Release

Previous studies identified partial inhibitors and allosteric modulators of 5-HT ([5-amino-3-(3,4-dichlorophenyl)-1,2-dihydropyrido[3,4-b]pyrazin-7-yl]carbamic acid ethyl ester [SoRI-6238], 4-(2-[bis(4-fluorophenyl)methoxy]ethyl)-1-(2-trifluoromethyl-benzyl)-piperidine [TB-1-099]) and dopamine transporters N-(Diphenylmethyl)-2-phenyl-4-quinazolinamine, [SoRI-9804]). IRP researchers report here the identification of three novel allosteric modulators of the dopamine transporter N-(2,2-Diphenylethyl)-2-phenyl-4-quinazolinamine [SoRI-20040], N-(3,3-Diphenylpropyl)-2-phenyl-4-quinazolinamine [SoRI-20041], [4-Amino-6-[(diphenylmethyl)amino]-5-nitro-2-pyridinyl]carbamic acid ethyl ester, [SoRI-2827]). Membranes were prepared from HEK cells expressing the cloned human dopamine (hDAT) transporter. [125I]RTI-55 binding and other assays followed published procedures. SoRI-20040, SoRI-20041 and SoRI-2827 partially inhibited [125I]RTI-55 binding with EC50 values ranging from ~1.4 uM to 3 uM and EMAX values decreasing as the [125I]RTI-55 concentrations increased. All three compounds decreased the [125I]RTI-55 Bmax and increased the apparent Kd in a manner well described by a sigmoid dose-response curve. In dissociation rate experiments, SoRI-20040 (10 uM) and SoRI-20041 (10 uM), but not SoRI-2827 (10 uM), slowed the dissociation of [125I]RTI-55 from hDAT by ~30%. Using rat brain synaptosomes, all three agents partially inhibited [3H]dopamine uptake with EC50 values ranging from 1.8 uM to 3.1 uM and decreased the VMAX value in a dose-dependent manner. SoRI-9804 and SoRI-20040 partially inhibited amphetamine-induced DAT-mediated release of [3H]MPP+ from rat caudate synaptosomes in a dose-dependent manner. Viewed collectively, the authors report several compounds that allosterically modulate hDAT binding and function, and identify novel partial inhibitors of amphetamine-induced dopamine release. Pariser, J.J., Partilla, J.S., Dersch, C.M., Ananthan, S., and Rothman R.B. J. Pharmacol. Exp. Ther., 326, pp. 286-295, 2008.

### Chronic Fenfluramine Administration Increases Plasma Serotonin (5-HT) to Non-Toxic Levels

Large elevations in blood serotonin (5-HT) can produce valvular heart disease in humans and laboratory animals. Accordingly, one prevailing hypothesis (i.e., the "5-HT hypothesis") suggests 5-HT transporter substrates like fenfluramine increase the risk for valvular heart disease by elevating plasma 5-HT, secondary to the release of 5-HT from platelets. The main purpose of this study was to determine if chronic administration of fenfluramine increases plasma 5-HT to concentrations that are associated with the development of valvular heart disease. To the best of the authors' knowledge, this is the first study to address this issue using an in vivo microdialysis method that measures plasma 5-HT in non-hypoxic rats. The IRP scientists examined the effects of chronic (+/-)-fenfluramine and fluoxetine on plasma levels of 5-HT and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in blood samples from conscious catheterized rats. Plasma indoles were measured by HPLC-ECD in dialysates of whole blood. Baseline plasma 5-HT was < 1.0 nM. Chronic fenfluramine (14-day minipump infusion) produced small increases in baseline plasma 5-HT (~2-to-4-fold), while chronic fluoxetine had no effect. Chronic fenfluramine and fluoxetine markedly decreased whole blood 5-HT, and reduced the ability of acute fenfluramine to evoke 5-HT release. Elevations in baseline plasma 5-HT produced by chronic fenfluramine are far below M levels necessary to produce valvular heart disease. Furthermore, chronic fenfluramine reduces the ability of acute fenfluramine to increase plasma 5-HT, suggesting the "5-HT hypothesis" can not explain the increased risk of valvular heart disease in patients treated with fenfluramine. Zolkowska, D., Baumann M.H., and Rothman R.B. J.

Pharmacol. Exp. Ther., 324, pp. 791-797, 2008.

### Drug Design and Synthesis Section, Chemical Biology Research Branch

#### Synthesis and Structure-Activity Relationships of a Potent mu-Agonist delta-Antagonist and an Exceedingly Potent Antinociceptive in the Enantiomeric 9-Substituted 5-(3-Hydroxyphenyl)-N-phenylethylmorphan Series

Both of the enantiomers of 5-(3-hydroxyphenyl)-N-phenylethylmorphan with C9a-methyl, C9-methylene, C9-keto and C9a- and C9b-hydroxy substituents were synthesized and pharmacologically evaluated. Three of the 10 compounds, (1R,5R,9S)-(-)-9-hydroxy-5-(3-hydroxyphenyl-2-phenylethyl-2-azabicyclo[3.3.1]nonane ((1R,5R,9S)-(-)-10),(1R,5S)-(+)-5-(3-hydroxyphenyl)-9-methylene-2-phenethyl-2-azabicyclo[3.3.1]nonane ((1R,5S)-(+)-14), and (1R,5S,9R)-(-)-5-(3-hydroxyphenyl)-9-methyl-2-phenethyl-2-azabicyclo[3.3.1]nonane ((1R,5S,9R)-(+)-15) had subnanomolar affinity at m-opioid receptors (Ki = 0.19, 0.19, and 0.63 nM, respectively). The (1R,5S)-(+)-14 was found to be a m-opioid agonist and a mu-, delta- and kappa-antagonist in [35S]GTP-g-S assays and was approximately 50-times more potent than morphine in a number of acute and subchronic pain assays including thermal and visceral models of nociception. The (1R,5R,9S)-(-)-10 compound with a C9-hydroxy substituent axially oriented to the piperidine ring (C9beta-hydroxy), was a mu-agonist about 500 times more potent than morphine. In the single-dose suppression assay it was greater than 1000 times more potent than morphine. It is the most potent known phenylmorphan antinociceptive. The molecular structures of these compounds were energy minimized with density functional theory at the B3LYP/6-31G* level, and then overlayed onto (1R,5R,9S)-(-)-10 using the heavy atoms in the morphan moiety as a common docking point. Based on modeling, the spatial arrangement of the protonated nitrogen atom and the 9beta-OH substituent in (1R,5R,9S)-(-)-10 may facilitate the alignment of a putative water chain enabling proton transfer to a nearby proton acceptor group in the mu-opioid receptor. Hiebel, A.-C., Lee, Y. S., Bilsky, E., Giuvelis, D., Deschamps, J.R., Aceto, M.D., May, E.L., Harris, L.S., Coop, A., Dersch, C.M., Partilla, J.S., Rothman, R B., Cheng, K., Jacobson, A.E., and Rice, K.C. J. Med. Chem., 50, pp. 3765-3776, 2007.

### Drug Design and Synthesis Section, Chemical Biology Research Branch

#### A Novel Divergent Synthesis of ortho-Hydroxy-e and -f Oxide-Bridged 5-Phenylmorphans

5-(2-Bromo-3-methoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-9-one was prepared in six steps from a known acetonitrile. Stereoselective reduction of the ketone furnished the corresponding - or -alcohols and their deprotonation, intramolecular cyclization, and demethylation gave ortho-hydroxy-e and -f oxide-bridged 5-phenylmorphans, respectively. This new synthetic route has the desired oxygenation pattern in place, eliminating the problematic diazonium reactions used in former syntheses. Zezula, J., Jacobson, A.E., and Rice, K.C. Heterocycles 71, pp. 881-889, 2007.

#### Opioid Ligands With Mixed Properties From Substituted Enantiomeric N-Phenethyl-5-Phenylmorphans. Synthesis of a micro-Agonist delta-Antagonist and delta-Inverse Agonists

Enantiomeric N-phenethyl-m-hydroxyphenylmorphans with various substituents in the ortho, meta or para positions of the aromatic ring in the phenethylamine side-chain (chloro, hydroxy, methoxy, nitro, methyl), as well as a pyridylethyl and a indolylethyl moiety on the nitrogen atom, were synthesized and their binding affinity to the mu-, delta- and kappa-opioid

receptors was examined. The higher affinity ligands were further examined in the [35S]GTPgS assay to study their function and efficacy. 3-((1R,5S)-(-)-2-(4-Nitrophenethyl)-2-aza-bicyclo[3.3.1]nonan-5-yl)phenol ((-)-10m) was found to be a mu-agonist and delta-antagonist in that functional assay and was about 50 fold more potent than morphine in vivo. 3-((1R,5S)-(-)-2-(4-Chlorophenethyl)-2-aza-bicyclo[3.3.1]nonan-5-yl)phenol ((-)-10i) and several other ligands displayed inverse agonist activity at the delta-opioid receptor. The absolute configuration of all of the reported compounds was established by chemical conversion to a compound with known absolute configuration. Cheng, K., Kim, I.-J., Lee, M.J., Adah, S.A., Raymond, T.J., Bilsky, E., Aceto, M.D., May, E.L., Harris, L.S., Coop, A., Dersch, C M., Rothman, R.B., Jacobson, A.E., and Rice, K.C. Org. & Biomolec. Chem., 5, pp. 1177-1190, 2007.

**A New Approach to the Synthesis of the Nonpeptide NOP Receptor Antagonist J-113397**

To obtain multi-gram quantities of J-113397, a competitive antagonist of the N/OFQ-NOP receptor system, we report a new synthesis that eliminated the need for chromatographic separation. N-Benzyl protected 4-oxopiperidinecarboxylate was used as the starting material to obtain an N-benzyl intermediate that could be resolved at a relatively early stage in the synthesis. The crucial step in the synthesis was reduction of the double bond of the -enaminoester functionality of 1-benzyl-4-(3-ethyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester, since Pd/C reduction gave inseparable mixtures. IRP scientits found that it could be reduced and epimerized to the desired trans diastereoisomer in a one-pot reaction by treatment with magnesium metal in methanol. Sulima, A., Folk, J., Jacobson, A.E., and Rice, K.C. Synthesis, 10, pp. 1547-1553, 2007.

**Synthesis and Pharmacological Effects of the Enantiomers of the N-phenethyl Analogues of the ortho and para e- and f-oxide-Bridged Phenylmorphans**

The N-phenethyl analogues of (1R*,4aR*,9aS*)-2-phenethyl-1,3,4,9a-tetrahydro-2H-1,4a-propanobenzofuro[2,3-c]pyridin-6-ol and 8-ol and (1R*,4aR*,9aR*)-2-phenethyl-1,3,4,9a-tetrahydro-2H-1,4a-propanobenzofuro[2.3-c]pyridin-6-ol and 8-ol, the ortho- (43) and para-hydroxy e- (20), and f-oxide-bridged 5-phenylmorphans (53 and 26) were prepared in racemic and enantiomerically pure forms from a common quaternary salt precursor. Optical resolutions were accomplished by salt formation with suitable enantiomerically pure chiral acids or by preparative HPLC on a chiral support. The N-phenethyl (-)- para-e enantiomer (1S,4aS,9aR-(-)-20) was found to be a mu-opioid agonist with morphine-like antinociceptive activity in a mouse assay. In contrast, the N-phenethyl (-)-ortho-f enantiomer (1R,4aR,9aR-(-)-53) had good affinity for the mu-opioid receptor (Ki = 7 nM) and was found to be a m-antagonist both in the [35S]GTP-g-S assay and in vivo. The molecular structures of these rigid enantiomers were energy minimized with density functional theory at the level B3LYP/6-31G* level, and then overlayed on a known potent mu-agonist. This superposition study suggests that the agonist activity of the oxide-bridged 5-phenylmorphans can be attributed to formation of a seven membered ring that is hypothesized to facilitate a proton transfer from the protonated nitrogen to a proton acceptor in the m-opioid receptor. Zezula, J., Singer, L. B., Przybyl, A.K., Hashimoto, A., Dersch, C.M., Rothman, R.B., Deschamps, J., Lee, Y.S., Jacobson, A.E., and Rice, K.C. Org. & Biomol. Chem., DOI: 10.1039/b803433h, 2008.

## Behavioral Neuroscience Research Branch

## Behavioral Neuroscience Section, Behavioral Neuroscience Research Branch

**Ventral Tegmental Glutamate: A Role in Stress-, Cue-, and Cocaine-induced Reinstatement of Cocaine-seeking**

Ventral tegmental dopamine neurons are activated by primary rewards and, when such rewards are predictable by reward-predicting stimuli. Glutamatergic input to the ventral tegmental area contributes to this activation: in animals trained to self-administer cocaine, cocaine-predictive cues trigger ventral tegmental glutamate release and dopaminergic activation. Mild footshock stress similarly causes glutamate release and dopaminergic activation in cocaine-trained but not cocaine-naive animals. The ability of cocaine-predictive and stress-associated cues to activate the dopamine system and to trigger cocaine craving appears to be related to changes in the ability of glutamate to activate dopaminergic neurons, changes known to be caused by experience with stress or with drugs of abuse. Wise, R. A. Neuropharmacology, 2008, [E-pub ahead of print].

**Intracranial Self-administration of MDMA into the Ventral Striatum of the Rat: Differential Roles of the Nucleus Accumbens Shell, Core, and Olfactory Tubercle**

Behavioral and anatomical data suggest that the ventral striatum, consisting of the nucleus accumbens and olfactory tubercle, is functionally heterogeneous. Cocaine and D-amphetamine appear to be more rewarding when administered into the medial olfactory tubercle or medial accumbens shell than into their lateral counterparts, including the accumbens core. IRP researchers sought to determine whether rats self-administer the popular recreational drug (+/-)-3,4-methylenedioxymethamphetamine (MDMA) into ventrostriatal subregions and whether the medial olfactory tubercle and medial accumbens shell mediate MDMA's positive reinforcing effects more effectively than their lateral counterparts. Rats receiving 30 mM MDMA into the medial olfactory tubercle, medial accumbens shell, or accumbens core, but not the lateral tubercle or lateral shell, showed higher self-administration rates than rats receiving vehicle. The medial shell supported more vigorous self-administration of MDMA at higher concentrations than the core or medial olfactory tubercle. In addition, intra-medial shell MDMA self-administration was disrupted by co-administration of the D1 or D2 receptor antagonists SCH 23390 (1-3 mM) or raclopride (3-10 mM). These data suggest that the ventral striatum is functionally heterogeneous. The medial accumbens shell appears to be more important than other ventrostriatal subregions in mediating the positive reinforcing effects of MDMA via both D1- and D2-type receptors. Together with previous data, our data also suggest that unidentified actions of MDMA interfere with the positive reinforcing effects of dopamine in the medial olfactory tubercle. Shin, R., Qin, M., Liu, Z-H., and Ikemoto, S. Psychopharmacology (Berl), 198(2), pp. 261-270, 2008.

**Dual Role of Medial A10 Dopamine Neurons in Affective Encoding**

Increasing evidence suggests that the activation of medial A10 neurons mediates positive affective encoding. However, little is known about the functions of the inhibition of midbrain dopamine neurons. Here IRP investigators show evidence suggesting that the inhibition of medial A10 neurons mediates a negative affective state, leading to negative affective encoding, whereas blunting the activation of medial A10 neurons disrupts positive affective encoding involving food reward. The authors used a microinjection procedure, in which the D(2) dopamine receptor agonist quinpirole was administered into the cell body region of the dopamine neurons, a procedure that reduces dopamine cell firing. Microinjections of quinpirole into the posteromedial ventral tegmental area, but not its more lateral counterparts, led to conditioned place aversion. Quinpirole administration to this site also decreased food intake and basal dopamine concentration in the ventromedial striatum, a major projection area of medial A10 neurons. In addition, moderate quinpirole doses that did not lead to conditioned place aversion or disrupt food intake abolished food-conditioned place preference, suggesting that blunting dopamine impulse activity in response to food reward

disrupts positive affective encoding in associated external stimuli. These data support the hypothesis that activation of medial A10 dopamine neurons mediates a positive affective state, leading to positive affective encoding, while their inhibition mediates a negative affective state, leading to negative affective encoding. Together with previous findings, the authors propose that medial A10 neurons are an important component of the mechanism via which animals learn to avoid negative incentive stimuli. Liu, Z-H., Shin, R., and Ikemoto, S. Neuropsychopharmacology, 2008, E-pub ahead of print.

## Neurobiology of Relapse Section, Behavioral Neuroscience Research Branch

### Context-induced Relapse to Drug Seeking: A Review

In humans, exposure to environmental contexts previously associated with drug intake often provokes relapse to drug use, but the mechanisms mediating this relapse are unknown. Based on early studies by Bouton & Bolles on context-induced 'renewal' of learned behaviors, we developed a procedure to study context-induced relapse to drug seeking. In this procedure, rats are first trained to self-administer drug in one context. Next, drug-reinforced lever responding is extinguished in a different (non-drug) context. Subsequently, context-induced reinstatement of drug seeking is assessed by re-exposing rats to the drug-associated context. Using variations of this procedure, we and others reported reliable context-induced reinstatement in rats with a history of heroin, cocaine, heroin-cocaine combination, alcohol and nicotine self-administration. Here, IRP scientists first discuss potential psychological mechanisms of context-induced reinstatement, including excitatory and inhibitory Pavlovian conditioning, and occasion setting. They then summarize results from pharmacological and neuroanatomical studies on the role of several neurotransmitter systems (dopamine, glutamate, serotonin and opioids) and brain areas (ventral tegmental area, accumbens shell, dorsal striatum, basolateral amygdala, prefrontal cortex, dorsal hippocampus and lateral hypothalamus) in context-induced reinstatement. The authors conclude by discussing the clinical implications of rat studies on context-induced reinstatement of drug seeking. Crombag, H.S., Bossert, J.M., Koya, E., and Shaham, Y. Philos Trans R Soc Lond B Biol Sci., 2008, [E-pub ahead of print].

### Role of Ventral Medial Prefrontal Cortex in Incubation of Cocaine Craving

Cue-induced drug-seeking in rodents progressively increases after withdrawal from cocaine, suggesting that cue-induced cocaine craving incubates over time. Here, IRP researchers explored the role of the medial prefrontal cortex (mPFC, a brain area previously implicated in cue-induced cocaine seeking) in this incubation. They trained rats to self-administer cocaine for 10 days (6h/day, infusions were paired with a tone-light cue), and then assessed after 1 or 30 withdrawal days the effect of exposure to cocaine cues on lever presses in extinction tests. The authors found that cue-induced cocaine-seeking in the extinction tests was higher after 30 withdrawal days than after 1 day. The time-dependent increases in extinction responding were associated with large (ventral mPFC) or modest (dorsal mPFC) increases in ERK phosphorylation (a measure of ERK activity and an index of neuronal activation). After 30 withdrawal days, ventral but not dorsal injections of muscimol+baclofen (GABAa+GABAb receptor agonists that inhibit neuronal activity) decreased extinction responding. After 1 withdrawal day, ventral but not dorsal mPFC injections of bicuculline+saclofen (GABAa+GABAb receptor antagonists that increase neuronal activity) strongly increased extinction responding. Finally, muscimol+baclofen had minimal effect on extinction responding after 1 day, and in cocaine-experienced rats, ventral mPFC injections of muscimol+baclofen or bicuculline+saclofen had no effect on lever presses for an oral sucrose solution. The present results indicate that ventral mPFC neuronal activity plays an important role in the incubation of cocaine craving. Koya, E., Uejima, J.L.,

Wihbey, K.A., Bossert, J.M., Hope, B.T., and Shaham, Y. Neuropharmacology, 2008, [E-pub ahead of print].

## In Vivo Electrophysiology Unit, Behavioral Neuroscience Research Branch

### Behavioral and Temperature Effects of Delta 9-tetrahydrocannabinol in Human-relevant Doses in Rats

Marijuana smoking dramatically alters responses to various environmental stimuli. To study this phenomenon, IRP scientists assessed how delta-9-tetrahydrocannabinol (THC), a primary psychoactive ingredient of marijuana, affects locomotor and brain (nucleus accumbens or NAcc), muscle and skin temperature responses to natural arousing stimuli (one-minute tail-pinch and one-minute social interaction with another male rat) and iv cocaine (1 mg/kg) in male rats. THC was administered at three widely varying doses (0.5, 2.0 and 8.0 mg/kg, ip), and the drug-induced changes in basal values and responses to stimuli were compared to those occurring following ip vehicle injections (control). Each stimulus in control conditions caused acute locomotor activation, a prolonged increase in brain and muscle temperature (0.6-1.0 degrees C for 20-50 min) and transient decrease in skin temperature (-0.6 degrees C for 1-3 min). While THC at any dose had a tendency to decrease spontaneous locomotion as well as brain and muscle temperatures, true hypothermia and hypoactivity as well as clearly diminished locomotor and temperature responses to all stimuli were only seen following the largest dose. In this case, temperature decreases in the NAcc were stronger than in the muscle, suggesting metabolic brain inhibition as the primary cause of hypoactivity, hypothermia and hyporesponsiveness. While weaker in strength and without associated vasodilatation, this response pattern is mimicked by general anesthetics, questioning to what extent the hypothermic action of THC is specific (i.e., mediated via endogenous cannabinoid receptors) or non-specific, reflecting drug interaction with membrane lipids or other receptors. In contrast, weaker behavioral and temperature effects of THC at lower doses resemble those of diazepam, whose locomotion- and temperature-decreasing effects are evident only in activated conditions, when rats are moving and basal temperatures are elevated. Smirnov, M.S. and Kiyatkin, E.A. Brain Research, 2008, [E-pub ahead of print].

### Sensory Effects of Intravenous Cocaine on Dopamine and Non-dopamine Ventral Tegmental Area Neurons

Intravenous (iv) cocaine mimics salient somato-sensory stimuli in their ability to induce rapid physiological effects, which appear to involve its action on peripherally located neural elements and fast neural transmission via somato-sensory pathways. To further clarify this mechanism, single-unit recording with fine glass electrodes was used in awake rats to examine responses of ventral tegmental area (VTA) neurons, both presumed dopamine (DA) and non-DA, to iv cocaine and tail-press, a typical somato-sensory stimulus. To exclude the contribution of DA mechanisms to the observed neuronal responses to sensory stimuli and cocaine, recordings were conducted during full DA receptor blockade (SCH23390+eticloptide). Iv cocaine (0.25 mg/kg delivered over 10 s) induced significant excitations of ~63% of long-spike (presumed DA) and ~70% of short-spike (presumed non-DA) VTA neurons. In both subgroups, neuronal excitations occurred with short latencies (4-8 s), peaked at 10-20 s (30-40% increase over baseline) and disappeared at 30-40 s after the injection onset. Most long-(67%) and short-spike (89%) VTA neurons also showed phasic responses to tail-press (5-s). All responsive long-spike cells were excited by tail-press; excitations were very rapid (peak at 1 s) and strong (100% rate increase over baseline) but brief (2-3 s). In contrast, both excitations (60%) and inhibitions (29%) were seen in short-spike cells. These responses were also rapid and transient, but excitations of short-spike units were more prolonged and sustained (10-15 s) than in long-spike cells. These

data suggest that in awake animals iv cocaine, like somato-sensory stimuli, rapidly and transiently excites VTA neurons of different subtypes. Therefore, along with direct action on specific brain substrates, central effects of cocaine may occur, via an indirect mechanism, involving peripheral neural elements, visceral sensory nerves and rapid neural transmission. Via this mechanism, cocaine, like somato-sensory stimuli, can rapidly activate DA neurons and induce phasic DA release, creating the conditions for DA accumulation by a later occurring and prolonged direct inhibiting action on DA uptake. By providing a rapid neural signal and triggering transient neural activation, such a peripherally driven action might play a crucial role in the sensory effects of cocaine, thus contributing to learning and development of drug-taking behavior. Brown, P.L. and Kiyatkin, E.A. Brain Research, 1218, pp. 230-249, 2008.

## Medicinal Chemistry Section, Medications Discovery Research Branch

### Labeling of Dopamine Transporter Transmembrane Domain 1 with the Tropane Ligand [125I]MFZ 2-24 Implicates Proximity of Cocaine and Substrate Active Sites

The novel photoaffinity ligand N-[4- (4-azido -3-[125I]-iodophenyl) butyl] -2-carbomethoxy-3-(4-chlorophenyl) tropane ([125I]MFZ 2-24) was used to investigate the site for cocaine binding on the dopamine transporter (DAT). [125I]MFZ 2-24 irreversibly labeled both rat striatal and expressed human DAT with high affinity and appropriate pharmacological specificity. Tryptic proteolysis of [125I]MFZ 2-24 labeled DAT followed by epitope- specific immunoprecipitation demonstrated that the ligand becomes adducted almost exclusively to transmembrane domains (TMs) 1-2. Further localization of [125I]MFZ 2-24 incorporation achieved by proteolyzing labeled wild type and methionine mutant DATs with cyanogen bromide identified the sequence between residues 68-80 in TM1 as the ligand adduction site. This is in marked contrast to the previously identified attachment of the photoaffinity label [125I]RTI 82 in TM6. Because [125I]MFZ 2-24 and [125I]RTI 82 possess identical tropane pharmacophores and differ only in the placement of the reactive azido moieties, their distinct incorporation profiles identify the regions of the protein adjacent to different aspects of the cocaine molecule. These findings thus strongly support the direct interaction of cocaine on DAT with TM1 and TM6, both of which have been implicated by mutagenesis and homology to a bacterial leucine transporter as active sites for substrates. These results directly establish the proximity of TMs 1 and 6 in DAT and suggest that the mechanism of transport inhibition by cocaine involves close interactions with multiple regions of the substrate permeation pathway. Parnas, M.L., Gaffaney, J.D., Zou, M.-F., Lever, J.R., Newman, A.H., and Vaughan, R.A. Molecular Pharmacology, 73, pp. 1141-1160, 2008.

### The Binding Sites for Cocaine and Dopamine in the Dopamine Transporter are Overlapping

Cocaine is a widely abused substance with psychostimulant effects attributed to inhibition of the dopamine transporter (DAT). Here, IRP investigators present molecular models for DAT binding of cocaine and its analogue CFT ((-)-2-carbomethoxy-3-(4-fluorophenyl)tropane or WIN 35,428) based on the high-resolution structure of the bacterial transporter homologue, LeuT. The authors'models suggest that the binding site for cocaine and CFT is deeply buried between transmembrane segments (TM) 1, 3, 6, and 8, and overlaps with the binding sites for the substrates, dopamine and amphetamine, as well as for benztropine-like DAT inhibitors. The models were validated by detailed mutagenesis, and by trapping the radiolabeled cocaine analogue [3H]CFT in the transporter through cross-linking of engineered cysteines or by engineering of a Zn2+ binding site situated extracellular to the predicted common binding pocket. Summarized, the data demonstrate for the first time the molecular

basis for the competitive inhibition of dopamine transport by cocaine and refutes the possibility of a dopamine-sparing cocaine antagonist. Beuming, T., Kniazeff, J., Bergmann, M.L., Shi, L., Gracia, L., Raniszewska, K., Newman, A.H., Javitch, J.A., Weinstein, H., Gether, U., and Loland, C.J. Nature Neuroscience, 11, pp. 780-789, 2008.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2008

## Program Activities

### New NIDA PAs and RFAs

On June 26, NIDA issued a PA entitled **Medications Development for Polydrug Addiction Treatment (R01) (PAS-08-186)**. Through this FOA, NIDA is seeking medication discovery and development research grant applications focused on the treatment of patients who are simultaneously addicted to multiple substances, including alcohol, tobacco, illicit drugs and/or prescription drugs. Novel proposals for clinical or preclinical testing of potential medications, as well as relevant animal model development and medicinal chemistry efforts are encouraged. This FOA will utilize the NIH Research Projects (R01) grant mechanism and runs in parallel with a FOA of identical scientific scope, **PAS-08-187**, that encourages applications under the NIH Exploratory/Developmental (R21) grant mechanism.

On June 26, NIDA issued a PA entitled **Medications Development for Polydrug Addiction Treatment (R21) (PAS-08-187)**. Through this PA, NIDA is seeking medication discovery and development research grant applications focused on the treatment of patients who are simultaneously addicted to multiple substances, including alcohol, tobacco, illicit drugs and/or prescription drugs. Novel proposals for clinical or preclinical testing of potential medications, as well as relevant animal model development and medicinal chemistry efforts are encouraged. This FOA will use the NIH Exploratory/Developmental (R21) grant mechanism and runs in parallel with a FOA of identical scientific scope, **PAS-08-186**, that encourages applications under the NIH Research Projects (R01) grant mechanism.

On July 25, 2008, NIDA issued a PA entitled **Drug Abuse Prevention Intervention Research (R01) (PA-08-217)**. The purpose of this FOA is to encourage Research Project Grant (R01) applications from institutions/organizations that propose to advance the science of drug abuse and drug-related HIV prevention through 1) the development of novel prevention approaches, 2) the testing of novel and adapted prevention intervention approaches 3) the elucidation of processes associated with the selection, adoption, adaptation, implementation, sustainability, and financing of empirically validated interventions, and 4) the development of new methodologies suitable for the design and analysis of prevention research studies. Programs of research are intended to provide pathways toward the discovery of population-level approaches for the prevention of drug abuse and dependence, drug-related problems (such as interpersonal violence, criminal involvement, and productivity loss), and drug related illness (such as comorbid drug and mental health problems or comorbid infections including HIV, hepatitis B, and hepatitis C). This FOA will utilize the NIH Research Project Grant (R01) award mechanism and runs in parallel with FOAs of identical scientific scope, **PA-08-218** and **PA-08-219**, that solicit applications under

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the Exploratory/Developmental Grant (R21) and Small Research Grant (R03) award mechanisms, respectively.

On July 25, 2008, NIDA issued a PA entitled **Drug Abuse Prevention Intervention Research (R21) (PA-08-218)**. The purpose of this FOA is to encourage Research Project Grant (R01) applications from institutions/organizations that propose to advance the science of drug abuse and drug-related HIV prevention through 1) the development of novel prevention approaches, 2) the testing of novel and adapted prevention intervention approaches 3) the elucidation of processes associated with the selection, adoption, adaptation, implementation, sustainability, and financing of empirically validated interventions, and 4) the development of new methodologies suitable for the design and analysis of prevention research studies. Programs of research are intended to provide pathways toward the discovery of population-level approaches for the prevention of drug abuse and dependence, drug-related problems (such as interpersonal violence, criminal involvement, and productivity loss), and drug related illness (such as comorbid drug and mental health problems or comorbid infections including HIV, hepatitis B, and hepatitis C). This FOA will utilize the NIH Exploratory/Developmental Grant (R21) award mechanism and runs in parallel with FOAs of identical scientific scope, **PA-08-217** and **PA-08-219**, that solicit applications under the Research Project Grant (R01) and Small Research Grant (R03) award mechanisms, respectively.

On July 25, 2008, NIDA issued a PA entitled **Drug Abuse Prevention Intervention Research (R03) (PA-08-219)**. The purpose of this FOA is to encourage pilot/feasibility R03 applications from institutions/organizations that propose to advance the science of drug abuse and drug-related HIV prevention through 1) the development of novel prevention approaches, 2) the testing of novel and adapted prevention intervention approaches 3) the elucidation of processes associated with the selection, adoption, adaptation, implementation, sustainability, and financing of empirically validated interventions, and 4) the development of new methodologies suitable for the design and analysis of prevention research studies. Programs of research are intended to provide pathways toward the discovery of population-level approaches for the prevention of drug abuse and dependence, drug-related problems (such as interpersonal violence, criminal involvement, and productivity loss), and drug related illness (such as comorbid drug and mental health problems or comorbid infections including HIV, hepatitis B, and hepatitis C). This FOA will utilize the NIH Small Research Grant (R03) award mechanism award mechanism and runs in parallel with FOAs of identical scientific scope, **PA-08-217** and **PA-08-218**, that solicit applications under the Research Project Grant (R01) and the Exploratory/Developmental Grant (R21) award mechanisms, respectively. The R03 grant mechanism supports different types of projects including pilot and feasibility studies; secondary analysis of existing data; small, self-contained research projects; development of research methodology; and development of new research technology. The R03 is intended to support small research projects that can be carried out in a short period of time with limited resources.

On April 23, 2008, NIDA issued an RFA entitled **Medications Development for Cannabis Related Disorders (R01) (RFA-DA-09-001)**. This FOA encourages research studies that focus on the identification, and preclinical and clinical evaluation of medications that can be safe and effective for the treatment of cannabis-use and -induced disorders, as well as their medical and psychiatric consequences. The studies can be preclinical or FDA-defined Phase I, Phase II or Phase III clinical trials.

On June 12, 2008, NIDA issued an RFA entitled **Pilot Clinical Trials of Pharmacotherapies for Substance Related Disorders (R01) (RFA-DA-09-005)**. The purpose of this FOA is to support pilot clinical studies of medications for investigation as possible treatments for Substance Related

Disorders (SRDs). Because the purpose of this FOA is to support pilot studies, preliminary studies are not required. This FOA does not support clinical studies of nicotine or alcohol related disorders, except as comorbid disorders with other SRDs. NIDA expects to receive grant applications for clinical research on medications for which some theoretical or limited preclinical or clinical information exists for investigation as possible treatments of individual SRDs, combinations of them (i.e., cocaine and alcohol use, cocaine and cannabis use) or comorbid with other psychiatric disorders, but which are not ready to be tested in a large and expensive randomized clinical trial. This FOA will not accept proposals that involve preclinical studies. NIDA will not accept applications testing medications that have already demonstrated safety and efficacy for the target disorder. Therefore, there must be a strong rationale for the medications proposed for testing, but no preclinical or clinical data are required or expected. This FOA will utilize the National Institutes of Health (NIH) research project grant (R01) granting mechanism.

On June 24, 2008, NIDA issued an RFA entitled **Criminal Justice Drug Abuse Treatment Studies 2 (CJ-DATS 2) (U01) (RFA-DA-09-006)**. Through this FOA, NIDA invites cooperative agreement applications to participate as Research Centers in the second phase of the national Criminal Justice Drug Abuse Treatment Studies (CJ-DATS 2). The goal of this cooperative research program is to develop and test systems-level models that integrate public health and public safety approaches for criminal justice-involved adults and adolescents with drug abuse and addictive disorders. Additional funds are being sought from other sources. This FOA will utilize the NIH Cooperative Research Project Grant (U01) award.

### Other Program Activities

On May 9, 2008 NIDA, in conjunction with a number of other NIH components issued a PA entitled **Collaborative HIV/AIDS Studies in the Middle East and North Africa (R21) (PAR-08-153)**. The aim of this FOA is to invite applications for collaborations for exploratory and developmental work on HIV/AIDS in the low and middle income countries of the Middle East and North Africa (MENA), as defined by the World Bank: Algeria, Djibouti, Egypt, Iran, Iraq, Jordan, Lebanon, Libya, Morocco, Oman, Syria, Tunisia, West Bank and Gaza, and Yemen. Specific areas of research include, but aren't limited to, epidemiologic studies, prevention research from both biomedical and social/behavioral perspectives, studies of social factors affecting the spread of HIV in the region, and research on women and youth. Collaborations must involve U.S. investigators from a partnering U.S. organization and one or more research teams in the MENA region. The collaborative effort supported through the R21 should help foster the development of HIV-relevant research infrastructure and expertise in the region and have the potential to lead to further research and improvements in public health. This FOA will use the NIH Exploratory/Developmental (R21) award mechanism.

On June 6, 2008, NIDA and NIAAA issued a PA entitled **Economics of Treatment and Prevention Services for Drug & Alcohol Abuse (R03) (PA-08-172)**. This Funding Opportunity Announcement (FOA) encourages Research Project Grant (R03) applications on the economics of prevention and treatment services for drug and alcohol abuse. Such research projects might emphasize any of the following subjects: (1) financing and purchasing of drug and alcohol treatment and prevention services, including studies of health insurance and payment mechanisms; (2) economic incentives used to improve the quality and economic efficiency of treatment and prevention services (3) alternative delivery systems and managed care; (4) cost-benefit, cost-effectiveness, or cost-utility analyses; (5) service costs, production, and economic efficiency; and (6) research to develop or improve methods to be used in the economic study of drug and alcohol services The R03 grant mechanism supports different types of projects including pilot and feasibility

studies; secondary analysis of existing data; small, self-contained research projects; development of research methodology; and development of new research technology. The R03 is intended to support small research projects that can be carried out in a short period of time with limited resources. This FOA will utilize the NIH Small Research Grant (R03) award mechanism and runs in parallel with FOAs of identical scientific scope, PA-08-174, that encourages applications under the R01 mechanism and PA-08-173 that encourages applications under the R21 mechanism.

On June 6, 2008, NIDA and NIAAA issued a PA entitled **Economics of Treatment and Prevention Services for Drug & Alcohol Abuse (R21) (PA-08-173)**. This Funding Opportunity Announcement (FOA) issued by the National Institute on Drug Abuse (NIDA) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) encourages Research Project Grant (R21) applications on the economics of prevention and treatment services for drug and alcohol abuse. Such research projects might emphasize any of the following subjects: (1) financing and purchasing of drug and alcohol treatment and prevention services, including studies of health insurance and payment mechanisms; (2) economic incentives used to improve the quality and economic efficiency of treatment and prevention services (3) alternative delivery systems and managed care; (4) cost-benefit, cost-effectiveness, or cost-utility analyses; (5) service costs, production, and economic efficiency; and (6) research to develop or improve methods to be used in the economic study of drug and alcohol services. This FOA will use the NIH Exploratory/Developmental (R21) grant mechanism and runs in parallel with a FOA of identical scientific scope, **PA-08-174**, that encourages applications under the R01 mechanisms and **PA-08-172** which encourages applications under the R03 mechanism.

On June 6, 2008, NIDA and NIAAA issued a PA entitled **Economics of Treatment and Prevention Services for Drug & Alcohol Abuse (R01) (PA-08-174)**. This Funding Opportunity Announcement (FOA) encourages Research Project Grant (R01) applications on the economics of prevention and treatment services for drug and alcohol abuse. Such research projects might emphasize any of the following subjects: (1) financing and purchasing of drug and alcohol treatment and prevention services, including studies of health insurance and payment mechanisms; (2) economic incentives used to improve the quality and economic efficiency of treatment and prevention services (3) alternative delivery systems and managed care; (4) cost-benefit, cost-effectiveness, or cost-utility analyses; (5) service costs, production, and economic efficiency; and (6) research to develop or improve methods to be used in the economic study of drug and alcohol services. This FOA will utilize the Research Project Grant (R01) grant mechanism and runs in parallel with a FOA of identical scientific scope, **PA-08-173**, which encourages applications under the R21 mechanism and **PA-08-172** which encourages applications under the R03 mechanism.

On June 24, 2008, NIDA, in conjunction with numerous other NIH components, issued a PA entitled **Exploratory Collaborations with National Centers for Biomedical Computing (R21) (PAR-08-183)**. This funding opportunity announcement (FOA) is for projects from individual-investigators or small groups to collaborate with the NIH Roadmap for Medical Research National Centers for Biomedical Computing (NCBCs). The intention of the collaborating projects is to engage researchers across the nation in building an excellent biomedical computing environment, using the computational tools and biological and behavioral application drivers of the funded NCBCs as foundation stones. This FOA is intended to support exploratory biomedical informatics and computational biology research--applications should be innovative, with high risk/high impact in new areas that are lacking preliminary data or development. Applications for R21 awards should describe projects distinct from those supported through the traditional R01 mechanism. For example,

long-term projects, or projects designed to increase knowledge in a well-established area will not be considered for R21 awards. This FOA will use the NIH Exploratory/Developmental (R21) grant mechanism and runs in parallel with a FOA of identical scientific scope, PAR-08-184, that solicits applications under the R01 mechanism.

On June 24, 2008, NIDA, in conjunction with numerous other NIH components, issued a PA entitled **Collaborations with National Centers for Biomedical Computing (R01) (PAR-08-184)**. This funding opportunity announcement (FOA) is for projects from individual-investigators or small groups to collaborate with the NIH Roadmap for Medical Research National Centers for Biomedical Computing (NCBCs). For a description of the NCBCs see bisti.nih.gov/ncbc/. The intention of the collaborating projects is to engage researchers across the nation in building an excellent biomedical computing environment, using the computational tools and biological and behavioral application drivers of the funded NCBCs as foundation stones. This Funding Opportunity Announcement (FOA) will utilize the R01 grant mechanism and runs in parallel with an FOA of identical scientific scope, **PAR-08-183** that solicits applications under the R21 mechanism, and which solicits innovative, high risk/high impact new areas that are lacking preliminary data or development.

On June 30, 2008, NIDA, in collaboration with several other NIH components, issued a PA entitled **Integrating Biobehavioral and Sociocultural Research to Prevent HIV Transmission and Infection (R01) (PA-08-188)**. This funding opportunity announcement (FOA) solicits Research Project (R01) grant applications from applicant organizations to develop theoretically grounded approaches to prevention of HIV infection and transmission that incorporate biobehavioral approaches in studies that are culturally appropriate. Biobehavioral approaches may be biomedical, or they may consist of behavioral interventions using biological markers of efficacy. Sociocultural appropriateness involves, at minimum, application of knowledge of the norms, beliefs and values of potential research subjects in varied contexts, and an appreciation of culture as dynamic. It is anticipated that such knowledge will improve both the quality and applicability of research among the diverse populations affected by the pandemic, in the US or abroad. Intervention and pre-intervention studies are welcomed, but descriptive ethnographic and epidemiological research is still needed in some areas. For example, descriptive research may delineate the impact of cultural variables on behaviors that impede or promote biological markers (e.g., seroconversion), lead to a better understanding of ethical concerns in biomedical preventive studies, or may illuminate as yet unrecognized issues concerned with adherence to a prevention interventions. Intervention studies should evaluate the efficacy of biomedical interventions, or of behavioral interventions that also use biological variables, in light of the sociocultural context. This FOA will utilize the R01 grant mechanism and runs in parallel with a FOA of identical scientific scope, **PA-08-189**, that encourages applications under the R21 mechanism.

On June 30, 2008, NIDA, in collaboration with several other NIH components, issued a PA entitled **Integrating Biobehavioral and Sociocultural Research to Prevent HIV Transmission and Infection (R21) (PA-08-189)**. This funding opportunity announcement (FOA) solicits Research Project (R21) grant applications from applicant organizations to develop theoretically grounded approaches to prevention of HIV infection and transmission that incorporate biobehavioral approaches in studies that are culturally appropriate. Biobehavioral approaches may be biomedical, or they may consist of behavioral interventions using biological markers of efficacy. Sociocultural appropriateness involves, at minimum, application of knowledge of the norms, beliefs and values of potential research subjects in varied contexts, and an appreciation of culture as dynamic. It is anticipated that such knowledge will improve both the quality and applicability of research among the diverse populations affected by

the pandemic, in the US or abroad. Intervention and pre-intervention studies are welcomed, but descriptive ethnographic and epidemiological research is still needed in some areas. For example, descriptive research may delineate the impact of cultural variables on behaviors that impede or promote biological markers (e.g., seroconversion), lead to a better understanding of ethical concerns in biomedical preventive studies, or may illuminate as yet unrecognized issues concerned with adherence to prevention interventions. Intervention studies should evaluate the efficacy of biomedical interventions, or of behavioral interventions that also use biological variables, in light of the sociocultural context. This FOA will utilize the R21 grant mechanism and runs in parallel with a FOA of identical scientific scope, **PA-08-188** that encourages applications under the R01 mechanism.

On July 2, 2008, NIDA, in collaboration with numerous other NIH components issued a PA entitled **Research Supplements to Promote Diversity in Health-Related Research (PA-08-190)**. The NIH recognizes a unique and compelling need to promote diversity in the biomedical, behavioral, clinical and social sciences research workforce. The NIH expects efforts to diversify the workforce to lead to the recruitment of the most talented researchers from all groups; to improve the quality of the educational and training environment; to balance and broaden the perspective in setting research priorities; to improve the ability to recruit subjects from diverse backgrounds into clinical research protocols; and to improve the Nation's capacity to address and eliminate health disparities. Through this FOA individuals may submit (an) application(s) if they are the Principal Investigator, at a domestic institution, who holds an active R00, R01 (or RL1), R10, R18, R22, R24, R35, R37, R43, R44, R41, R42, DP1, DP2, P01 (or PL1), P20, P30, P40, P41, P50, P51, P60, U01 (or UL1), U10, U19, U41, U42, U54. Because policies may vary among awarding components regarding eligibility of Small Grant Awards (R03), Academic Research Enhancement Awards (R15), Support of Continuous Research Excellence (SC1, SC2, SC3), or Exploratory/Developmental Grants (R21) for supplements under this program, grantees holding those awards must check with the appropriate awarding component before submitting an application for a supplement.

On July 15, 2008, NIDA, in collaboration with numerous other NIH components issued a PA entitled **Technological Innovations for Interdisciplinary Research Incorporating the Behavioral and Social Sciences (STTR [R41/R42]) (PAR-08-201)**. The purpose of this Funding Opportunity Announcement (FOA) is to solicit Small Business Technology Transfer (STTR) grant applications from small business concerns (SBCs) for development of new, innovative technologies for research integrating human social and/or behavioral science with other disciplines. This FOA will utilize the STTR (R41/R42) grant mechanisms for Phase I, Phase II, and Fast-Track applications and runs in parallel with a FOA of identical scientific scope, **PAR-08-202** that encourages applications under the Small Business Innovation Research (SBIR) (R43/R44) grant mechanisms.

On July 15, 2008, NIDA, in collaboration with numerous other NIH components issued a PA entitled **Technological Innovations for Interdisciplinary Research Incorporating the Behavioral and Social Sciences (SBIR [R43/R44]) (PAR-08-202)**. The purpose of this Funding Opportunity Announcement (FOA) is to solicit Small Business Innovation Research (SBIR) grant applications from small business concerns (SBCs) for development of new, innovative technologies for research integrating human social and/or behavioral science with other disciplines. This FOA will utilize the SBIR (R43/R44) grant mechanisms for Phase I, Phase II, and Fast-Track applications and runs in parallel with a FOA of identical scientific scope, **PAR-08-201**, which solicits applications under the Small Business Technology Transfer (STTR) (R41/R42) grant mechanisms.

On July 22, 2008, NIDA, in conjunction with numerous other NIH components

issued a PA entitled **Methodology and Measurement in the Behavioral and Social Sciences (R01) (PAR-08-212)**. The goal of this Funding Opportunity Announcement (FOA) is to encourage research that will improve the quality and scientific power of data collected in the behavioral and social sciences, relevant to the missions of the participating NIH Institutes and Centers. The participating NIH Institutes and Centers invite qualified researchers to submit research grant applications aimed at improving and developing methodology and measurement in the behavioral and social sciences through innovations in research design, data collection techniques, measurement, and data analysis techniques. Research that addresses methodology and measurement issues in diverse populations, issues in studying sensitive behaviors, issues of ethics in research, issues related to confidential data and the protection of research subjects, and issues in developing interdisciplinary, multimethod, and multilevel approaches to behavioral and social science research is particularly encouraged, as are approaches that integrate behavioral and social science research with biological, physical, or computational science research or engineering. This FOA will utilize the NIH Research Project Grant (R01) mechanism and runs in parallel with **PAR-08-213** and **PAR-08-214** which solicit applications under the Exploratory/Developmental (R21) and Small Research Grant (R03) award mechanisms, respectively.

On July 22, 2008, NIDA, in conjunction with numerous other NIH components issued a PA entitled **Methodology and Measurement in the Behavioral and Social Sciences (R21) (PAR-08-213)**. The goal of this Funding Opportunity Announcement (FOA) is to encourage research that will improve the quality and scientific power of data collected in the behavioral and social sciences, relevant to the missions of the participating NIH Institutes and Centers. The participating NIH Institutes and Centers invite qualified researchers to submit research grant applications aimed at improving and developing methodology and measurement in the behavioral and social sciences through innovations in research design, data collection techniques, measurement, and data analysis techniques. Research that addresses methodology and measurement issues in diverse populations, issues in studying sensitive behaviors, issues of ethics in research, issues related to confidential data and the protection of research subjects, and issues in developing interdisciplinary, multimethod, and multilevel approaches to behavioral and social science research is particularly encouraged, as are approaches that integrate behavioral and social science research with biological, physical, or computational science research or engineering. This FOA will use the NIH Exploratory/Developmental (R21) grant mechanism and runs in parallel with **PAR-08-212** and **PAR-08-214**, which solicit applications under the NIH Research Project Grant (R01) and Small Research Grant (R03) award mechanisms, respectively.

On July 22, 2008, NIDA, in conjunction with numerous other NIH components issued a PA entitled **Methodology and Measurement in the Behavioral and Social Sciences (R03) (PAR-08-214)**. The goal of this Funding Opportunity Announcement (FOA) is to encourage research that will improve the quality and scientific power of data collected in the behavioral and social sciences, relevant to the missions of the participating NIH Institutes and Centers. The participating NIH Institutes and Centers invite qualified researchers to submit research grant applications aimed at improving and developing methodology and measurement in the behavioral and social sciences through innovations in research design, data collection techniques, measurement, and data analysis techniques. Research that addresses methodology and measurement issues in diverse populations, issues in studying sensitive behaviors, issues of ethics in research, issues related to confidential data and the protection of research subjects, and issues in developing interdisciplinary, multimethod, and multilevel approaches to behavioral and social science research is particularly encouraged, as are approaches that integrate behavioral and social science research with biological, physical, or computational science research or engineering. The R03 grant mechanism supports different types of projects

including pilot and feasibility studies; secondary analysis of existing data; small, self-contained research projects; development of research methodology; and development of new research technology. The R03 is intended to support small research projects that can be carried out in a short period of time with limited resources. This FOA will utilize the NIH Small Research Grant (R03) award mechanism and runs in parallel with **PAR-08-213** and **PAR-08-212**, which solicit applications under the Exploratory/Developmental (R21) and NIH Research Project Grant (R01) award mechanisms, respectively.

On August 1, 2008, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Research Training Grants (T32) (PA-08-226)**. NIH will award Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Research Training Grants (T32) to eligible institutions as the primary means of supporting predoctoral and postdoctoral research training to help ensure that a diverse and highly trained workforce is available to assume leadership roles related to the Nation's biomedical, behavioral and clinical research agenda. The primary objective of the T32 program is to prepare qualified individuals for careers that have a significant impact on the health-related research needs of the Nation. This program supports predoctoral, postdoctoral and short term research training programs at domestic institutions of higher education with the T32 funding mechanism. Note that programs solely for short-term research training should not apply to this announcement, but rather the separate (T35) NRSA Short-Term Institutional program exclusively reserved for short-term programs (see **PA-08-227**). This Funding Opportunity Announcement (FOA) will utilize the Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Research Training Grants (T32).

On August 1, 2008, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Ruth L. Kirschstein National Research Service Award Short-Term Institutional Research Training Grants (T35) (PA-08-227)**. The NIH will award Ruth L. Kirschstein National Research Service Award (NRSA) Short-Term Institutional Research Training Grants (T35) to eligible institutions to develop or enhance research training opportunities for individuals interested in careers in biomedical, behavioral and clinical research. Many of the NIH Institutes and Centers (ICs) use this grant mechanism exclusively to support intensive, short-term research training experiences for students in health professional schools during the summer. In addition, the Short-Term Institutional Research Training Grant may be used to support other types of predoctoral and postdoctoral training in focused, often emerging scientific areas relevant to the mission of the funding IC. The proposed training must be in either basic, behavioral or clinical research aspects of the health-related sciences. This program is intended to encourage graduate and/or health professional students to pursue research careers by exposure to and short-term involvement in the health-related sciences. The training should be of sufficient depth to enable the trainees, upon completion of the program, to have a thorough exposure to the principles underlying the conduct of research. This Funding Opportunity Announcement (FOA) will utilize the Ruth L. Kirschstein National Research Service Award (NRSA) Short-Term Institutional Research Training Grants (T35).

On July 31, 2008, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Fogarty International Research Collaboration - Basic Biomedical (FIRCA-BB) Research Award (R03) (PAR-08-222)**. This Funding Opportunity Announcement (FOA) facilitates collaborative basic biomedical research between scientists supported by the National Institutes of Health (NIH) and investigators in low- to middle-income countries (LMIC). All non-AIDS-related biomedical research topics that are supported by the NIH, including basic, clinical, and applied research that does not involve behavioral or social science topics and techniques, are eligible for

inclusion under the FIRCA-BB program. For behavioral and social science (BSS) research, see the companion Funding Opportunity Announcement (FOA), the "Fogarty International Research Collaboration - Behavioral and Social Sciences (FIRCA-BSS) Research Award" program, (**PAR-08-223**). Special consideration will be given to proposed research that addresses significant global health problems, particularly those of high relevance to an LMIC country or region.

On July 31, 2008, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Fogarty International Research Collaboration - Behavioral and Social Sciences (FIRCA-BSS) Research Award (R03) (PAR-08-223)**. This Funding Opportunity Announcement (FOA) facilitates collaborative behavioral and social sciences research between scientists supported by the National Institutes of Health (NIH) and investigators in low- and middle-income countries (LMIC). For basic biomedical research, see the companion Funding Opportunity Announcement (FOA), "Fogarty International Research Collaboration - Basic Biomedical Sciences (FIRCA-BB) Research Award (**PAR-08-222**)". Special consideration will be given to proposed research that addresses significant global health problems, particularly those of high relevance to an LMIC country or region.

On August 1, 2008, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Using Systems Science Methodologies to Protect and Improve Population Health (R21) (PAR-08-224)**. This FOA solicits Exploratory/Developmental (R21) applications from institutions/organizations that propose to apply one or more specific system science methodologies (identified in Section I.1 - "Background", of this announcement) to public health and health care systems problems and contribute knowledge that will enhance effective decision making around the development of and prioritization of policies, interventions, and programs to improve population health, especially where resources are limited and only a limited number of programs/policies/interventions can be implemented. Applicants are encouraged to submit projects that tackle "policy resistant" health problems (i.e., ones in which the effects of planned interventions, programs or policies tend to be delayed, diluted or defeated by responses of the system to the intervention itself) using a systems science methodology. This FOA will use the NIH Exploratory/Developmental (R21) grant mechanism.

On August 15, 2008, NIDA, in collaboration with a number of other NIH components, issued a PA entitled **Reducing Risk Behaviors by Promoting Positive Youth Development (R01) (PA-08-241)**. This purpose of this Funding Opportunity Announcement is to encourage Research Project Grant (R01) applications from institutions/organizations that propose to enhance our understanding of effective positive youth development programs and the mechanisms responsible for positive health and developmental outcomes. This will be accomplished through the development, implementation, and evaluation of new or improved positive youth development programs, the evaluation of existing "successful" programs, or the evaluation of effective, evidence-based, gender-inclusive programs that are adapted, translated, or disseminated for new populations of youth and adolescents. This FOA will utilize the Research Project Grant (R01) grant award mechanism and runs in parallel with a FOA of identical scientific scope, **PA-08-242**, that encourages applications under the R03 mechanism.

On August 15, 2008, NIDA, in collaboration with a number of other NIH components, issued a PA entitled **Reducing Risk Behaviors by Promoting Positive Youth Development (R03) (PA-08-242)**. This purpose of this Funding Opportunity Announcement is to encourage Research Project Small (R03) Grant applications from institutions/organizations that propose to enhance our understanding of effective positive youth development programs and the mechanisms responsible for positive health and developmental outcomes. These studies may include the evaluation of particular components

of new or existing youth development programs thought to be responsible for positive development; the examination of child and adolescent assets, behaviors, and development that influence positive youth trajectories; and the evaluation of family, community, or social assets and liabilities that contribute to or hamper youth development. Investigators and/or colleagues should have a strong knowledge of child development. The R03 grant mechanism supports a variety of projects including pilot and feasibility studies; secondary analysis of existing data; small, self-contained research projects; development of research methodology; and development of new research technology. The R03 small grant mechanism is intended to support small scale research projects that can be carried out in two years or less with limited resources. This FOA will utilize the Research Project Small (R03) Grant award mechanism and runs in parallel with a FOA of similar scientific scope, **PA-08-241**, that encourages applications under the R01 mechanism.

On August 14, 2008, NIDA, in collaboration with NIMH and NIAAA issued a PA entitled **National Cooperative Drug Discovery and Development Groups (NCDDDG) for the Treatment of Mental Disorders, Drug or Alcohol Addiction (U01/U19) (PAR-08-238)**. The purpose of the National Cooperative Drug Discovery and Development Group (NCDDDG) Program is to create multidisciplinary research groups or partnerships for the discovery of pharmacological agents to treat and to study mental illness, drug or alcohol addiction. The objectives of this program are to: accelerate innovative drug discovery; develop pharmacologic tools for basic and clinical research on mental disorders, or drug or alcohol addiction; develop and validate models for evaluating novel therapeutics for mental disorders; and support early phase human clinical testing to rapidly assess the safety and efficacy of promising drug candidates and new indications for IND-ready drugs for the treatment of mental disorders or alcohol addiction. The National Institute of Mental Health (NIMH), the National Institute on Drug Abuse (NIDA), and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) invite applications to advance the discovery, preclinical development, and proof of concept testing of new, rationally based candidate medications to treat mental disorders or drug or alcohol addiction, and to develop novel ligands as tools to further characterize existing or to validate new drug targets. Partnerships between academia and industry are strongly encouraged. This funding opportunity announcement (FOA) will utilize the Cooperative Agreement (U01) and multi-project Cooperative Agreement (U19) grant mechanisms. In addition, this FOA runs in parallel with an FOA of similar scientific intent for small businesses, **PA-08-142** and **PA-06-028** using the Small Business Innovation Research (SBIR [R43/R44]) and the Small Business Technology Transfer (STTR [R41/R42]) grant mechanisms.

On June 18, NIDA, in conjunction with NCI, issued an RFA entitled **Improving Effectiveness of Smoking Cessation Interventions and Programs in Low Income Adult Populations (R01) (RFA-CA-08-022)**. This funding opportunity announcement (FOA), encourages research grant applications for projects designed to improve outcomes of smoking cessation in low income adult populations within the United States. Despite significant progress in reducing the prevalence of smoking in the United States, smoking continues to represent a major threat to public health. In addition, decreases in smoking have not been consistent across the population and marked disparities exist with smoking prevalence continuing to remain high among low income adults. The long-term goal is to facilitate a significant reduction in smoking prevalence among low income adults, thereby reducing the excess disease burden of tobacco use within these groups and decreasing the prevalence of smoking in the United States as a whole. This FOA is intended to support human research only. This FOA will utilize the NIH research project R01 grant mechanism and runs in parallel with a FOA of identical scientific scope, **RFA-CA-08-023**, that solicits applications under the R21 exploratory grant mechanism.

On June 18, NIDA, in conjunction with NCI, issued an RFA entitled **Improving Effectiveness of Smoking Cessation Interventions and Programs in Low Income Adult Populations (R21) (RFA-CA-08-023)**. This funding opportunity announcement (FOA), encourages research grant applications for projects designed to improve outcomes of smoking cessation in low income adult populations within the United States. Despite significant progress in reducing the prevalence of smoking in the United States, smoking continues to represent a major threat to public health. In addition, decreases in smoking have not been consistent across the population and marked disparities exist with smoking prevalence continuing to remain high among low-income adults. The long-term goal is to facilitate a significant reduction in smoking prevalence among low-income adults, thereby reducing the excess disease burden of tobacco use within these groups and decreasing the prevalence of smoking in the United States as a whole. This FOA is intended to support human research only. This FOA will utilize the R21 grant mechanism and runs in parallel with a FOA of identical scientific scope, **RFA-CA-08-022**, that solicits applications under the R01 grant mechanism.

On July 16, 2008, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Implementation Planning Grants for Educational, Behavioral, or Social Studies for Translation of Genetic Factors in Common Diseases (U34) (RFA-DK-08-003)**. Through this FOA, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) on behalf of the NIH Genes, Environment and Health Initiative solicits Implementation Planning Grant (U34) applications from institutions/organizations that propose to plan for multicenter research on a) educational and communication initiatives for health care providers and consumers regarding interpretation of and findings from genetic studies of common diseases and the results of their dissemination and b) behavioral or psychosocial aspects of clinical application of genetic findings. Areas of interest include, but are not limited to: research on patient or provider education regarding genetic findings or clinical outcomes of genetic testing; research on patient or provider perceptions of environmental or other risk factors that may have specific interactions with gene variants; and assessments of responses to use of personal genetic information in clinical care and disease prevention. The proposed research must focus on using findings from genetic studies of common diseases with complex genetic etiology in clinical settings. This FOA will support planning and preliminary or feasibility studies for investigator-initiated, multi-center clinical studies through an implementation planning (U34) grant. The U34 planning grant is designed to: (1) permit early peer review of the rationale for the proposed clinical study; (2) permit assessment of the design/protocol of the proposed study; (3) provide support for the development of a complete study protocol and associated documents including a manual of operations, (4) support the development of other essential elements required for the conduct of a clinical study, and (5) carry out key preliminary or feasibility studies. Completion of the required products of a U34 grant is a prerequisite for submission of a multi-center clinical study cooperative agreement (U01) application, which will support the actual conduct of the study. This FOA will utilize the U34 grant mechanism and runs in parallel with an FOA, **RFA-DK-08-004**, that solicits applications under the R21 mechanism.

On July 9, 2008, NIDA, in collaboration with numerous other NIH components issued an RFA entitled **Translation of Common Disease Genetics into Clinical Applications (R21) (RFA-DK-08-004)**. Through this FOA, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) on behalf of the NIH Genes, Environment and Health Initiative, solicits Exploratory/Developmental Clinical Research Grant (R21) applications from institutions/ organizations that propose a) clinical studies using information from genome wide association or other genetic studies in common diseases; b) development and assessment of diagnostic, clinical trial, epidemiologic and risk

analytic tools for use in clinical research or practice; and c) cost-effectiveness studies of clinical applications of genetic information. Areas of interest include, but are not limited to: development of diagnostic or other risk factor algorithms that incorporate genetic data; pilot interventional studies using findings from genetic studies of common diseases or outcomes related to genetic testing for variants identified in common diseases; pilot research on clinical modification of environmental factors known to interact with specific genes variants identified in common diseases; and cost effectiveness studies. The proposed research must focus on using findings from genetic studies of common diseases with complex genetic etiology in clinical or public health settings. Through a Exploratory/Developmental Clinical Research (R21) grant, this FOA will support efforts to produce data that may be useful or pivotal in eventually designing large scale clinical trials or studies. This FOA will utilize the R21 grant mechanism.

On August 15, 2008, NIDA, in collaboration with a number of other NIH components, issued an RFA entitled **Exceptional, Unconventional Research Enabling Knowledge Acceleration (EUREKA) (R01) (RFA-GM-09-008)**. This FOA solicits Research Project Grant (R01) applications from institutions/organizations proposing exceptionally innovative research on novel hypotheses or difficult problems, solutions to which would have an extremely high impact on biomedical or biobehavioral research that is germane to the mission of one or more of the participating NIH Institutes. This FOA is for support of new projects, not continuation of projects that have already been initiated. It does not support pilot projects, i.e., projects of limited scope that are designed primarily to generate data that will enable the PI to seek other funding opportunities. This FOA will utilize the NIH Research Project Grant (R01) award mechanism.

## Other Program Activities

### Clinical Trials Network (CTN) Update

**SBIR:** Four proposals were awarded under the NIH SBIR Contract Solicitation for "Development of Web-based Training on Addiction Medicine for Pain Management Providers" and "Development of Web-based Skills Training for Primary Care Physicians on Screening, Brief Intervention, Referral and Treatment of Substance Abuse."
A Phase II proposal was awarded under topic 089, "Development of Practical Training Materials for Evidence-Based Treatment."

**Protocols:** A total of 32 protocols have been initiated since 2001. Over 9,000 participants have enrolled in studies. Of these studies, 22 have completed data lock; one is in the follow-up phase; and three are currently enrolling. Six protocols are in the development phase.

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

**Protocol CTN 0001**, Buprenorphine/Naloxone versus Clonidine for Inpatient Opiate Detoxification

**Protocol CTN 0002**, Buprenorphine/Naloxone versus Clonidine for Outpatient Opiate Detoxification

**Protocol CTN 0005**, MI (Motivational Interviewing) To Improve Treatment Engagement and Outcome in Subjects Seeking Treatment for Substance Abuse

**Protocol CTN 0006**, Motivational Incentives for Enhanced Drug Abuse Recovery: Drug Free Clinics

**Protocol CTN 0007**, Motivational Incentives for Enhanced Drug Abuse Recovery: Methadone Clinics

*Primary outcome papers are published or in press for:*

**Protocol CTN 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 0019**, Reducing HIV/STD Risk Behaviors: A Research Study for Women in Drug Abuse Treatment

*In addition, the primary outcome papers from the following protocols are under journal review:*

**Protocol CTN 0003**, Bup/Nx: Comparison of Two Taper Schedules

**Protocol CTN 0010**, Buprenorphine/Naloxone Facilitated Rehabilitation for Opioid Dependent Adolescents/Young Adults

**Protocol CTN 0015**, Women's Treatment for Trauma and Substance Use Disorder: A Randomized Clinical Trial

**Protocol CTN 0018**, Reducing HIV/STD Risk Behaviors: A Research Study for Men in Drug Abuse Treatment

**Protocol CTN 0019**, Reducing HIV/STD Risk Behaviors: A Research Study for Women in Drug Abuse Treatment

**Protocol CTN 0021**, Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome for Spanish-Speaking Individuals Seeking Treatment for Substance Abuse. This is the first Spanish-only protocol in the CTN

*The following protocols have locked the data:*

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

**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 ended new enrollment and is in the follow-up 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).

*Three 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 June 30, 2008, there were 797 randomized participants. CCTN 0027A, START Pharmacogenetics: Exploratory Genetic Studies In Starting Treatment With Agonist Replacement Therapies. Nearly all subjects randomized into the main study are accepting enrollment in this ancillary genetics study.

**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. As of June 30, 2008, there were 540 randomized participants.

CTN 0030A, Collection of Economic Data for the Prescription Opioid Addiction Treatment Study. This ancillary study is conducted in collaboration and support with NIDA DESPR.

CTN 0030B, Effects of Chronic Opioids is conducted in collaboration and support 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.

**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 June 30, 2008, at the three Wave 1 sites, 52 participants have been randomized to either the STAGE-12 or the TAU condition. Staff from the Wave 2 sites was trained in Rockville, MD, August 6-8, 2008, and recruitment commenced in September 2008.

CTN 0031A, 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 July 9, 2008, 34 participants have been enrolled in this ancillary study.

CTN 0031B, 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 0031C, 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. This project is supported by supplemental funds from DESPR. 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 to be submitted to DESPR in 2008.

*Six 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, and whether a simple prevention intervention might decrease their sexual risk behavior. The protocol seeks to enroll more than 1,200 participants across approximately twelve sites in the US. The twelve sites have been selected. The protocol has been submitted to the Western IRB for approval. The goal is to start enrolling patients by fall 2008.

CTN 0032A, 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 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, which is in the protocol development phase, will test the effectiveness of the addition of exercise in improving drug abuse treatment outcomes.

In addition to the primary CTN trials, there are currently three secondary analyses that combine analysis 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).

There are also 37 funded studies supported by independent grants that use CTN studies as a platform for research, and 21 completed, ongoing, or planned studies funded as supplements to the clinical trials.

Cecelia Spitznas of DCNBR/BITB and Thomas Brady of DESPR in conjunction with NIDA's Office of Science Policy and Communication are developing A Clinician's Guide to Screening and Brief Intervention and Referral (SBIRT) for Adults in Primary Care. This document will be available over the NIDA website and its purpose is to serve as a resource for providers interested in initiating substance use screening, intervention and referral programs.

Drs. Lisa Onken, DCNBR, and Minda Lynch, DBNBR, have continued to provide input for NIDA on the Roadmap initiative, **"Understanding and Incenting Behavior Change."** This initiative will be part of a broader transformative R01 program designed to "stimulate disruption of existing paradigms or creation of paradigms where none exists. The Transformative R01 Program (T-R01s) will allow highly creative, "out-of-the-box" projects to be supported." (see http://nihroadmap.nih.gov/)

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### NIDA's New and Competing Continuation Grants Awarded Since May 2008

**Arria, Amelia M.** -- University of Maryland, College Park
*Drug Abuse Trajectories in the Transition to Adulthood: Risk Factors and Outcomes*

**Ator, Nancy A.** -- Johns Hopkins University
*The Reinforcing and Discriminative Stimulus Effects of Orally Administered MDMA*

**Barbee, Scott Alan** -- University of Denver
*P-Body and Mirna-Mediated Regulation of Neuroplasticity*

**Bechara, Antoine** -- University of Southern California
*Changes in Addictive Behaviors after Brain Lesions*

**Becker, James T.** -- University of Pittsburgh at Pittsburgh
*Cerebral Blood Flow in HIV/AIDS and Drug Abuse Detected by CASL MRI*

**Berman, Joan W.** -- Yeshiva University
*Dopamine Alters CNS Migration of Uninfected and HIV Infected Leukocytes to SDF-1*

**Bevins, Rick A.** -- University of Nebraska, Lincoln
*Altering Nicotine Reward through Conditioning*

**Bickel, Warren K.** -- University of Arkansas Medical Sciences, Little Rock

*Executive Function Therapy for Stimulant Addiction*

**Bogen, Debra L.** -- Children's Hospital Pittsburgh/UPMC Health System
*Methadone Maintenance Therapy: A Breastfeeding Intervention for Pregnant Women*

**Bolanos-Guzman, Carlos A.** -- Florida State University
*Ontogeny of Physical versus Emotional Stress and Reward Pathways*

**Bongiovanni, Michele Bongiovanni** -- Medical University of South Carolina
*Sex Differences in the Effects of Stress on Cocaine Seeking*

**Booth, Robert E.** -- University of Colorado, Denver
*Structural Barriers to HIV Prevention and Treatment with IDUS in Ukraine*

**Brady, Kathleen T.** -- Medical University of South Carolina
*D-Cycloserine Facilitation of Cocaine-Cue Extinction*

**Brown, Sandra A.** -- University of California, San Diego
*Genetics of Adolescent Antisocial Drug Dependence*

**Bulte, Jeff W.** -- Johns Hopkins University
*Developing MPI for Non-Invasive and Quantitative Imaging of Stem Cells*

**Capaldi, Deborah M.** -- Oregon Social Learning Center, Inc.
*Adjustment Problems and Substance Use in Three Generations*

**Carr, Kenneth D.** -- New York University School of Medicine
*CNS Mechanisms That Modulate Reward*

**Cheer, Joseph Francois Rene** -- University of Maryland, Baltimore
*Cannabinoid Receptor Mechanisms in Accumbal Encoding of Extinction Learning*

**Chen, Li Min** -- Vanderbilt University
*High Resolution fMRI of Nociception in Sii of Monkeys*

**Chen, Yuan** -- City of Hope/Beckman Research Institute
*A High Throughput Screening Assay for the Identification of Sumoylation Inhibitor*

**Chinman, Matthew J.** -- Rand Corporation
*Enhancing Prevention Capacity with Developmental Assets and Getting to Outcomes*

**Clark, David J.** -- Stanford University
*Opioid Efficacy in Humans: A Twin Study*

**Clatts, Michael C.** -- University of Puerto Rico Medical Sciences
*Diffusion of HIV among Drug Using Men in SE Asia*

**Conner, Bradley T.** -- University of California, Los Angeles
*The Effect of Treatment Motivation on Drug Use Treatment Success*

**Cooper, Donald C.** -- University of Texas SW Medical Center/Dallas
*Pathway Specific Ecstasy-Induced Plasticity of Excitability in the Subiculum*

**Cravatt, Benjamin F.** -- Scripps Research Institute
*Toward a Potent and Selective Inhibitor for Every Mammalian Serine Hydrolase*

**Daughters, Stacey B.** -- University of Maryland, College Park
*Behavioral Depression Treatment for African American HIV-Infected Substance Users*

**Davidson, Beverly L.** -- University of Iowa
*MIRNA-Mediated Modulation of Neural Progenitor Cell Fate*

**De Bellis, Michael D.** -- Duke University
*Prefrontal Function in Adolescent Limited vs. Life Course Persistent SUD*

**De La Garza, Richard** -- Baylor College of Medicine
*Rivastigmine as a Treatment for Methamphetamine Dependence*

**Delaney-Black, Virginia** -- Wayne State University
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**Gelberg, Lillian** -- University of California Los Angeles
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**Martins, Silvia Saboia** -- Johns Hopkins University
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**Salvemini, Daniela** -- Saint Louis University
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**Staley, Julie K.** -- Yale University
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**Steketee, Jeffery D.** -- University of Tennessee Health Science Center
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**Wang, Ning** -- National Center/AIDS/STD Control/Prevention
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**Weiss, Friedbert** -- Scripps Research Institute
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# Director's Report to the National Advisory Council on Drug Abuse - September, 2008

## Extramural Policy and Review Activities

### Receipt, Referral, and Review

NIDA received 1426 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 1281 applications.

OEA arranged and managed 33 grant review meetings in which 663 applications were evaluated. OEA's reviews included applications in chartered, standing review committees and Special Emphasis Panels (SEPs). In addition, OEA's Contracts Review Branch (CRB) arranged and managed 23 contract proposal and contract proposal concept reviews.

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 29 Special Emphasis Panels 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 (R01)
Requests for Applications (RFAs)
Loan Repayment Program

OEA managed the following RFA reviews:

- DA08-003: 2008 NIDA Avant-Garde Award Program for HIV/AIDS Research (DP1)
- DA08-007: The Interaction of HIV, Drug Use, and the Criminal Justice System (R01)
- DA08-008: Research on HIV/AIDS and Drug Use in the Multicenter AIDS Cohort Study (MACS) (R03)
- DA08-009: HIV-1 and Host Genetics in Drug Using Populations and Model Organisms (R01)
- DA08-010: The National Institute on Drug Abuse HIV/AIDS Pilot Proteomics Centers (P20)
- DA08-011: Drug Interactions in Substance Abusers With HIV Infection and Other Comorbid Conditions (R01)

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- DA08-012: Resource Core Transdisciplinary Prevention Research Centers (P30)
- DA08-013 /014 /015: Substance Abuse and Glial Regulation of Nervous System Function (R03, R21, R01)
- DA08-016 /017: Non-Coding RNAs And Other Post-Transcriptional Regulatory Mechanisms in Neuroplasticity and Addiction (R01, R03)
- DA08-020: Facilitating Self-Control of Substance Abuse Related Brain Activity Through Real-Time Monitoring of fMRI Signals (R21/R33)-NIAAA Review
- DA08-021: Screening, Brief Intervention and Referral to Treatment (SBIRT) for Drug Abuse in General Medical Settings (R01)
- DA08-022: Exploratory Centers For Translational Research on the Clinical Neurobiology of Drug Addiction (P20)
- DA08-024 /025: Extinction and Pharmacotherapies for Drug Addiction (R03, R01)

Completed Concept and Contract Reviews from the Contracts Review Branch since the last Council are as follows:

**Concept Reviews (R&D)**

- N01DA-9-5547: Measuring Propensity to and Severity of Addiction

**Concept Reviews SBIR Phase I**

- N43DA-9-5545: Innovative Technologies to Support Economic Research in the Drug Abuse Treatment System
- N43DA-9-5541: Instrument Development
- N43DA-9-5542: Rapid Assessment Tools of Sexual and Drug Use Risk Behaviors
- N43DA-9-5543: Electronic Drug Abuse Treatment Referral Systems for Physicians
- N43DA-9-5544: Virtual Reality Simulations to Train Caregivers/Providers
- N43DA-9-5546: Improvement of Reliability and Validity of Reporting of Sensitive Data
- N43DA-9-8884: Development of Therapeutic Agents for Substance Use Disorders
- N43DA-9-8885: Pharmaceutical Approaches for Development of Pharmacotherapies for Drug Addiction
- N43DA-9-8886: Design and Synthesis of Treatment Agents for Drug Abuse
- N43DA-9-8887: Repository for Substance Abuse Brain Imaging Data (SBIR/STTR)
- N43DA-9-8888: Web Based Cognitive/Neuropsychological Testing for Substance Abuse
- N43DA-9-1138: Development of Science Education Materials or Programs
- N43DA-9-7768: Screening, Characterization and Validation Assays for Protein Capture Reagents
- N43DA-9-7769: Tool Development for New or Improved Capture Reagents

**Phase II SBIR Contract Reviews**

- N44DA-8-2210: Development of SA Training Methods
- N44DA-8-5536: Develop State-of-the-Art Mechanisms for Epidemiological Research

### R&D and non-R&D Contract Reviews

- NO1DA-8-1137: International Research Training and Support
- NO1DA-8-5540: CJDATS 2: Coordinating Center and Data and Safety Monitoring Board Support
- NO1DA-8-7766: Synthetic Peptides & Other Drugs of Abuse - Purity Determination, Stability Testing & Quantitative Analysis
- NO1DA-8-8877: Receptor Profiling
- NO1DA-8-8878: Medications Development for Stimulant Dependence 3 (MDS 3)
- NO1DA-8-8880: Toxicological Evaluations of Potential Medications to Treat Drug Abuse

### Certificates of Confidentiality

Between March 21, 2008 and August 4, 2008, OEA processed 109 Certificate applications, including 20 for extension of expiration dates and 7 for amended protocols.

### 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 NIDA's International Program, the NIDA Networking Project, NIH Public Access Policy, protection of sensitive data and information used in research, Notice on modified application submission, referral and review for appointed NIH study section members, and the latest on Enhancing Peer Review.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2008

## Congressional Affairs (Prepared August 29, 2008)

### Appropriations

**FY 2008 --** On June 30, 2008, the President signed into law H.R. 2642 (now Public Law 110-252), the Supplemental Appropriations Act, 2008, which included $150 million for NIH. NIDA's allocation from this total was $5.3 million.

**FY 2009 -- House --** On June 19, 2008, 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. Full Committee action was scheduled for June 26. The Committee met but adjourned before taking action on the FY2009 Labor, HHS, Education appropriations bill. Further House appropriations action is pending.

**FY 2009 -- Senate --** In the Senate, June 26, 2008 saw the Senate Appropriations Committee pass its Labor/HHS bill for FY 2009. This bill includes an increase of $1.025 billion for NIH, for a total of $30,254,524,000. The full committee passed the bill it received from the subcommittee, amended to require the Secretary, HHS, to issue an Advanced Notice of Proposed Rulemaking for public comment in advance of modifying regulations to strengthen federal oversight, including requirements for financial disclosure to institutions, governing conflicts of interest among extramural investigators receiving grant support from NIH.

### Hearings, Briefings, and Events of Interest

**U.S. Senators visit new IRP facility -** On June 2, 2008, NIH hosted a visit by Senators Barbara Mikulski (D-MD) and Ben Cardin (D-MD) to the NIH Biomedical Research Center on the Bayview Campus of the Johns Hopkins University. Presenters included Drs. Elias A. Zerhouni, Director, NIH; Richard Hodes, Director, NIA, and Mark Mattson, Chief, Laboratory of Neurosciences, NIA; Nora Volkow, Director, NIA, Elliott Stein, Chief, Neuroimaging Research Branch, NIDA.

**Vaccine Development Discussed at Friends of NIDA Congressional Briefing -** The Friends of the National Institute on Drug Abuse (NIDA) hosted its eleventh congressional briefing on July 29. The educational event, titled **"Developing New Tools to Prevent and Treat Addiction: Vaccine Development on the Horizon,"** was held in conjunction with the Congressional Addiction, Treatment and Recovery Caucus. Attendance was again very strong, indicating continued significant congressional interest in addiction issues.

The expert panel outlined the growing body of research on vaccines used as an

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addiction treatment and prevention tool. This innovative approach has the potential to profoundly impact the public's health, as drugs of abuse have powerful influences over behavior through their actions on the brain, particularly in those circuits involved in reward and motivation. Immunization is a strategy that seems ideally suited to address this problem. NIDA has embraced the concept and is guiding, in collaboration with pharmaceutical companies, an important vaccine development effort.

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. Michael Owens, PhD, Professor and Director of the Center for Alcohol and Drug Abuse and a Wilbur Mills Endowed Chair in Alcohol and Drug Abuse Prevention, then discussed developing research on antibody-based medications for use in treating methamphetamine addiction. Next, Thomas Kosten, MD, Professor of Psychiatry and Neuroscience at Baylor College of Medicine and Research Director of the VA National Substance Use Disorders Quality Enhancement Research Initiative, shared his results from clinical trials with potential vaccines for treating cocaine addiction. Finally, Dorothy Hatsukami, PhD, Professor in both the Departments of Psychiatry and Psychology at the University of Minnesota and Director of the Tobacco Research Program and Associate Director of the Masonic Cancer Center, discussed her studies of vaccine development for the treatment of nicotine dependence. Photos and presentations from the briefing can be found at http://www.thefriendsofnida.org/briefing-2008-07.php.

### Bills of Interest

[For the full text and additional information about any bill, go to the Library of Congress website at http://thomas.loc.gov].

**Potential Institute Name Change - H.R.1348/S. 1011 -** On March 6, 2007, Representatives Patrick Kennedy (D-RI) and John Sullivan (R-OK) introduced H.R.1348, to redesignate the National Institute on Drug Abuse as the National Institute on Diseases of Addiction, and to redesignate the National Institute on Alcohol Abuse and Alcoholism as the National Institute on Alcohol Disorders and Health. Similarly, on March 28, Senators Joseph Biden (D-DE), Edward Kennedy (D-MA) and Michael Enzi (R-WY) introduced S. 1011, the Recognizing Addiction as a Disease Act of 2007, which would make the same changes. In a press release, Senator Biden said the intent of the legislation is to recognize addiction as a preventable and treatable neurobiological disease, and to better identify the roles and missions of our research institutes. "Addiction is a neurobiological disease - not a lifestyle choice - and it's about time we start treating it as such," said Sen. Biden. "We must lead by example and change the names of our Federal research institutes to accurately reflect this reality. By changing the way we talk about addiction, we change the way people think about addiction, both of which are critical steps in getting past the social stigma too often associated with the disease." The House bill was referred to the Health Subcommittee of the Energy and Commerce Committee; the Senate bill was marked up and passed by the Health, Education, Labor and Pensions Committee on June 27, 2007. The bill has been placed on the Senate calendar under General Orders. The bill is currently being "held" by Senator Jim DeMint (R-SC). He must release his hold if the bill is to receive full consideration in the Senate.

**Stem Cells - H.R. 3/S. 5 -** On January 5, 2007, Representative Diana DeGette (D-CO) introduced H.R. 3, the Stem Cell Research Enhancement Act of 2007. The Senate companion, S. 5, was introduced on January 4, 2007, by Senate Majority Leader Harry Reid (D-NV). The bills would require the Secretary of HHS to conduct and support research using human embryonic stem cells regardless of the date on which such cells were derived. Both the

House and Senate passed their bills. The Senate bill was amended prior to floor consideration. As amended, the bill would also require the Secretary to conduct and support research involving methods of obtaining pluripotent stem cells that do not involve the use of human embryos. The House passed the amended Senate bill, thus sending the bill to the President. The President vetoed the bill. Concurrent with his veto, the President issued an Executive Order requiring the Secretary of HHS to enhance funding for research on alternative methods to derive pluripotent stem cells that do not involve human embryos.

**Stem Cells - S. 30 -** On April 11, 2007, the Senate passed S. 30, the Hope Offered Through Principled and Ethical Stem Cell Research Act, by a roll call vote of 70-28. The bill, introduced on March 29, 2007, by Representative Norm Coleman (R-MN) would require the Secretary to support research to develop pluripotent stem cells using methods that do not involve either the creation of, harm to, or destruction of human embryos. As mentioned above re: S.5, the President issued an Executive Order requiring the Secretary of HHS to enhance funding for research on alternative methods to derive pluripotent stem cells that do not involve human embryos.

**Genetic Non-discrimination - H.R. 493/S. 358 -** On January 16, 2007, Representative Louise Slaughter (D-NY) introduced H.R. 493, the Genetic Information Nondiscrimination Act of 2007. The Senate companion, S. 358, was introduced by Senator Olympia Snowe (R-ME) on January 22, 2007. These bills, which would prohibit discrimination in health insurance and employment on the basis of predictive genetic information, are identical to legislation passed by the Senate during the 109th Congress. The bills would prohibit health insurers in both the group and individual markets from (1) using genetic information to impose enrollment restrictions or to adjust premium or contribution amounts, (2) requesting genetic testing or results except as necessary for treatment, payment, or health care operations, or (3) requesting or requiring the use of genetic information for the purposes of underwriting. The bills define a genetic test as an analysis of human DNA, RNA, chromosomes, proteins, or metabolites that detects genotypes, mutations, or chromosomal changes. The House passed its original bill on April 25, 2007. On April 24, 2008, the Senate passed an amended version of the House bill; the House passed the final bill on May 1. The President signed the bill into law (P.L. 110-233) on May 21.

**Insurance Parity for Mental Health and Substance Abuse - H.R. 1424/S.558 -** On February 12, 2007, Senator Pete Domenici (R-NM) introduced the Mental Health Parity Act of 2007, a bill to provide parity between health insurance coverage of mental health benefits and benefits for medical and surgical services. On March 9, 2007, Representative Patrick Kennedy (D-RI) introduced the Paul Wellstone Mental Health and Addiction Equity Act of 2007, to amend section 712 of the Employee Retirement Income Security Act of 1974, section 2705 of the Public Health Service Act, and section 9812 of the Internal Revenue Code of 1986 to require equity in the provision of mental health and substance-related disorder benefits under group health plans. The Senate passed its bill in September of 2007; the House passed its bill on March 5, 2008. Compromise language has been agreed to, but has yet to come to a vote in either the House or Senate. Congressional leaders are on record hoping to pass the legislation before Congress adjourns this fall. (NOTE: The Medicare Improvements for Patients and Providers Act of 2008, which was passed by Congress in July [P.L. 110-275] includes some parity provisions within the Medicare program.)

**Community Re-entry for Prisoners - H.R. 1593/S. 1060 -** On March 20, 2007, Representative Danny Davis (D-IL) introduced the Second Chance Act of 2007, to reauthorize the grant program for reentry of offenders into the community in the Omnibus Crime Control and Safe Streets Act of 1968, to improve reentry planning and implementation, and for other purposes. The

Senate version of this bill was introduced by Senator Joe Biden (D-DE) on March 29, 2007. The bills include a strong focus on drug treatment in the criminal justice system, and consultation with NIDA is required in several bill sections. The House passed its bill in November, the Senate passed its bill in March of 2008, and the President signed it into law (P.L 110-199).

**Tobacco - H.R. 1108/S. 625 -** On February 15, 2007, Representative Henry Waxman (D-CA) introduced H.R. 1108, the Family Smoking Prevention and Tobacco Control Act - a bill to protect public health by providing the Food and Drug Administration with certain authority to regulate tobacco products. Senator Edward Kennedy (D-MA) introduced an identical bill in the Senate. The House bill (as amended in Committee) passed on July 30, 2008, and action is still pending in the Senate.

**Crack vs. Powder Cocaine -** Several bills have been introduced to address the sentencing differences for those convicted of selling or possessing different forms of cocaine. Most attempt to equalize penalties. Representative Roscoe Bartlett (R-MD) introduced H.R. 79, the Powder-Crack Cocaine Penalty Equalization Act of 2007. Representative Charles Rangel (D-NY) introduced H.R. 460, the Crack-Cocaine Equitable Sentencing Act of 2007. Representative Bobby Scott (D-VA) introduced H.R. 5035, the Fairness in Cocaine Sentencing Act of 2008. Senator Jeff Sessions (R-AL) introduced S. 1383, the Drug Sentencing Reform Act of 2007. Senator Orrin Hatch (R-UT) introduced S. 1685, the Fairness in Drug Sentencing Act of 2007. Senator Joseph Biden introduced S. 1711, the Drug Sentencing Reform and Cocaine Kingpin Trafficking Act of 2007. All of these bills have been referred to their appropriate committees and further action is pending.

**Freedom of Information -** Several bills designed to broaden accessibility to government information were introduced last year (H.R. 1309, H.R. 1326, S. 849, S. 2427). Senator Patrick Leahy introduced S. 2488, the Open Government Act of 2007, to combine various proposals, which passed the House and Senate and became law in December 2007. The law aims to promote accessibility, accountability and openness in government by strengthening Section 522 of Title 5, U.S. Code (the Freedom of Information Act).

**Small Business - Senate -** On July 30, the Senate Committee on Small Business and Entrepreneurship (Senator John Kerry [D-MA], Chairman) held a mark up hearing and reported favorably S. 3362, a bill to reauthorize and improve the SBIR and STTR programs, Reauthorization Act of 2008. S. 3362 would reauthorize SBIR until 2022 and STTR until 2023. It would increase the set-aside for SBIR by 0.1% each year to 3.5% by 2022 for all participating agencies except for the NIH, and double the set-aside for STTR from the current 0.3% to 0.6% by 2014 for all agencies. The measure would increase the SBIR and STTR awards to $150,000 for phase I and to $1,000,000 for phase II, not to exceed 50% of the guideline. The bill would allow the NIH to award up to 18% of SBIR funds to companies majority-owned and controlled by multiple venture capital firms. Other agencies would be allowed to use up to 8% of their funds to award such venture-backed small businesses. S. 3362 includes numerous provisions aimed at strengthening outreach and commercialization pilot initiatives, Federal and state technology partnership programs, and encouraging participation from rural communities. The measure would also require agencies to collect additional data on SBIR applicants. Under section entitles "NIH Cures Pilot," an advisory board would be established at the National Academies to periodically evaluate the SBIR program at all NIH institutes. S. 3362 differs substantially from its House companion, H.R. 5819, passed in April 2008. Any further action is pending. House -- H.R. 5819 - On April 17, 2008, Representative Nydia Velazquez introduced the SBIR/STTR Reauthorization Act, to amend the Small Business Act to improve the SBIR program and the STTR program, and for other purposes. The bill would

reauthorize the programs until 2010 with allocation levels remaining at 2.5 percent for SBIR and 0.3 percent for STTR. The bill increases the award levels for SBIR and STTR Phase I at $300,000 and Phase II at $2,200,000. The measure would require the establishment of an advisory board at each participating agency to review quarterly reports and make necessary recommendations. Additionally, the bill would expand the eligibility criteria to allow small business concerns with multiple venture capital investment and ownership to apply for awards. Further, H.R.5819 would provide flexibility to applicants for cross-over between the programs and to apply directly for Phase II awards. During committee markup, 15 amendments were adopted, some of which would provide for a preference in awarding grants to businesses owned by veterans, that are located in areas with high unemployment, working on rare-disease or nanotechnology-related research topics, or that have taken steps to increase energy efficiency and reduce carbon emissions. Finally, the bill would require rendering final decisions on applications within 90 days after closing of the solicitation, with some exceptions. The bill passed the House on April 23.

**HIV/AIDS -** On July 30, the President signed H.R. 5501, the Tom Lantos and Henry J. Hyde United States Global Leadership Against HIV/AIDS, Tuberculosis and Malaria Reauthorization Act of 2008 as P.L. 110-293. Research-related provisions would require the Director, NIH Office of AIDS Research, to (1) expedite the implementation of the Federal strategic plan regarding the conduct and support of research on, and the development of, a microbicide to prevent HIV transmission, (2) review and revise, as appropriate, the plan to prioritize funding and activities relative to their scientific urgency and potential market readiness, and (3) consult with the Global AIDS Coordinator, the Director, CDC, the Administrator, USAID, the microbicide community, and health advocates. Further, the Director, NIAID, acting through the Institute's Director of the Division of AIDS, would be required to carry out research on, and development of, safe and effective methods for use by women to prevent HIV transmission, including microbicides.

**H.R. 3749 -** On October 4, 2007, Representative Darlene Hooley (D-OR) introduced H.R. 3749, the Methamphetamine Prevention Enhancement Act, to amend the Public Health Service Act to provide for the establishment of a Drug-Free Workplace Information Clearinghouse, to authorize programs to prevent and improve treatment of methamphetamine addiction, and for other purposes. The bill was referred to the Committee on Energy and Commerce.

**H.R. 3992 -** On October 30, 2007, Representative Bobby Scott (D-VA) introduced the Mentally Ill Offender Treatment and Crime Reduction Reauthorization and Improvement Act of 2007, to amend Title I of the Omnibus Crime Control and Safe Streets Act of 1968 to provide grants for the improved mental health treatment and services provided to offenders with mental illnesses, and for other purposes. The bill passed the House in January, 2008. See S. 2304.

**H.R. 4053 -** On November 1, 2007, Representative Shelley Berkley (D-NV) introduced the Mental Health Improvement Act of 2007, to improve the treatment and services provided by the Department of Veterans Affairs to veterans with post-traumatic stress disorder and substance use disorders, and for other purposes. The bill was referred to the Committee on Veterans Affairs, Subcommittee on Health. See S. 2162.

**H.R. 4129 -** On November 8, 2007, Representative Hilda Solis (D-CA) introduced the Homeless Access to Recovery through Treatment Act, to amend the Public Health Service Act to strengthen and expand substance abuse and mental health services to persons experiencing homelessness in the United States. The bill was referred to the Committee on Energy and Commerce.

**H.R. 4232 -** On November 15, 2007, Representative Patrick Kennedy (D-RI)

introduced H.R. 4232, the Improving the Quality of Mental and Substance Use Health Care Act of 2007, to improve mental and substance use health care in the U.S. The bill was referred to the Committee on Energy and Commerce.

**H.R. 4848 -** On February 6, 2008, Representative Pete Stark (D-CA) introduced legislation to extend parity in the application of certain limits to mental health benefits and for other purposes. The bill passed the House on February 8, 2008.

**H.R. 5176 -** On January 29, 2008, Representative Gene Green (D-TX) introduced the Community Mental Health Services Improvement Act," to amend the Public Health Service Act with respect to mental health services. The Bill was referred to the Committee on Energy and Commerce, Subcommittee on Health. See S. 2182.

**H.R. 5554 -** On March 6, 2008, Representative Michael Michaud (D-ME) introduced the Veterans Substance Use Disorders Prevention and Treatment Act of 2008, to amend Title 38, United States Code, to expand and improve health care services available to veterans from the Department of Veterans Affairs for substance use disorders, and for other purposes. The Committee on Veterans Affairs held subcommittee and committee hearings, the bill was reported favorably (as the Justin Bailey Veterans Substance Use Disorder Prevention and Treatment Act of 2008), and passed the House on May 20. The bill was referred to the Senate, where action is pending.

If enacted into law, this bill would require that each VA medical center provide ready access to a full continuum of care for substance use disorders for veterans in need of such care. Under the legislation, this continuum of care is defined as including:

Screenings for substance use disorder in all settings
Detoxification and stabilization services
Intensive outpatient care services
Relapse prevention services
Outpatient counseling services
Residential substance use disorder treatment for veterans with severe recurring substance abuse or substance dependence
Pharmacological treatment to reduce cravings, including opioid substitution therapy
Coordination with groups providing peer to peer counseling
Short-term, early interventions for substance use disorders
Marital and family counseling

The VA Secretary would also be required to reach out to veterans who served in Operation Enduring Freedom or Operation Iraqi Freedom to increase awareness of the availability of care, treatment and services from the VA for substance use disorders. The bill also authorizes a $1.5 million per year pilot program to test the feasibility of providing veterans who seek treatment for substance use disorders access to a computer-based self-assessment, education, and specified treatment program through a secure Internet website operated by the VA. Finally, the bill requires the Secretary of the VA to include a detailed report to Congress on the care, treatment and services provided by the VA during the most recently completed fiscal year. The report must include data from each VA medical facility, including information about the number of veterans who received substance use disorder screening; the number of veterans for whom a disorder was identified after a screening at a VA facility; the number of veterans who were referred by a VA facility for care, treatment or services; the number of veterans who actually received care, treatment or services; and the availability of the full continuum of care.

**H.R. 5613 -** On March 3, 2008, Representative John Dingell (D-MI) introduced the Protecting the Medicaid Safety Net Act of 2008, to extend certain moratoria

and impose additional moratoria on certain Medicaid regulations through April 1, 2009. The seven regulations targeted by this bill seek to limit certain types of services reimbursable under Medicaid provided by addiction treatment, mental health treatment and other healthcare providers. Reimbursement payments under Medicaid for targeted case management, rehabilitation, school-based transportation and outreach, hospital outpatient and other services provided through the health care system would be restricted under the proposed rules. The bill passed the House on April 23 and was referred to the Senate. See also S. 2819.

**H.R. 5619 -** On March 13, 2008, Representative Rick Boucher (D-VA) introduced the Combat Methamphetamine Enhancement Act of 2008, to enhance the ability to combat methamphetamine. The bill was referred to the Committees on Energy and Commerce and Judiciary. See S. 2071.

**H.R. 5835 -** On April 17, 2008, Representative Jan Schakowsky (D-IL) introduced the Health Promotion Funding Integrated Research, Synthesis, and Training Act, or the Health Promotion FIRST Act, to provide for increased planning and funding for health promotion programs of the Department of Health and Human Services. The bill would require OBSSR to develop, and periodically review and as appropriate revise, a plan on how to best develop the basic science of health promotion through the NIH agencies. The bill would also authorize $30 million for FY 2009 to conduct or support early research programs and research training regarding health promotion. The bill was referred to the Committee on Energy and Commerce.

**H.R. 5842 -** On April 17, 2008, Representative Barney Frank (D-MA) introduced the Medical Marijuana Patient Protection Act, to provide for the medical use of marijuana in accordance with the laws of the various States. The bill was referred to the Committee on Energy and Commerce.

**H.R. 5843 -** On April 17, 2008, Representative Barney Frank (D-MA) introduced the Act to Remove Federal Penalties for the Personal Use of Marijuana by Responsible Adults, to eliminate most Federal penalties for possession of marijuana for personal use, and for other purposes. The bill was referred to the Committees on Energy and Commerce, and Judiciary.

**H.R. 5989 -** On May 7, 2008, Representative Patrick Kennedy (D-RI) introduced H.R. 5989, the National Neurotechnology Initiative Act. The Senate companion, S. 2989, was introduced by Senator Patty Murray (D-WA) on the same day. This legislation would require the Secretary of HHS to implement a National Neurotechnology Initiative and establish a National Neurotechnology Coordinating Office within HHS to coordinate all activities. The legislation would authorize the Blueprint for Neuroscience Research which already exists at NIH and would require that, in carrying out the Small Business Innovation Research Program and the Small Business Technology Transfer Program and responsibilities, IC directors, where appropriate, give high priority to small businesses that participate in or conduct neurotechnology research and development projects and annually report to the Office established above. H.R. 5989 was referred to the House Committee on Energy and Commerce. S. 2989 was referred to the Senate Committee on Health, Education, Labor and Pensions (HELP).

**H.R. 6215 -** On June 9, 2008, Representative Frank Pallone (D-NJ) introduced H.R. 6215, the Advancing Fetal Alcohol Spectrum Disorders (FASD) Research, Prevention, and Services Act, to amend the Public Health Service Act to reauthorize and extend the Fetal Alcohol Syndrome prevention and services program. H.R. 6215 would require the NIH Director, in coordination with the Interagency Coordinating Committee on Fetal Alcohol Syndrome, to establish a research agenda for FASD and award grants, contracts or cooperative agreements to public or private nonprofit entities to carry out the agenda. H.R. 6215 would reauthorize the Interagency Coordinating Committee on Fetal

Alcohol Syndrome, led by the National Institute on Alcohol Abuse and Alcoholism, to coordinate activities among the Federal agencies. H.R. 6215 was referred to the House Committees on Energy and Commerce and Education and Labor.

**H.R. 6281 -** On June 17, 2008, Representative Elton Gallegly (R-CA) introduced the High School Sports Anti-Drug Act, a bill to provide states with the resources needed to rid our schools of performance-enhancing drug use. The bill was referred to the House Committee on Education and Labor. See. S. 1470

**H.R. 6353 -** On June 24, 2008, Representative Bart Stupak (D-MI) introduced the Ryan Haight Online Pharmacy Consumer Protection Act of 2008, to amend the Controlled Substances Act to address online pharmacies. The bill was referred to the Committees on Energy and Commerce, and Judiciary. See S. 980

**H.R. 6498 -** On July 15, 2008, Representative Patrick Kennedy (D-RI) introduced the Genomics and Personalized Medicine Act of 2008, a bill to secure the promise of personalized medicine for all Americans by expanding and accelerating genomics research and initiatives to improve the accuracy of disease diagnosis, increase the safety of drugs, and identify novel treatments, and for other purposes. The bill was referred to the Committees on Ways and Means, and Energy and Commerce.

**H.R. 6680 -** On July 30, 2008, Representative Jose Serrano (D-NY) introduced H.R. 6680, the Community AIDS and Hepatitis Prevention Act. Provisions would provide that "notwithstanding any other provisions for law, nothing shall prohibit the use of Federal funds to establish or carry out a program of distributing sterile syringes to reduce the transmission of bloodborne pathogens, including HIV and viral hepatitis." H.R. 6680 was referred to the House Committee on Energy and Commerce.

**H. Res. 1359 -** On July 21, 2008, Representative Maxine Waters (D-CA) introduced a resolution expressing support for the goals and ideals of National Clinicians HIV/AIDS Testing and Awareness Day and encouraging that (1) primary care physicians and other clinicians nationwide become actively involved in HIV/AIDS awareness, testing, treatment, and referral services; (2) the media educate clinicians and the public to the benefits of HIV testing; and (3) individuals get tested and educate themselves about HIV/AIDS prevention and treatment. H. Res. 1359 was referred to the House Committee on Energy and Commerce.

**S. 2162 -** On October 15, 2007, Senator Daniel Akaka (D-HI) introduced the Veterans Mental Health Improvements Act of 2007, to improve the treatment and services provided by the Department of Veterans Affairs to veterans with post-traumatic stress disorder and substance use disorders, and for other purposes. On April 8, 2008, the bill was reported out by the Committee on Veterans Affairs and passed the Senate on June 3. See H.R. 4053.

**S. 2182 -** On October 17, 2007, Senator Jack Reed (D-RI) introduced the Community Mental Health Services Improvement Act, to amend the Public Health Service Act with respect to mental health services. The bill was referred to the Committee on Health, Education, Labor and Pensions. See H.R. 5176.

**S. 2237 -** On October 25, 2007, Senator Joseph Biden (D-DE) introduced the Crime Control and Prevention Act of 2007, an omnibus bill to fight crime. The legislation includes several drug-related programs. The bill was referred to the Committee on the Judiciary.

**S. 2274 -** On October 31, 2007, Senator Joseph Biden introduced the Dextromethorphan Abuse Reduction Act of 2007, to amend the Controlled Substances Act to prevent the abuse of dextromethorphan, and other

purposes. The bill was referred to the Committee on the Judiciary.

**S. 2304 -** On November 5, 2007, Senator Pete Domenici (R-NM) introduced the Mentally Ill Offender Treatment and Crime Reduction Reauthorization and Improvement Act of 2007, to amend Title I of the Omnibus Crime Control and Safe Streets Act of 1968 to provide grants for the improved mental health treatment and services provided to offenders with mental illnesses, and for other purposes. On April 1, 2008, the bill was reported out by the Committee on the Judiciary and placed on the legislative calendar. See H.R. 3992.

**S. 2819 -** On April 3, 2008, Senator Jay Rockefeller (D-WV) introduced the Economic Recovery in Health Care Act of 2008, to preserve access to Medicaid and the State Children's Health Insurance Program during an economic downturn, and for other purposes. The bill was referred to the Committee on Finance. See H.R. 5613.

**S. 2988 -** On May 7, 2008, Senator Joseph Lieberman (I-CT) introduced the Accelerating Cures Act of 2008" to amend the Public Health Service Act to enhance public and private research efforts to develop new tools and therapies that prevent, detect, and cure diseases. The bill was referred to the Committee on Health, Education, Labor and Pensions.

**S. 2989 -** On May 7, 2008, Representative Patrick Kennedy (D-RI) introduced H.R. 5989, the National Neurotechnology Initiative Act. The Senate companion, S. 2989, was introduced by Senator Patty Murray (D-WA) on the same day. This legislation would require the Secretary of HHS to implement a National Neurotechnology Initiative and establish a National Neurotechnology Coordinating Office within HHS to coordinate all activities. The legislation would authorize the Blueprint for Neuroscience Research which already exists at NIH and would require that, in carrying out the Small Business Innovation Research Program and the Small Business Technology Transfer Program and responsibilities, IC directors, where appropriate, give high priority to small businesses that participate in or conduct neurotechnology research and development projects and annually report to the Office established above. H.R. 5989 was referred to the House Committee on Energy and Commerce. S. 2989 was referred to the Senate Committee on Health, Education, Labor and Pensions (HELP).

**S. 3173 -** On June 20th, Senator Jay Rockefeller (D-WV) introduced S. 3173, the "Keeping Families Safe Act of 2008." S. 3173 seeks to better allow children currently in foster care to be placed with a parent living in a residential treatment facility that provides drug and alcohol addiction treatment services. Under the legislation, the current law would be amended to add residential family addiction treatment centers to the list of child-care institutions that can receive foster care maintenance payments. The bill was referred to the Committee on Finance.

**S. 3379 -** On July 31, 2008, Senator John Kerry introduced the SERV Act, to provide grants to establish veterans treatment courts. The bill was referred to the Committee on the Judiciary.

**S. 3387 -** On July 31, 2008, Senator Orrin Hatch (R-UT) introduced for himself and Senator Christopher Dodd (D-CT) S. 3387, the National Pain Care Policy Act of 2008. Among other provisions, the bill would amend the Public Health Act to require the Director of the NIH to establish a new office to be known as the Pain Consortium. The Consortium would be required to (1) establish and maintain a national agenda for basic and clinical research on the causes and treatments of pain, (2) coordinate pain research and related training and other activities across programs at the NIH, (3) convene an annual conference, and (4) undertake other appropriate actions. The bill would also require the NIH Director to establish an advisory committee to the Consortium, known as the National Pain Care Research Advisory Committee. S. 3387 was referred to the

Senate Committee on Health, Education, Labor, and Pensions.

**S. 3408 -** On July 31, 2008, Senator Max Baucus (D-MT) introduced S. 3408, the Comparative Effectiveness Research (CER) Act of 2008. The bill would establish a nonprofit corporation called the Health Care Comparative Effectiveness Research Institute to contract with appropriate Federal agencies or the private sector to conduct comparative effectiveness research. The Institute would be responsible for (1) establishing and carrying out a research project agenda [in carrying out a research agenda, Institute must give preference for contracts to Federal government agencies with experience in conducting CER], (2) establishing a methodology committee to develop scientifically-based methodological standards for comparative clinical effectiveness research [would be required to consult or contract with IOM, AHRQ, NIH (can contract with one or more) in developing and updating standards], and (3) ensuring that there is a process for peer-review of the research [Institute would be authorized to use existing peer-review processes used by entities with which the Institute contracts]. Provisions would also establish a Board of Governors comprised of 21 members, including the Secretary of HHS, the Director of AHRQ, and the Director of NIH, to oversee the Institute's activities. The legislation would create the Comparative Effectiveness Research Trust Fund in the U.S. Treasury. Total funding for the first year (FY 2009) would be $5 million, and funding would increase to $300 million a year by the year 2013. Funding for the Institute would sunset after 10 years. S. 3408 was referred to the Senate Committee on Finance.

**S.Res. 614 -** On July 16, 2008, Senator Joe Biden (D-DE) introduced this resolution, designating the month of August 2008 as National Medicine Abuse Awareness Month.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2008

## International Activities

### Funding Initiatives

***Online International Master of Science in Addiction Studies Now Accepting Applications***

The University of Adelaide, King's College London, and Virginia Commonwealth University have created the International Programme in Addiction Studies (IPAS), an online, 12-month intensive graduate program available to students from all countries. The NIDA International Program provided initial funding to support planning for the IPAS. The program is designed to develop professionals who are fully prepared to assume leadership roles in the addictions field throughout the world. Students will study the scientific basis of addiction, comparative epidemiology, evidence-based interventions (including pharmacological, psychosocial, and public health approaches), research methodology, and addictions policy. Lecturers will be selected from among the world's leading authorities in each of these subject areas, while program directors will be faculty members of the three participating universities. The firm scientific grounding of the program, covering a range of areas from treatment to policy, and its unique international perspective make it appropriate for recent graduates and professionals working in a range of fields such as health, law enforcement, policy, and education. Graduates of the program will be able to: (1) translate research on addiction into more effective treatment and prevention practices; (2) translate research into more effective policies at the local, state, national, and/or international level to address public health issues; and (3) become specialists in addiction by integrating program material into their profession/practice.

### NIDA International Forum

***NIDA International Forum Focuses on Evidence-Based Interventions for Addictions***

More than 200 registrants from 53 countries participated in the 13th NIDA International Forum, which was held June 13-17, 2008, in San Juan, Puerto Rico. The meeting, *Globally Improving and Applying Evidence-Based Interventions for Addictions,* was sponsored by the NIDA International Program and focused on the benefits of multidisciplinary, public health approaches to drug abuse research, prevention, and treatment. Opening the Plenary Session, NIDA Deputy Director Dr. Timothy P. Condon highlighted recent advances in NIDA-supported addiction research that have provided new insights into the complex neurophysiological, genetic, and epigenetic components of drug abuse and addiction. Dr. Vladimir B. Poznyak, World Health Organization, addressed ways to strengthen the public health approach to drug dependence. Dr. Gilberto Gerra, United Nations Office on Drugs and Crime, described the evidence supporting the existence of genetic, familial, and community-level risk

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factors for substance abuse and dependence and called for increased advocacy, outreach, training, and dissemination efforts to implement evidence-based addiction prevention and treatment programs in health care systems, schools, and social programs. Dr. Tom Babor, University of Connecticut, reviewed the ways public policy influences drug abuse treatment and population health. NIDA International Program Director Dr. Steven W. Gust called for a new era of scientific diplomacy, describing research that found U.S. science and technology is highly respected internationally, even in regions where public opinions of U.S. foreign policy are extremely low. Dr. Gust summarized research that documented benefits to the U.S. scientific community from contributions by foreign scientists, particularly by creating opportunities to conduct research in parts of the world critical to scientific advancement. The NIDA International Program supports activities designed to promote scientific diplomacy, and Dr. Gust outlined major initiatives to foster publication of international research; develop web-based communication and training tools; and support international research through fellowships, exchanges, and training and research grants. Presenters in concurrent workshops illustrated numerous ways researchers and service providers can forge partnerships; integrate public policy, science, and practice; and implement effective -- and cost-effective -- programs to prevent and treat drug abuse and addiction. More than 130 meeting participants presented their research at a joint NIDA International Forum/College on Problems of Drug Dependence (CPDD) international poster session. During that Forum poster session, representatives from 10 NIDA components (IP, ARP, CCTN, DBNBR, DCNBR, DESPR, DPMCDA, IRP, Special Populations, and Women and Sex/Gender Differences Research Program) and the Fogarty International Center presented posters summarizing the units' goals, research interests, international focus, and international funding priorities.

***NIDA International Program Presents Awards of Excellence***

During the 2008 NIDA International Forum, the NIDA International Program presented awards to honor mentors, researchers, and binational collaborative teams whose efforts support the International Program mission.

The *Excellence in Mentoring* award was presented to Linda B. Cottler, Ph.D., M.P.H., Washington University School of Medicine, for her work directing NIDA- and NIH-supported training programs in comorbidity, biostatistics, and epidemiology and in developing a bioethics incubator in India.

Juana M. Tomas-Rossello, M.D., Ph.D., United Nations Office on Drugs and Crime (UNODC), was honored for *Excellence in International Leadership* for her role in creating and operating the UNODC TreatNet, an international network of resource centers that synthesize and disseminate best practices and lessons learned on drug abuse treatment and rehabilitation.

The binational research team of Perry F. Renshaw, M.D., Ph.D., Mclean Hospital Brain Imaging Center, and In Kyoon Lyoo, M.D., Ph.D., Seoul, South Korea, National University Medical School, received the *Excellence in Collaborative Research Award* for their work employing innovative imaging techniques that allow them to take very sensitive measurements of small regions in the brain. The team's studies investigate how drug addiction and mood disorders alter brain structure and chemistry, documenting age-dependent neurobiological deficits in the frontal regions of adolescent methamphetamine users, and suggesting that some deficits recover with abstinence while others do not.

## NIDA-Supported Meetings

***NIDA Supports International Poster Session at Society for Prevention Research***

Thirty scientists from around the world presented their research at the International Poster Session cosponsored by the NIDA International Program

and Division of Epidemiology, Services and Prevention Research, Prevention Research Branch in conjunction with the 16th Annual Meeting of the Society for Prevention Research (SPR). Half of the scientists--all international researchers--received NIDA travel awards to present research conducted by international researchers or binational teams on drug abuse prevention research completed in international settings. The other 15 researchers were U.S. researchers whose research was conducted in other countries or as part of a binational team. The session attracted about 150 SPR registrants and was very well received. The SPR meeting, which was held May 28-30, 2008, in San Francisco, focused on research in prevention science designed to aid understanding of the ways in which social and physical settings matter in designing interventions and understanding intervention impact. Other conference themes included: (1) how and under what conditions research is used to influence policies and practices or how policy priorities shape what researchers study; (2) the role of culture, ethnicity, and health disparities in prevention research; (3) the developmental period of emerging adulthood, which extends roughly through the ages 18 to 29; and (4) advances in epidemiology, etiology, efficacy trials, effectiveness trials, dissemination, and innovative methods.

## Fellowships

### *INVEST Fellow Will Focus on HIV Prevention in Tajikistan*

Makhbatsho Bakhromov, M.D., MSc., HIV/AIDS Coordinator for the Tajikistan National Coordinating Committee to Prevent HIV/AIDS, Tuberculosis, and Malaria, has been selected as a NIDA INVEST Fellow. He will work with Nabila El-Bassel, D.S.W., Columbia University, to use qualitative research methods to adapt a network-oriented peer education HIV prevention intervention for use in Tajikistan. Dr. Bakhromov will then pilot test the adapted intervention to obtain preliminary data and assess its feasibility for implementation in Dushanbe, Tajikistan, and develop a grant application to scale-up the intervention in a randomized clinical trial. The fellowship builds on Dr. Bakhromov's existing collaboration with Dr. El-Bassel and her colleagues at Columbia. The intervention, based on Project Shield, will use network members to educate their drug and sexual network partners and reach injection drug use and sexual partners who are not currently accessing public health services. Dr. Bakhromov will conduct the pilot test in collaboration with a Dushanbe nongovernmental organization that distributes condoms, syringes, and health information to injection drug users. A graduate of Tajik Medical University, Dr. Bakhromov received a Muskie Fellowship in 2004 to obtain his master's degree in International Health Policy and Management from Brandeis University. He implemented a national development program for Tajik health professionals and coauthored an article on HIV/AIDS risks among Tajik migrants in Moscow [J. Immigr. Minor. Health. 2008 Oct;10(5):461-8].

### *DISCA Partners Explore Role of Acculturation, Stress, and Family Functioning on Prevention Interventions*

Juan-Luis Recio, Ph.D., emeritus associate professor at Universidad Complutense de Madrid, has received a NIDA Distinguished International Scientist Collaboration Award (DISCA) to collaborate with Flavio Marsiglia, Ph.D., Arizona State University - Tempe. Dr. Recio will conduct a small drug abuse and HIV feasibility pilot study in Phoenix, Arizona, with a sample of Latino youth and their family members. The research partners will then use a longitudinal approach to explore the interaction among family functioning, acculturation, and acculturative stress to design and test a culturally grounded and family-based drug use and HIV/AIDS prevention intervention.

## International Visitors

On May 7, 2008, Dale Weiss from the NIDA International Program met with Tomotaka Sobue and Yumiko Mochizuki-Kobayashi from the Japanese National

Cancer Center. The two visitors were here as part of a tour arranged by the National Cancer Institute to examine NCI's tobacco control programs. The visitors were particularly interested in NIDA's tobacco prevention and control research and how it informs the overall US tobacco related policies.

Also on May 7, 2008, visitors from the Indonesian organization Yayasan Cinta Anak Bangsa (YCAB) visited NIDA. YCAB is an independent organization whose main focus is primary drug prevention in schools and communities. The visitors met with representatives from NIDA's Division of Epidemiology, Services, and Prevention Research.

Dr. Sandeep Chawla Chief of the Policy Analysis and Research Branch of the United Nations Office on Drugs and Crime met with Steve Gust, Ph.D. and Dale Weiss, IP on July 16, 2008. Dr. Chawla explained the wide reaching work done by his office and Dr. Gust outlined NIDA's mission and goals.

### Other International Activities

Dr. Joe Frascella, Director, DCNBR, participated in the 2nd annual conference sponsored by the Norlien Foundation entitled **"Building Blocks for a Healthy Future II"** and gave a plenary address entitled "Addiction: A Bio-developmental Perspective" in Red Deer, Alberta Canada on June 10, 2008.

Dr. Woody Lin, DCNBR, participated in the **"Traditional Chinese Medicine Research"** Roundtable held on June 16-17, 2008 at NIH. The conference sought to foster US-China collaboration in research on traditional Chinese Medicine and included the participation of Michael O. Leavitt, Secretary, U.S. Department of Health and Human Services, NIH and FDA. A Memorandum was signed during the meeting the describes participants' (HHS and the Chinese counterpart) areas of mutual interest, including acupuncture research, safety and efficacy of Chinese herbal medicine, and methodology development.

Dr. Woody Lin participated in a cross-NIH meeting on global health organized by the NIH Fogarty International Center titled **"China's Health: Looking Ahead"** on July 16, 2008. Other attendees included Dr. Betty Tai, Director of NIDA's Center of Clinical Trial Network and Dr. Steve Gust, Director of NIDA's International Office. The keynote speaker was Dr. Lincoln Chen, the director of Chinese Medical Board of New York, a Rockefeller family-founded entity actively involved in studying policy, medical education and medical sciences in Asia. This organization also provides funding for research in these areas. China's role in global health was presented and discussed. In addition to the background introduction, Dr. Chen highlighted four areas relevant to public health concerns in the United States: 1) public health as related to cigarette smoking and migrant health, 2) potential of traditional Chinese medicine, 3) the large size of clinical trial centers located in China, and 4) the large scientific talent pool in China.

Dr. Vishnu Purohit, DBNBR, participated in the Annual International Cannabinoid Research Society Symposium (ICRS), which was held in Aviemore, Scotland, June 25-29, 2008. The title of his presentation was "Opportunities for International Collaboration on Cannabinoid Research at National Institute on Drug Abuse/National Institutes of Health".

Dr. Jag Khalsa, DPMCDA, (along with several NIDA colleagues including NIDA Director, Dr. Nora Volkow and NIDA funded researchers) visited with clinicians/researchers in Iceland, July 1-4, 2008, to begin working on collaborations on research on drug abuse and co-occurring infections and other issues.

Dr. Ivan Montoya, DPMCDA, co-chaired with Francisco Cumsille from the Organization of American States a 2-day meeting of the Latin American Network of Drug Abuse Epidemiology 9REDLA) that took place in San Juan

(Puerto Rico) on June 11 and 12, 2008. The panel of presenters included drug abuse epidemiology experts from 10 countries of the Americas and Puerto Rico.

Dr. Meyer Glantz (DESPR) represented NIDA at the 2008 World Mental Health Consortium annual meeting in Annapolis, Maryland. The Consortium is a collaboration of the World Health Organization, NIMH and NIDA, and other mental health institutions. The Consortium members sponsor and conduct the World Mental Health Survey, a multi-site investigation of the prevalence and concomitants of mental and substance use disorders in 32 countries. The United States component of the survey, the National Comorbidity Survey-Replication, has completed data collection and is currently analyzing and publishing its findings.

Dr. Yonette Thomas, Chief, ERB, DESPR, gave a plenary presentation on "The Epidemiology of Drug Abuse" at the Fourth Regional Workshop of the Project AD/CAM/04/H90: Establishment of a network of treatment, rehabilitation and social reinsertion for Central America on June 11, 2008 in San Salvador, El Salvador.

Ana Anders, SPO, participated in the planning and development of a Drug Abuse and Addiction Prevention and Treatment Training Conference for Central America and the Caribbean with the United Nations Office of Drugs and Delinquency, The National Hispanic Science Network and SAMHSA on June 10-13, 2008 in El Salvador.

Dr. Elizabeth Ginexi, DESPR, and Dr. Richard Jenkins, DESPR on May 7, 2008 met with visitors Bobby Hartanto and Rofikoh Rokhim from Yayasan Cinta Anak Bangsa, a Non-Governmental Organization in Indonesia. They are interested in partnering with international prevention researchers to help with training and implementation of effective prevention programs.

Dr. Belinda Sims, DESPR, Dr. Augie Diana, DESPR, Dr. Wilson M. Compton, Director, DESPR, and Dr. Yonette Thomas, Chief, ERB, DESPR, and Dr. Steve Gust, International Office, met with Paul Griffiths from the European Monitoring Centre for Drugs and Drug Addiction on June 19, 2008.

Dr. Bruce Hope, IRP, presented a seminar entitled "Neuronal Ensembles and Context-specific Sensitization to Cocaine" at the Department of Neuroscience, Karolinska Instituet, Stockholm, Sweden, on May 29-30, 2008. Dr. Yavin Shaham visited the Weizmann Institute of Science in Rehovot, Israel to discuss current collaborative research and to present a lecture on "Neurobiology of Relapse to Abused Drugs" on June 9-11, 2008.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2008

## Meetings/Conferences

The National Institute on Drug Abuse (NIDA) convened a two-day Blending Conference at the Duke Energy Center in Cincinnati, Ohio on June 2-3, 2008 titled: **"Blending Addiction Science and Treatment: The Impact of Evidence-Based Practices on Individuals, Families and Communities."** In this seventh NIDA Blending Conference, the successful and unique two-day event provided an opportunity for over 1,100 clinicians and researchers to collectively examine cutting edge approaches for treating and preventing drug abuse and addiction. Plenary presenters included Nora Volkow, M.D., Kathleen Brady, M.D., Ph.D., Dennis Daley, Ph.D. and Deni Carise, Ph.D. Session topics ranged from the latest findings on the role of genetics, experimental vaccines and the Blending Team products addressing motivational interviewing, buprenorphine, and motivational incentives. The NIDA planning committee of this conference included Drs. Timothy P. Condon, Cindy Miner and Denise Pintello. Nearly 75% of the participants completing the evaluation reported that they were planning to make changes in their treatment/practice based on the information presented at the NIDA Blending Conference.

NIDA, in collaboration with the Center for Substance Abuse Treatment (CSAT), and the National Association of State Alcohol and Drug Abuse Directors (NASADAD) held a meeting **"Enhancing Services Using Addiction Treatment and Prevention Research"** on June 8, 2008, in Montgomery, Alabama. NIDA's Deputy Director, Dr. Timothy P. Condon, presented NIDA's most recent science advances regarding addiction research; Dr. Frank Vocci, DPMCDA Director, provided an overview of the development of medications for assisted treatment; Dr. Elizabeth Robertson, DESPR, presented prevention research; and the members from the adolescent buprenorphine treatment Blending Team discussed CTN protocol results.

NIDA sponsored a **Mentored-K Awardee Meeting** on July 24-25, 2008, at the Bethesda North Marriott Hotel & Conference Center. The goal was to help new scientists in their transition to independence. Participants had the opportunity to hear from the NIDA Director about research highlights and priorities and to interact with Division Directors, Program, Review, and Grants Management staff. They also had the benefit of practical advice and presentations from former K-awardees, and senior researchers on topics ranging from grant writing to negotiating with your institution to team science. The meeting was organized by Drs. Mimi Ghim, Diane Lawrence, Eliane Lazar-Wesley, Aria Crump, Susan Weiss, Ms. Anna Staton and Ms. Usha Charya on behalf of the Research Training Committee.

The National Institute on Drug Abuse organized a program at this year's **American Psychological Association (APA) Annual Meeting** in Boston, Massachusetts, August 14-17, 2008. A number of NIDA staff presented on a wide range of session topics, such as: Do Drugs of Abuse Produce Cognitive

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Rigidity?; Potential of Universal Childhood Prevention to Reduce Later Criminal Behavior; and Biological Basis of Sex Differences in Drug Abuse: A Translational Perspective. NIDA also co-sponsored an Early Career Investigator Poster Session with APA's Divisions 28 and 50 and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as part of the two Divisions' Social Hour.

Dr. Augusto Diana, DESPR, Dr. Marsha Lopez, DESPR, and Dr. Aleta Meyer, DESPR, convened a two-day science meeting titled **"Can Physical Activity and Exercise Prevent Substance Use? Promoting a Full Range of Science to Inform Prevention"** on June 5-6, 2008, in Bethesda, MD. The goal of the meeting was to promote examination of the potential role of physical activity in substance use prevention. For the purposes of this meeting, physical activity was conceptualized broadly across types (e.g., sports, exercise, dance, martial arts, outdoor adventure) and across development (e.g., open-ended free play in early childhood, physical education and sports team participation during school years, healthy leisure activities in adulthood). Dr. Nora Volkow, Director of NIDA, and Dr. Wilson Compton, Director of DESPR, welcomed the meeting participants and gave opening remarks. Expert panels presented a full range of potential neurobiological, developmental, social, and environmental processes associated with physical activity and the onset and progression of drug use. Staff from other Divisions within NIDA, the National Cancer Institute, and USDA, contributed as panel moderators: Dr. Karen Sirocco (DCNBR), Dr. Minda Lynch (DBNBR), Dr. Frank Perna (NCI), Dr. Audie Autienza (NCI), and Dr. Shirley Gerrior (USDA).

A CCTN-DCNBR joint workshop was held May 20, 2008. The title of the workshop was **"Pain, Stress and Healthier Life Choices with an Eastern Approach."** Drs. Lixing Lao and Kevin Chen (University of Maryland School of Medicine) discussed how acupuncture and/or meditation are useful in 1) coping with pain or stress; 2) a choice for healthier lifestyles; and 3) managing addiction. They also discussed the concerns and challenges in experimental design and project implementation and how evidence-based studies can be carried out.

Drs. Mary Kautz, of DCNBR, and Allison Chausmer Hoffman, of DBNBR, organized a symposium titled **"Virtual Reality and Drug Cue Reactivity"** that was held on July 16, 2008 at the Neuroscience Center, Rockville, MD. The meeting was sponsored by the Translationally Oriented Approaches, Devices and Strategies (TOADS) Workgroup and the Nicotine/Tobacco Interest Group. A major purpose was to take a translational approach to basic human research on virtual reality and smoking cues, and explain how this emerging technology may be used as a new, innovative tool exploring nicotine addiction, cue reactivity, and potential research and treatment applications. The speakers were Drs. Patrick Bordnick (University of Houston), Mark Wiederhold (Virtual Reality Medical Center), and Michael Saladin (Medical University of South Carolina).

The **National CTN Steering Committee Meetings** were held June 3-6, 2008 in Cincinnati, Ohio. The following meetings/committees convened:

CTP and PI Caucuses
Steering Committee
Executive Committee
Research Utilization Committee
Research Development Committee
Node Coordinator Workgroup
CTN 0027 - START Study Team
CTN 0031 - STAGE-12 Study Team
CTN 0033 - Meth Use among American Indians Study Team
Marinol Concept Group
Pharmacotherapy Special Interest Group

Two workshops were held during the CTN Steering Committee Meetings:

**Publishing Workshop** Practitioners and principal investigators joined together in Cincinnati during the CTN Steering Committee meeting to promote the involvement of more people in publishing opportunities. The workshop titled "Share Your Knowledge by Publishing and Presenting" was sponsored by the CTN Publications Committee and organized by Steven Sparenborg of the CCTN. Speakers were Greg Brigham, Steering Committee Co-Chair and Principal Investigator at Maryhaven, Inc. of Columbus, Ohio; Susan Gordon, Research Director at Seabrook House in Seabrook, New Jersey; and Louise Haynes, Director of Research at the Lexington/Richland Alcohol and Drug Abuse Council in Columbia, South Carolina; and Steven Sparenborg Program Officer, Psycho-Pharmacology Team, CCTN. Principal Investigators were urged to invite the participation of staff and practitioners in the publishing process.

**Posttraumatic Stress Disorder (PTSD) and Substance Use Disorders (SUD) Workshop** Some soldiers returning from combat duty in Iraq and Afghanistan show signs and symptoms of post traumatic stress disorder (PTSD) and many research and treatment resources in the country are increasing their level of research on this condition in order to better serve our veterans. A substantial proportion of veterans with PTSD also have comorbid substance use disorders. CTN Node PI Kathleen Brady, M.D., Ph.D. and Co-PI Andrew Saxon, M.D. have treated subjects with PTSD who are comorbidly dependent on cocaine, alcohol, or nicotine and presented results of their research with these subjects at the Clinical Trials Network Steering Committee meeting on June 4, 2008 in Cincinnati, Ohio. They educated the CTN on the gravity of the situation among veterans and the paucity of effective treatments for PTSD. Dr. Saxon's research focused on the integration of evidence-based smoking cessation treatments into ongoing mental health care for PTSD patients in a Veterans Health Clinic and was published in 2007. Dr. Brady studied a small sample of PTSD subjects (mostly females who had been sexually assaulted) who were dependent on cocaine. She found that a combination of cognitive behavioral therapy for cocaine use and exposure therapy for PTSD significantly reduced symptoms of both disorders during treatment and at a follow-up visit. In a different sample, she found that the use of the SSRI sertraline improved PTSD symptoms in nearly all treated subjects and improved drinking outcomes in subjects with early onset PTSD and later onset alcoholism.

NIDA's Special Populations Office (SPO), NIDA convened the **NIDA Research Development Diversity Programs Meeting** on May 19-20, 2008 in Silver Spring, Maryland. The meeting's key priorities were to discuss and assess funding programs coordinated through the SPO including: Diversity Supplements, Minority Institutions Drug Abuse Research Program (MIDARP) and Summer Research with NIDA. PIs and former trainees/recipients presented on their experiences and provided viable feedback. Additionally, an array of NIDA staff provided information on funding and career development activities and the grant application and review process.

The Special Populations Office (SPO) and the African American Researchers and Scholars Workgroup (AARSWG) convened a one day **"Mini Medical School on Addiction"** at Morehouse School of Medicine in Atlanta, Georgia on July 21, 2008 for health care professionals, researchers, and members of the

community interested in understanding the needs of substance abusers and addiction in the African American community. Scientists and physicians lectured on topics that covered the process of addiction, psychopharmacology, addiction treatment and services, issues arising from substance abuse and its research implications, HIV/AIDS and other related co-morbidities. The AARSWG presented an award of exemplary leadership to Dr. Lula Beatty, Chief, Special Populations Office, NIDA.

Lula Beatty, Ph.D. and staff of the Special Populations Office assisted the African American Researchers and Scholars Workgroup (AARSWG) with the development and coordination of the first **Addiction Research Training Institute (ARTI)**, which was held on July 22-25, 2008 at Morehouse School of Medicine in Atlanta, Georgia. The ARTI was designed to train early/new investigators to become funded researchers in the area of substance abuse and addiction in African Americans. The trainees included twenty post-doctoral fellows and junior faculty members from several academic institutions. Training sessions included presentations on an array of current research findings and opportunities, grant writing and publication workshop, and a mentored critique of the trainees' research proposals.

The Special Populations Office supported the Native American /Alaska Native Researchers and Scholars Workgroup (NAANRSWG) first **"Native to Native Mentoring Program,"** developed to increase the number of Native Americans and Alaska Natives pursuing research careers and in the field of substance abuse and addiction. The meeting was an adjunct to the annual Association of American Indian Physicians (AAIP) meeting held in Couer d' Alene, Idaho on July 24 - 29, 2008. Wilson Compton, M.D., Director of DESPR, provided a presentation titled, "Drug Addiction: A Biobehavioral Disorder". Kathy Etz, Ph.D. (DESPR) also attended this meeting and met with the NAANRSWG and their mentees to discuss research opportunities and future activities that will be supported by NIDA.

NIDA's Women & Sex/Gender Differences Program awarded 27 **Women & Gender Junior Investigator Travel Awards** for the annual meeting of the College on Problems of Drug Dependence (CPDD), June 15-21, 2007, Quebec City, Canada. These $750 awards provide travel support to first author junior investigators who make presentations on the topic of women and/or sex/gender differences. These travel awards have been made annually beginning in 1999, and are designed to promote entry of junior investigators into drug abuse research on women and sex/gender differences. A brochure listing all the awardees since 1999 was made available at CPDD. To further promote research in this field, NIDA published a mini-program book, Focus on Women & Sex/Gender Differences, for the CPDD meeting. Excerpted from the CPPD program book, it contains only those program listings related to women and sex/gender differences. It also contains the CPDD abstracts on women and sex/gender differences, information about the Women & Gender Junior Investigator Travel Awardees presentations, announcement of the travel award program for CPDD 2009, and information on current NIDA funding opportunity announcements in this area. These efforts were led by Dr. Cora Lee Wetherington and Dr. Samia Noursi who were assisted by Dr. Lynda Erinoff and Dr. Joe Frascella.

The American Psychological Association (APA) held its annual convention in Boston, Massachusetts, from August 14-17, 2008. Drs. Harold Perl and Teri Levitin taught their annual half-day course on NIH program issues and preparing grant applications **"Inside the Black Box at NIH [NIDA & NIAAA]: Grant Writing Tips They Didn't Teach You in Graduate School"** as a pre-conference workshop on August 13, 2008. Dr. Harold Perl also gave the talk entitled, "Implementation Science: Transforming Evidence Into Real-World Practice" as part of the symposium "Evidence Based Practice: Cutting Edge Issues", at the APA on Saturday August 16, 2008. As in previous years,

NIDA (in collaboration with NIAAA) and APA Divisions 50 (Addictions) and 28 (Psychopharmacology and Substance Abuse) organized a Poster Session/Social Hour focusing on Early Career Investigators, on August 14, 2008.

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Dr. Timothy P. Condon, Deputy Director, NIDA, presented "A Recovery Research Agenda: Where We Are and Where We Want to Go" at the Northeast Addiction Technology Transfer Center Recovery symposium: "Aligning Concepts, Aligning Practice, Aligning Contexts - Building a Blueprint for Recovery," on May 2, 2008, in Philadelphia, Pennsylvania.

Dr. Timothy P. Condon chaired a session titled "Emerging Trends in Drug Abuse: Monitoring to Stay Ahead of the Curve" at the "Advancing Psychiatric Practice Through the Science of Addition: A Research Track from the National Institute on Drug Abuse" during the American Psychiatric Association (APA) Annual Meeting on May 7, 2008, in Washington, D.C.

Dr. Timothy P. Condon presented the keynote address, "Advances in Drug Abuse and Addiction from NIDA: Implications for Treatment" at the 2008 Chief Resident Immersion Training (CRIT) Program, "Addiction Medicine: Improving Clinical and Teaching Skills for Generalists" on May 19, 2008, in Cape Cod, Massachusetts.

Dr. Timothy P. Condon presented "Using the Science of Addiction to Improve Treatment Outcomes in Criminal Justice Populations" at the National Association of Drug Court Professionals 14th Annual Training Conference, on May 29, 2008, in St. Louis, Missouri.

Dr. Timothy P. Condon gave the plenary address entitled "Research and Asian American and Pacific Islander (AAPI) Substance Abuse Treatment" at the National Asian Pacific American Families Against Substance Abuse National Conference, on June 6, 2008, in Los Angeles, California.

Dr. Timothy P. Condon presented a NIDA Research Update at the National Association of State Alcohol and Drug Abuse Directors 2008 Annual Conference, "Enhancing Services Using Addiction Treatment and Prevention Research," on June 8, 2008, in Montgomery, Alabama.

Dr. Timothy P. Condon presented "NIDA Progress, Priorities & Plans for the Future" at the 2008 NIDA International Forum: Globally Improving and Applying Evidence-Based Interventions for Addictions, on June 14, 2008, in San Juan, Puerto Rico.

Dr. Timothy P. Condon presented "Using the NIH Roadmap and NIDA Funding Opportunities to Advance Drug Abuse Research" at the College On Problems Of Drug Dependence Annual Meeting, on June 15, 2008, in San Juan, Puerto Rico.

Dr. Timothy P. Condon presented "Principles of Drug Abuse Treatment for Criminal Justice Populations" at the National Committee on Community Corrections, on June 20, 2008, in Washington, D.C.

Dr. Timothy P. Condon presented "NIDA's Blending Research and Practice Initiative" at the 2008 State Associations of Addiction Services (SAAS) National Conference & Network for the Improvement of Addiction Treatment (NIATx) Summit, on June 23, 2008, in Orlando, Florida.

Dr. Timothy P. Condon presented "Understanding Drug Abuse and Addiction Through Research" at the US-Mexico 7th Bi-National Drug Demand Reduction Conference: Unifying Efforts Toward best Practices, on July 23, 2008, in Monterrey, Mexico.

Dr. Cindy Miner, Deputy Director, OSPC participated as a Judge at the Intel International Science and Engineering Fair held May 12-16, 2008, in Atlanta,

Georgia.

Dr. Cindy Miner presented "Neurobiology of Addiction: Principles for Treatment and Prevention" and also participated in a Policy Panel entitled "What Works" at the Idaho Conference on Alcohol and Drug Dependency on May 19, 2008, in Boise, Idaho.

Dr. Cindy Miner presented "Understanding the Neurobiology of Addiction and Co-Morbid Mental Illness at the NAMI New Jersey 2008 Annual Conference on June 8, 2008, in Jamesburg, New Jersey.

Dr. Cindy Miner presented an update on "NIDA Initiatives and Research Training" at the AACAP NIDA K12 Annual Retreat on June 12, 2008, in Miami Beach, Florida.

Dr. Cindy Miner participated in a Grantwriting Workshop at the CPDD 70th Annual Scientific Meeting on June 17, 2008, in San Juan, Puerto Rico.

Dr. Cindy Miner presented "Neurobiology of Addiction: Principles for Treatment and Prevention at the NAADAC, KAAP and NALGAP 2008 Annual Conference on August 28, 2008, in Overland Park, Kansas.

Dr. Gayathri J. Dowling, OSPC, presented "Substance Abuse among Older Adults - An Overview" at the Conference on Substance Abuse and Older Adults on June 19, 2008 in State College, Pennsylvania.

Dr. Gayathri J. Dowling presented "Careers at the NIH: How did I get here?" at the University of California Washington Center on July 15, 2008, in Washington, D.C.

Dr. Ruben Baler, OSPC, presented "How can science help us navigate around the dangers of abuse and addiction?" at the 2008 mid-year CADCA Training Institute (Youth Leadership Forum) on July 28-31, 2008, in Palm Spring, California.

Brian Marquis presented a NIDA Goes Back to School workshop at the Students Against Destructive Decisions (SADD) National Conference in Phoenix, Arizona, on June 24, 2008. SADD promotes programming that includes targeting all forms of drug use. SADD has grown to become the nation's dominant peer-to-peer youth prevention organization with thousands of chapters in middle schools, high schools and colleges.

Dr. Da-Yu Wu, DBNBR, helped organized the NIH symposium "Challenges and Promise of Cell-Based Therapies" held May 6, 2008.

Dr. Christine Colvis, DBNBR, attended the Molecular Libraries Screening Centers Network Steering Committee Meeting in Nashville, TN May 12-14, 2008.

Dr. Da-Yu Wu helped organize the NIH workshop "Transforming Regenerative Medicine: An Interdisciplinary Approach", May 19-20, 2008.

Drs. Da-Yu Wu and Susan Volman, DBNBR, organized the NIDA Neuroscience Consortium Cutting Edge seminar on "Zebrafish Modeling of in vivo Gene Detection, Manipulation and Regulation in Drug Addiction", August 14, 2008.

Drs. Timothy P. Condon, NIDA Deputy Director and David Shurtleff, Director, DBNBR, co-organized and co-chaired a symposium entitled "A Roadmap to NIH and NIDA Funding Opportunities and Research Resources" at the College on Problems of Drug Dependence, June, 15, 2008. San Juan, Puerto Rico. Drs. Joni Rutter, Jonathan Pollock, Minda Lynch and Betty Tai presented current state of NIH Roadmap and Trans-NIH initiatives that are of interest to the drug abuse research community.

Dr. Joni Rutter, DBNBR, presented a talk entitled "Genetic Resources and Initiatives at NIH and NIDA "at the 70th Annual CPDD Scientific Meeting, June 14-19, Puerto Rico.

Dr. Jonathan Pollock presented a talk entitled "Mouse Resources: Taking Advantage of the NIH KOMP GENSAT and Collaborative Cross Projects for Drug Abuse Research" at the 70th Annual CPDD Scientific Meeting, June 14-19, Puerto Rico.

Dr. Minda Lynch, DBNBR, presented a talk entitled "An Update on the Approved Behavioral Change" at the 70th Annual CPDD Scientific Meeting, June 14-19, Puerto Rico.

Drs. Paul Schnur and David Shurtleff, DBNBR, co-organized and co-chaired a symposium entitled; "Understanding Extinction Learning and Its Translation to Drug Addiction" at the College on Problems of Drug Dependence, June, 16, 2008, San Juan Puerto Rico.

Dr. David Shurtleff, Director, DBNBR, gave a presentation at the NIDA/CPDD Grant-Writing Workshop entitled: "Research Funding Opportunities: The Role of NIDA Program" June 17, 2008 San Juan, Puerto Rico.

Drs. Joni Rutter and Ivan Montoya, DPMCDA, co-chaired symposium entitled "Pharmacogenetics of Medications for the Treatment of Addictions" at the 70th Annual CPDD Scientific Meeting, June 14-19, 2008, San Juan, Puerto Rico.

Dr. Christine Colvis, DBNBR, participated in a site visit of the Broad Institute for the Molecular Libraries Probe Production Centers Network in Boston, MA on June 13, 2008.

Dr. Christine Colvis participated in a site visit of Boston University for the Molecular Libraries Probe Production Centers Network in Boston, MA June 16, 2008.

Drs. Christine Colvis and David Shurtleff co-chaired and Dr. Colvis gave a presentation at an International Narcotics Research Conference workshop on the NIH Molecular Libraries Program in Charleston, SC on July 16, 2008.

Dr. Christine Colvis served as a reviewer for an NIDDK collaborative bridging project in their Nuclear Receptor Signaling Atlas program.

Dr. Jonathan Pollock, DBNBR, attended the KOMP Research Network Y2 Review, May 12, Rockville, MD.

Dr. Jonathan Pollock participated in the International Knockout Mouse Consortium meeting held May 13, 2008 in Toronto, Canada.

Dr. Jonathan Pollock participated in the Mouse Phenotyping Workshop at the Jackson Laboratory, Bar Harbor, ME on July 29, 2008.

Dr. John Satterlee, DBNBR, attended "Epigenetics of Aging and Age-related Diseases" July 15-16, 2008 Bethesda, MD.

Dr. John Satterlee attended "Computing the Future: Systems Biology and the NIH" June 26, 2008, Bethesda, MD.

Dr. David Thomas, DBNBR, was a conference organizer and made the closing remarks at The NIH Pain Consortium 3rd Annual Symposium on Advances in Pain Research, May 22, 2008, Bethesda, MD.

Dr. David Thomas was a session chair and conference organizer of the symposium: Mechanisms and Management of Pain in the Elderly, June 31-July 1, 2008, Bethesda, MD.

Dr. David Thomas was a co-chair of a workshop titled: Bridging Basic Pain

Research, Conventional Pain Treatments and VR Pain Treatments, at the 13th Annual Cybertherapy meeting, June 22, 2008, San Diego CA.

Dr. David Thomas was a co-chair of a symposium titled: Pain Research, at the 13th Annual Cybertherapy meeting, June 24, 2008, San Diego CA.

Drs. Cora Lee Wetherington, DBNBR, and Jill Becker (University of Michigan) co-organized the symposium, "Sex Differences in the Causes and Consequences of Drug Abuse," for the second annual meeting of the Organization for the Study of Sex Differences, June 4-7, 2008, New Orleans, LA. Dr. Wetherington co-chaired the symposium with Ellen Witt (NIAAA) who made opening remarks. Speakers: Linda Spear (SUNY-Binghamton), Marc Kaufman (Harvard Medical School), Amy Wisniewski (University of Oklahoma Health Sciences Center), and Jill Becker (University of Michigan). Dr. Wetherington served as the symposium discussant.

Dr. Cora Lee Wetherington led the Q&A breakout session on women and sex/differences research at NIDA's Mentored K Awardees Meeting: Making the Transition to Independence, July 24-25, 2008, Bethesda, MD.

Drs. Cora Lee Wetherington and Wendy Lynch (University of Virginia) co-organized and co-chaired the symposium, "Biological Basis of Sex Differences in Drug Abuse: A Translational Perspective," at the annual American Psychological Association meeting, August 14-17, 2008, Boston, MA. Speakers: Marilyn Carroll, Ph.D. (University of Minnesota), Aimee McRae (Medical University of South Carolina), Marc Potenza (Yale University School of Medicine), Larry Cahill (UC Irvine).

Drs. Minda Lynch and Steve Grant, DCNBR, chaired a symposium at the annual American Psychological Association Meeting in Boston, MA (August, 2008) entitled "Do Drugs of Abuse Produce Cognitive Rigidity?" with presentations by David Q. Beversdorf, M.D.: Diminished Cognitive Flexibility During Cocaine- A Noradrenergically-mediated Shift in Addiction; Hans C. Breiter, M.D.: Choice Behavior in Cocaine Abusers is More 'Lawful' than Non-abusing Controls - Paradoxical Loss of Variability in Response to Emotional Stimuli.; Martin P. Paulus, M.D.: Rigid Cognitive Strategies in Methamphetamine Abusers as a Consequence of Failure to Recruit Frontal Regions Mediating Behavioral Flexibility; and Geoffrey Schoenbaum, M.D., Ph.D.: Amygdaloidal Control of Behavioral Inflexibility in Reward Responding - Animal Models of Chronic Cocaine and Shifts in Stimulus-reward Learning.

Dr. Allison Chausmer Hoffman, DBNBR, organized a Cutting Edge seminar on "Nicotine and Neuroplasticity" on May 28, 2008. This event was sponsored by the Neuroscience Consortium.

Dr. Allison Chausmer Hoffman organized a special tour of the National Museum of Health and Medicine, May 29, 2008.

Dr. Allison Chausmer Hoffman organized a seminar by Douglas Tipperman of SAMHSA on "Tobacco and the Media" on July 15, 2008. This event was hosted by the NIDA Nicotine/Tobacco Interest Group.

Dr. Allison Chausmer Hoffman and Dr. Mary Kautz, DCNBR, co-organized a symposium on Virtual Reality and Drug Cue Reactivity on July 16, 2008. This event was jointly hosted by the Translationally Oriented Approaches, Devices and Strategies (TOADS) Workgroup and the NIDA Nicotine/Tobacco Interest Group.

Drs. Samia Noursi and Cora Lee Wetherington, Women and Sex/Gender Differences Research Program, presented a poster at NIDA's International Forum at the College on Problems of Drug Dependence (CPDD), June 14-19, 2008 in San Juan, Puerto Rico. The poster described NIDA's Women and Sex/Gender Differences Research Program and presented analyses of the

posters focused on women and sex/gender differences, presented in 2006 and 2007 CPDD International Forums.

Dr. Joe Frascella, Director, DCNBR, participated in a symposium at the CPDD annual meeting entitled "Of Vice and Men: Shared Brain Vulnerabilities for Drug and Non-drug (Food, Sex, and Gambling) Rewards and gave a presentation entitled "Shared Brain Vulnerabilities in Obesity and Addiction" in San Juan, Puerto Rico on June 15, 2008.

Dr. Laurence Stanford, Deputy Director, DCNBR, was a participant in the Dana Foundation Speaking of Science Symposium entitled "The Teen Brain" at the Dana Center on May 27th, 2008 in Washington, DC.

Dr. Laurence Stanford presented a talk entitled "NIH Grant Writing and Funding Mechanisms" at the National Hispanic Science Network Summer Research Training Institute on June 11th, 2008 in Houston, Texas.

Dr. Laurence Stanford served as a member of the NIH Pediatric Device Working Group and participated in the Interagency Pediatric Device Development Workshop on July 23rd, 2008 in Bethesda, Maryland.

Dr. Karen Sirocco, DCNBR, organized and moderated a panel entitled "Potential Role of Physical Activity on Attention and Other Cognitive Processes: A New Paradigm for Drug Abuse Prevention?" at the NIDA meeting entitled "Can Physical Activity and Exercise Prevent Drug Abuse? Promoting a Full Range of Science to Inform Prevention" held on June 5 and 6th, 2008 in Bethesda, Maryland.

Dr. Cecelia Spitznas, DCNBR, lectured on behavioral and integrative treatment research at the National Hispanic Scientist Network Summer Research Training Institute on June 12, 2008 in Houston Texas. A major purpose of this NIDA supported program is to train junior investigators interested in addressing drug abuse and associated problems for Latino/Hispanic ethnic minorities.

Drs. James Bjork, DCNBR, and Minda Lynch, DBNBR, co-chaired a symposium "Adults are from Mars, and Adolescents are from Venus" at the annual meeting of the College on Problems of Drug Dependence on June 16, 2008 in San Juan, Puerto Rico. The speakers were Janet Neisewander (Arizona State University), Sari Izenwasser (University of Miami), Nicole Schramm Sapyta (Duke University), and Yasmin Hurd (Mount Sinai School of Medicine).

Dr. Harold Gordon, DCNBR, participated in a workshop convened on July 18, 2008 by the National Sleep Awareness Roundtable for the purpose of understanding how sleep disorders impact health or disease conditions.

Dr. Harold Gordon participated in the roundtable discussion on Human Genetics in the NIDA "Mentored K Awardees Meeting: Making the Transition to Independence" that was held at the Bethesda North Marriott Hotel & Conference Center, Bethesda, MD on July 24-25, 2008. Drs. James Bjork, Steven Grant and Mary Kautz also participated in the meeting.

Dr. Steven Grant, DCNBR, gave a presentation titled "Clinical Neuroscience of Addiction: Advances and Prospects" in the symposium "What is the Fundamental Nature of Addiction?" at the Annual Meeting of the American Psychological Association in Boston, Mass on August 14-18, 2008. The symposium was chaired by Meyer Glantz (DESPR) and the other speakers included Wilson Compton, (DESPR), Kevin Conway (DESPR) and Robert F. Krueger (University Minnesota).

Dr. Steven Grant gave a presentation entitled "Brain Mechanisms of Inhibitory Control Deficits in Drug Abusers and TBI" at the MindKnit Conference on US-Japan Goodwill Exchange for Technology and Research on Persons with TBI, Autism, and Special Needs, in Rockville, MD on July 14, 2008.

Dr. David McCann, DPMCDA, gave a presentation entitled "Medications Discovery for Drug Addiction Treatment: Methods, Results and Future Directions" at the Annual Meeting of the International Study Group Investigating Drugs as Reinforcers (ISGIDAR) on June 14, 2008 in San Juan, PR.

A symposium on Preclinical Research on the Discovery of Glutamatergic Therapeutics for the Treatment of Addiction, organized and co-chaired by Dr. David A. White, DPMCDA and Dr. Anthina Markou, University of California, San Diego was held on June 19, 2008 at the Annual Meeting of the College on the Problem of Drug Dependence (CPDD) in San Juan, PR. The participants and their presentation titles included: Dr. Bryan K. Yamamoto, Boston University School of Medicine, "Possible Glutamatergic Targets for the Treatment of High Dose Substituted Amphetamine Exposure;" Dr. Ainhoa Bilbao, Central Institute of Mental Health, Mannheim, Germany, "The Role of NMDA and AMPA Receptors in Cocaine Addiction;" Dr. Karen K. Szumlinski, University of California, Santa Barbara, "mGluR-Homer-P13K Signaling Mechanisms in Addiction-Related Behaviors;" and Dr. Carrie Jones, Vanderbilt University School of Medicine, "Allosteric Modulators of mGluRs as a Novel Approach to Treatment of Drug Abuse and Other CNS Disorders." Dr. Markou was the discussant.

At the annual meeting of the American Psychological Association on August 14, 2008, Dr. Jane B. Acri, DPMCDA, and Dr. Nancy Mello (McLean Hospital, Harvard University) co-chaired the Jack Mendelson Memorial Symposium: Recent Advances in the Development of Medications for Drug Abuse Treatment. Presenters included Dr. James H. Woods (University of Michigan) on Drug and Environment-Induced Changes in Behavior, Dr. Jack Bergman (McLean Hospital, Harvard University) on Recent Candidate Medications for Stimulant Abuse: Preclinical Evaluation in Nonhuman Primates, Dr. Richard Foltin (Columbia University) on Novel Laboratory Models in Medication Development, Dr. Leonard Howell (Emory University) on Nonhuman Primate Neuroimaging and Cocaine Medication Development, Dr. Richard Rothman, IRP, on Dual DA/5-HT Releasers: Potential Treatment Agents for Stimulant Addiction, and Dr. Frank Vocci, Director, DPMCDA, on Remediation of Cognitive Deficits as a Target for the Treatment of Stimulant Dependence.

Dr. Ivan Montoya, DPMCDA, and Joni Rutter, DCNBR, co-chaired a symposium at the CPDD meeting in San Juan, Puerto Rico. The title was "Pharmacogenetics of Medications for the Treatment of Addictions". The panel of presenters included Drs. Caryn Lerman from University of Pennsylvania, Thomas Kosten from Baylor College of Medicine, Mary Jeanne Kreek from The Rockefeller University, Bernard Le Foll from the University of Toronto, and George Uhl from the NIDA IRP.

Robert Walsh and Ivan Montoya from DPMCDA co-chaired a workshop at the CPDD meeting in San Juan, Puerto Rico. The focus was to discuss tools and strategies to ensure compliance with current regulations for clinical trials of pharmacotherapies for drug abuse. The panel of presenters included Drs. Frances Levin from Columbia University and Eric Strain from Johns Hopkins University, as well as the co-chairs.

Dr. Ivan Montoya substituted for Dr. Petra Jacobs to co-chair with Dr. Frances Levin a symposium at the CPDD meeting in San Juan (Puerto Rico). The title was "Advances in the Development of Medications for Comorbid ADHD and Substance Use Disorders." The panel of presenters included Drs. Brooke Molina from the U. of Pittsburgh, Himanshu Upadhyaya from the Medical University of South Carolina, Paula Riggs from the University of Colorado, Frances Levin from Columbia University, and Timothy Wilens from Harvard Medical School.

Dr. Wilson M. Compton, Director, DESPR, presented a plenary lecture "Drug Abuse and Addition: Neuroscience Update" and chaired a breakout session on

re-entry programs for the Federal Judiciary Training on July 17, 2008 in Boston, Massachusetts. He also presented the same plenary lecture to the Federal Probation and Parole Association on August 13, 2008 in Charlotte, North Carolina.

Dr. Wilson M. Compton presented "Dimensional Models of Marijuana Use, Abuse and Addiction" at the American Psychological Association meeting on August 14, 2008 in Boston, Massachusetts.

Dr. Wilson M. Compton served as discussant on a panel on the social epidemiology of drug abuse at the meeting of the Society for Epidemiological Research on June 25, 2008 in Chicago, Illinois.

Dr. Wilson M. Compton presented, chaired sessions and served as discussant in panels at the annual meetings of the American Psychiatric Association, on May 7, 2008 in Washington, D.C. and at the Society for Prevention Research on May 27, 2008 in San Francisco, California.

Dr. Wilson M. Compton presented on treatment of addiction as a plenary speaker both at the US-Mexico Bi-National Conference on July 25 in Monterrey, Mexico and at the meeting of the Association of American Indian Physicians on July 28, 2008 in Coeur d'Alene, Idaho.

Dr. Wilson M. Compton presented to the National Youth Leadership Forum on July 21, 2008 in Vienna, Virginia.

Dr. Redonna K. Chandler, Chief, SRB, DESPR, presented "Treatment is Key: Addressing Drug Abuse in Criminal Justice Settings" at the National Association of Drug Court Professionals 14th Annual Conference on May 29, 2008 in Saint Louis, Missouri.

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 on May 28, 2008 in Saint Louis, Missouri.

Dr. Redonna K. Chandler co-chaired AcademyHealth Behavioral Health Services Research Interest Group Meeting entitled "Embedding Services Research Questions into Comparative Effectiveness Studies from the Start," on June 10, 2008 in Washington, D.C.

Dr. Elizabeth Robertson, Chief, PRB, DESPR, presented a talk titled "What Do We Do Besides Talking to You?" to visiting scholars from the Pennsylvania State University, on May 6, 2008 in Washington, D.C.

Dr. Elizabeth Robertson and Dr. Richard Spoth of Iowa State University, co-lead a roundtable symposium titled "Lost in Translation" at the 16th Annual Meeting of the Society for Prevention Research on May 28, 2008 in San Francisco, California.

Dr. Elizabeth Robertson presented a paper titled "Emerging Principles of Prevention at the joint NASADAD/NIDA/SAMHSA meeting: Blending Research and Practice: Enhancing Services Using Addiction Treatment and Prevention Research" on June 8, 2008 in Montgomery, Alabama.

Dr. Elizabeth Robertson presented two workshops "Research to Practice and Back Again" at the CADCA Mid-year Seminar on July 29, 2008 in Palm Springs, California.

Dr. Elizabeth Robertson presented a session titled "Principles of Prevention" at the National Prevention Network, 21st Annual Prevention Research Conference on August 25, 2008 in Indianapolis, Indiana.

Dr. Yonette Thomas Chief, ERB, DESPR and Dr. Wilson Compton, Director, DESPR, participated in a panel on "Social Epidemiology and Behavioral Health:

Methodological Approaches, Problems, and Promise" at the Society for Epidemiological Research on May 25, 2008 in Chicago, Illinois.

Dr. Yonette Thomas presented on "The Epidemiology of Drug Abuse" at the summer institute of the National Hispanic Science Network on June 10, 2008 in Houston, Texas.

Dr. Dionne Jones, Deputy Chief, SRB, DESPR, gave a presentation on "Disparities in HIV/AIDS and Substance Abuse in the US: Research Needs" at the Meeting on Cultures in Context: HIV and Substance Abuse Research in the Southeast, on June 12, 2008 in Nashville, Tennessee.

Dr. Dionne Jones gave a presentation on "Funding Opportunities in DESPR" at the NIDA Research Development Diversity Programs Workshop on May 19, 2008 in Silver Spring, Maryland.

Dr. Dionne Jones gave a presentation on "Funding Opportunities for Health Disparities Research at NIDA: Helpful Hints for Investigators" at a Research Workshop: On the Road to NIH Funding, on May 6, 2008 in Richmond, Virginia.

Dr. Dionne Jones chaired a panel, "Substance Abuse Treatment for Adolescents: Addressing Health Disparities" at the Joint Meeting for Adolescent Treatment Effectiveness Conference, on March 25, 2008 in Washington, DC.

Dr. Dionne Jones facilitated a round table discussion on grant writing at a professional development workshop for diversity investigators, sponsored by the National Institute on Neurological Disorders and Stroke on March 3, 2008 in Washington, D.C.

Dr. Tom Brady, DESPR, and Dr. Richard A. Denisco, DESPR, coordinated a one-day NIDA Workshop "Screening for Drug Use in General Medical Settings" on May 12, 2008 in Bethesda, Maryland.

Dr. Tom Brady, DESPR, and Dr. Richard A. Denisco, DESPR, coordinated a meeting co-sponsored by NIDA and ONDCP titled "Identifying Prescription Drug Abuse in Medical Settings: Challenges and Opportunities" on May 19, 2008 in Bethesda, Maryland.

Dr. Tom Brady, DESPR, and Dr. Redonna K. Chandler, Chief, SRB, DESPR, managed a two-day conference "Enhancing Practice Improvement: NIDA Community-Based Grantee Meeting", on May 22 and 23, 2008 in Bethesda, Maryland.

Dr. Sarah Q. Duffy, DESPR, served as chair and discussant in sessions on Substance Abuse and Technology Adoption at the American Society of Health Economists meeting on June 23-25, 2008 in Durham, North Carolina. Dr. Tom Brady developed and chaired a symposium on adolescent health at the Academy Health Annual Research Meeting titled "Continuing Care for Adolescents with Substance Use Disorders: Opportunities for Health Services Research" on June 9, 2008 in Washington, D.C.

Dr. Aleta Meyer, DESPR gave an opening plenary titled "Federal Funding to Support Research of Adventure Programming and Experiential Education: The Why's and How To's" at the Research and Evaluation of Adventure Programming (REAP) Symposium on March 20, 2008 in Santa Fe, New Mexico.

Dr. Aleta Meyer led a workshop titled "Exploring Connections between Healthy Living and Substance Use Prevention Research" at the annual conference for USDA's Children-Youth-and-Families-At-Risk (CYFAR) on May 8, 2008 in San Antonio, Texas.

Dr. Eve Reider, Deputy Chief, PRB, DESPR, was a discussant for the symposium "Understanding Risky Sexual Behavior During Emerging Adulthood" the at the 16th Annual Meeting of the Society for Prevention Research on May 28, 2008 in

San Francisco, California.

Dr. Belinda Sims chaired a research roundtable entitled "Context and Beyond: NIH Priorities for Prevention Research." at the 16th annual meeting of the Society for Prevention Research on May 28, 2008 in San Francisco, California. Discussants included Dr. Aria Crump, DESPR and Dr. LeShawndra Price, DESPR.

Dr. Belinda Sims and Dr. Aria Crump co-chaired a discussion session at the 16th annual meeting of the Society for Prevention Research entitled "The Federal Grants Process: You Have Questions, We Have Answers" on May 28, 2008 in San Francisco, California.

Dr. Aleta Meyer led a roundtable discussion titled "Preventing Substance Use and Risky Sexual Behavior in College Contexts" at the annual meeting of the Society for Prevention Research on May 30, 2008 in San Francisco, California.

Dr. Elizabeth Ginexi, DESPR, served as the discussant for a paper symposium titled "Can You Sit Still and Raise Your Hand? Self-Regulation as a Focus for School Readiness Interventions." at the 16th annual meeting for the Society for Prevention Research on May 29, 2008 in San Francisco, California.

Dr. Aria Crump, DESPR chaired a symposium entitled "Drug Prevention Program Effects on Early Adult Outcomes: A Growing Body of Evidence" at the 16th Annual Meeting of the Society for Prevention Research on May 29, 2008 in San Francisco, California.

Dr. Eve Reider, Deputy Chief, PRB, DESPR, presented on NIDA's Prevention Research Branch activities at the Community Epidemiology Work Group meeting on June 12, 2008 in Bethesda, Maryland.

Dr. Peter Hartsock, DESPR, met with the University of Texas School of Public Health's Center for Health Promotion and Prevention Research on May 2-3, 2008 in Houston Texas to plan research activities on the U.S.-Mexico border and east Africa. Also planned was a convocation of all living Surgeons General in Houston this coming February. The convocation will focus on wellness and healthy life styles.

Dr. Peter Hartsock, DESPR, and NIDA grantee Dr. Martina Morris of the University of Washington, met with IOM and USAID to present latest research modeling findings on the "HIV Superway" on March 20, 2008 in Washington, D.C. Findings included that concurrent sexual partnerships account for 50% of sexually-transmitted HIV cases.

Dr. Betty Tai, Director, CCTN, co-chaired, along with Juana Tomas-Rosello (UNODC), the symposium, "Implementing Evidence-Based Practice Treatments: The Clinical Trials Network and TreatNet Models" at the NIDA International Forum held June 13-17, 2008 in San Juan, Puerto Rico. The symposium's goal was to describe two different models designed to integrate research findings into the practices of community-based treatment providers. Speakers included Dr. Jose Szapocznik (University of Miami), Dr. Jeffrey Seltzer (North Shore-Long Island Jewish Hospital), Dr. Richard Rawson (University of California at Los Angeles) and Dr. Min Zhao (Shanghai Jiao Tong University).

Dr. Paul Wakim, CCTN, organized and chaired an invited session at the 29th Annual Meeting of the Society for Clinical Trials, May 18-21, 2008, in St. Louis, Missouri. The title of the session was "Interim Look(s): Practical Recommendations". The three invited speakers were Drs. David DeMets (University of Wisconsin-Madison), John Lachin (George Washington University) and Peter Ouyang (Johnson & Johnson). Dr. Wakim was the discussant.

Dr. Harold Perl, CCTN, served on the faculty for the two annual NIH Regional

Seminars on Program Funding and Grants, sponsored by the NIH Office of Extramural Research (OER). These seminars are intended to help demystify the application and review process, clarify Federal regulations and policies, and highlight current areas of special interest or concern. The seminars serve the NIH mission of providing education and training for the next generation of biomedical and behavioral scientist. The faculty of NIH policy, grants management, review, and program staff provide a broad array of expertise and encourage personal interaction between themselves and seminar participants. The two 2008 seminars convened in San Antonio, Texas from March 25-27, 2008 and in Chicago, Illinois on June 18-20, 2008. Dr. Perl also led a Webinar training seminar on NIH Program Funding and Grants for faculty and staff at California State University - Fresno on June 9, 2008. He will lead a second Webinar training seminar on October 16, 2008 for faculty and staff at Texas A&M International University.

Dr. Petra Jacobs, CCTN, participated in the meeting of the Workshop Selection Committee of the American Association for the Treatment of Opioid Dependence (AATOD), August 15, 2008, in New York, NY.

Dr. Lula Beatty, Chief, Special Populations Office (SPO), attended the program directors meeting of the NINDS Specialized Neuroscience Research Programs on April 28, 2008 in Bethesda, Maryland.

Dr. Lula Beatty presented an overview of NIDA and moderated a session on health disparities at the CSAT satellite program at CPDD on June 14, 2008 in San Juan, Puerto Rico.

Dr. Lula Beatty participated in the program of the Underrepresented Populations Committee at CPDD on June 15 in San Juan, Puerto Rico.

Dr. Lula Beatty moderated a session titled "Strengthening Families - Connecting Fathers" at the African American Health Marriage Initiative conference (Building Strong and Healthy Families: Connecting Marriage Research to Practice Conference) on June 17, 2008 in Chapel Hill, North Carolina.

Dr. Lula Beatty served as a poster judge for the NCI Cancer Health Disparities Summit held on July 14-16, 2008 in Bethesda, Maryland.

Dr. Lula Beatty presented a talk titled "Getting Help: NIDA Research on Access to Services" at the convention of the Association of Black Psychologists on July 31, 2008 in Oakland, California.

Dr. Lula Beatty participated in the following activities at the American Psychological Association convention held August 13-17, 2008 in Boston, MA: Chaired a session titled "Impact of Criminalization on Women's Identity and Treatment Needs," chaired a federal panel (and hosted a NIDA roundtable) on research opportunities sponsored by the APA Women's Program Office, and presented a talk titled "The Role of Neuropsychology in Health Disparities Research: Focus on Addiction."

Dr. Lula Beatty participated as a faculty member at the inaugural meeting of the Committee on Women in Psychology's Leadership Institute for mid-career women. The workshop, convened as an American Psychological Association preconference activity, was held August 12, 2008 in Boston, Massachusetts.

Flair Lindsey, SPO, coordinated the 12th annual Summer Research with NIDA program, which enabled high school and undergraduate students to engage in drug abuse research with a number of NIDA grantees for 8-10 weeks over the summer. This year, 55 students and 32 investigators participated.

Flair Lindsey presented an overview of NIDA Diversity-supported programs and activities to students at the Johns Hopkins Bloomberg School of Public Health's

"Addiction, Infectious Disease and Public Health Conference" on April 21, 2008 in Baltimore, Maryland.

Ana Anders was a guest speaker for participants in the NIH Hispanic Youth Initiative at Lipsett Auditorium on July 14, 2008 in Bethesda, Maryland.

Ana Anders presented at the Hispanic Association of Colleges and Universities (HACU) meeting, which was hosted by NIMH on July 23, 2008 in Bethesda, Maryland.

Dr. Teri Levitin, Director, OEA, served on the faculty for the Association for Psychological Science 19th annual convention workshop on "Grant Getting for Graduate Students and New Faculty" in May 2008 in Chicago, IL.

Dr. Levitin co-organized and with other NIH staff presented a workshop on social and behavioral research and the grant review process at NIH and NIDA at the American Sociological Association 103rd annual meeting in Boston, MA in August 2008.

Dr. Levitin co-taught a course on grant writing at the American Psychological Association 116th annual meeting as part of the APA's continuing education workshop program. This meeting took place in August in Boston.

Dr. Gerald McLaughlin, OEA, co-managed the Mitochondria Interest Group (MIG), whose January 2008 Symposium associated with a MIG-nominated WALS speaker, helped to promote an active trans-NIH Roadmap initiative. Dr. McLaughlin's nomination for the 2008-2009 WALS series, Dr. Leonard Guarante of MIT, has also been selected for a WALS lecture and Dr. McLaughlin is co-arranging a mini-symposium associated with Dr. Guarante's SIRTUINS, Aging and Disease lecture in November 2008.

Dr. Gerald McLaughlin co-founded and co-chairs the NIH-wide Scientific Program and Review Interest Group (SPRIG) whose theme in 2007-2008 was Springboards to Science Leadership and Management, arranged several lecture-discussion sessions including a June session on Peer Review and Leadership, and is co-defining the 2008-2009 SPRIG series theme, tentatively, managing innovative transformative research.

Dr. Mark Swieter, OEA, was a speaker at the Grant Writing Workshop presented at CPDD's 70th annual scientific meeting in San Juan, Puerto Rico, June 14-19, 2008.

Dr. Kristen Huntley, OEA, and Dr. Mark Swieter co-chaired a career development workshop with the theme "Promotions and Tenure in Tight Times." Panelists were Drs. Bill Dewey, Linda Dykstra, Carl Latkin, Kathy Sanders-Phillips, and Sharon Walsh. The workshop was presented at CPDD's 70th annual scientific meeting in San Juan, Puerto Rico, June 14-19, 2008.

Dr. Nadine Rogers, OEA, and Dr. Mark Swieter co-chaired a workshop "What's New at NIDA and NIH" at CPDD's 70th annual scientific meeting in San Juan, Puerto Rico, June 14-19, 2008.

Dr. Eliane Lazar-Wesley, OEA, presented at two workshops, "Promotions and Tenure in Tight Times" and "What's New at NIDA and NIH" at CPDD's 70th annual scientific meeting in San Juan, Puerto Rico, June 14-19, 2008.

Dr. Eliane Lazar-Wesley presented "Peer Review Issues" for the Penn State Prevention and Methodology Training Program in Bethesda, Maryland on May 7, 2008.

Dr. Eliane Lazar-Wesley co-organized and made a presentation "Peer-Review Workshop" at the NIDA sponsored Mentored K Awardees meeting: Making the Transition to Independence, in Bethesda, Maryland on July 24, 2008.

Dr. Rita Liu, OEA, presented at two workshops, "Promotions and Tenure in Tight Times" and "What's New at NIDA and NIH" at CPDD's 70th annual scientific meeting in San Juan, Puerto Rico, June 14-19, 2008.

Dr. Jose Ruiz, OEA, delivered a presentation entitled, "The NIH, NIDA, and the Review Process: Focus on Undergraduate Institutions and Students," at St. Mary's College of Maryland on May 28, 2008.

Dr. Gerald McLaughlin, OEA, co-coordinated several events for the University of Iowa's DC Area Alumni Club related to the spring 2008 Iowa floods.

Dr. Amy Newman, IRP, was invited to give a seminar at the University of Mississippi, School of Pharmacy entitled "Dopamine D3 Receptor Antagonists as Potential Therapeutic Agents for Addiction" in March 2008.

Dr. Amy Newman was invited to give a NIDA Director's Seminar entitled "Molecular Tools to Study Drug Addiction" in April 2008.

Dr. Bruce Hope, IRP, presented a talk entitled "Neuronal Ensembles & Context-specific Sensitization to Cocaine" at the Plasticity & Repair in Neurodegenerative Disorders Workshop at the UCLA Conference Center at Lake Arrowhead, CA on May 15-18, 2008.

Dr. Yavin Shaham, IRP, was invited to present a seminar entitled "Neurobiology of Relapse to Drug Use" at the Neuroscience Seminar Series at the University of Minnesota, Minneapolis, MN, on May 22-23, 2008.

Dr. Kenner Rice, IRP, presented the A. Nelson Voldeng Memorial Lecture "Corticotropin Releasing Hormone (CRH) Agonist and Antagonists as Drugs and Research Tools" at the University of Arkansas, School of Pharmacy, Department of Pharmaceutical Sciences, Little Rock, AK in May 2008.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2008

## Media and Education Activities

### Press Releases

April 1, 2008 - **NIH Research Suggests Stimulant Treatment for ADHD Does Not Contribute to Substance Abuse Later in Life.** Treating children as early as age six or seven with stimulants for Attention-Deficit Hyperactivity Disorder (ADHD) is not likely to increase risk of substance abuse as adults, according to two studies funded by the National Institutes of Health (NIH). However, the studies also showed treatment with stimulants did not prevent substance abuse later in adulthood. The studies, conducted by researchers at New York University School of Medicine (NYU) and the Massachusetts General Hospital/Harvard Medical School (Mass General) were published in this month's American Journal of Psychiatry.

April 2, 2008 - **NIDA Researchers Identify Genetic Variant Linked to Nicotine Addiction and Lung Cancer.** Scientists have identified a genetic variant that not only makes smokers more susceptible to nicotine addiction but also increases their risk of developing two smoking-related diseases, lung cancer and peripheral arterial disease. The research was supported by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health (NIH).

May 8, 2008 - **First Addiction Science Award to be Given to Students at International Science Fair.** This year, for the first time, three students will receive awards for exemplary projects in Addiction Science at the Intel International Science and Engineering Fair (ISEF), the world's largest science competition for high school students. The Addiction Science award is co-sponsored by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health (NIH), and Scholastic, the global children's publishing, education and media company.

May 16, 2008 - **Discovery of Possible Link Between Protein Deletion and Addiction Wins Top Honors at ISEF:** *Texas High School Senior Wins First-Ever NIDA Scholastic Addiction Science Award.* An ambitious exploration of the basic mechanisms underlying addiction received top honors in the new Addiction Science category at the Intel International Science and Engineering Fair (ISEF), the world's largest science competition for high school students. The project, The Novel Role of the GluCl ; Ion Channel and Diazepam Binding Genes in Alcohol Addiction, was developed by Kapil Vishveshwar Ramachandran, a 16-year-old senior from Westwood High School in Austin, Texas.

May 25, 2008 - **Scientists Identify a Brain Mechanism Underlying Persistent Cocaine Craving.** Scientists have identified a mechanism in the brain that helps to explain why craving for cocaine, and the risk of relapse,

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seems to increase in the weeks and months after drug use is stopped. The research was supported by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health. The study, published in the May 25 issue of the journal Nature, "reveals a novel mechanism for why cocaine craving intensifies after cessation of drug use and suggests a new target for the development of medications to decrease the risk of relapse in abstinent cocaine abusers," says NIDA Director Dr. Nora Volkow.

May 28, 2008 - **NIDA to Highlight Latest Drug Abuse Research at Cincinnati Conference.** The National Institute on Drug Abuse (NIDA), a component of the National Institutes of Health, will convene a 2-day conference to explore how the latest scientific findings in drug abuse can fill the current gap between research and clinical treatment practices. The conference is part of NIDA's Blending Initiative, designed to stimulate engaging dialogue between those who work with substance abusers in communities with those engaged in the latest treatment research.

June 2, 2008 - **NIDA Highlights Best Drug Abuse Treatment Approaches at Blending Conference.** The most difficult challenge in finding substance abuse treatment for a loved one is how to know which programs have a proven track record. That is just one of the topics being discussed today at the conference *"Blending Addiction Science and Treatment: The Impact of Evidence-Based Practices on Individuals, Families and Communities."* Held at the Duke Energy Center in Cincinnati, the conference is hosted by the National Institute on Drug Abuse (NIDA), a component of the National Institutes of Health. It is part of NIDA's Blending Initiative, in which teams of experts create clinical tools based on the latest treatment research.

June 2, 2008 - **Clusters of Genetic Variants Linked to Distinct Treatment Responses for Smoking Cessation.** Scientists have identified distinct clusters of genetic markers associated with the likelihood of success or failure of two smoking cessation treatments, nicotine replacement therapy (NRT) and the medication bupropion (Zyban). This study, supported by the National Institute on Drug Abuse (NIDA) and the National Cancer Institute (NCI), part of the National Institutes of Health (NIH), was published in the June issue of the journal *Archives of General Psychiatry.*

June 5, 2008 - **NIDA Explores Exercise as Drug Abuse Prevention Tool.** It is well known that exercise is an important part of a healthy lifestyle but can exercise programs actually reduce the likelihood of drug abuse and thus prevent addiction? The National Institute on Drug Abuse (NIDA), part of the National Institutes of Health (NIH), is holding a seminal conference on June 5-6 to explore a possible role for physical activity in substance abuse prevention. As part of this effort, NIDA announced a $4 million grant initiative to spur further research on this emerging area of investigation.

June 30, 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 NIDA, is published in the July 1, 2008 issue of the open access journal PLoS Medicine.

### Research News

April 15, 2008 - **NIDA NewsScan #52** - Research News

**Activities**

**Planned Meetings**

**Publications**

**Staff Highlights**

**Grantee Honors**

- Psychological Trait Helps Identify Boys at Risk of Substance Use Disorder
- Fluoxetine Does Not Add to Benefit of Cognitive Behavior Therapy for Depression in Adolescents with Substance Abuse Disorder
- "Missing Piece" of Receptor Decreases Effects of Nicotine
- HCV Infection Associated with Increased Diabetes Risk in Older Persons With or At Risk of HIV Infection, Particularly Obese Individuals
- Anxiety Sensitivity Impacts Smoking Cessation
- Adolescent Male Rats Self-Administer Nicotine More Than Their Adult Counterparts

June 9, 2008 - **NIDA NewsScan #53** - Research News

- Intensive Foster Care Program Reduces Delinquency and Improves School Engagement for Girls
- Intervention Prevents Disruption of Stress Hormone Levels in Preschoolers in Foster Care
- Health Plans More Likely to Focus on Identifying Enrollees with Mental Illness than Substance Use Disorders
- Brain Regions Associated with Cue-Induced Cigarette Cravings Independent of Withdrawal
- Prerelease Treatment with Buprenorphine-Naloxone Reduces Drug Use in Inmates Re-Entering the Community
- Pharmacology Modules Help Students Learn Basic Science Concepts
- Methamphetamine Use Increases Risk of Unsafe Heterosexual Behaviors

### Interviews & Articles of Interest

March 17, 2008, National Public Radio/"Talk of the Nation" -- Interview with Nora D. Volkow, M.D. about the effects of cognitive-enhancing drugs.

April 3, 2008, Associated Press -- Interview with Nora D. Volkow, M.D. about DeCODE smoking/lung cancer study.

April 7, 2008, *Wall Street Journal* -- Interview with Nora D. Volkow, M.D. about the science of addiction and drug use on college campuses.

April 14, 2008, CN8-The Comcast Network/"Arthur Fennell Reports" -- Interview with Wilson Compton, M.D. about teen drug abuse trends.

May 21, 2008, *U.S. News & World Report*, "What Parents Need to Know About Pot," -- Interview with Nora D. Volkow, M.D. about the effects of marijuana on the brain.

June 12, 2008, USA Today, "Report: Marijuana Potency Rises," -- Interview with Nora D. Volkow, M.D. about marijuana potency.

June 21, 2008, National Journal, "Juiced on the Job," -- Interview with Nora D. Volkow, M.D. on performance-enhancing drugs used in the workplace.

July 9, 2008, SAMHSA's Center for Substance Abuse Treatment (CSAT) - Taped panel discussion that included Timothy P. Condon, Ph.D. for the Road to Recovery broadcast which will air in September during Recovery Month.

July 10, 2008, Bloomberg News -- Interview with Nora D. Volkow, M.D. about gene variation found linked to early onset smoking.

Dr. Steven Grant, DCNBR, was interviewed by Michael Payne of the APA Monitor for an article on the neurobiology of tobacco addiction on May 1, 2008.

Dr. Steven Grant provided background information about the link between use

of marijuana and mental health problems for CNN Medical News on May 6, 2008.

Dr. Joe Frascella, Director, DCNBR, was interviewed for an article in the New Yorker Magazine on drug and other behavioral addictions on August 5, 2008.

Dr. George Uhl, IRP, was interviewed or appeared in several media outlets regarding his article on molecular genetics of successful smoking cessation published in Archives of General Psychiatry including Time, ABC News, the Washington Post, and the Boston Globe.

### Additional Highlights

March 13, 2008 - Dr. Timothy P. Condon highlighted the role of science and the research conducted by NIDA to understand and prevent inhalant abuse at a press briefing on inhalant use hosted by the National Inhalant Prevention Coalition in Washington, D.C.

The first ever Addiction Science Awards were bestowed to three high school students as part of the **INTEL International Science and Engineering Fair**, the world's largest competition for high school science projects, that took place in May in Atlanta, GA. Judges included Dr. Cindy Miner and Dr. Ruben Baler from OSPC along with two NIDA grantees, Dr. Rochelle Schwartz-Bloom from Duke and Dr. Michael Kuhar from Emory. Carol Krause, NIDA's communications director, coordinated the judging activities during the competition and arranged for the three winners to travel to NIH on August 11 to meet scientists from NIDA, present their projects to Dr. Volkow and Dr. Zerhouni, and receive their award plaques and prize money.

The PILB press team coordinated a press event at **International AIDS Conference**, held in Mexico City on August 7, 2008. 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. After the media roundtable, ten additional interviews were scheduled, as well as a live interview on CNN Mexico the night before. The media roundtable included reporters from Africa, Colombia, Switzerland and the U.S.

#### Brain Awareness Week

On August 4, 2008, Dr. Roger Sorensen, DBNBR, presented the exhibit "Welcome to Roger's Party" at the Substance Abuse Education Fair held during the 2008 Jeter's Leaders Leadership Conference at the University of Texas at Arlington. Supported by the Turn 2 Foundation, Jeter's Leaders (founded by Derek Jeter of the New York Yankees) is a program designed to promote healthy lifestyles, academic achievement and social change activism among high school students. Students were invited to the exhibit booth for an interactive discussion on the physical and societal harms of substance abuse, and obtained information on drug abuse and addiction through NIDA publications.

### Recent and Upcoming NIDA Exhibits at the Following Conferences

National Association of Drug Court Professionals (NADCP) 14th Annual Training Conference, St. Louis, MO - 5/28-31/08

NIDA Blending Conference, Cincinnati, OH - 6/2-3/08

American College Health Association (ACHA) 2008 Annual Meeting, Orlando, FL - 6/3-7/08

National Alliance on Mental Illness (NAMI) Annual Convention, Orlando, FL - 6/13-16/08

Joint Conference of the State Associations of Addiction Services (SAAS) and the Network For the Improvement of Addiction Treatment (NIATx), Orlando, FL - 6/22-25/08

American Academy of Nurse Practitioners (AANP) 23rd National Conference, National Harbor, MD - 6/26/08-7/1/08

National Association of School Nurses (NASN) 14th Annual Conference, Albuquerque, NM - 6/27/08-7/1/08

American Academy of Family Physicians (AAFP) Family Medicine Residents and Students National Conference, Kansas City, MO - 7/30/08-8/2/08

American Probation and Parole Association (APPA) 33rd Annual Training Institute, Las Vegas, NV - 8/3-6/08

American Psychological Association (APsychA) 116th Annual Convention, Boston, MA - 8/14-17/08

NAADAC The Association for Addiction Professionals Annual Conference, Overland Park, KS - 8/28-31/08

NIDA Medicalization Conference, Washington, DC - 9/1/08

12th Annual United States Conference on AIDS (USCA), Miami Beach, FL - 9/18-21/08

Latino Behavioral Health Institute (LBHI) 14th Annual Conference, Los Angeles, CA - 9/23-25/08

Annual World Employee Assistance Professionals Association (EAPA) Conference, Atlanta, GA - 10/16-18/08

American Public Health Association (APHA) 136th Annual Meeting and Exposition, San Diego, CA - 10/25-29/08

American Academy of Child and Adolescent Psychiatry (AACAP) 55th Annual Meeting, Chicago, IL - 10/28/08 - 11/2/08

National Middle School Association (NMSA) 35th Annual Conference and Exhibit, Denver, CO - 10/30/08 - 11/1/08

Treatment Conference, Washington, DC - 12/1/08

American Academy of Addiction Psychiatry (AAAP) 19th Annual Meeting and Symposium, Boca Raton, FL - 12/4-7/08

# Director's Report to the National Advisory Council on Drug Abuse - September, 2008

## Planned Meetings

NIDA is once again organizing a mini-convention, **Frontiers in Addiction Research**, at this year's Society for Neuroscience (SfN) meeting. In addition to the presentation of the 2008 Waletzky Memorial Award, the mini-convention will include an Early Career Investigators Poster Session, as well as presentations on the following topics:

- Epigenetics and Brain Function
- Multilevel Multimodal Imaging of Gene Expression, Cells, Neurons, and Circuitry
- Will Power: What Really Governs Our Choices, and
- Cortical Development and Substance Abuse

The mini-convention will take place at the Renaissance Washington DC hotel on Friday, November 14, 2008. NIDA will also have an exhibit booth at the SfN meeting, November 16-19, 2008.

Cecelia Spitznas, Shoshana Kahana and Lisa Onken of DCNBR/BITB in collaboration with Eve Reider and Elizabeth Robertson of DESPR/PRB are collaborating with other NIH institutes, and representatives of the DOD and VA to develop a meeting for Fall 2008. The meeting's working title is **Designing a Research Agenda to Prevent and Treat Substance Abuse and Related Consequences for Military Service Members, Veterans and their Families**. The meeting will help determine next steps for research related to actual and potential substance abuse and related comorbidities which are consequences of the Afghan and Iraq wars.

Dr. Steven Grant, DCNBR, and Dr. Rita Goldstein (Brookhaven National Laboratories) co-organized and will co-chair with a symposium entitled **"Functional Neuroimaging Evidence for a Brain Network Underlying Impaired Insight (into illness) in Drug Addiction"** at the annual meeting of the Society for Neuroscience to be held in Washington, DC on November 15-29, 2008. The speakers will be A.D. "Bud" Craig (Barrow Neurological Institute), Antoine Bechara (University of Southern California)., Hugh Garavan (Trinity College), and Anna Rose Childress (University of Pennsylvania).

The next **National CTN Steering Committee Meetings** are planned for October 21-23, 2008 in Bethesda, MD.

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## Publications

### NIDA Publications

**Drugs, Brain and Behavior - The Science of Addiction (Spanish)**
NIH Pub. No.: 08-5605S
This is the Spanish translation of "The Science of Addiction," NIDA's 30-page, full-color booklet that explains in layman's terms how science has revolutionized our understanding of drug addiction as a brain disease that affects behavior. It uses simple language, diagrams, and graphics to help people understand how drugs change the brain in structure and in function. The booklet explores some of the reasons that people take drugs, helps explain why some people become addicted while others do not, and demonstrates how addiction, like other chronic diseases, may be prevented and treated.

**College on Problems of Drug Dependence**
NIH Pub. No.: 08-6408
This publication is more than just a "proceedings" from a meeting--it is valued as one of the only research tools and references for scientists and other professionals in the drug abuse field. It is the most comprehensive gathering of scientific information on all aspects of substance abuse and is invaluable to researchers and other scientists.

**Heads Up: Real News About Drugs and Your Body: Student Compilation**
This booklet is a collection of articles designed to teach youth in grades 6-12 about how drugs of abuse affect the brain and body. Topics covered are The Science of Addiction, Tobacco Addiction and Secondhand Smoke, Stress and Drug Abuse, and Health Literacy and Drug Abuse. These articles were distributed in Scholastic magazines nationwide during the 2007/2008 school year.

**Heads Up: Real News About Drugs and Your Body: Teacher Compilation**
This booklet provides skill-building extension activities and further resources for teachers. Topics covered are The Science of Addiction, Tobacco Addiction and Secondhand Smoke, Stress and Drug Abuse, and Health Literacy and Drug Abuse. These "teacher editions" were distributed nationwide during the 2007/2008 school year with Scholastic student magazines containing Heads Up articles.

**Monitoring the Future National Results on Adolescent Drug Use - Overview of Key Findings: 2007**
NIH Pub. No.: 08-6418
Provides a summary of drug use trends from a survey of 8th, 10th, and 12thgrade students nationwide. Also includes perceived risk, personal disapproval, and perceived availability of each drug by this group.

**National Survey Results from the Monitoring the Future 2007, Volume**

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**I: Secondary Students**
NIH Pub. No.: 08-6418A
Reports on the prevalence of drug use among students in 8th, 10th, and 12th grades. Trends are analyzed to understand the changing drug abuse problem and to formulate appropriate prevention and treatment polices.

**National Survey Results from the Monitoring the Future 2007, Volume II: College Students and Adults Ages 19-40**
NIH Pub. No.: 08-6418B
Reviews trends in drug use by populations based on gender, college plans, regions of the country, population density, race/ethnicity, and parents' education. Trends are analyzed to understand the changing drug abuse problem and to formulate appropriate prevention and treatment polices.

**Brain Power! NIDA Junior Scientists**
NIDA has reprinted its award winning curricula, "Brain Power! NIDA Junior Scientists" for grades 2-3 and 4-5. These curricula, developed for teachers, span 5 class periods each and cover a variety of neuroscience/drug abuse topics relevant to the particular age. For example, the curriculum for grades 2-3 covers scientific inquiry, basic brain biology, neurotransmission, medicines and drugs, and the science related to smoking. All topics are covered in an age appropriate manner and each session includes activities for both the classroom and home. Each topic also includes a parent newsletter and trading cards for the kids. The materials are available for free from NIDA's Research Dissemination Center.

## *NIDA NOTES*

***NIDA NOTES,* Vol. 22, No. 1 Innovations Special Issue**
**NIH Pub. No. 08-6455, August 2008**
This special issue features recent groundbreaking discoveries in drug abuse research that connect to the work of scientists across many disciplines. The lead story describes findings about receptors on neurons and glial cells that offer promise for pain relief without the negative side effects of currently used opioids. The Director's Perspective looks at how NIDA fosters interdisciplinary, breakthrough work; it describes two innovative NIDA programs: Cutting-Edge Basic Research Awards (CEBRA) and the Translationally Oriented Approaches, Devices and Strategies (TOADS) Workgroup. Other research reports discuss optical technologies that expand research and therapeutic possibilities by revealing neural circuits in living animals; discoveries of an unexpected role for the immune system in eliminating extra synapses during brain development; and work in genetics that identifies dozens of genes that influence vulnerability to drug dependence and indicates parts of the brain beyond the dopamine reward system that may contribute to addiction risk. The issue also announces the winners of the first Addiction Science Award for high school student at the Intel International Science and Engineering Fair.

## NIDA Journal of Addiction Science and Clinical Practice

**Addiction Science and Clinical Practice Volume 4, Number 2**
NIH Pub. No.: 08-6452, June, 2008
The issue's feature article is a comprehensive discussion by Dr. Seddon R. Savage and colleagues on the challenges of using opioids to treat pain in patients with substance use disorders. Addressing an audience of addiction specialists, the authors describe the nature and physiological basis of pain, explore its interrelationships with substance use, present methodical approaches to the evaluation and treatment of pain and co-occurring substance use disorder, and discuss the clinical and ethical challenges that both pain management specialists and addiction professionals face when treating this

population. Drs. Linda A. Dimeff and Marsha M. Linehan describe Dialectical Behavior Therapy (DBT), a treatment originally developed for suicidal patients with severe psychosocial disorders. The authors discuss their modification of DBT for treating substance abusers, DBT's strategies for promoting abstinence and preventing relapse, and the clinical trials that demonstrate the therapy's efficacy. Finally, Dr. Kyle Kampman discusses current research efforts toward developing effective medications for stimulant dependence.

### CTN-Related Publications

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

Data from fourteen CTN trials are now available on the CTN Data Sharing Web Site. Another three data sets will be available by the end of December 2008. Currently more than 120 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. Starting next year, flat file postings of the current data sets will also be available on the CTN Data Sharing website.

### International Publications

***NIDA International Program 2007 Annual Report***
The 2007 Annual Report demonstrates how each NIDA International Program activity independently addresses one aspect of addiction's impact on public health and simultaneously supports the wider network of NIDA's international activities and partners.

***NIDA International Program E-News Letter***
**August 2008** - This issue reported on the NIDA International Forum, the NIDA International Program Awards of Excellence, the Institute's international research interests and opportunities, and the IP 2007 Annual Report. The issue also announced the Mentor International Prevention Awards and provided links to the newly published UNAIDS 2008 Report on the Global AIDS Epidemic and the United Nations Office on Drugs and Crime World Drug Report 2008.

**June 2008** - This issue reported on the International Poster Session at the Society for Prevention Research meeting and the inauguration of the International Programme in Addiction Studies, an online, 12-month master's degree program offered jointly by the University of Adelaide, King's College London, and Virginia Commonwealth University. The issue also announced the second round of NIDA/CICAD Research Awards for pre- or postdoctoral students from Latin America who are conducting research in any area of the drug use field.

### Other Publications

A research monograph entitled "Drug Addiction - From Basic Research to Therapies" edited by Drs. Rao S. Rapaka and Wolfgang Sadee was recently published. This resulted from a NIDA-AAPS symposium. Springer-Verlag, 2008.

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## Staff Highlights

### Staff Honors and Awards

#### 2008 NIDA DIRECTOR'S AWARDS

*NIDA Director's Award for Innovation* **Carol Krause --** *"For employing innovative thinking and novel methods in facilitation of the NIDA Science Fair"*

### Group Awards

**The CCTN Data Share Workgroup**
Carol Cushing, Ronald Dobbins, Mary Ellen Michel, Ph.D., Harold Perl, Ph.D., Carmen Rosa, and Paul Wakim, Ph.D.

**The GEI Exposure Biology Program**
Kevin Conway, Ph.D., J.C. Comolli, Harold Gordon, Ph.D., Mary Kautz, Ph.D., Minda Lynch, Ph.D., Jonathan Pollock, Ph.D., Susan Volman, Ph.D., and Kay Wanke, Ph.D.

**The Physical Activity Meeting Team**
Nicolette Borek, Ph.D., Kristopher Bough, Ph.D., Usha Charya, B.A., Wilson Compton, M.D., M.P.E., Augie Diana, Ph.D., Gayathri J. Dowling, Ph.D., Joseph Frascella, Ph.D., Dorie Hightower, Sharan Jayne, Carol Krause, Marsha Lopez, Ph.D., Minda Lynch, Ph.D., Aleta Meyer, Ph.D., Lisa Onken, Ph.D., Nancy Pilotte, Ph.D., Elizabeth Robertson, Ph.D., Paul Schnur, Ph.D., Karen Sirocco, Ph.D., and Yonette Thomas, Ph.D.

**The IRP Administrative Management Branch**
Janice Carico, Tracey Coleman-Rawlinson, Kandi Culbertson, Diane French, Grant Greenwaldt, Thomas Haines, Timothy Kirkendall, John Kunzelman, Carol Lindsay, Randall Smith, Massoud Vahabzadeh, Ph.D., and Sheila Zichos.

**The Neuro-Genetic Addiction Course Team**
Beth Babecki, Usha Charya, Kevin Conway, Ph.D., Steven Grant, Ph.D., Raul Mandler, M.D., Lucinda Miner, Ph.D., Amrat Patel, Ph.D., Jonathan Pollock, Ph.D., Joni Rutter, Ph.D., David Shurtleff, Ph.D., Laurence Stanford, Ph.D., George R. Uhl, M.D., Ph.D., Susan Volman, Ph.D., Kay Wanke, Ph.D., Naimah Weinberg, M.D.

**The Information Resources Management Branch**
Marguerite Lewis, Tina McDonald-Bennett, Michael Wright, and Berhane Yitbarek.

**The National Science Fair Team**
Patricia Anderson, Ruben Baler, Ph.D., Gayathri J. Dowling, Ph.D., Mark Fleming, Dorie Hightower, Carol Krause, Jan Lipkin, Sheryl Massaro, Lucinda

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Nathan M. Appel, Ph.D.
Janelle Barth
Aria Crump, Sc.D.
Allison Chausmer Hoffman, Ph.D.
Steven Grant, Ph.D.
Eliane Lazar-Wesley, Ph.D.
David Liu, M.D.
Marisela Morales, Ph.D.
Linda Thomas

**NIDA EEO Award**
Michelle K. Leff, M.D.

**30 Years of Government Service Awards**
Loretta Beuchert
Nora Chiang
Jag H. Khalsa
Shou-Hua Li
Geraline Lin
Frank Vocci

### Other Staff Awards

**Dr. Betty Tai** received the 2008 NIH Director's Award in recognition of her exceptional work in supporting the comprehensive trans-NIH assessment of the system of research support, of which peer review is a major component.

**Dr. Betty Tai** received the 2008 NIH Director's Award for her leadership in developing an effective Clinical Trial Network (CTN) focused on treating addictions and dependence on drugs.

**Dr. Betty Tai** received the 2008 J. Michael Morrison Award for advancing drug abuse research through work within the NIDA Drug Development Program and for expert and enthusiastic leadership of the Drug Abuse Treatment Clinical Trial Network.

At the 2008 American Psychological Association Convention in August 2008, **Dr. Meyer Glantz**, DESPR, received a Special Presidential Citation for Distinguished Service to Divisions 50 and 28 for "extraordinary work in supporting early career psychologists in addiction, psychopharmacology, and substance abuse research.' Dr. Glantz has supported early career psychologists in the field of substance abuse research and treatment through his work with the APA dissertation awards, the College of Professional Psychology, and the NIDA/NIAAA-Divisions 50 & 28 Early Career Poster Presentations.

**Dr. Richard A. Jenkins**, DESPR, received the Award for Distinguished Contributions to Practice in Community Psychology (2008), Society for Community Research & Action (Division 27 of American Psychological Association).

**Dr. Lula Beatty**, Chief, Special Populations Office (SPO), was inducted as a Fellow for Division 45: Society for the Psychological Study of Ethnic Minority Issues at the American Psychological Association meeting on August 15, 2008 in Boston, Massachusetts.

**Ana Anders, M.S.W.** SPO, was selected to be a member of the NIH Hispanic

Employee Committee.

**Dr. Joni Rutter**, DBNBR, received the NIH Director's award for Implementation of Roadmap Programs, July 21, 2008 in Bethesda, MD.

**Dr. John Satterlee**, DBNBR, received the NIH Director's Award for NIH Roadmap Epigenomics Program efforts.

**Dr. John Satterlee** received the NIH Blueprint Directors Award for Blueprint Neuroplasticity RFA efforts.

**Dr. John Satterlee** received the NIH Blueprint Directors Award for work on the Blueprint Neuroplasticity Workshop team.

**Dr. Da-Yu Wu**, DBNBR, received two Blueprint team awards one as part of the Gene Expression team and one as part of the hESC Workshop Planning team.

**Dr. Christine Colvis**, DBNBR, received the NIH Director's award for Implementation of Roadmap Programs, July 21, 2008 in Bethesda, MD.

**Dr. Jonathan Pollock**, DBNBR, received the NIH Director's award as part of the Genome Wide Association Studies Policy Development Team, July 21, 2008 in Bethesda, MD.

**Dr. Jonathan Pollock** received the NIH Blueprint award for "Effective and dedicated teamwork in the creation of and funding of the Blueprint Neurodevelopment Circuits Initiative", July 24, 2008 in Bethesda, MD.

**Dr. Karen Skinner**, DBNBR, received the NIH Director's award for outstanding leadership, vision, dedication and oversight in developing the Neuroscience Information Framework, July 21, 2008 in Bethesda, MD.

**Dr. David Shurtleff**, Director, DBNBR, received the NIH Director's award for outstanding leadership, vision, dedication and oversight in developing the Neuroscience Information Framework, July 21, 2008 in Bethesda, MD.

**Dr. Kristopher Bough**, DPMCDA, received an "Excellence in Mentoring" award for helping design and implement a comprehensive training and mentoring program in review management techniques for new reviewers at the FDA, May 16, 2008.

**Dr. Jag Khalsa**, DPMCDA, received the Life Time Achievement Award for his dedication and developing research programs in drug abuse and infections, by the American Sikh Council on Religion and Education (SCORE), June 11, 2008, in a ceremony on the Capitol Hill attended by several US Congressmen and Senators.

**Dr. Khalsa** received the award from the US Congressman Joe Wilson of South Carolina.

**Dr. Rita Liu**, OEA, received the 2008 J. Michael Morrison Award from CPDD, for outstanding scientific administration. This award is given biennially to individual(s) recognized for his/her/theirs extraordinary achievements in administering drug abuse research related activities.

**Dr. Meenaxi Hiremath**, OEA, received the NIH Director's Award for her work on the DEAS Re-engineering Team.

**Dr. Stephen Heishman**, IRP, served as the NIDA liaison on the 2008 update of the PHS Clinical Practice Guideline: Treating Tobacco Use and Dependence. He attended the release of the Guideline on May 7, 2008 at the headquarters of the American Medical Association in Chicago. A summary of the Guideline was published in the American Journal of Preventive Medicine, as cited below:

**Dr. Kenner Rice**, IRP, was inducted into the Medicinal Chemistry Hall of Fame

of the American Chemical Society Division of Medicinal Chemistry, 2007 as one of only 33 living members.

**Dr. Teruo Hayashi**, a Staff Scientist within the Cellular Pathobiology Section, Cellular Neurobiology Research Branch, IRP, was honored on July 14, 2008 for his poster presentation entitled "A Novel Molecular Chaperone Sigma-1 Receptor: Potential Therapeutic Target for Neuropsychiatric Disorders", and received "Best Poster Award" at the XXVII Collegiums International Neuro-Psychopharmacologicum Annual Meeting, which was held from July 13-17, 2008 in Munich, Germany. This award is made on the basis of the study's scientific excellence.

### Staff Changes

**Christine Colvis, Ph.D.** has joined the Office of the Director as the Director of Program Integration. She will be facilitating collaboration across NIDA's Divisions, Offices and Centers as well as across the NIH with an emphasis on program development and will continue to represent NIDA on a number of trans-NIH program teams. Christine received her Ph.D. in Biochemistry and Molecular Biology from Oregon Health Sciences University in 1998. After earning her degree, Christine came to the NIH as a fellow in the National Eye Institute's Intramural Research Program where she was studying proteomics of cataracts. Christine has been a program director at NIDA in the Genetics and Molecular Neurobiology Research Branch in the Division of Basic Neuroscience and Behavioral Research since 2001. She has helped to build NIDA's portfolio in several areas including proteomics, epigenetics and non-coding RNAs and represents NIDA on several NIH Roadmap Programs.

**Ananth Charya, M.P.H.** joined NIDA in May 2008 as a Health Program Specialist and is assisting with NIH Roadmap Initiatives and trans-Institute activities. He is originally from the Washington, DC Metro area. He received his Bachelors of Science degree in Neurobiology and Physiology and Bachelors of Arts in Economics from the University of Maryland- College Park in 2002. After college, Ananth worked at Georgetown University Medical Center in the Department of Pharmacology where he performed research involving molecular mechanisms regulating neuronal cell death and survival after continuous seizure activity. After Georgetown, Ananth worked at the Walter Reed Army Institute of Research, where he used neurobiological assays to examine the effects of chronic low dose chemical nerve agent exposure. In 2008, he received his Masters of Science in Public Health from George Washington University.

**Diane Lawrence, Ph.D.** has joined the NIDA AIDS Research Program as an Associate Director. She will be helping to coordinate program efforts within NIDA and across other NIH ICs and DHHS agencies, particularly in the area of basic and clinical HIV and neuroAIDS research. Her goal is to facilitate communication and team building in order to develop initiatives that bring the best HIV research to NIDA. Diane has been a Program Official at NIDA for the past three years, during which time she coordinated efforts to develop initiatives, helped build a research portfolio in basic neuroAIDS research, and managed a fellowship and training portfolio. Prior to joining NIDA, she spent five years in NINDS doing intramural research on neuroAIDS and gaining experience in program, review, and communications. Diane received her B.A. in Psychology and Biological Sciences from Carnegie Mellon University in 1989 and her Ph.D. from the University of Rochester Neuroscience Program, where she had an interest in psychoneuroimmunology and was funded by a NIDA training grant to study opioid receptor expression on T cells. After NIDA-supported postdoctoral training at Temple University to get more experience with in vivo models of immunology and pharmacology, she shifted her focus back to neuroscience. Diane began a second postdoc at the Fox Chase Cancer Center, where she studied infectious diseases and immune responses within

the brain using both transgenic mouse model systems and neurons in culture.

**Albert Avila Ph.D.** recently joined DBNBR. Dr. Avila received a B.S. in Psychobiology and a B.A. in English Literature from the University of California, Los Angeles, and a Ph.D. in pharmacology from Georgetown University in 2003. His doctoral research focused primarily in the area of neuropsychopharmacology and immunology, specifically studying the effects of cocaine, cocaine withdrawal, and stress on the immune system. Upon graduating from Georgetown, he received a National Institutes of Health Intramural Research Training Award for postdoctoral research in the area of pain transmission and control at the National Institute of Dental and Craniofacial Research, NIH. In 2004, he became the Director of the NIDCR Office of Education, directing the intramural research training program for NIDCR. The following year Dr. Avila became an Extramural Program Officer for the NIDCR Training and Career Development Branch where he managed grants and fellowships for dental and graduate students, postdocs, and junior investigators who are conducting oral and craniofacial related-research. At NIDA, he will be working with Beth Babecki and Charlie Sharp, managing training and fellowship grants as well as working with research grants in the area of stress and immunology.

**Elena Koustova, Ph.D.** recently joined DBNBR. Elena earned her bachelor's degree in physiology at Moscow State University. She then went on to receive her Ph.D. in neurosciences, also from Moscow State. She completed her postdoctoral studies at the Laboratory of Neuroscience (NIDDK) at NIH, were she was involved in developing animal models of neuroAIDS and behavioral phenotyping of genetically manipulated animals. Later, she held a professorship at The F. Edward Hebert School of Medicine (Bethesda, MD), and served as an R&D Director at DOV Pharmaceutical Inc (Somerset, NJ). She pioneered research in posttranslational and epigenetic regulation in hypovolemic/full body ischemia states, and participated in development of clotting agents that are currently utilized by US Marine Corps. At DOV, Elena directed preclinical discovery and development of triple reuptake inhibitors, securing the progression of two compounds into currently conducted clinical trials. The transition from academic to industrial research was so perspective-changing, that Elena pursued formal business education and earned an MBA degree from Gallup (Princeton, NJ), specializing in Organizational Innovation. Elena holds three patents as a single inventor and multiple patents as a team contributor. Her research is described in more than 70 articles and book chapters, public press, and even a Doonesbury cartoon strip. Elena is working in the Genetics and Molecular Neurobiology Branch of DBNBR on molecular neurobiology, SBIR and other initiatives programs combining her business and scientific background.

**Dr. Shoshana Kahana** joined DCNBR's Behavioral & Integrative Treatment Branch on August 3, 2008. Prior to coming to NIDA, Dr. Kahana was a Visiting Scientist in the Psychosocial Stress and Related Disorders Branch at NIMH. Dr. Kahana received her doctoral degree in Clinical Psychology from Case Western Reserve University and completed postdoctoral work at Case Western, as well as Brown University. Her primary research interests are focused on (behavioral) interventions for comorbid conditions, specifically traumatic stress and drug use, in adolescent and adult populations. In addition, some of her work examines risk and protective factors for treatment noncompliance among youth with chronic health conditions, as well as the effects of treatment choice/preference on outcome among adult sexual assault victims diagnosed with PTSD.

**Dr. Guifang Lao, M.D., Ph.D.** has joined DPMCDA as a Health Scientist Administrator/ Program Officer, in the Medical Consequences of Drug Abuse Branch. Dr. Lao received her M.D. and M.Sc. in Biochemistry from China, Ph.D. in Microbiology and Biochemistry from the Cornell University, completed a

postdoctoral fellowship at NINDS, and worked in the Department of Radiology at the NIH Clinical Center. Her research interests are in the areas of clinical medicine, clinical molecular biology, immunology, neuroscience, protein chemistry, and non-invasive techniques of assessing medical consequences. Dr. Lao will be developing new programs of research on medical consequences of drug abuse and co-occurring infections including one on new and innovative non-invasive methods of assessing clinical consequences of drugs of abuse and infections.

**Stephanie Older** joined the Public Information and Liaison Branch of OSPC in June 2008 as the Deputy Press Officer. Her experience includes work for both corporate and non profit organizations, most notably as the media liaison for the National Breast Cancer Coalition. She has also conducted media outreach for the Social Security Administration's Medicare Assistance Program and the National Health Council's "Putting Patients First" national media campaign. Stephanie holds a law degree from the University of Baltimore as well as a B.A. in communication from the University of Pennsylvania. Before joining NIDA, she worked as Attorney-Adviser to an Associate Chief Judge at the U.S. Department of Labor. After working on cases involving Black Lung Disease and workman's compensation issues, Stephanie decided she missed the media element of public health work, and wants to apply her well developed organizational skills to help with NIDA's press outreach.

**Dr. Ericka Boone** joined the Science Policy Branch of OSPC in August 2008 as a Health Scientist Administrator. She received her Ph.D. in Biobehavioral Health from The Pennsylvania State University in 2000. Most recently, she conducted research at the University of Illinois at Chicago focusing on the physiology, neurobiology and development of socially monogamous traits, including parenting and pair-bonding behaviors, in prairie voles. She was particularly interested in the role of early experience and neuropeptides such as oxytocin and vasopressin in the development of these behaviors. Dr. Boone has over 10 years experience synthesizing, conducting and analyzing basic and clinical research information in the areas of social neuroscience, genetics, molecular biology and drug abuse.

**Kyle C. Stump, DVM, DACLAM** was appointed the Animal Program Director for NIDA IRP in March 2008. He is a graduate of Michigan State University College of Veterinary Medicine and completed a postdoctoral fellowship at the Johns Hopkins University School of Medicine, Division of Comparative Medicine. He is a board certified diplomate of the American College of Laboratory Animal Medicine. Prior to his appointment at the IRP, Dr. Stump was the Senior Animal Program Veterinarian for the National Cancer Institute and the Chief of Veterinary Medicine and Surgery at the University of Maryland School of Medicine.

The CCTN is pleased to welcome **Dr. Udi Ghitza** as a member of the Behavioral and Social Science Team. Before coming to the CCTN, Dr. Ghitza worked in the Intramural Program of NIDA with Drs. Kenzie Preston and Yavin Shaham. Dr. Ghitza received his Ph.D. in psychology from Rutgers University, with a specialization in behavioral neuroscience/ biological psychology. He has done work on animal models of drug abuse, as well as clinical studies of behavioral and pharmacological therapies. In his behavioral neuroscience research, he used a rat relapse model to examine the cellular and neuroanatomical mechanisms underlying relapse to drug- and high-fat food-seeking behavior. In clinical trials research, he evaluated behavioral and pharmacological treatments for cocaine and heroin abuse.

**Captain Kesinee (Kay) Nimit, M.D.** retired after 21 years of service in the PHS Commissioned Corps, including 19 years at NIDA. During her service, she received a Unit Commendation, the Commendation Medal four times (1991, 1994, 1997, and 2000), the Regular Corps Ribbon, and the Bicentennial Unit Commendation. Dr. Nimit received her Doctor of Medicine Degree from Mahidol

University School of Medicine in Bangkok, completed a Pediatric Residency at St. Agnes Hospital/Johns Hopkins Hospital and is Board Certified in Pediatrics. Dr. Nimit provided pediatric clinic care at the Navy Medical Center in Bethesda one morning each week in addition to her work in managing peer review. Dr. Nimit's career at NIDA has primarily been in the area of clinical research where she has a well-earned reputation as a dedicated, hardworking professional who always conducts herself to meet the highest standards. She has provided a very positive interface with the extramural community of researchers, as evidenced by the many unsolicited notes of praise sent to her. Her sustained excellence will be missed.

**Dr. Richard Hawks** has retired from his position as Deputy Director, DPMCDA after 36 years of exceptional service to the Federal Government. Dr. Hawks received his Ph.D. from Duke University in organic chemistry in 1970 and completed a postdoctoral appointment at the Research Triangle Institute in North Carolina working on cannabinoid chemistry. He began his career as a chemist with the Federal Government in 1972 with the Division of Narcotic Addiction and Drug Abuse, National Institute of Mental Health (the Division which became NIDA). Dr. Hawks also served as Chief of the Chemistry and Pharmaceutics Branch of the Medications Development Division and Chief of the Research Technology Branch in the Division of Preclinical Research at NIDA. Dr. Hawks was closely involved with the establishment and evolution of the NIDA's medications development program and made tremendous contributions in the areas of chemistry, pharmaceutics, and project management and budget.

**Dr. Ivan Montoya** will serve as Acting Deputy Director, DPMCDA. Dr. Montoya received his M.D. from the University of Antioquia (Colombia), a Masters in Public Health (M.P.H.) from The Johns Hopkins School of Public Health, and completed residency training in Psychiatry at the San Vicente de Paul Hospital (Colombia) and the University of Maryland Hospital (Baltimore). He was a Hubert H. Humphrey Fellow in Drug Abuse at The Johns Hopkins School of Public Health and a Visiting Postdoctoral Fellow at NIDA's Intramural Research Program. He has been the Director of the Public Mental Health Program at the University of Antioquia (Colombia), Director of the Practice Research Network of the American Psychiatric Association, consultant for the World Health Organization's Pan American Health Organization, and Clinical Director of the Pharmacotherapies and Medical Consequences Grants of NIDA's DPMCDA. He has published extensively in the areas of etiology, prevention, treatment (pharmacological and non-pharmacological), and medical consequences of drug abuse.

# Director's Report to the National Advisory Council on Drug Abuse - September, 2008

## Grantee Honors

**Dr. Gilbert Botvin** received the 2008 Special Recognition Award from the Society for Prevention Research, for service to the society as founding editor of the Prevention Science journal and Editor-in Chief from 2002-2006. Dr. Botvin is Professor of Psychology and Director of the Institute for Prevention Research at Weill Medical College, Cornell University.

**Beth Dannhardt**, Director of Triumph Treatment Services in Yakima, Washington, and the alternate CTP representative for the Pacific Northwest Node, has been selected as the recipient of the 2007 Nichols Leadership Award. The Nichols Leadership Award is presented annually by Residence XII, a specialty chemical dependence treatment program for women and families in Kirkland, Washington, and one of the Pacific Northwest Node's CTPs, to an individual, or group, who has consistently demonstrated community leadership to better meet the needs of chemically dependent women and their families. Triumph Treatment Services operates the oldest gender-specific chemical dependency treatment program for women and their children in the state of Washington. Beth was honored with a reception and award presentation at Residence XII on May 30, 2008.

**Dr. Marion Forgatch**, Oregon Social Learning Center, received the 2008 International Collaborative Prevention Research Award from the Society for Prevention Research, for contributions to the field of prevention science in the area of international collaboration.

**Dr. Mark Greenberg**, Pennsylvania State University, received the 2008 Friend of ECPN (Early Career Preventionist Network) Award from the Society for Prevention Research, for supporting and encouraging early career persons or issues.

**Shelly Greenfield, M.D., M.P.H.** (Co-PI of the Northern New England Node) recently received the Massachusetts Psychiatric Society 2008 Outstanding Psychiatrist Award for Research. Dr. Greenfield received the honor in recognition of her contributions to the field of substance abuse research, with a particular focus on gender differences in the prevention and treatment of substance use disorders.

**Dr. Michael Hecht** of Pennsylvania State University presented a paper at the 2008 Annual International Communication Association Convention in Montreal, Quebec, Canada held May 22-26 2008. The paper by Matsunaga, M., Ndiaye, K., Hecht, M.L., & Elek, E.E. (May 2008), "Punctuated Equilibria of Ethnic Identity Development: The Case of Mexican-Heritage Youth in the United States," received an award as the top paper in intercultural communication.

**Dr. Stephen T. Higgins**, Professor of Psychiatry and Psychology and Director of the Substance Abuse Research and Treatment Center at the University of

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Vermont has received the distinguished honor of being invited to present a G Stanley Hall lecture at the 2008 Annual APA Conference. His lecture will be on Reinforcement and Substance Use Disorders.

**Dr. Sheppard Kellam**, American Institutes for Research and Professor Emeritus, Johns Hopkins Bloomberg School of Public Health, received the 2008 Presidential Award from the Society for Prevention Research, for a major lifetime contribution to prevention science research.

**Dr. Stefan Kertesz** was invited to serve on a federal panel to advise HHS Assistant Secretary for Planning and Evaluation regarding evaluation of a novel service model for homeless persons: medical respite services.

**Dr. Stephanie Lanza**, Scientific Director of the NIDA-funded Penn State University Methodology Center (P50) and PI for the Methodology Center's annual Summer Institute on Longitudinal Methods (R13), was presented the Early Career Prevention Network (ECPN) Early Career Award at the annual meeting for the Society for Prevention Research in San Francisco, CA on May 29, 2008. This award is bestowed to someone who has shown a commitment to prevention science through outstanding research, policy or practice.

**Edythe London, Ph.D.** gave the Marian Fischman Memorial Award Lecture entitled "Brain Imaging and Addiction" at the College on Problems of Drug Dependence on June 16, 2008 in San Juan, Puerto Rico.

**Dr. Thomas E. Prisinzano**, Associate Professor of Medicinal Chemistry at the University of Kansas, received the 2008 Matt Suffness Award from the American Society of Pharmacognosy (ASP). He accepted the Award and presented a lecture at the 7th Joint Meeting of AFERP, ASP, GA, and PSE August 3 - 8, 2008 in Athens, Greece. Dr. Prisinzano's studies have shown that structural modification of natural ligands from S. divinorum can lead to potential new medications for the treatment of drug dependence and pain. His group is now working to identify, synthesize and evaluate biased agonists for opioid receptors as potential analgesics with reduced side effects. Salvia divinorum, a hallucinogenic mint plant native to Oaxaca, Mexico. The award is presented to young natural product scientists within 12 years of receiving their doctorate and within 10 years of gaining their first independent position and is intended to provide a special, timely forum for them to present their research. The Award also recognizes and honors the memory of Dr. Matt Suffness. Dr. Suffness served as the Society's President in 1989-1990, during which time he initiated the "Young Investigator's Symposium" which now bears his name. Dr. Suffness is best known for his commitment to the development of taxol as an anticancer drug. He edited the book entitled Taxol - Science and Applications, which was published shortly before his death in 1995.

**Dr. Richard Spoth**, Iowa State University, received the 2008 Prevention Science Award from the Society for Prevention research, in recognition of a significant body of research that has applied scientific methods to test preventive interventions or policies.

**Dr. Melissa Tibbits, Dr. Michael Cleveland, Dr. Monique Faulk,** and **Dr. Amy Syvertsen**, current and former fellows on the NIDA supported Prevention and Methodology Training program at Pennsylvania State University, along with pre-doctoral student **Joche Gayles** won the 2008 SPR Sloboda & Bukoski Cup, an annual Society for Prevention Research competition where independent groups of scientists, each working with the same data set prior to the conference, conduct a study that is presented at SPR and evaluated by a panel of judges and audience members on the quality of the research and presentation.