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Research Findings - Basic Neurosciences Research

Pregnancy & Cigarette Smoking

Children of women who smoked during pregnancy are at increased risk of dependence when smoking is initiated during adolescence. Studies conducted in experimental animals demonstrate that gestational nicotine exposure attenuated dopamine release induced by nicotine delivered during adolescence. In a recent study, NIDA supported researchers report that exposing pregnant rats to nicotine for a period equivalent to the three trimesters of human brain development period reduced nicotine cholinergic receptor (nAChR) expression in dopaminergic regions during adolescence. This reduction reflects lower nAChR subunits transcript levels and fewer neurons in the VTA, as well as other undefined mechanisms. These data indicate that gestational nicotine exposure affected the developmental regulation of nAChR expression and these effects can endure at least into adolescence. These findings are important from a public health perspective because the down-regulation of nAChR expression during brain development may result in heightened vulnerability to dependence on cigarette smoking that affects adolescent offspring of women who smoked tobacco during pregnancy. Chen, H., Parker, S.L., Matta, S.G., and Sharp, B.M. Gestational Nicotine Exposure Reduces Nicotinic Cholinergic Receptor (nAChR) Expression in Dopaminergic Brain Regions of Adolescent Rats. European Journal of Neuroscience, 22, pp. 380-388, 2005.

Cocaine and Progression of HIV

Cocaine is associated with an increased risk for, and progression of, clinical disease associated with human immunodeficiency virus (HIV) infection. In a recent study, NIDA supported researchers, Dr. Michael Roth and his associates at UCLA report findings of their studies designed to investigate the biological interactions between cocaine and HIV infection. These investigations were conducted using a hybrid human-mouse model in which human peripheral blood mononuclear cells (huPBL) were implanted into severe combined immunodeficiency mice (huPBL-SCID) and then infected with a HIV reporter virus. Systemic administration of cocaine significantly increased the percentage of HIV-infected PBL and viral load in huPBL-SCID mice suggesting a dynamic interaction between drug exposure and viral infection. They also report that despite the capacity for cocaine to increase corticosterone and adrenocorticotropic hormone levels in control mice, the hypothalamic pituitary-adrenal axis was suppressed in HIV-infected animals, and corticosterone levels were further decreased when animals were exposed to HIV and cocaine. Activating huPBL in vitro in the presence of cocaine increased expression of CC chemokine receptor 5 (CCR5) and CXC chemokine receptor 4 (CXCR4) co-receptors. Expression of CCR5 was also increased at early time-points in the huPBL-SCID mouse model following systemic exposure to cocaine. This effect

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preceded the boost in viral infection and waned as HIV infection progressed. In addition, they report that a selective sigma -1 antagonist, BD1047, blocked the effects of cocaine on HIV replication in the huPBL-SCID mouse. This is consistent with a previous finding that cocaine' s immunosuppressive effects in vitro are mediated by sigma-1 receptors. Thus, these findings suggest that systemic exposure to cocaine can enhance HIV infection in vivo by activating sigma-1 receptors and by modulating the expression of HIV co-receptors. Roth, M.D., Whittaker, K.M., Choi, R., Tashkin, D.P., and Baldwin, G.C. Cocaine and _-1 Receptors Modulate HIV Infection, Chemokine Receptors, and the HPA Axis in the huPBL-SCID Model. Journal of Leukocyte Biology, 78, pp. 1198-1203, 2005.

Opiate Modulation of Immunity and Antiviral Action

Numerous investigators have provided information on opiate inhibition of antiviral activity, especially in regards to anti-HIV action. Wang and his collaborators have continued to define this relationship and have provided an in-depth understanding of the mechanism of this action at the molecular level of cellular activity. Opiates have profound effects on the function of human immune cells and are a possible cofactor in the immunopathogenesis of human immunodeficiency virus (HIV) disease. Wang et al. investigated the impact of morphine on CD8(+) T cell-mediated, noncytotoxic, anti-HIV activity in latently infected human immune cells. Morphine inhibited the noncytotoxic, anti-HIV activity of CD8(+) T cells in HIV latently infected cells (U1 and J1.1). Naltrexone abolished the morphine-mediated, inhibitory effect on the noncytotoxic, anti-HIV activity of CD8(+) T cells. Interferon-gamma (IFN-gamma), a potent antiviral cytokine produced by CD8(+) T cells, was partially responsible for CD8(+) T cell-mediated, noncytotoxic, anti-HIV activity. The anti-HIV activity of IFN-gamma was also compromised by morphine treatment. Further, morphine attenuated CD8(+) T cell-mediated suppression of the HIV long-terminal repeat promoter activation. Morphine also inhibited CD8(+) T cell-induced expression of the signal transducer and activator of transcription-1, an important transcriptional factor in the IFN signaling pathway. These data provide additional evidence to support the notion that opioids play a role in impairing the anti-HIV function of the immune system. Wang, X., Tan, N., Douglas, S.D., Zhang, T., Wang, Y-J. and Ho, W-Z. Morphine Inhibits CD8+ T Cell-mediated, Noncytolytic, Anti-HIV Activity in Latently Infected Immune Cells. Journal of Leukocyte Biology, 78, pp. 772-776, 2005.

Morphine Withdrawal Contributes to Th Cell Differentiation by Biasing Cells Toward the Th2 Lineage

The consequences of drug withdrawal on immune functioning have only recently been appreciated; however, given the wide variety of use and abuse of opiate analgesics, understanding the decrements to immune function that withdrawal from these drugs cause is of crucial importance. The immune system functions in many ways to combat diseases. There are lymphocytes that combat viruses/bacteria upon entry and others that develop antibody production to combat them. The entry of virus/bacteria into the host is met by Th1-type cells to keep down the proliferation of the invader. Th2 cells and B-cells act together to produce antibodies, a later event in host defense. Numerous investigators are observing a change in the profile of Th1/Th2 type cell when drugs are administered. Many other compounds act similarly in altering the body' s host defense mechanism. Although most investigators look at the early actions of drugs on T-cell maturation, a recent study has observed similar profile alterations when a chronically-administered-drug is withdrawn. Thus, it may be as important to be aware of disease states during drug withdrawal as it is to oversee potential infectious situations following opiate administration following surgery or other drug use situations. Kelschenbach, J.,

Barke, R.A. and Roy, S. Morphine Withdrawal Contributes to Th Cell Differentiation by Biasing Cells Toward the Th2 Lineage. The Journal of Immunology, 175, pp. 2655-2665, 2005.

Neuroprotection by Pharmacologic Blockade of the GAPDH Death Cascade

NIDA supported investigator, Dr. Solomon Snyder and his colleagues, have identified a key biochemical pathway that plays a role in mediating cell death and may provide potential treatment for neurodegenerative diseases. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is normally involved in sugar metabolism. However, under certain conditions of cell stress GAPDH is nitrosylated by nitric oxide. Nitrosylation of GAPDH abolishes its enzymatic activity and converts it to a cell death molecule by binding to SIAH (sevenless in absentia homolog), a ubiquin E3 ligase. Nitrosylated GAPDH acting as chaperone binds to SIAH causing the GAPDH/SIAH complex to translocate to the cell nucleus where degradation of SIAH targets produces cell death. Now Dr. Snyder and his colleagues show that both deprenyl, a drug used to treat Parkinson' s disease and a related agent, TCH346, block cell death by preventing nitrosylation of GAPDH and subsequent translocation of SIAH to the nucleus in both macrophage cell lines treated with LPS and in dopamine neurons treated with MPTP, a toxin that damages dopamine neurons. In cultures of cerebellar granule cells deprenyl prevented apoptotic cell death elicted by etoposide. This work suggests that deprenyl may not only be effective for treating Parkinson disease but may also be useful in treating other neurodegenerative disorders. Hara, M.R., Thomas, B., Cascio, M.B., Bae, B-I., Hester, L.D., Dawson, V.L., Dawson, T.M., Sawa, A. and Snyder, S.H. Neuroprotection by Pharmacologic Blockade of the GAPDH Cascade. Proceedings of the National Academy of Science of the United States of America, 103, pp. 3887-3889, 2006.

A Nitric Oxide (NO) Signaling Pathway Controls CREB-Mediated Gene Expression in Neurons

Neurotrophins such as BDNF are thought to mediate the actions of drugs of abuse such as cocaine. The actions of neurotrophins are in part mediated by activating the transcription factor, CREB (cyclic AMP Response Element Binding protein) to alter gene expression. In the classical model, phosphorylation of CREB on serine 133 by CREB kinases causes CREB to associate with CBP (CREB binding protein) and bind to CRE to initiate transcription. Recent work by the laboratory of Dr. Solomon Snyder in collaboration with the laboratories of Dr. David Ginty and Dr. Ted Dawson at Johns Hopkins Medical Center suggest that phosphorylation is not required for activation of CREB. Transcriptional activation by CREB remains even when phosphorylation of CREB 133 is blocked. Instead Dr. Snyder and his colleagues show that binding of CREB to CRE is blocked by inhibitors of nitric oxide synthase (NOS) in a calcium dependent manner and that NO is sufficient to induce CREB binding to CRE. Furthermore, CREB dependent transcription is absent in mice lacking the nNOS, the neuronal form of nitric oxide synthase. Because nNOS acts either by activating cyclic GMP or by nitrosylating proteins, Dr. Snyder and his colleagues tested whether CREB binding is mediated by either one of these signaling pathways. Inhibitors of cyclic GMP dependent protein kinase did not abolish CREB binding to CRE in response to BDNF. Although Dr. Synder and his colleagues did not find CREB to be nitrosylated following neurotrophin treatment, they suggest that inactivation of histone deacetylase 2 by nitrosylation permits histone 3 and histone 4 to become acetylated, enabling CREB to bind CRE. These results suggest that the binding of CREB to CRE is independent of the ras/erk pathway and is mediated by nitrosylation of nuclear proteins. Riccio, A., Alvania, R.S., Lonze, B.E., Ramanan, N., Kim, T., Huang, Y., Dawson, T.M., Snyder, S.H., and Ginty, D.D. A Nitric Oxide Signaling

Pathway Controls CREB-Mediated Gene Expression in Neurons. Molecular Cell, 21(2), pp. 283-294, 2006.

p11: A New Link Between Serotonin and Depression

Therapeutic modulation of serotonin metabolism is used to treat a number of neuropsychiatric disorders. The 5-HT1B serotonin receptor subtype, which regulates serotonin neurotransmission, has been implicated in a variety of behaviors including depression, anxiety, sleep, and drug addiction. Using a protein interaction screen, Dr. Greengard and coworkers discovered that the p11 protein specifically binds to the 5-HT1B receptor. Further experiments indicated that the mRNA transcripts of these two genes are expressed in similar patterns in rat brain, the two proteins bind to one another in vivo, and both proteins co-localize on the cell surface. The p11 protein contains calcium-binding motifs, and can translocate proteins to the plasma membrane. Does p11 play a role in depression? Dr. Greengard found that p11 mRNA levels in the brain were reduced in post-mortem patients who suffered from major depression, as well as in a mouse model of depression. Interestingly, p11 mRNA levels increase in response to imipramine and to electroconvulsive therapy, both of which are treatments for depression. Does experimental manipulation of p11 levels alter behavior with respect to depression? Dr. Greengard used genetic techniques to decrease and increase p11 levels in living animals. In some brain regions, mice with genetic inactivation of p11 function had fewer binding sites for a chemical antagonist which binds the 5-HT1B serotonin receptor. These animals also exhibited higher levels of depression-like states and were less responsive to a sweet reward. In contrast, animals overexpressing p11 had more 5-HT1B serotonin receptors. These mice had decreased levels of behaviors associated with depression and anxiety, and behaved more like animals treated with antidepressants. Dr. Greengard' s work establishes a role for p11 modulation of 5-HT1B serotonin receptor levels, leading to alterations in depression-related behavior. This work reveals that the tricyclic antidepressant imipramine functions through p11 and the 5-HT1B serotonin receptor to ameliorate depression. The identification of p11 and its 5-HT1B regulatory role enhances our understanding of how serotonin receptors are regulated and may lead to the identification of new therapies for the treatment of a variety of diseases of the brain, including depression and drug addiction. Svenningsson, P., Chergui, K., Rachleff, I., Flajolet, M., Zhang, X, El Yacoubi, M., Vaugeois, J-M., Nomikos, G.G., and Greengard, P. Alterations in 5-HT1B Receptor Function by p11 in Depression-Like States. Science, 311, pp. 77-80, 2006.

Opiate Reward is Mediated by the Neurotransmitter Norephinephrine

Opiate reward is the pleasure one experiences upon taking an opiate such as morphine. Over thirty years ago, the neurotransmitters norepinephrine (NE) and dopamine (DA) were linked to opiate reward, and the role of DA in this process has been well characterized. However, a conclusive role for NE in this process has not been established. Dr. Palmiter and co-workers investigated opiate reward in mice lacking NE. NE is normally synthesized from DA by dopamine beta-hydroxylase (DBH), so mice with a genetic disruption of the DBH gene lack NE. DBH mutant animals were tested using a conditioned place preference paradigm, in which the animals were treated with morphine in a specific environmental milieu. If morphine treatment is perceived by the animals as pleasurable, the animals will prefer the environmental conditions that coincide with treatment. If it is not perceived as pleasurable the animals will be indifferent to these conditions, and if the treatment is perceived as unpleasant, the animals will avoid these environmental conditions. Normal mice prefer the environment associated with morphine treatment, but DBH mutant animals show no such preference, suggesting that they do not experience

opiate reward. Dr. Palmiter then restored NE to the DBH mutant animals by treatment with a compound called DOPS, which can be converted to NE without the need for the DBH enzyme. DBH mutant mice treated with DOPS now prefer the environment associated with the morphine treatment, indicating that NE is required for the animals to experience opiate reward. Dr. Palmiter then investigated where NE is required in the brain to mediate opiate reward, and found that restoration of norepinephrine signaling only to a specific region of the brain called the Nucleus Tractus Solitarus was sufficient to allow opiate reward. This work conclusively demonstrates a crucial role for the neurotransmitter norepinephrine in mediating opiate reward, and will lead to a deeper understanding of the molecules and brain regions that mediate behavioral responses to drug taking. Olson, V.G., Heusner, C.L., Bland, R.J., During, M.J., Weinshenker, D., and Palmiter, R.D. Role of Noradrenergic Signaling by the Nucleus Tractus Solitarius in Mediating Opiate Reward. Science, 311, pp. 1017-1020, 2006.

Suppression of Dynorphin by DeltaFosB Results in Opioid Addiction

Chronic exposure to drugs of abuse like cocaine induces upregulation of the transcription factor deltaFosB, which acts as a molecular switch for addiction in the nucleus accumbens (NAc). Whether morphine addiction shares the same molecular mechanism as cocaine, and if it does, how this mechanism functions in morphine addiction is not clear. Nestler and colleagues at the University of Texas Southwestern Medical Center tackled this question in a NIDA funded research project. Using a bitransgenic mouse line that inducibly overexpresses deltaFosB in the NAc and dorsal striatum and using viral-mediated gene transfer to specifically express it only in the NAc, Nestler demonstrated that deltaFosB is necessary and sufficient to mediate all aspects of the addictive effect of opioids. Thus, deltaFosB overexpression in the NAc increased the sensitivity of the mice to the rewarding effects of morphine and led to exacerbated physical dependence, but also reduced their sensitivity to the analgesic effects of morphine and led to faster development of analgesic tolerance. Furthermore, Dr. Nestler and his colleagues report that the endogenous opioid peptide dynorphin seemed to be at least one of the main targets through which deltaFosB produced this behavioral phenotype: first, the action of deltaFosB is dependent on its expression in dynorphin expressing neurons in NAc, but not in other neurons that do not express dynorphin. Second, the induction of deltaFosB within dynorphin neurons in the NAc alone, in response to the chronic opioid administration, is sufficient to cause many of the various types of behavioral plasticity altered by the abuse. Third, deltaFosB has been shown to bind to the dynorphin gene promoter in cultured neurons, and the researchers suggest a direct action of deltaFosB on suppressing dynorphin expression, which results in opioid addiction. Together, these experiments demonstrated that deltaFosB in the NAc, at least partly through the repression of dynorphin expression, mediates several major features of opiate addiction. Zachariou, V., Bolanos, C.A., Selley, D.E., Theobald, D., Cassidy, M.P., Kelz, M.B., Shaw-Lutchman, T., Berton, O., Sim-Selley, L.J., Dileone, R.J., Kumar, A. and Nestler, E.J. An Essential Role for _FosB in the Nucleus Accumbens in Morphine Action. Nature Neuroscience, 9, pp. 205-211, 2006.

Cocaine-induced Dendritic Spine Formation in D1 and D2 Dopamine Receptor-Containing Medium Spiny Neurons in Nucleus Accumbens

Drug addiction is a chronic relapsing disease suggesting that drugs of abuse produce long lasting changes in the brain. The mechanism by which drugs of abuse produce these long lasting changes in the brain even after the drug is no longer present is not clear. In this study, Dr. Lee and colleagues examined

nerve cells in a region of the brain called the nucleus accumbens (NAcc) either 2 days or 30 days after the last exposure to cocaine, which had been administered for 4 weeks prior to removal. They were specifically looking at nerve cells, medium spiny neurons (MSN) that contain several projections called spines. There are two primary classes of MSNs in the NAcc: the dopamine receptor D1-containing cells and the D2 receptor-containing cells. In their analysis, about 50% of the MSNs contain only D1 receptors, 35-40% contain only D2 receptors and 10-15% contain both types of receptors. Using innovative analytical techniques, they found that while there was an increase in the number of spines in both D1 and D2-containing cells two days after the last administration of cocaine, only the increase seen in D1-containing cells persisted to day 30, although at a reduced level than was seen at two days. Another change that they saw in the D1-containing cells that coincided with the persistence of spines was the induction of another important molecule that has been implicated in longer-term effects of cocaine, deltaFosB. Not only did they see an induction, but deltaFosB persisted to a greater extent in the D1-containing cells after 30 days than it did in the D2-containing cells, much like the pattern they see with the spine persistence. Further study is needed to determine whether deltaFos B directly regulates cell morphological changes. Lee, K-W., Kim, Y., Kim, A.M., Helmin, K., Nairn, A.C. and Greengard, P. Cocaine-induced Dendritic Spine Formation in D1 and D2 Dopamine Receptor-containing Medium Spiny Neurons in Nucleus Accumbens. Proceedings of the National Academy of Sciences of the United States of America, 103, pp. 3399-3404, 2006.

Mechanism of Synaptic Plasticity Modulated by Postsynaptic Events

Long term synaptic modulation requires presynaptic structural changes induced by postsynaptic activity. The molecular mechanisms by which postsynaptic modifications lead to precisely coordinated changes in presynaptic structure and function are unknown. To address this issue, NIDA funded researchers at Stanford University, led by Craig Garner and Robert Malenka, examined the presynaptic consequences of postsynaptic expression of members of the membrane-associated guanylate kinase family of synaptic scaffolding proteins, by postsynaptic expression of synapse-associated protein 97 (SAP97). Previous studies suggested that SAP97 can influence synaptic AMPA receptors when overexpressed postsynaptically in culture, and perhaps also affect presynaptic function. In the present study, the investigators engineered overexpression of SAP97 in vivo and probed the cellular events that alter presynaptic structure. They found that compared with other SAP family members, namely SAP90/PSD-95 and SAP102, postsynaptic expression of SAP97 has the most potent presynaptic effect, dramatically increasing levels of the active zone protein Bassoon and the vesicle proteins synapsin and synaptophysin. Recruitment of these presynaptic proteins dramatically affects presynaptic function, as evidenced by a marked increase in N-(3-triethylammoniumpropyl)-4-(6-(4-(diethylamino)phenyl) hexatrienyl) pyridinium dibromide (FM4-64) dye uptake. Furthermore, increasing postsynaptic SAP97 also causes a selective increase of several binding partners including the AMPAR subunit GluR1 and the scaffold proteins ProSAP2, Shank1a, and SPAR/SPAL (spine-associated RapGAP/SPA-1-like protein). In addition, they report that the transsynaptic effects of postsynaptic SAP97 require multiple cell adhesion and signaling molecules including cadherins, integrins, and EphB receptor/ephrinB. These results suggest that SAP97 plays a central role in coordinating the growth and functional organization of the presynaptic and postsynaptic components of synapses during both development and synaptic plasticity. Regalado, M.P., Terry-Lorenzo, R.T., Waites, C.L., Garner, C.C. and Malenka, R.C. Transsynaptic Signaling by Postsynaptic Synapse-Associated Protein 97. The Journal of Neuroscience, 26, pp. 2343-2357, 2006.

Cell Signaling Events in Neural Circuit Associated with Appetite in the Brain

Hedonic or motivated aspects of feeding are mostly mediated by perifornical lateral hypothalamic (LH) neurons. Endogenous cannabinoids and anorexigenic hormone leptin have opposing effects on these neurons, with opposite effects on feeding behavior; but the cellular mechanisms of these endogenous food intake modulators are not known. Using electrophysiology on acute brain slice preparation and aided by single cell RT-PCR and immunohistochemistry, NIDA funded researchers at Columbia University led by Lorna Role report that depolarization of LH neurons elicits a cannabinoid receptor CB1-mediated suppression of inhibition in local circuits thought to be involved in appetite and "natural reward." The depolarization-induced decrease in inhibitory tone to LH neurons is blocked by leptin. Leptin inhibits voltage-gated calcium channels in LH neurons via the activation of janus kinase 2 (JAK2) and of mitogen activated protein kinase (MAPK). Importantly, these researchers further suggest that these signaling cascades activated by leptin suppresses motivated feeding through the reduction of endogenous cannabinoids in the brain. The present study provides mechanistic evidence on how the integration of endocannabinoid and leptin signaling regulates the excitability of lateral hypothalamic neurons in appetite-related circuits. Jo, Y-H., Chen, Y-J.J., Chua, S.C. Jr., Talmage, D.A. and Role, L.W. Integration of Endocannabinoid and Leptin Signaling in an Appetite-Related Neural Circuit. Neuron, 48, pp. 1055-1066, 2005.

Allelic Expression Imbalance of Human mu Opioid Receptor (OPRM1) Caused by Variant A118G

The mu opioid receptor is the primary target for opioid drugs and plays a key role in addiction and pain perception. The single nucleotide polymorphism A118G, leads to an Asn40Asp substitution with uncertain functions, and an allele frequency range of 10-32%. Wolfgang Sadee and his colleagues have measured allele specific mRNA expression of OPRM1 in human autopsy brain tissues, using A118G as a marker. In 8 heterozygous samples measured, the A118 mRNA allele was 1.5-2.5 fold more abundant than the G118 allele. Inserting C118 or T118 into OPRM1 failed to affect mRNA expression compared with the wild-type A118. These results demonstrate that substitution with G118 alone, in the absence of any other regulatory regions, causes a significant change in mRNA expression. No differences in mRNA stability between the two variants were detected, indicating partial defects in transcription or mRNA maturation. Western blotting also demonstrated a much lower protein yield for the G118, indicating that the variant appears to affect translation or post-translational processing and turnover of OPRM1 protein. This study indicates that the OPRM1-G118 is a functional variant with deleterious effects on both mRNA and protein yield. Clarifying the functional relevance of polymorphisms associated with susceptibility to a complex disorder such as drug addiction and pain provides a foundation for clinical association studies. Zhang, Y., Wang, D., Johnson, A., Papp, A. and Sadee, W. Allelic Expression Imbalance of Human mu Opioid Receptor (OPRM1) Caused by Variant A118G. Journal of Biological Chemistry, 280, pp. 32618-32624, 2005.

Cocaine-Seeking Behavior and AMPA Receptor Trafficking in the Nucleus Accumbens

Work in Yavin Shaham's lab at the NIDA IRP demonstrated that cocaine-seeking behavior increases progressively over the first three months of withdrawal from cocaine self-administration in rats, a phenomenon termed "incubation of cocaine craving." NIDA researcher Marina Wolf and her colleagues sought to determine if increased cell surface expression of

glutamate AMPA receptors in the nucleus accumbens (NAc), leading to increased excitatory drive to NAc neurons, might underlie the behavioral changes observed during the incubation of cocaine craving. AMPA receptor subunits on the cell surface were distinguished from those inside the cell, where they are not active, using a membrane-impermeant cross-linking agent that selectively modifies surface proteins. Rats were trained to self-administer cocaine (6 hrs/day/10 days) and tested for drug-seeking behavior on day 1 or 45 of withdrawal. Rats tested on withdrawal day 45 responded significantly more than those tested on withdrawal day 1. Other rats were treated identically for protein cross-linking studies showed a robust increase (~500%) in total GluR1 protein levels (surface + intracellular) on day 45 compared with day 1, but no change in the surface/intracellular ratio. This indicates that NAc neurons are producing more GluR1 and transporting the same proportion of GluR1 to the surface, resulting in an increase in absolute levels of GluR1 on the surface. This would be expected to enhance the responsiveness of NAc neurons to glutamate inputs from cortical and limbic regions that trigger drug-seeking behavior. Interestingly, the same cross-linking assay showed that behavioral sensitization to cocaine is accompanied by different changes that also result in a net increase in AMPA receptor surface expression. Boudreau, A.C. and Wolf, M.E. Behavioral Sensitization to Cocaine Is Associated with Increased AMPA Receptor Surface Expression in the Nucleus Accumbens. Journal of Neuroscience, 25, pp. 9144-9151, 2005. A goal of future studies is to determine if AMPA receptor trafficking represents a "link" between locomotor sensitization and incubation of cocaine craving. Conrad, K.L., Marinelli, M. and Wolf, M.E. Cocaine-Seeking Behavior and AMPA Receptor Trafficking in the Nucleus Accumbens. Society for Neuroscience Abstract, Program No. 1030.1, 2005.

Delta Opioid Receptor Ligands Modulate Anxiety-Like Behaviors in the Rat

Dr. Unterwald of Temple University School of Medicine examined the role of the delta opioid receptor in regulating anxiety-like behavior in male Sprague-Dawley rats. Using an elevated plus maze, the effects of the selective delta opioid receptor antagonist naltrindole (1 or 5 mg/kg) and agonist SNC80 (1, 5 or 20 mg/kg) on anxiety-like behavior were measured. Anxiety was also measured following administration of diazepam (3 mg/kg) and amphetamine (1 mg/kg) and compared to the effects of SNC80. Locomotor activity following administration of naltrindole, SNC80, diazepam, and amphetamine was measured. Finally, the defensive burying paradigm was used to confirm the findings from the elevated plus maze. Results demonstrated that SNC80 produced dose-dependent anxiolytic effects similar to that of the classical antianxiety agent, diazepam. Administration of naltrindole caused anxiogenic behavior in rats further supporting the involvement of the delta opioid receptor system in regulating anxiety. Naltrindole also blocked the anxiolytic effects of SNC80. Amphetamine had no effect on anxiety-like behavior. SNC80 induced hyperactivity similar to amphetamine at the doses tested, while naltrindole and diazepam did not significantly affect locomotor activity. Although SNC80 can increase locomotor activity, control experiments reported herein indicate that hyperlocomotion is not sufficient to produce an anxiolytic response on the elevated plus maze. Together with the results from the defensive burying paradigm, this suggests that the effects of SNC80 on reducing anxiety are independent of its effects on locomotion. Collectively these data show that the delta opioid receptor system can regulate anxiety-like behavior in an anxiolytic (agonist) and anxiogenic (antagonist) manner. Perrine, S.A., Hoshaw, B.A. and Unterwald, E.M. Delta Opioid Receptor Ligands Modulate Anxiety-like Behaviors in the Rat. British Journal of Pharmacology, pp. 1-9, 2006 [Epub ahead of print].

Endocannabinoids Act on Inhibitory Interneurons and Modulate

an Intrinsic Population Rhythm of Hippocampal Neurons

Assessment of single neuronal behavior reveals that endocannabinoids (eCB) fine-tune the dynamic status of synaptic activity, strength and plasticity of hippocampal neurons. Upon afferent activation, the principal neuron discharges an action potential. By releasing eCBs, it sends a retrograde feedback signal to inhibitory interneurons, which in turn affects the discharge pattern and intensity of the principal neurons they innervate. This phenomenon, known as depolarization suppression of inhibition (DSI), is observed wherever the eCBs affect the theta rhythm wave, an intrinsic neuronal population rhythm of hippocampal neurons. Theta rhythms are behaviorally relevant electrical oscillations in the mammalian brain, particularly in the hippocampus, and metabotropic glutamatergic and/or cholinergic inputs often drive these oscillations via the activity of inhibitory postsynaptic potentials (IPSPs). Dr. Alger' s recent work shows that perisomatic-targeting interneurons, whose output is inhibited by endocannabinoids, are the likely source of theta IPSPs. Under conditions that block all glutamate receptors, theta rhythm IPSPs induced by muscarinic acetylcholine receptors in hippocampal CA1 region can be transiently interrupted by action potential-induced, retrograde endocannabinoid release. Simultaneous recordings from pyramidal cell pairs reveal synchronous theta-frequency IPSPs in neighboring pyramidal cells, suggesting that these IPSPs may help entrain or modulate small groups of pyramidal cells. With the capability of rapidly switched-on by afferent inputs and switched-off by the eCB-mediated retrograde feedback DSI, the intrinsic neuronal network may constitute the fundamental mechanism for temporal coding and decoding in the hippocampus. Disruption of theta rhythm might be one mechanism by which cannabinoid drugs cause cognitive dysfunction. Reich, C.G., Karson, M.A., Karnup, S.V., Jones, L.M. and Alger, B.E. Regulation of IPSP Theta Rhythm by Muscarinic Receptors and Endocannabinoids in Hippocampus. Journal of Neurophysiology, 94, pp. 4290-4299, 2005.

Estradiol Selectively Reduces the Stimulated Release of GABA in Rat Striatum

NIDA-supported research has shown that females (rats and humans) appear to be more sensitive to the effects of psychostimulants than males. Research conducted in Dr. Jill Becker' s laboratory suggests that the naturally occurring higher concentrations of estrogen in females relative to males may be related to this observation. Becker and her colleagues ovariectomized female rats, replaced the estradiol in some of them, and monitored the efflux of GABA, taurine, and glutamate in the striatum after local application of 75 mM K+. They found that GABA and taurine were both enhanced in the striatum after the K+ challenge, but that the increase in GABA was much less in rats that also were given estradiol; glutamate did not change after challenge in either group. As GABA is the predominant inhibitory transmitter in the brain, this finding may be important for our understanding of how estradiol can alter neurotransmission and how that may be related to the differential effects of stimulants on males and females. Hu, M., Watson, C.J., Kennedy, R.T. and Becker, J.B. Estradiol Attenuates the K+ -induced Increase in Extracellular GABA in Rat Striatum. Synapse, 59, pp. 122-124, 2006.

Estrogen Neuroprotection from HIV Protein-Induced Oxidative Stress

Estrogen replacement therapy in older women is associated with improvement of symptoms of dementia and Parkinson' s Disease, so it is believed that estradiol may have neuroprotective qualities in some circumstances. Although the mechanisms of such neuroprotection are unknown, it is possible that estradiol acts as a free-radical scavenger to reduce oxidative stress. Some HIV

infected patients experience similar neurological problems, likely involving glutamate and/or oxidative stress-mediated neurotoxicity that may be caused in part by extracellular HIV proteins gp120 and Tat. This study used human neuronal cells grown in culture to test whether estrogen could reverse damage by tat and gp120, as well as the free-radical generator SIN-1. Both tat and gp120, alone and combined, increased oxidative stress as measured by a fluorescent indicator. This increase was greatly diminished in the presence of estradiol but not progesterone or estradiol plus a selective antagonist. When exposed to tat or gp120, synaptosomes made from rat striatal tissue showed reduced dopamine uptake, and this effect was blocked by preincubation with estradiol. Reduced dopamine transporter activity in the striatum is a component of HIV-associated neuropathology; so together these findings suggest that estradiol may be a useful strategy for neuroprotection in the context of HIV-associated neurological disease. Wallace, D.R., Dodson, S., Nath, A. and Booze, R.M. Estrogen Attenuates gp120- and Tat(1-72)-Induced Oxidative Stress and Prevents Loss of Dopamine Transporter Function. Synapse, 59, pp. 51-60, 2006.

Opioid-Induced Tolerance and Dependence In Mice Is Modulated by the Distance Between Pharmacophores in a Bivalent Ligand Series

Given the mounting evidence for involvement of opioid receptors in the tolerance and physical dependence of μ opioid receptor agonists, Portoghese and his collaborators investigated the possible physical interaction between μ and opioid receptors by using bivalent ligands. Based on reports of suppression of antinociceptive tolerance by the antagonist naltrindole (NTI), bivalent ligands (μ- agonist-antagonist series, MDAN series) that contain different length spacers, and pharmacophores derived from NTI and the μ agonist oxymorphone, have been synthesized and evaluated. Chronic i.c.v. studies revealed that MDAN ligands whose spacer was 16 atoms or longer produced less dependence than either morphine or μ monovalent control (MA-19). On the other hand, both physical dependence and tolerance were suppressed at MDAN spacer lengths of 19 atoms or greater. When the spacer length was longer than 22 (MDAN-19 to -21), neither tolerance nor dependence were observed, which is in harmony with the idea that these bivalent ligands bridge neighboring μ and opioid receptors effectively. The mechanism by which the bridging of the μ- heterodimer suppress tolerance and dependence is not understood. A possible explanation is that the μ- heterodimer is the fundamental signaling unit that mediates tolerance and dependence through specific signal transducer(s) that recognize and couple to the heterodimer but not μ receptor monomers/homomers. The finding that receptor knockout mice do not become tolerant is consistent with this concept. Given these results, it appears reasonable that bridging μ- heterodimers by MDAN ligands would negatively modulate such putative transducers, thus reducing tolerance and dependence. These data also suggest that physical interaction between the μ and opioid receptors modulates μ-mediated tolerance and dependence and MDAN-21 offers an approach for the development of potent, bioavailable analgesics devoid of these side effects. Daniels, D.J., Lenand, N.R., Etienne, C.L., Law, P-Y., Roenig, S.C. and Portoghese, P.S. Opioid-induced Tolerance and Dependence in Mice is Modulated by the Distance Between Pharmacophores in a Bivalent Ligand Series. Proceedings of the National Academy of Sciences of the United States of America, 102, pp. 19208-19213, 2005.

Neurokinin 1 Receptor (NK1R) Internalization is Inhibited Both in vivo and in vitro by mu- and delta-Opioid Agonists

Opioid mu- and delta- receptors are thought to inhibit neurotransmitter release in primary afferents, which results in analgesia. NIDA grantees Drs. Tony Yaksh

and Juan Carlos Marvizon and their colleagues have examined the effect of opiates on NK1R internalization in spinal cord slices and in vivo. In slices, pain fiber stimulation induced NK1R internalization that was abolished by the mu agonist [D-Ala(2), N-Me-Phe(4), Gly-ol(5)]-enkephalin (DAMGO) and decreased by the delta agonist [D-Phe(2,5)]-enkephalin (DPDPE). In vivo, hind paw compression-induced NK1R internalization was significantly reduced by morphine, DAMGO, and DPDPE, but not by a kappa-opioid agonist. All effects were reversed by naloxone. These results demonstrate that mu- and delta-opioid agonists produce clear NK1R internalization that is associated with their analgesic properties. Kondo, I., Marvizon, J.C.G., Song, B., Salgado, F., Codeluppi, S., Hua, X-Y. and Yaksh, T.L. Inhibition by Spinal µ- and _-Opioid Agonists of Afferent-Evoked Substance P Release. Journal of Neuroscience, 25, pp. 3651-3660, 2005.

Salvinicins A and B, New Neoclerodane Diterpenes from Salvia Divinorum

Salvia divinorum is used in traditional spiritual practices of the Mazatecs to produce "mystical" or hallucinogenic experiences. The active ingredients of this plant are Salvinorin A as well as Salvinorin B. A dose of 200- 250 ug, when smoked, produces profound hallucinations lasting up to 1 hour. Salvia divinorum and one of its constituents, Salvinorin A, are gaining popularity as recreational drugs. Young adults and adolescents smoke the leaves and leaf extracts of the plant to induce powerful hallucinations. Currently this plant and its active constituents are not regulated in the United States and are easily available through the Internet. Given its potential for abuse, as well as its unique pharmacological properties as a potent selective kappa opioid receptor agonist, the authors have studied the chemistry and pharmacology associated with constituents of Salvia divinorum. Previous phytochemical investigations of S. divinorum resulted in the identification of several neoclerodane diterpenes present in the leaves. In a recently published paper, NIDA researchers report the identification of two new neoclerodane diterpenes with opioid receptor activity. Salvinicins A and B are unique neoclerodanes that possess a 3,4-dihydroxy-2,5-dimethoxytetrahydrofuran ring. The absolute stereochemistry of these molecules has been assigned through X-ray crystallographic analysis. Harding, W.W., Tidgewell, K., Schmidt, M., Shah, K., Dersch, C.M., Snyder, J., Parrish, D. Deschamps, J.R., Rothman, R.B., and Prisinzano, T.E. Salvinicins A and B, New Neoclerodane Diterpenes from Salvia Divinorum. Organic Letters, 7, pp. 3017-3020, 2005.

FAAH Inhibition

There is considerable interest in understanding the "background" or tonal level of endocannabinoids and their activity in the human brain, in terms of their production on demand, followed by their retrograde activation of the presynaptic cannabinoid receptor CB1 which triggers cannabinoid signaling processes, and their subsequent inactivation by metabolic processes. Levels of one particular endocannabinoid, anandamide, are regulated by the mammalian serine enzyme known as fatty acid amide hydrolase (FAAH), which has been cloned, characterized by crystallography and molecular modeling studies, and its distribution mapped in the human brain. Pharmacological inhibitors of this enzyme can increase the available concentration of anandamide, offering a potential for therapeutic targets of pain management and sleep disorders. Consequently, there are academic and commercial efforts currently directed at designing various chemical classes of inhibitors. One such inhibitor is URB597, developed with NIDA funding by Dr. Daniele Piomelli and Dr. Giorgio Tarzia. This compound inhibits the enzyme with nM affinity; it does not bind the CB1 receptor, does not produce typical THC-like behavioral effects in animals, but does produce anxiolytic effects in rats. There are two recent findings reported by these investigators and their collaborators that contribute to the

understanding of URB597 pharmacology. The first is that single intravenous injections of URB597 into rat midbrain produce a significant increase in anandamide concentration after two hours, along with an increase in both serotonin and noradrenergic neuron firing. When URB597 was given intraperitoneally to rodents, it produced behavioral results (decreases in immobility and forced swimming), also produced by the antidepressant desipramine. URB597 did not produce conditioned place preference as did delta-9-THC, and did not generalize to the cannabinoid agonist WIN 55,212. The above neuronal and behavioral effects were blocked by the CB1 antagonist SR141716. URB597 was also shown to be inactive at a battery of receptors, including serotonin, adrenergic, dopaminergic, cannabinoid, nicotinic, and muscarinic, and inactive as well at the SERT, NET, and DAT transporters. Secondly, URB597 has been shown to have a role in reducing mechanical and thermal allodynia, using Freund' s adjuvant in the rat paw to induce an inflammatory pain response. It did not reduce the pain withdrawal threshold fourteen days following sciatic nerve ligation, used as a neuropathic pain model. The response shown in the two inflammatory pain models was dose-dependent, and blocked by co-administration of the cannabinoid antagonists AM 251 and SR144528. Overall, these results suggest an association between FAAH inhibitors and inflammatory pain, as well as with anxiety/mood modulation in animal models. Gobbi, G., Bambico, F.R., Mangieri, R., Bortolato, M., Campolongo, P., Solinas, M., Cassano, T., Morgese, M.G., Debonnel, G., Duranti, A., Tontini, A., Tarzia, G., Mor, M., Trezza, V., Goldberg, S.R., and Cuomo, V. Antidepressant-like Activity and Modulation of Brain Monoaminergic Transmission by Blockade of Anandamide Hydrolysis. Proceedings of the National Academy of Sciences of the United States of America, 102, pp. 18620-18625, 2005; Jayamanne, A., Greenwood, R., Mitchell, V.A., Aslan, S. Piomelli, D., and Vaughan, C.W. Actions of the FAAH Inhibitor URB597 in Neuropathic and Inflammatory Chronic Pain Models. British Journal of Pharmacology, 147, pp. 281-288, 2006.

Director's Report to the National Advisory Council on Drug Abuse - May, 2006

Research Findings - Basic Behavioral Research

Enhanced Neuronal Activity in the Nucleus Accumbens Accompanies Relapse to Cocaine Self-Administration

When rats are trained to respond for i.v. drug administration, and subsequently withdrawn, they resume drug self-administration ("relapse") when returned to the environment where they previously received the drug. Researchers have identified a number of cellular changes that may contribute to relapse after a period of abstinence. For example, changes in the nucleus accumbens (NAc) are seen in gene expression, GABA concentration, and neuronal structure. Electrophysiological recording from the NAc of rats self-administering i.v. cocaine has revealed patterns of firing that are associated with anticipation of drug reward, and with response-reinforcement associations. Four well-defined types of firing patterns occur within seconds of drug reinforcement: Some cells increase their activity preceding the reinforced response and some increase or decrease immediately following the response. A fourth type exhibits a dual peak increase. Two other patterns have been identified that are long-duration cyclic discharges that span the inter-infusion interval of self-administration. Dr. Regina Carelli and her colleagues sought to determine whether these firing patterns show neuroadaptations that might be involved in relapse to drug seeking. She trained animals to self-administer cocaine and identified the six neuronal patterns described above on the basis of cell firing on the last self-administration session. After a one-month break, animals were tested in a one-hour self-administration session. Recordings from the NAc revealed significant increases in the number, percentage and strength of short-duration patterned discharges, and also in the long-term cyclic alterations associated with cocaine. The findings are significant in that the short discharges preceding drug administration are believed to encode cocaine-seeking behaviors, and the long-term firing patterns have been hypothesized to convert declining drug levels into increased motivation for more drug. The observation that these electrophysiological correlates are enhanced and associated with increased drug seeking during relapse suggests that these signals may be the output pathway for cellular, molecular and genetic changes seen during psychostimulant withdrawal. Hollander, J.A. and Carelli, R.M. Abstinence from Cocaine Self-administration Heightens Neural Encoding of Goal-directed Behaviors in the Accumbens. Neuropsychopharmacology, 30, pp. 1464-1474, 2005.

An Animal Model of Disruption of Maternal Behavior and Intergenerational

Pregnant women who use cocaine are more likely to abuse or neglect their children and to exhibit deficits in bonding and interacting with their infants. In addition, numerous studies have shown an intergenerational transfer of

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childhood maltreatment: daughters with a history of abuse or neglect are more likely to exhibit these same behaviors in rearing their own offspring. Dr. Josephine Johns and her colleagues have developed a rat model to investigate the causal factors involved in disruption of maternal behavior and intergenerational transfer. During gestation, they treated rat dams with cocaine, or with saline, or merely handled them as a control condition. Then, after the litters were culled to form comparable sized groups, the dams reared either their natural or cross-fostered litters such that some pups that were not themselves exposed to cocaine were reared by cocaine exposed dams and vice versa. Measures of maternal behavior were then collected on postpartum days 1, 5, 10, and 15. Subsequently, first generation daughters from these various litters were bred with no cocaine exposure, and their maternal behavior towards their natural litters was also studied. The authors found: 1) Dams treated with cocaine, regardless of whether they reared exposed or unexposed pups, showed disruption of the onset of maternal behavior, with a diminishing effect over the postpartum period; 2) Pups prenatally exposed to cocaine were treated differently by all dams, regardless of their own treatment condition. Overall, the dams had a tendency to spend less time caring for these pups, consistent with other animal studies suggesting that drug-exposed rat pups have attributes that may make them vulnerable to neglect; 3) Intergenerational deficits in maternal behavior were apparent in the first generation daughters. This effect largely resulted from prenatal exposure to cocaine, but it was also influenced by the treatment of the dams that had reared them. Johns, J.M., Elliott, D.L., Hofler, V.E., Joyner, P.W., McMurray, M.S., Jarrett, T.M., Haslup, A.M., Middleton, C.L., Elliott, J.C. and Walker, C.H. Cocaine Treatment and Prenatal Environment Interact to Disrupt Intergenerational Maternal Behavior in Rats. Behavioral Neuroscience, 119, pp. 1605-1618, 2005.

Personality Factors Influence the Effects of Acute Amphetamine

Individual differences in the drug-induced positive mood and other subjective effects of d-amphetamine have been linked to personality traits related to sensation seeking. The present study by Harriet de Wit and colleagues extended these associations to separate personality traits of reward sensitivity, physical fearlessness, and impulsivity. A total of 128 healthy volunteers were given oral doses of d-amphetamine (10 and 20 mg) or placebo in counterbalanced order. Their responses to the drug were measured using the Profile of Mood States, Addiction Research Center Inventory, and Drug Effects Questionnaire. Participants also completed the Multidimensional Personality Questionnaire Brief Form to assess personality traits related to reward sensitivity, physical fear (or harm avoidance), and impulsivity. De Wit reports three main findings from this study. First, compared to individuals with high trait physical fear, individuals with low trait physical fear reported greater positive activational responses to low-dose d-amphetamine, showing greater energy, intellectual activation, euphoria, vigor, arousal, elation, friendliness, positive mood, and less fatigue and sedation. Second, individuals with high trait reward sensitivity had marginally greater positive responses as well as drug liking and drug wanting after the 20 mg dose. Third, individuals with high mental imagery/_flexibility had greater positive drug responses to both doses, and these effects were more significant at the lower dose. These findings indicate that the subjective effects of amphetamine vary as a function of specific personality traits in healthy volunteers. White, T.L., Lott, D.C. and de Wit, H. Personality and the Subjective Effects of Acute Amphetamine in Healthy Volunteers. Neuropsychopharmacology, 31, pp. 1064-1074, May 2006.

Psychological Processes Underlying Risky Decisions

Poor self- control or disinhibition is a characteristic feature of young adults with

drug addiction. NIDA researcher Julie Stout and her colleagues recently applied mathematical decision models with a simulated gambling task (SGT) to investigate the processes underlying decision making in 66 drug abusers and 58 control participants. The mathematical model enabled these investigators to separately examine the effects of wins and losses on the SGT. The investigators also assessed impulsivity, social deviance and harm avoidance. The results of the study showed that drug abusers differed from controls in SGT performance and in the processes underlying performance. The results showed also that individual differences, such as personality and drug abuse characteristics, are related to SGT performance. For the men, for example, drug group participants performed more poorly than did controls. Moreover, male drug abusers were more influenced by rewards than by punishments, consistent with other studies that have found drug abusers are hypersensitive to rewards and relatively insensitive to future consequences. In contrast to the findings from men, the performance of women was not straightforward. Control women performed at chance level, which is unusual for a control group on this task. By contrast, performance of the drug-abusing women fell below that of control men, but was slightly better than that of the drug-abusing men. Overall the findings suggest a difference between men and women in their approach to the SGT. Thus, generalizations from studies that have focused on male participants may not be germane to understanding cognitive aspects of drug abuse in women. Finally, individual differences in the decision processes used in performing the SGT task are related not only to drug abuse but also to personality factors. Stout, J.C., Rock, S.L., Campbell, M.C., Busemeyer, J.R. and Finn, P.R. Psychological Processes Underlying Risky Decisions in Drug Abusers. Psychology of Addictive Behaviors, 19, pp. 148-157, 2005.

Upregulation of Ionotropic Glutamate Receptor Subunits within Specific Mesocortico-limbic Regions during Chronic Nicotine Self-Administration

Little is known about the effects of chronic nicotine treatment on glutamate receptors. A model of chronic nicotine self-administration (SA) using rats, which emulates important aspects of nicotine intake by humans, has recently been employed by Burt M. Sharp and colleagues to determine whether glutamate receptor subunits are affected when animals freely take nicotine via the i.v. route of administration. In this study, two groups of rats could press a lever in their home cages to receive an infusion of either 0.03 mg/kg nicotine or saline. The investigators reported that animals working for nicotine responded twice as much than those working for saline. After 18 days of this SA procedure, ionotropic glutamate receptor subunit levels were determined in brain regions within the mesocorticolimbic system with Western blot techniques. In prefrontal cortex, the levels of NMDA receptor subunit 2A (NR2A) and NR2B were increased by 67% ($p<0.04$) and 83% ($p<0.027$), respectively, compared to saline controls. In the ventral tegmental area, glutamate receptor subunit 2/3 (GluR2/3) increased by 34% ($p<0.011$). By contrast, nicotine SA did not affect expression of these NMDA receptor subunits in the dorsal striatum or nucleus accumbens. These findings suggest that chronic nicotine SA selectively increases ionotropic glutamate receptor subunits in specific areas of the brain. Wang, F., Chen, H., Steketee, J.D. and Sharp, B.M. Upregulation of Ionotropic Glutamate Receptor Subunits within Specific Mesocorticolimbic Regions during Chronic Nicotine Self-Administration. Neuropsychopharmacology, advance online publication, 1 February 2006.

Potentiation of Cocaine-Primed Reinstatement of Drug Seeking in Female Rats During Estrus

Researchers at the Medical University of South Carolina previously reported that cue-induced reinstatement of cocaine-seeking was greater in male than in female rats at the highest (1.0 mg/kg) and lowest training dose (0.25 mg/kg),

but did not differ at the intermediate training doses (0.4, 0.5, 0.6 mg/kg). At the lowest training dose, females in estrus failed to exhibit reinstatement. (Fuchs, R.A., Evans, A., Mehta, R.H., Case, J. M., and See, R.E. Influence of Sex and Estrous Cyclicity on Conditioned Cue-induced Reinstatement of Cocaine-seeking Behavior in Rats. Psychopharmacology, 179, pp.662-672, 2005.) In a follow up study, the researchers sought to determine whether sex and estrous cycle phase play a role in cocaine-primed reinstatement. Following the acquisition of cocaine self-administration (0.5 mg/kg per infusion) and subsequent extinction, reinstatement was assessed with a priming infusion of i.p. cocaine (0, 5.0 or 10.0 mg/kg) in males and in females tested in either the diestrus, proestrus, or estrus phase. Both males and females exhibited a dose-related increase in reinstatement. The effects, however, were opposite those previously observed under conditioned cue-reinstatement. At the 10.0 mg/kg priming dose, females in estrus were more susceptible to reinstatement than both males and non-estrus females (that did not differ). These sex differences in cocaine-induced versus conditioned cue-induced reinstatement could have implications for sex differences in relapse in humans, suggesting perhaps that the factors leading to relapse may differ in males and females. The neuroendocrine basis for the sex differences observed in the present study is unknown, although prior work has shown that dopamine transmission in the prefrontal cortex is associated with cocaine-primed reinstatement, whereas dopamine transmission in the basolateral amygdala is associated with conditioned cue-reinstatement. Further investigation into sex differences and hormonal factors involved in these brain regions and the relationship to reinstatement is warranted. Kippen, T.E., Fuchs, R.A., Mehta, R.H., Case, J.M., Parker, M.P., Bimonte-Nelson, H.A. and See, R.E. Potentiation of Cocaine-primed Reinstatement of Drug Seeking in Female Rats During Estrus. Psychopharmacology, 182, pp. 245-252, 2005.

Exogenous Estrogen Enhances Reinstatement of Cocaine-Seeking Behavior in Ovariectomized Female Rats

In recent studies from the Medical University of South Carolina, reinstatement of cocaine-seeking behavior was found to be affected by phase of the estrous cycle. In a separate investigation by researchers at the University of Minnesota, the role of estrogen as a modulator of reinstatement of cocaine-seeking behavior has been explicitly examined by comparing reinstatement in ovariectomized female rats administered estrogen replacement (OVX+EST), OVX females administered vehicle (OVX+VEH), and sham-operated females administered vehicle (SH+VEH). In the first of two experiments, in the OVX+EST females EST was administered long-term, during training of self-administration, maintenance, extinction and reinstatement. Results indicated that cocaine-primed reinstatement of responding was greater in the OVX+EST and the SH+VEH females than in the OVX+VEH females, indicating that estrogen mediates cocaine-primed reinstatement of responding. In order to distinguish between estrogen's effects on motivation versus learning, in the second experiment, EST was administered short-term, over 3 days prior to and during the reinstatement phase in OVX+EST. As in the first experiments, greater reinstatement occurred in the OVX+EST females compared to OVX+VEH controls. Comparison of OVX+EST rats in the two experiments (i.e., those receiving long versus short-term EST), however, revealed no differences in reinstatement, suggesting to the authors that estrogen's enhancing effects on reinstatement reflects a direct effect of estrogen's enhancement of motivation for cocaine as opposed to an effect of estrogen on associative learning. Larson, E.B., Roth, M.E., Anker, J.J. and Carroll, M.E. Effect of Short- vs. Long-term Estrogen on Reinstatement of Cocaine-seeking Behavior in Female Rats. Pharmacology, Biochemistry and Behavior, 82, pp. 98-108, 2005.

Nicotine Reward More Influenced by Dose Instructions in Female Than Male Smokers

Studies on smoking behavior have shown that females are more sensitive to the non-pharmacological cues associated with nicotine and less sensitive to nicotine dose compared to males. These findings suggest that different interventions may be effective in smoking cessation strategies for men and women. Ken Perkins and his colleagues investigated the effects of accurate or inaccurate instructions about nicotine content on smoking reward. The investigators report that accurate instructions increased smoking reward more in women than in men. In a follow-up study, these investigators enrolled 60 subjects who smoked more than 10 cigarettes per day for at least one year to assess the influence of dose instruction versus no instruction on male and female smokers. Subjects were abstinent overnight and were randomly assigned to one of four conditions on the study day. Subjects smoked either a normal cigarette with 0.6mg nicotine (nic) or a de-nicotinized brand with <0.05 mg. Half of each group was given instructions and half were not. After two puffs, they completed the Rose Sensory Questionnaire to assess smoking reward, and the Diener and Emmons Mood Scale. Craving was also measured and smoking behavior was quantified by number of puffs and latency to first puff during a 30-min ad lib smoking period. Data analysis revealed the following: For women, nic increased reward only in the presence of dose instructions, whereas for men, nic increased reward only in the absence of dose instructions. Nic increased positive affect overall. Craving decreased from baseline to post-puffs, but this decrease was greater for men than for women. Also, for men but not women, nic decreased craving in the presence, but not the absence, of instructions (opposite from the observation for smoking reward). In the 30-min ad lib smoking period, nic decreased the latency to the first puff for women, only in the presence of dose instruction; this effect was not seen in men. These observations add to a rapidly accumulating body of evidence that women's smoking behavior is guided by a different set of influences from those that are important for men. Perkins, K.A., Doyle, T., Ciccocioppo, M. Conklin, C., Sayette, M. and Caggiula, A. Sex Differences in the Influence of Nicotine Dose Instructions on the Reinforcing and Self-reported Rewarding Effects of Smoking. Psychopharmacology, 184, pp. 600-607, 2006.

Sibutramine Decreases the Appetitive and Consummatory Aspects of Feeding in Baboons

This study examined how sibutramine (0.06-4.0 mg/kg, i.m.), a clinically effective weight-loss medication that increases extracellular serotonin and norepinephrine levels, affected the appetitive and consummatory aspects of feeding of nonhuman primates (baboons) with task-dependent 24-hour access to food. Sibutramine effects were compared to those of dexfenfluramine (2.0-6.0 mg/kg, p.o.), which primarily increases extracellular serotonin levels. The baboons had to complete a two-response sequence to obtain food: responding on one lever during a 30-min appetitive phase was required before animals could start a consumption phase, where responding on a second lever led to food delivery. Responding during the appetitive phase resulted in presentations of food-related light stimuli only. Both males and females ate significantly less when treated with dexfenfluramine, but not sibutramine. Animals also ate fewer meals when treated with dexfenfluramine, but not with sibutramine. Although sibutramine had no effect on number of light presentations and did not alter performance during the appetitive phase, it did reduce consummatory behavior. Sibutramine increased the latency to the first meal of the session in females, but not males. By contrast, dexfenfluramine increased the latency to the first meal of the session, and decreased both appetitive and consummatory behavior in males and females. The presence of sibutramine's gender-specific effects suggests that sex may play a role in determining its effects on feeding behavior. The behavioral mechanism by which sibutramine decreases food intake appears distinct from anorectic drugs such as dexfenfluramine. That is, sibutramine has its anorectic effect by reducing consummatory behavior

(eating), whereas dexfenfluramine reduces both consummatory and appetitive behavior (food seeking). Applied to drug abuse, this behavioral paradigm might be useful for understanding appetitive drug seeking and consummatory drug taking. Foltin, R.W. Effects of Sibutramine on the Appetitive and Consummatory Aspects of Feeding in Non-human Primates. Physiology and Behavior, 87, pp. 280-286, 2006.

Individual Differences in Anxiety and Stress Reactivity May Predict Nicotine Self-Administration

Previous research has revealed that anxiety, stress, and nicotine dependence interact in complex ways. Recently, NIDA grantee Dr. Richard De La Garza examined the relationship between anxiety and nicotine reinforcement by comparing self-administration behavior in Wistar-Kyoto (WK) rats, known to be anxiety prone and hyperresponsive to stress. These animals were compared to Wistar (W) controls in responding for a non-drug reinforcer (sucrose) and for self-administration of nicotine. Analysis revealed that W rats made significantly more responses and worked harder to obtain sucrose than did WK animals. In addition, over the course of 24 days of nicotine self-administration,W rats showed an increase in drug intake that significantly exceeded the stable intake of WK rats by Day 14. Taken together, these findings suggest a reduced motivation by WK rats for both non-drug and drug reinforcers. Moreover, further analysis showed that both groups had similar response rates for sucrose when low levels of effort were required, and that group differences were not seen until the response requirement increased to more than 23 lever presses for each sucrose delivery. To account for differences in responding for nicotine, the authors suggest that lower levels of responding for nicotine by WK rats might be attributable to drug-induced activation of endogenous stress systems, which would serve to reduce the reinforcing value of nicotine. De La Garza, R. Wistar Kyoto Rats Exhibit Reduced Sucrose Pellet Reinforcement Behavior and Intravenous Nicotine Self-administration. Pharmacology, Biochemistry and Behavior, 82, pp. 330-337, 2005.

Cocaine Impairs Social Communication in Baboons

Drugs of abuse have been observed to disrupt social behavior among non-human primates. Drugs like cocaine might produce these effects by altering the way in which nonhuman primates communicate. Recently, NIDA grantees Robert Hienz and Elise Weerts examined cocaine's effects on discriminations of socially important vocal communication - grunts - in baboons. Grunts are natural calls that are associated with differing motivational and/or social contexts, such as affiliation, dominance or aggression, and they also serve to identify the caller. Acoustically, they resemble human vowel sounds. Previously, these investigators reported that cocaine disrupted the baboons' perception of human vowel sounds. In the recent study they extended their research by testing digitized versions of baboon grunts that were recorded in the natural environment. Animals were trained to release a lever when they heard a different, or "target" grunt, inserted in a consecutive sequence of standard grunts. Cocaine was administered intramuscularly at doses between 0.032 and 0.56 mg/kg. Each dose was tested twice, with lower doses examined first to avoid the development of psychostimulant sensitization. Prior to drug administration, the four male baboons discriminated target vocalizations at the 80% correct level. Following cocaine, discrimination was significantly impaired, but interestingly, this effect was much greater than had previously been seen with human vowel sounds. Although these auditory stimuli are acoustically similar, the authors suggest that grunts are more affected because they are biologically and socially significant for the species. The detection of species-specific vocalizations may represent a more specialized perceptual process than the general process invoked by human vowel sounds. If similar drug effects occur with human cocaine use, it is possible that subtle social communications

may be impaired and thus contribute to the addictive process. Hienz, R.D. and Weerts, E.M. Cocaine's Effects on the Perception of Socially Significant Vocalizations in Baboons. Pharmacology, Biochemistry and Behavior, 81, pp. 440-450, 2005.

Differential Responsivity to Non-Drug Reinforcers Predicts Vulnerability for Relapse in Female Rats

Previous studies have demonstrated that rats that freely explore novel environments, rats that have high activity levels, rats that are impulsive and rats that have a preference for highly palatable tastes readily acquire drug self-administration. Recently, Marilyn Carroll and colleagues examined the maintenance of i.v. cocaine intake and subsequent drug-primed relapse after an extended period of abstinence. In this study, female rats were allowed six hours per day access to running wheels for 21 days and then divided into groups that had high wheel running rates (H) or low rates (L) on the basis of a median split (mean revolutions/day). Patterns of wheel running over the 21 days increased in animals that were subsequently assigned to an H group, while steady rates were observed in the L group. Also, the investigators found that H rats took significantly more cocaine (0.4 mg/kg/infusion) over 14 days on a fixed ratio reinforcement schedule, than their low wheel running counterparts. Following self-administration tests, rats were withdrawn from cocaine by replacing saline in the infusion cannulae for 22 days. In response to a priming dose of cocaine on Day 23, both groups showed drug seeking by increasing their responses on the lever previously associated with drug, but the H group had a 7-fold increase over their prior response rates during extinction, as compared to a 3-fold increase by L animals. These differences cannot be accounted for by responses during extinction because both groups showed similar response rates during this phase. These findings support previous observations suggesting that inherent differences in an individual's behavior for non-drug reinforcers predict the propensity to engage in drug taking and drug seeking. Still to be determined is whether the increased vulnerability seen in maintenance and reinstatement reflects inherent differences in the sensitivity of motivational systems or more rapid neuroadaptations to cocaine exposure. However, as non-drug rewards and drugs of abuse activate similar neurobiological substrates, and H animals showed an escalating pattern of running wheel behavior, these animals may experience deprivation of hedonic effects produced by running. The authors suggest that they may show higher rates of drug intake and relapse in order to compensate for this loss. Larson, E.B. and Carroll, M.E. Wheel Running as a Predictor of Cocaine Self-administration and Reinstatement in Female Rats. Pharmacology Biochemistry and Behavior, 82, pp. 590-600, 2005.

Subthalamic Nucleus Lesions Enhance the Effects of Cocaine in Rats

The subthalamic nucleus (STN) is traditionally thought to be involved in motor control and has recently become a target for treatment of Parkinson's disease. Less attention has been paid to the role of STN in motivated behaviors, but recent reports suggest that it does have a role: in rats, bilateral lesions of the STN increase responding for food rewards, and high frequency stimulation of the STN has been reported to alter mood and motivation in patients treated for Parkinson's disease. Several years ago, Drs. Uslaner and Robinson noted that c-fos expression, a measure of neural activation, was robustly induced in STN in response to amphetamine or cocaine. They later found that this response increases after a sensitizing regimen of repeated drug administration. Now they have shown more directly that the STN plays an important role in motivational processes and the response to drugs of abuse. Rats received bilateral lesions of the STN and were tested for the psychomotor-activating effects of cocaine, the rate at which they acquired cocaine self-administration, and the motivation for

cocaine as assessed with a progressive ratio schedule. STN lesions produced a dose-dependent increase in all of these measures. In addition, STN lesions enhanced the ability of cocaine to induce c-fos expression in the nucleus accumbens and caudate-putamen, structures known to be involved in mediating the psychomotor-activating and incentive motivational effects of drugs of abuse. These findings suggest that engagement of the STN normally serves to dampen psychomotor-activating and incentive motivational effects of drugs of abuse, and that the STN may serve as a novel target for therapeutic interventions aimed at treating drug dependence. Uslaner, J.M., Yang P. and Robinson, T.E. Subthalamic Nucleus Lesions Enhance the Psychomotor-activating, Incentive Motivational, and Neurobiological Effects of Cocaine. Journal of Neuroscience, 25, pp. 8407-8415, 2005.

Mechanisms of Orexin Action in Addiction-Related Neuroadaptations and Behaviors

The orexins (also known as hypocretins) are hypothalamic neuropeptides that were originally identified for their role in arousal and feeding. More recently, several lines of evidence have implicated orexin, and particularly a subset of the orexin neurons that project to the VTA as playing a role in drug addiction. Dr. Antonello Bonci's laboratory has recently investigated the nature of neuroadaptations produced by orexin A input to the VTA and how these are involved in behavioral sensitization to cocaine. The first set of experiments was carried out in brain slices, where orexin effects on synaptic function were explored in dopaminerigic neurons of the VTA. They found that orexin A input to the VTA: (1) potentiates NMDA receptor-mediated excitation in glutamatergic neurons; (2) increases the number of NMDA receptors, causing them to be inserted into the postsynaptic membrane, thereby increasing their availability; and (3) caused a longer-term potentiation of synaptic currents mediated by the AMPA glutamate receptors. They then investigated whether orexin signaling in the VTA was required for the long-term plasticity associated with the development of behavioral sensitization to cocaine. When an orexin A antagonist was given just before cocaine injections during a 5 day sensitization procedure, behavioral sensitization was blocked and the signature synaptic plasticity did not develop. Taken together, these results suggest that orexin produces a fast increase in NMDA receptor function, leading to a longer-term increase in AMPA receptor plasticity, which is associated with behavioral sensitization. In the context of results from a recent study in Dr. Gary Aston-Jones' laboratory, which showed that orexin injections into the VTA could reinstate drug seeking in drug-free rats, results from the current study indicate the cellular mechanisms that precipitate arousal-induced relapse to drug taking during abstinence. All of the recent studies showing a role for orexin in drug addiction indicate that this peptide may provide a target for addiction medications. Borgland, S.L., Taha, S.A., Sarti, F., Fields, H.L. and Bonci, A. Orexin A in the VTA is Critical for the Induction of Synaptic Plasticity and Behavioral Sensitization to Cocaine. Neuron, 49, pp. 589-601, 2006.

Nicotine Induces a Distinctive Gene Expression Profile in Adolescent Rat Forebrain

Smoking is typically initiated in adolescence, but comparatively few studies in animals have investigated whether the adolescent brain responds differently to nicotine than the adult brain. Differences in behavioral responses to nicotine have been observed in adolescent as compared to adult rats. Previously, these authors showed that adolescent rats fail to display long-term contextual cue conditioning, suggesting that neural plasticity related to memory formation may be different in the younger animals. In the current report, they examined the expression of a number of early response genes (arc, c-fos and NGFI-B) that have been implicated in synaptic plasticity and addiction, following acute nicotine in adolescent and adult rats. Baseline expression of arc and c-fos was

higher in adolescent brains compared with adults. Following acute nicotine treatment, they found a higher induction of arc mRNA in the prefrontal cortex, and especially in orbitofrontal areas, of adolescents compared to adults. c-fos and NGFI-B were also upregulated by nicotine, but not in an age-related manner. They also measured the induction of these same genes in somatosensory cortex. As in the PFC, baseline levels were also higher in adolescents, but nicotine-induced expression was lower than in adults. Furthermore, in contrast to studies with other drugs of abuse, upregulation of these genes by nicotine was less pronounced in the ventral and dorsal striatum. These results indicate that in adolescence, the activity of specific early response genes is higher in brain regions critical for emotional regulation and decision making, which are known from other studies to be less mature at this age, and that nicotine affects arc in these areas more robustly in adolescents than in adults. Arc is a dendritically targeted gene that is important for synaptic plasticity involved in learning and memory, and it known to be upregulated by amphetamine and cocaine in various brain regions. These new results for nicotine suggest that adolescence may be a neurobiologically vulnerable period for nicotine exposure. Perhaps more importantly, the finding that nicotine has a more profound effect on cortical as compared to striatal regions in both age groups may indicate that addiction to nicotine, even more than to other drugs of abuse, depends on alterations of representations of reward value and other cognitive and attentional functions. Schochet, T.L., Kelley, A.E. and Landry, C.F. Differential Expression of arc mRNA and Other Plasticity-related Genes Induced by Nicotine in Adolescent Rat Forebrain. Neuroscience, 135, pp. 285-297, 2005.

The Cannabinoid System Affects Anxiety-Like Behavior Induced by Nicotine in Mice

The overlapping distribution of cannabinoid CB1 receptors and nicotinic acetyl choline receptors, along with other observations, suggests there may be functional interactions between these two systems. Dr. Rafael Maldonado and his colleagues have explored this interaction in a study on anxiety-like behaviors in mice using the elevated plus maze to study the anxiolytic or anxiogenic effects of various pharmacological treatments, relative to vehicle treatment. This apparatus has 4 arms - two that are enclosed and two that are open - and is suspended 30 cm above the ground. Less anxious animals spend more of their time on the maze and enter more often into the open arms than do more anxious animals. In a previous study, this group established that a single low dose of nicotine (0.05 mg/kg, s.c.) produced anxiolytic-like effects, whereas a high dose (0.8 mg/kg) was anxiogenic. In this study, they showed that pretreatment with the CB1 antagonist, rimonabant, dose-dependently abolished the anxiolytic effects of low-dose nicotine and increased the anxiogenic effects of the high dose. Treatment with _9-THC, a cannabinoid agonist, had no effect on the anxiolytic effects of nicotine, but attenuated the anxiogenic effects. They also tested a combination of subthreshold nicotine and _9-THC, which produced an anxiolytic-like response. The results of these studies indicate that the endogenous cannabinoid system regulates the effects of nicotine on anxiety-like behavior, and in particular that CB1 receptors must be active for nicotine to have an anxiolytic effect. The elucidation of this interaction between nicotine and the endogenous cannabinoid system provides support for the use of cannabinoid antagonists in the treatment of tobacco addiction. Balerio, G.N., Aso, E. and Maldonado, R. Role of the Cannabinoid System in the Effects Induced by Nicotine on Anxiety-like Behaviour in Mice. Psychopharmacology (Berlin), 184, pp. 504-513, 2006.

Morphine Conditioned Place Preference is Disrupted by Inhibition of Protein Synthesis During Memory Recall

A consensus is emerging that established memories of different sorts undergo

a process called "reconsolidation" each time they are recalled. During recall and reconsolidation, memories can be disrupted by interfering events and pharmacological treatments, including inhibition of protein synthesis. Because craving and relapse are frequently evoked by the recall of memories associated with previous drug experience, the reconsolidation process offers an opportunity for disrupting these memories and potentially reducing relapse to drug seeking. In this study, Dr. Cristina Alberini and her colleagues used a rat model of drug seeking to test whether inhibiting protein synthesis after the reactivation of the memory trace can weaken the memory of a drug experience. They first established conditioned place preference for morphine (mCPP) over 4 days of treatment. One week later, the investigators attempted to disrupt memory reconsolidation in two different types of recall experiments. In the first, animals were tested in a contextual recall test; that is, they were tested for recall of the morphine-associated compartment. Immediately after this recall test, they were injected with either anisomycin or cycloheximide, two commonly used protein synthesis inhibitors. However, upon retesting the next day, the animals showed undisrupted mCPP. For the second experiment, the rats were given a new conditioning trial one week later, and then injected with inhibitor. In this case, when they were retested 24 hrs later for contextual recall, their memory was significantly impaired. With this single injection of inhibitor, recall was significantly recovered one week later, but with two injections, 5 hrs apart after the reconditioning trial, memory disruption persisted for at least 4 wks (the last time point tested). Thus, unlike with other types of memories that have been tested in similar paradigms, established mCPP did not become labile after contextual recall, but only after the concomitant re-experience of both the conditioning context and the drug. They then used focal injections of protein synthesis inhibitors and showed that an established mCPP was disrupted after the conditioning session if protein synthesis was blocked in the hippocampus, basolateral amygdala, or nucleus accumbens, but not in the ventral tegmental area. This study complements other recent studies that also showed disruption of drug-associated memories during recall. Although there are differences among the results of these studies that raise critical questions that can only be answered by further research, together they suggest the intriguing possibility that novel treatments with the goal of weakening memories for the drug experience might be developed to reduce the risk of relapse. Milekic, M.H., Brown, S.D., Castellini, C. and Alberini, C.M. Persistent Disruption of an Established Morphine Conditioned Place Preference. Journal of Neuroscience, 26, pp. 3010-3020, 2006.

Director's Report to the National Advisory Council on Drug Abuse - May, 2006

Research Findings - Behavioral and Brain Development Research

Methamphetamine and Other Substance Use during Pregnancy: Preliminary Estimates from the Infant Development, Environment, and Lifestyle (IDEAL) Study

Methamphetamine use is a continuing problem in several regions of the United States yet few studies have focused on prenatal methamphetamine exposure. Dr. Barry Lester and his colleagues are conducting a study to estimate the prevalence and correlates of alcohol, tobacco, and other substance use-including methamphetamine-during pregnancy in four areas of the country (Los Angeles, CA; De Moines, IA; Tulsa, OK; and Honolulu, HI). The sample consists of the first 1632 eligible mothers who consented to participate in a large-scale multi-site study focused on prenatal methamphetamine exposure. This unselected screening sample includes both users and nonusers of alcohol, tobacco, methamphetamine, and other drugs. Substance use was determined by maternal self-report and/or GC/MS confirmation of a positive meconium screen. Overall, 5.2% of women used methamphetamine at some point during their pregnancy. One quarter of the sample smoked tobacco, 22.8% drank alcohol, 6.0% used marijuana, and 1.3% used barbiturates prenatally. Less than 1% of the sample used heroin, benzodiazapenes, and hallucinogens. Multivariate modeling results showed that tobacco smokers and illicit drug users were more likely to be single and less educated, have attended less than 11 prenatal visits, and utilize public financial assistance. IDEAL is the first large-scale investigation to report the prevalence of methamphetamine use during pregnancy in areas of the United States where methamphetamine is a notable concern. Given that this research extends and confirms previous findings showing that high-risk groups of pregnant women can be identified on the basis of basic demographic characteristics, targeted interventions are greatly needed to reduce serious adverse outcomes associated with prenatal alcohol and tobacco use. Arria, A.M., Derauf, C., Lagasse, L.L., Grant, P., Shah, R., Smith, L., Haning, W., Huestis, M., Strauss, A., Grotta, S. D., Liu, J. and Lester, B. Methamphetamine and Other Substance Use during Pregnancy: Preliminary Estimates from the Infant Development, Environment, and Lifestyle (IDEAL) Study. Maternal Child Health Journal, pp. 1-10, January 5, 2006 [Epub ahead of print].

Cocaine Exposure During Pregnancy and Neonatal Outcomes

Data in this report are for newborns in the Maternal Lifestyle Study, a multi-site longitudinal investigation of health and development following prenatal drug exposure. Associations between cocaine exposure in utero and newborn conditions were examined. One of the strengths of this study is its large sample size; these analyses were carried out for 717 cocaine-exposed infants

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and 7442 infants not exposed to cocaine. Cocaine-exposed infants were about 1.2 weeks younger, weighed 536 grams less, measured 2.6 cm shorter, and had head circumference 1.5 cm smaller than nonexposed infants. Results did not confirm previous reports in the literature of abnormal anatomic outcomes. Central and autonomic nervous system symptoms were more frequent in the exposed group (i.e., jittery/tremors, high-pitched cry, excessive suck, hyperalertness, and autonomic instability); they were usually transient. No differences were detected in organ systems by ultrasound examination. Exposed infants had more infections, including hepatitis, syphilis, and HIV. Exposed infants were also less often breastfed, had more child protective services referrals, and were more often not living with their biological mother. Bauer, C.R., Langer, J.C., Shankaran, S., et al. Acute Neonatal Effects of Cocaine Exposure During Pregnancy. Archives of Pediatrics and Adolescent Medicine, 159, pp. 824-834, 2005.

Anthropometric and Dysmorphologic Assessments in 6-Year-Old Children

Anthropometric and dysmorphologic assessments were carried out for 154 6-year-old children prenatally-exposed to cocaine (PCE) and 131 high-risk controls of similar race and social class. Dose-response relationships were observed for adjusted mean height z scores and for weight-for-height z scores, with higher cocaine exposure associated with lower height and lower weight for height. Severity of marijuana use also predicted lower height for age but greater weight for height. Higher average alcohol exposure throughout pregnancy and 3rd trimester predicted lower head circumference and weight z scores, respectively. After controlling for covariates, higher average prenatal cigarette exposure predicted higher incidence of cranial facial abnormalities. First trimester alcohol exposure predicted greater rates of ear abnormalities and third trimester marijuana exposure predicted greater rates of chest and head shape abnormalities. There was not an increased rate of minor anomalies among the PCE cohort, nor was a consistent phenotype identified, leading the authors to conclude that prenatal cocaine exposure is negatively related to specific growth outcomes, including standardized height and weight-for-height, but is not associated with a systematic pattern of structural abnormalities. The dysmorphologic examination utilized a standardized checklist of presence or absence of 271 common dysmorphic characteristics. The authors discuss limitations of the study in detail, such as implications for generalizability as a result of exclusion of children with birth defects (including suspected or diagnosed fetal alcohol syndrome) prior to recruitment. Minnes, S., Robin, N.H., Alt, A.A., et al. Dysmorphic and Anthropometric Outcomes in 6-Year-Old Prenatally Cocaine-Exposed Children. Neurotoxicology and Teratology, 28, pp. 28-38, 2006.

Prenatal Marijuana Exposure Relative to Visuospatial Working Memory and Neural Activity in Young Adults

From their longitudinal cohort study of the long-term sequelae of prenatal marijuana exposure, Dr. Peter Fried and colleagues have reported on visuospatial working memory performance and neural activity in 18-22 year-old young adults followed since birth. Given the longitudinal nature of the data collection, detailed information is available in many areas, including prenatal drug history, detailed cognitive/behavioral performance from infancy to young adulthood, and current and past drug usage. Thirty-one participants (16 prenatally-exposed to marijuana and 15 prenatally nonexposed to marijuana) performed a visuospatial 2-back task while neural activity was imaged with functional magnetic resonance imaging (fMRI). No significant task performance differences were observed when comparing controls versus exposed participants. However, multiple regression analyses (including controls with no

exposure) revealed that as the amount of prenatal marijuana exposure increased, there was significantly more neural activity in the left inferior and middle frontal gyri, left parahippocampal gyrus, left middle occipital gyrus and left cerebellum. There was also significantly less activity in right inferior and middle frontal gyri. Included among the factors controlled in the analyses was current drug use. The authors interpret the results to suggest that prenatal marijuana exposure alters neural functioning during visuospatial working memory processing in young adulthood. Smith, A.M., Fried, P.A., Hogan, M.J. and Cameron, I. Effects of Prenatal Marijuana on Visuospatial Working Memory: An fMRI Study in Young Adults. Neurotoxicology and Teratology, 28, pp. 286-295, 2006.

Prenatal Exposure to Substances of Abuse in Children Residing in Russian Orphanages

Over 600,000 children reside in institutional care in Russia, most of them in baby homes and orphanages. The actual prevalence of fetal alcohol spectrum disorders (FASD) and exposure to drugs of abuse among these children is unknown. In this study, a team of researchers from Boston and the Murmansk Region of Russia, led by Dr. Laurie Miller from Tufts-New England Medical Center conducted a systematic survey of phenotypic features associated with prenatal alcohol exposure among institutionalized Russian children and related these findings to their growth, development, medical, and social histories. Phenotypic screening was conducted for all 234 children residing in three baby homes in the Murmansk region of Russia (mean age 21+12.6 months). These baby homes care not only for orphaned children but also abandoned and relinquished children and children whose parents' rights were terminated. Phenotypic expression scores were devised based on facial dysmorphology and other readily observable physical findings. Growth measurements from birth, time of placement in the baby home, and at present were analyzed. In addition, the charts of 64% of the children were randomly selected for retrospective review. Information collected included maternal, medical, developmental, and social histories. Thirteen percent of children had facial phenotype scores highly compatible with prenatal alcohol exposure and 45% had intermediate facial phenotype scores. These scores correlated with maternal gravidity and age. At least 40% of mothers in whom history was available ingested alcohol during pregnancy; some also used illicit drugs and tobacco. Z scores for growth measurements corresponded to phenotypic score, as did the degree of developmental delay. Children with no or mild delay had significantly lower phenotypic scores than those with moderate or severe delay ($p = 0.04$); more than 70% of children with high phenotypic scores were moderately or severely delayed. More than half of residents of the baby homes in Murmansk, Russia, have intermediate (45%) or high (13%) phenotypic expression scores suggesting prenatal exposure to alcohol. Despite good physical care, stable daily routine, availability of well-trained specialists, and access to medical care, these vulnerable children show significant growth and developmental delays compared with their institutionalized peers. Miller, L.C., Chan, W., Litvinova, A., Rubin, A., Comfort, K., Tirella, L., Cermak, S., Morse, B., Kovalev, I., and Boston-Murmansk Orphanage Research Team. Fetal Alcohol Spectrum Disorders in Children Residing in Russian Orphanages: A Phenotypic Survey. Alcohol: Clinical and Experimental Research, 30 (3), pp. 531-538, 2006.

Testing for Fetal Exposure to Illicit Drugs Using Umbilical Cord Tissue

This study investigated the feasibility of using umbilical cord tissue as a means of assessing fetal drug exposure. Comparisons were made for paired specimens of meconium and umbilical cord tissue from 118 pregnancies with high suspicion of illicit drug use by the mothers. Each specimen was tested for

amphetamines, opiates, cocaine, cannabinoids, and phencyclidine using a screening assay, with confirmation assessment carried out using gas chromatography/mass spectrometry (GC/MS). The agreement of drug screening results between umbilical cord and meconium was above 90% for all drugs tested. Agreement was 96.6% for amphetamines, 94.9% for opiates, 99.2% for cocaine, and 90.7% for cannabinoids (no PCP-positive samples were detected). Using meconium as the standard, umbilical cord screening sensitivity ranged from 75 to 95.2% and specificity from 91.2 to 100%. The investigators conclude that umbilical cord tissue performed as well as meconium, and that cord tissue may have some practical advantages over meconium. This research group is continuing its investigations into testing of umbilical cord tissue. Montgomery, D., Plate, C., Alder, S.C., Jones, M., Jones, J., and Christensen, R.D. Testing for Fetal Exposure to Illicit Drugs Using Umbilical Cord Tissue vs. Mecomium. Journal of Perinatology, 26, pp. 11-14, 2006.

Caregiver Substance Abuse Associated with Violence Exposure among Young Urban Children

Dr. Delaney-Black and her colleagues at Wayne State University examined the relative importance of caregiver substance abuse as a correlate of child-reported exposure to violence in this study of 407 female African-American primary caregivers and their children 6 to 7 years of age. The association between child report of violence and exposure to substance abuse by others (both within and outside the home) was considered after controlling for variance accounted for by child characteristics, caregiver characteristics, home environment, and neighborhood environment (including neighborhood crime). Caregiver alcohol abuse, children's witnessing of drug use in the home, and children's witnessing of drug deals all explained significant additional variance in violence exposure. These findings suggest that for early elementary-age children, meaningful prevention of violence exposure may be possible via addressing their exposure to substance abuse in their home and community. Ondersma, S.J., Delaney-Black, V., Covington, C.Y., Nordstrom, B. and Sokol, R.J. The Association between Caregiver Substance Abuse and Self-Reported Violence Exposure among Young Urban Children. Journal of Traumatic Stress, 19 (1), pp. 107-118, 2006.

Maternal Acceptance Moderates Relationship Between Community Violence Exposure and Child Functioning

Children in the United States are exposed to considerable community violence that has been linked to child functioning, however, not all those exposed experience negative outcomes. Dr. Delaney-Black and her colleagues examined the potential buffering or moderating role of maternal acceptance in the relationship between child-reported community violence exposure (reports of witnessing and being a victim of community violence) and internalizing and externalizing problems. In a sample of 268 urban African American first graders community violence exposure was significantly related to symptoms of post-traumatic stress, but did not correlate with either internalizing or externalizing problems for all children, after control for demographics, maternal mental health, and general life stress. However, children's perceptions of maternal acceptance moderated the relationship between violence exposure and internalizing and externalizing problems that included being withdrawn, anxious-depressed, and demonstrating delinquent behavior. Children with the lowest levels of self-reported maternal acceptance were most impacted by community violence. In this sample of urban first graders, low levels of maternal acceptance placed children at greater risk for adverse outcomes associated with community violence exposure compared to moderate and high levels of maternal acceptance. Bailey, B.N., Hannigan, J.H., Delaney-Black, V., Covington, C.Y., Covington, C.Y. and Sokol, R.J. The Role of Maternal

Acceptance in the Relation between Community Violence Exposure and Child Functioning. Journal of Abnormal Child Psychology, pp. 1-14, February 9, 2006 [Epub ahead of print].

Maternal Behavior among Drug Using Mothers

In this report, Dr. Rina Eiden and her colleagues examined the association between maternal cocaine use and maternal behavior in an infant feeding context. The investigators also tested a conceptual model predicting maternal insensitivity during mother-infant interactions. The analyses involved 130 mother-infant dyads (68 cocaine-exposed and 62 noncocaine-exposed) recruited after birth and assessed at 4-8 weeks of infant age. Results indicated that when the effects of prenatal cocaine use were examined in the context of polydrug use, maternal psychopathology, maternal childhood history, and infant birth weight, only postnatal cocaine use and maternal depression/anxiety were unique predictors of maternal insensitivity during the mother-infant interactions. Eiden, R.D., Stevens, A., Schuetze, P. and Dombkowski, L.E. A Conceptual Model for Maternal Behavior Among Polydrug Cocaine-Using Mothers: The Role of Postnatal Cocaine Use and Maternal Depression. Psychology of Addictive Behaviors, 20, pp. 1-10, 2006.

Genomic Screen for Loci Associated with Tobacco Usage in Native American Population

The prevalence of tobacco usage in Native American adults and adolescents is higher than any other racial or ethnic group, yet biological risk and protective factors underlying tobacco use in this ethnic group remain unknown. A genome scan for loci associated with tobacco use phenotypes was performed with data collected from a community sample of Mission Indians residing in Southwest California. This study used a structured diagnostic interview to define two tobacco use phenotypes: 1) any regular tobacco usage (smoked daily for one month or more) and 2) persistent tobacco usage (smoked at least 10 cigarettes a day for more than one year). Heritability was determined and a linkage analysis was performed, using genotypes for a panel 791 microsatellite polymorphisms, for the two phenotypes using variance component methods implemented in SOLAR. Analyses of multipoint variance component log of the odds (LOD) scores for the two tobacco use phenotypes revealed two scores that exceeded 2.0 for the regular use phenotype: one on chromosomes 6 and one on 8. Four other loci on chromosomes 1,7,13 and 22 were found with LOD scores between 1.0 and 1.5. Two loci of interest were found on chromosomes 1 and 4 for the persistent use phenotype with LOD scores between 1.3-1.5. Bivariate linkage analysis was conducted at the site on chromosome 4 for persistent tobacco use and an alcohol drinking severity phenotype previously identified at this site. The maximum LOD score for the bivariate analysis for the region was 3.4; however, there was insufficient power to exclude coincident linkage. While results do not provide evidence for linkage to specific chromosomal regions these results do identify regions of interest in the genome in this Mission Indian population for tobacco usage, some of which were identified in previous genome scans of non-native populations. Additionally, these data lend support for the hypothesis that cigarette smoking, alcohol dependence and other consumptive behaviors may share some common risk and/or protective factors in this Mission Indian population. Ehlers, C.L. and Wilhelmsen, K.C. Genomic Screen for Loci Associated with Tobacco Usage in Mission Indians. BMC Medical Genetics, 7(9), 2006.

Gender Differences in the Prediction of Condom Use Among Incarcerated Juvenile Offenders

Dr. Angela Robertson and her colleagues at Mississippi State University

examined the predictive value of the Information-Motivation-Behavioral Skills (IMB) model of HIV prevention for sexually active juvenile offenders at risk for substance abuse and explored gender differences in IMB model constructs for condom-protected vaginal intercourse. Self-report measures of HIV/AIDS knowledge, pro-condom peer influence, risk perception, condom attitudes, condom use self-efficacy, frequency of vaginal intercourse, and frequency of condom-protected vaginal intercourse were collected from predominantly African-American detainees 13-18 years of age. Analysis consisted of structural equation models for the combined sample (N = 523) and for separate gender groups (328 males and 195 females). In the combined model, condom use was significantly predicted by male gender, peer influence, positive condom attitudes, and condom self-efficacy. In separate gender analyses, condom use among adolescent males was predicted by peer influence (modestly) and by positive condom attitudes, whereas condom use among females was predicted by peer influence, self-efficacy, and condom attitudes. Compared with males, females reported significantly greater knowledge, less peer influence, higher perceived risk for infection, more positive condom attitudes, and more self-efficacy, but they reported less condom use. The authors conclude that females may find it difficult to use condoms consistently despite their awareness of their efficacy. Power imbalances or other dynamics operating in their relationships with males need further exploration. Gender differences in the relationship between condom self-efficacy and condom use were masked in the analysis of the total sample, indicating the value of testing theories of HIV prevention separately by gender. Robertson, A.A., Stein, J.A., and Baird-Thomas, C. Gender Differences in the Prediction of Condom Use among Incarcerated Juvenile Offenders: Testing the Information-Motivation-Behavior Skills (IMB) Model. Journal of Adolescent Health, 38 (1), pp. 18-25, 2006.

HIV and HCV Testing for Young Injection Drug Users in Rhode Island

Young injection drug users (IDU) are at risk for both human immunonodeficiency virus (HIV) and Hepatitis C infections (HCV). Rates of HIV testing have been widely documented, but limited information exists regarding HCV screening rates. Dr. David Pugatch and colleagues in Rhode Island recruited 86 IDUs 18-25 years of age from drug detoxification programs and street outreach to examine rates of HIV and HCV testing. Forty-nine percent of participants had been tested for HIV and HCV, 38.4% for HIV only, 2.3% for HCV only and 10.5% had not been tested for either HIV or HCV. Participants were more likely to have been tested for HIV than for HCV (87.2% vs. 51.2%, $p < .001$). Participants recruited through street outreach were more likely to have been tested for HCV than those recruited from drug detoxification programs (64.2% vs. 30.3%, $p = .002$). Results from this study suggest that young injectors may be under-screened for HCV. Pugatch, D., Anderson, B.J., O'Connell, J.V., Elson, L.C. and Stein, M.D., HIV and HCV Testing for Young Drug Users in Rhode Island. J of Adolescent Health, 38(3), pp. 302-304, 2006.

Neuropsychological Predictors of BOLD Response during a Spatial Working Memory Task in Adolescents: What Can Performance Tell Us About fMRI Response Patterns?

Dr. Susan Tapert and her colleagues at the University of California, San Diego explored the relationship between neuropsychological test performance and fMRI activation on a spatial working memory task in 49 typically developing adolescents. They found that neuropsychological performance negatively predicted fMRI activation, suggesting that those adolescents with better neuropsychological abilities needed to recruit fewer neural resources to perform the task. Nagel, B.J., Barlett, V.C., Schweisburg, A.D. and Tapert, S.F. J. Clin. Exp. Neuropsychol. 27(7), pp. 823-839, 2005.

Components of the Cerebellar Vermis Mediate Cocaine's Persisting and Acute Effects

The dopamine transporter (DAT) is thought to play a critical role in mediating the reinforcing and subjective effects of cocaine. It has been known for many years that the affinity of drugs for the DAT is positively correlated with their capacities to maintain self-administration behavior in animals. The knowledge that the primate cerebellar vermis (lobules II-III and VIII-IX) was reported to contain axonal dopamine transporter immunoreactivity (DAT-IR), and that this region has connections to midbrain dopaminergic cell body regions led a team of researchers at McLean Hospital in Boston to 1) apply BOLD-fMRI technology to determine whether cocaine-related cues activated DAT-IR-enriched vermis regions in cocaine abusers and 2) perform PET imaging in healthy subjects to determine whether the DAT-selective ligand [11C]altropane accumulated in those vermis regions. They found that cocaine-related cues selectively induced BOLD activation in lobules II-III and VIII-IX in cocaine users, and, at early time points after ligand administration, appreciable [11C]altropane accumulation was observed in lobules VIII-IX, possibly indicating DAT presence in this region. These findings, when combined with the established roles for the vermis as a locus of sensorimotor integration and motor planning, and findings of increased vermis activation in substance abusers during reward-related and other cognitive tasks, led the McLean team to propose that the vermis be considered one of the structures involved in cocaine- and other incentive-related behaviors. Anderson, C.M., Maas, L.C., Frederick, B. deB., Bendor, J. T., Spencer, T. J., Livni, E., Lukas, S.E., Fischman, A.J., Madras, B.K., Renshaw, P.F. and Kaufman, M.J. Cerebellar Vermis Involvement in Cocaine-Related Behaviors. Neuropsychopharmacology, advance online publication, pp. 1-9, October, 12 2005.

Visuospatial Memory Deficits Emerging During Nicotine Withdrawal in Adolescents with Prenatal Exposure to Active Maternal Smoking

Preclinical (animal) studies have previously shown that the effects of nicotine withdrawal are more pronounced in adolescents that were exposed to nicotine prenatally than in those that were exposed only in adolescence. In this study, Dr. Leslie Jacobsen and her colleagues examined visuospatial and verbal memory in 35 adolescent tobacco smokers with prenatal exposure to nicotine and 26 adolescent smokers with no prenatal exposure. They found that adolescents with prenatal exposure had greater deficits in visuospatial memory than adolescent smokers that had not been exposed to nicotine during gestation and that these deficits were accompanied by altered activation patters in the hippocampus bilaterally and the left parahippocampal gyrus. Jacobsen, L.K., Slotkin, T.A., Westerveld, M., Mencl, W.E. and Pugh, K.R. Neuropsychopharmacology. 2005. http://www.acnp.org/citations/Npp102105055322/default.pdf.

A Shift from Diffuse to Focal Cortical Activity with Development

Dr. B.J. Casey and colleagues used fMRI to investigate the potential changes that occur in neural processing associated with performing a cognitive control task with developmental time. In this combined longitudinal and cross-sectional study, they found that performance on the task did not change between the ages of 9 and 11 although reaction time did. In terms of brain activation patterns, there was a decrease in diffuse activation in the dorsolateral prefrontal cortex and an increase in focal activation in ventral prefrontal regions, suggesting a refinement in the neural circuitry needed to perform the task. Durston, S., Davidson, M.C., Tottenham, N., Galvan, A., Spicer, J., Fossella, J.A., and Casey, B.J. Developmental Science. 9(1), pp. 1-20, 2006.

Mapping Brain Maturation

Dr. Elizabeth Sowell and her colleagues at the University of California Los Angeles have investigated the regional development of gray and white matter during the development of healthy children using structural MRI. This team of investigators has now extended these studies to structural brain development in early-onset schizophrenia, fetal alcohol syndrome, ADHD, and Williams syndrome. In this paper, Dr. Sowell and colleagues review their findings on brain development in these groups of individuals, comparing differences in the development of specific regions of the brain in the different groups and relating them to the possible cellular changes that underlie them as well as to the cognitive and behavioral changes that occur during childhood and adolescence. Toga, A.W., Thompson, P.M. and Sowell, E.R. Trends in Neuroscience. 29(3), pp. 148-159, 2006.

Director's Report to the National Advisory Council on Drug Abuse - May, 2006

Research Findings - Clinical Neuroscience Research

Cognitive Function and Nigrostrial Markers in Abstinent Methamphetamine Abusers

Johanson and colleagues at Wayne State University in collaboration with investigators at University of Michigan, Haight Ashbury Free Clinics, and Cambridge University used Positron Emission Tomography (PET) to investigate the integrity of dopaminergic terminals and cognitive function in abstinent methamphetamine abusers (MA). Striatal levels of membrane Dopamine transporters (DAT) and vesicular monoamine transporters (VMAT2) were assessed using [11C] methylphenidate and [11C]dihydrotetrabenazine. Tests of motor function, memory, learning, attention, and executive function were also administered to evaluate cognitive function. Mean abstinence from methamphetamine was 3 years and ranged from 3 months to up to 10 years. Both DAT and VMAT2 were lower in MA than controls (-15% DAT, -10% VMAT2) across all striatal regions. MA performed more poorly than controls on 3 of the 12 cognitive tasks, but MA performance was still within normative range. Reductions in VMAT2 in human MA support pre-clinical studies indicating toxic effects of methamphetamine on dopaminergic nerve terminals. Although the failure to find more substantial changes in the PET or cognitive measures may have been due to the length of abstinence, there were no correlations of the PET or cognitive measures with the length of abstinence. The relatively small magnitude of the effects on the integrity of dopaminergic terminals raise questions as to whether clinical signs of dopaminergic deficiency will be evident in former methamphetamine abusers. Johanson, C.E., Frey, K.A., Lundahl, L.H. Keenan, P., Lockhart, N., Roll, J., Galloway, G.P., Koeppe, R.A., Kibourn, M.R., Robbins, T. and Schuster, C.R. Psychopharmacology, 185, pp. 327-338, 2006.

Ambiguity in Groups of Emotional Faces Recruits Ventromedial Prefrontal Cortex

Paulus and colleagues at the University of California, San Diego, used fMRI in a social neuroscience study of affective appraisal of the mood of a group of people. Affective neuroimaging research often uses individual faces as stimuli when exploring the neural circuitry involved in social appraisal, but single face paradigms may not generalize to settings where multiple faces are simultaneously processed. In this study groups of multiple matrices of affective faces were briefly presented during fMRI scans. Subjects were asked to decide whether there were more angry or happy faces (emotional decision) or whether there were more male or female faces (gender decision). In each condition, the array contained either an equal (ambiguous trials) or an unequal (unambiguous trials) distribution of one affect or gender. Ambiguous trials relative to unambiguous trials activated regions implicated in conflict monitoring and cognitive control, including the dorsal anterior cingulate cortex (ACC),

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dorsolateral PFC, and posterior parietal cortex. The ventromedial PFC (including the ventral ACC) was activated specifically by ambiguous affective decisions compared with ambiguous gender decisions. This supports the dissociation of the ACC into dorsal cognitive and ventral affective divisions, and suggests that the ventromedial PFC may play a critical role in appraising affective tone in a complex display of multiple human faces. This study forms the foundation for investigating whether drug abusers show impairment in brain systems involved in affective appraisal of groups. Since many treatment approaches involve group therapy, such a dysfunction could have substantial implications for treatment development. Simmons, A., Stein, M.B., Matthews, S.C., Feinstein, J.S. and Paulus, M.P. Neuroimage, 29(2), pp. 655-661, 2006.

Prefrontal and Temporal Gray Matter Density Decreases in Opiate Dependence

Renshaw and colleagues at McLean Hospital used structural brain imaging to study gray matter density alteration in opiate-dependent subjects. There have only been a few studies performed to date and these have had varied findings. This method is suitable for studying whole brain-wise structural brain. The current study used voxel-based morphometry (VBM) determination of gray matter density that was made in 63 opiate-dependent subjects and 46 age- and sex-matched healthy comparison subjects. Relative to healthy comparison subjects, opiate-dependent subjects exhibited decreased gray matter density bilaterally in the prefrontal cortex, insula, superior temporal cortex, as well as the left fusiform cortex and right uncus. It remains to be determined whether gray matter density decreases in prefrontal and temporal cortex are associated with behavioral and neuropsychological dysfunction in opiate-dependent subjects. Lyoo, I.K., Pollack, M.H., Silveri, M.M., Ahn, K.H., Diaz, C.I., Hwang, J., Kim, S.J., Yurgelun-Todd, D.A., Kaufman, M.J. and Renshaw, P.F. Psychopharmacology, 184(2), pp. 139-144, 2006.

Increased White Matter Hyperintensities in Male Methamphetamine Abusers

Renshaw and colleagues at McLean Hospital used structural MRI to assess the prevalence, severity, and location of white matter signal hyperintensities (WMH) in methamphetamine (MA) abusers. Axial T-2 weighted images and fluid attenuated inversion recovery axial images were obtained using a 3T MR scanner from 33 MA abusers and 32 age- and gender-matched healthy comparison subjects. The severity of WMH was assessed separately for deep and periventricular WMH. Ordinal logistic regression models were used to assess the odds ratio for WMH. MA abusers had greater severity of WMH than the healthy comparison subjects (odds ratio: 7.06, 8.46, and 4.56 for all, deep, and periventricular WMH, respectively). Severity of deep WMH correlated with total cumulative dose of MA ($p = 0.027$). These differences were mainly due to increased WMH in male MA abusers. There was greater severity of WMH in male than female MA abusers (odds ratio = 10.00). Male MA abusers had greater severity of WMH than male comparison subjects (odds ratio = 18.86), but there was no significant difference in WMH severity between female MA abusers and female comparison subjects. Increased WMH in MA abusers may be related to MA-induced cerebral perfusion deficits. The lower severity of WMH in female MA abusers may be due to estrogen's protective effect against ischemic or neurotoxic effects of MA. Bae, S.C., Lyoo, I.K., Sung, Y.H., Yoo, J., Chung, A., Yoon, S.J., Kim, D.J., Hwang, J., Kim, S.J. and Renshaw, P.F. Drug And Alcohol Dependence, 81(1), pp. 83-88, 2006.

Grey and White Matter GABA Level Differences in the Human Brain Using Two-Dimensional, J-Resolved Spectroscopic Imaging

Renshaw and colleagues at McLean Hospital used a magnetic resonance spectroscopy (MRS) method to determine brain gamma-aminobutyric acid (GABA) levels. Two-dimensional, J-resolved chemical-shift imaging sequence on a 4T scanner was used to MRS images on a 4 T scanner from six healthy subjects. Using image segmentation and a linear-regression analysis relating brain GABA level to tissue-type, a consistent and significant ($n = 6$, $p < 0.01$) elevation of mean GABA levels was measured in the cortical grey matter (0.96 +/- 0.24 mm) compared with white matter (0.44 +/- 0.16 mm) across all six subjects. The results suggest an approximately two-fold elevation of GABA levels in cortical grey matter compared with white matter in vivo. Our findings are consistent with ex vivo studies in the literature of both animal and human brain and demonstrate the significant potential of this technique for detecting and quantifying tissue-specific neurochemical pathology in vivo. Jensen, J.E., Frederick, B.D. and Renshaw, P.F. NMR In Biomedicine, 18(8), pp. 570-576, 2005.

Neural Correlates of Direct and Reflected Self-Knowledge

D'Esposito and colleagues at University of California, Berkeley, in collaboration with investigators at Stanford University, used fMRI to compare brain mechanisms mediating direct appraisals of self (i.e., an individual's own self-beliefs) versus reflected appraisals (i.e., an individual's perception of how others view him or her). One experiment compared the common and distinct neural bases of direct appraisals of the self, close others, and normative judgments of trait desirability. All three judgment types activated medial prefrontal cortex (MPFC) to a similar degree. A second experiment examined the common and distinct neural bases of (1) direct appraisals of self, a close other or a non-close other, and (2) reflected appraisals made from the perspective of a close or a non-close other. Consistent with the first study all judgment types activated MPFC. Direct appraisals of the self as compared to others more strongly recruited MPFC and right rostrolateral PFC. Direct appraisals as compared to reflected appraisals recruited regions associated with a first-person perspective (posterior cingulate), whereas reflected as compared to direct appraisals recruited regions associated with emotion and memory (insula, orbitofrontal, and temporal cortex). These results support models suggesting that MPFC mediates meta-cognitive processes that may be recruited for direct and reflected self appraisals depending upon the demands of a specific task. This type of social neuroscience study forms the foundation of future studies that can assess whether drug abusers have altered brain mechanisms for self-knowledge. Such studies provide insights that can be used to direct new treatment approaches. Ochsner, K.N., Beer, J.S., Robertson, E.R., Cooper, J.C., Gabrieli, J.D.E., Kihsltrom, J.F. and D'Esposito, M. Neuroimage, 28(4), pp. 797-814, 2005.

Neural Responses to Acute Cocaine Administration in the Human Brain Detected by fMRI

Risinger and colleagues at the Medical College of Wisconsin used an improved fMRI method for the reduction of susceptibility artifacts to investigate responses to acute cocaine administration in human cocaine users. Intravenous administration of cocaine (20 mg/70 kg) activated a set of hierarchical brain networks in the anterior prefrontal cortex (aPFC) of Brodmann area 10 (BA10) and orbitofrontal cortex (OFC), regions that had previously been difficult to image using BOLD fMRI. In addition, mesolimbic and mesocortical dopaminergic projection regions exhibited both positive or negative BOLD responses over time. This study provides further evidence that dopaminergic pathways and the hierarchical brain networks participate in mediating cocaine reward, associative learning, motivation, and memory in brains of human cocaine addicts. Kufahl, P.R., Li, Z., Risinger, R.C., Rainey, C.J., Wu, G.H., Bloom, A.S. and Li, S.J. Neuroimage, 28(4), pp. 904-914, 2005.

Cognitive Neuroscience of Emotional Memory

K. LaBar of Duke University reviewed the literature on psychological and neural mechanisms underlying emotional retention advantages in the human brain. A major conclusion was that emotion - memory interactions occur at various stages of information processing, from the initial encoding and consolidation of memory traces to their long-term retrieval. The amygdala is a brain structure that directly mediates aspects of emotional learning and facilitates memory operations in other regions, including the hippocampus and prefrontal cortex. Recent advances are revealing new insights into the reactivation of latent emotional associations and the recollection of personal episodes from the remote past. LaBar, K. Nature Reviews Neuroscience, 7(1), pp. 54-64, 2006.

Prefrontal Grey-Matter Changes In Short-Term and Long-Term Abstinent Methamphetamine Abusers

Renshaw and colleagues at McLean Hospital in collaboration with investigators in South Korea used structural MRI to determine the effect of methamphetamine abuse on grey matter density in methamphetamine abusers. Using voxel-based morphometry, grey-matter density in 29 methamphetamine abusers was compared to 20 healthy comparison subjects. In addition, grey-matter density changes and performance on the Wisconsin Card Sorting test (WCST) was compared between 11 short-term (< 6 months) and 18 long-term (>= 6 months) abstinent methamphetamine abusers. Methamphetamine abusers had lower grey matter density in the right middle frontal cortex (corrected $p < 0.05$) and more total errors in the WCST ($p < 0.01$) than healthy comparison subjects. Grey-matter density decreases in the right middle frontal cortex correlated with total errors in the WCST in methamphetamine abusers ($r = -0.45$). Long-term abstinent abusers had significantly less right middle frontal grey-matter density decreases ($p < 0.01$) and total errors in the WCST ($p < 0.01$) than short-term abstinent abusers, but more than the healthy comparison subjects. Thus, methamphetamine abusers have prefrontal grey-matter deficit, which may, in part, recover with long-term abstinence. Kim, S.J., Lyoo, I.K., Hwang, J., Chung, A., Sung, Y.H., Kim, J., Kwon, D.H., Chang, K.H. and Renshaw, P.F International Journal of Neuropsychopharmacology, 9(2), pp. 221-228, 2006.

Nicotine and Cognitive Efficiency In Alcoholics and Illicit Stimulant Abusers: Implications Of Smoking Cessation For Substance Users In Treatment

Nixon and colleagues at the University of Kentucky investigated whether nicotine could have a confounding effect on studies of cognition in detoxified substance users. In the current study of 87 participants, behavioral and electrophysiological indices of cognitive efficiency were measured in tobacco smokers from four groups: alcoholics, illicit stimulant abusers, concurrent abusers, and control subjects. They hypothesized that acute nicotine administration would modify cognitive deficits in alcoholics and illicit stimulant abusing groups. An adaptation of the Rapid Visual Information Processing task was administered after stabilization of nicotine levels via a high- or low-dose transdermal nicotine patch. Across groups, increased nicotine dose was associated with decreased reaction time ($p = .03$). Increasing doses of nicotine were associated with increased correct responding within the alcoholic group ($p = .02$). No significant differences in electrophysiology were observed. These results suggest that nicotine may modify cognitive efficiency in alcoholics and illicit stimulant abusers. These results are relevant to both the design of experimental work and the treatment of alcohol and illicit stimulant dependence. Further work is needed to determine whether this effect

predominantly reflects facilitation of cognition function or alleviation of nicotine withdrawal. Ceballos, N.A., Tivis, R., Lawton-Craddock, A.and Nixon, S.J. Substance Use & Misuse, 41(3), pp. 265-281, 2006.

Sex, Stress, and Fear: Gender and Individual Differences In Conditioned Learning

LaBar and colleagues at Duke University investigated the relationship among sex, stress hormones, and fear conditioning in humans in order to elucidate factors that contribute to individual variation in emotional learning. Forty-five healthy adults (22 females) underwent differential delay conditioning, using fear-relevant conditioned stimuli and a shock unconditioned stimulus. Salivary cortisol samples were taken at baseline and after acquisition training and a 24-h-delayed retention test. Acquisition of conditioning significantly correlated with postacquisition cortisol levels in males, but not in females. This sex-specific relationship was found despite similar overall levels of conditioning, unconditioned responding, and cortisol. There was no effect of postacquisition cortisol on consolidation of fear learning in either sex. These findings have implications for the understanding of individual differences in fear acquisition and risk factors for stress-elicited relapse in substance abusers. Zorawski, M., Cook, C.A., Kuhn, C.M. and LaBar, K.S. Cognitive Affective & Behavioral Neuroscience, 5(2), pp. 191-201, 2005.

Capacity Differences Predict Working Memory Performance and Prefrontal Activity Following Dopamine Receptor Stimulation

D'Esposito and colleagues at the University of California, Berkeley used fMRI to test the relationships between dopamine, pre-frontal cortical (PFC) function, and individual differences in working memory capacity. Subjects performed a verbal delayed-recognition task after taking either the dopamine receptor agonist bromocriptine or a placebo. Behavioral effects of bromocriptine treatment depended on subjects' working memory spans, with the greatest behavioral benefit for lower span subjects. After bromocriptine, PFC activity was positively correlated with a measure of cognitive efficiency (Reaction Time slope) during the probe period of the task. Less efficient subjects with slower memory retrieval rates had greater PFC activity, whereas more efficient subjects had less activity. After placebo, these measures were uncorrelated. These results support the role of dopamine in verbal working memory and suggest that dopamine may modulate the efficiency of retrieval of items from the contents of working memory. Individual differences in PFC dopamine receptor concentration may thus underlie the behavioral effects of dopamine stimulation on working memory function. These results suggest that the effects of drugs of abuse on working memory may be the result of an interaction between pre-existing cognitive capacity and drug-induced alterations in dopaminergic function. Gibbs, S.E.B. and D'Esposito, M. Cognitive Affective & Behavioral Neuroscience 5(2), pp. 212-221, 2005.

Human Striatal Activation Reflects Degree of Stimulus Saliency

Berns and colleagues at Emory University used fMRI to determine whether the striatum responds in an all-or-none fashion to salient events or instead responds in a graded fashion to the degree of saliency associated with an event. Salient stimuli are characterized by their capability to perturb and seize available cognitive resources. Although the striatum and its dopaminergic inputs respond to a variety of stimuli categorically defined as salient, including rewards, the relationship between striatal activity and saliency is not well understood. Twenty healthy participants performed a visual classification task in which they identified single digits as odd or even numbers. An auditory tone preceded each number, which was occasionally, and unexpectedly, substituted

by a novel sound. The novel sounds varied in their ability to interrupt and reallocate cognitive resources (i.e., their saliency) as measured by a delay in reaction time to immediately subsequent numerical task-stimuli. Striatal activity increased proportionally to the degree to which an unexpected novel sound interferes with the current cognitive focus, even in the absence of reward. These results suggest that activity in the human striatum reflects the level of saliency associated with a stimulus, perhaps providing a signal to reallocate limited resources to important events. These results provide a framework to interpret the alterations in striatal function observed in drug addicts. Zink, C.F., Pagnoni, G., Chappelow, J., Martin-Skurski, M. and Berns, G.S. Neuroimage, 29(3), pp. 977-983, 2006.

Perfusion Functional MRI Reveals Cerebral Blood Flow Pattern Under

Detre and colleagues at the University of Pennsylvania used a quantitative and noninvasive neuroimaging technique, arterial spin-labeling perfusion MRI, to measure cerebral blood flow (CBF) changes associated with mild to moderate stress. Mild stress was induced by a mental arithmetic task with performance monitoring, and the degree of stress was verified by self-report of stress and emotional state and measures of heart rate and salivary-cortisol level. Changes in CBF induced by the stress task were positively correlated with subjective stress rating in the ventral right prefrontal cortex (RPFC) and left insula/putamen area. The ventral RPFC along with right insula/putamen and anterior cingulate showed sustained activation after task completion in subjects reporting a high stress level during arithmetic tasks. Variations of baseline CBF in the ventral RPFC and right orbitofrontal cortex were found to correlate with changes in salivary-cortisol level and heart rate caused by undergoing stress tasks. Right prefrontal activation could not be attributed to increased cognitive demand accompanying stress tasks and extended beyond neural pathways associated with negative emotions. These results provide evidence that psychological stress induces negative emotion and vigilance and that the ventral RPFC plays a key role in the central stress response. Wang. J.J., Rao, H.Y., Wetmore, G.S., Furlan, P.M., Korczykowski, M., Dinges, D.F. and Detre, J.A. Proceedings National Academy of Sciences, USA, 102(49), pp. 17804-17809, 2005.

Gender and Functional Asymmetry of Ventromedial Prefrontal Cortex

Bechara and colleagues at the University of Iowa investigated whether gender plays a role in the development of defects in social conduct, emotional functioning and decision-making, following unilateral VMPC damage. A previous lesion study found that the more right-sided sector of the ventromedial prefrontal cortices (VMPCs) was critical for social/emotional functioning and decision-making than the left side. However, all but one of the subjects in that study were men, and the one woman did not fit the pattern very well. The study sample consisted of same-sex pairs of men or women patients who had comparable unilateral VMPC damage in either the left or right hemisphere. Two male pairs and one female pair were formed, and authors included two additional women with unilateral right VMPC damage (8 patients in all). The domains of measurement covered social conduct, emotional processing and personality, and decision-making. A systematic effect of gender was found on the pattern of left-right asymmetry in VMPC. Men had severe function defects following unilateral right VMPC damage, but not following left-sided damage. In contrast, functional defects were only found in women with unilateral left VMPC damage, whereas with right-sided damage the defects were mild or absent. The findings suggest that asymmetric, gender-related differences exist in the neurobiology of left and right VMPC sectors and as a result men and women may use different strategies to solve similar problems that parallel differences

in information processing between hemispheres. Such differences could reflect. Tranel, D., Damasio, H., Denburg, N.L. and Bechara, A. Brain 128(12), pp. 2872-2881 2005.

Prefrontal GABA Levels in Cocaine-Dependent (CD) Subjects Increase with Pramipexole and Venlafaxine Treatment

Streeter and colleagues at McLean Hospital used proton (H-1) Magnetic Resonance Spectroscopy (MRS) to measure changes in GABA levels in CD subjects at baseline and after 8 weeks of treatment with pramipexole, venlafaxine, or placebo. There is evidence that prefrontal lobe GABA levels are low in cocaine-dependent (CD) individuals, and treatment with GABA agonists decreases cocaine self-administration. GABA levels in the prefrontal lobe were measured before and after treatment. Only Pramipexole-treated subjects had significantly increased brain GABA levels compared to placebo ($p=0.031$). Mean percentage changes in GABA levels were as follows: pramipexole +17.0 +/- 28.0%, venlafaxine +13.0 +/- 11.0%, and placebo -2.1 +/- 19.5%. Despite significant changes in GABA levels, there were no significant differences in the number of urine samples positive for cocaine metabolites. This study demonstrates that H-1 MRS can measure changes in GABA levels following pharmacologic treatment. The increase in GABA levels, although significant, is modest compared to other MRS studies of depression or epilepsy, associated with clinical improvements. The failure to see larger increases in GABA levels and an associated reduction in cocaine consumption may reflect the relatively low doses of medication used. Streeter, C.C., Hennen, J., Ke, Y., Jensen, J.E., Sarid-Segal, F., Nassar, L.E., Knapp, C., Meyer, A.A., Kwak, T., Renshaw, P.F. and Ciraulo, D.A. Psychopharmacology, 182(4), pp. 516-526, 2005.

Using Cognitive Models to Map Relations Between Neuropsychological Disorders and Human Decision-Making Deficits

Bechara and collegues used a cognitive model to analyze performance in a complex decision-making task (the Iowa gambling task). This model dissociates performance into three different underlying psychological components: the relative impact of rewards and punishments on evaluations of options; the rate that the contingent payoffs are learned; and the consistency between learning and responding. Findings from 10 studies are organized by distilling the observed decision deficits into the three basic components and locating the neuropsychological disorders in this component space. The results reveal a cluster of populations characterized by making risky choices despite high attention to losses, perhaps because of difficulties in creating emotive representations. These findings demonstrate the potential contribution of cognitive models in building bridges between neuroscience and behavior. Yechiam, E., Busemeyer, J.R., Stout, J.C. and Bechara, A. Psychological Science, 16(12), pp. 973-978, 2005.

Cerebral Metabolic Dysfunction and Impaired Vigilance in Recently Abstinent Methamphetamine Abusers

London and colleagues at the University of California, Los Angeles investigated the relationship between cognitive impairment and cerebral abnormalities in limbic and paralimbic cortices and hippocampus in methamphetamine (MA) abusers. Cerebral glucose metabolism was assessed with [F-18]fluorodeoxyglucose positron emission tomography in 17 abstinent (4 to 7 days) methamphetamine users and 16 control subjects performing an auditory vigilance task and obtained structural magnetic resonance brain scans. Error rates on the task were related to regional radioactivity and hippocampal morphology. Methamphetamine users had higher error rates than control

subjects on the vigilance task. The groups showed different relationships between error rates and relative activity in the anterior and middle cingulate gyrus and the insula. Whereas the MA user group showed negative correlations involving these regions, the control group showed positive correlations involving the cingulate cortex. Across groups, hippocampal metabolic and structural measures were negatively correlated with error rates. Dysfunction in the cingulate and insular cortices of recently abstinent MA abusers may contribute to impaired vigilance and other cognitive functions requiring sustained attention. Furthermore, hippocampal structural integrity predicts task performance in methamphetamine users as well as control subjects. London, E.D., Berman, S.M., Voytek, B., Simon, S.L., Mandelkern, M.A., Monterosso, J., Thompson, P.M., Brody, A.L., Geaga, J.A., Hong, M.S., Hayashi, K.M., Rawson, R.A. and Ling, W. Biological Psychiatry, 58(10), pp. 770-778, 2005.

Psychological and Cognitive Effects of Long-Term Peyote Use among Native Americans

Halpern and colleagues at McLean Hospital investigated the long-term, residual psychological and cognitive effects of hallucinogens. The Rand Mental Health Inventory (RMHI), and ten standard neuropsychological tests of memory and attentional/executive functions were administered to three groups of Navajo Native Americans, age 18-45. The groups were: 1) 61 Native American Church members who regularly ingested peyote, a hallucinogen-containing cactus, 2) 36 individual with past alcohol dependence, but currently sober at least 2 months, and 3) 79 individuals reporting minimal use of peyote, alcohol, or other substances. Compared to Navajos with minimal substance use, the peyote group showed no significant deficits on the RMHI or any neuropsychological measures, whereas the former alcoholic group showed significant deficits ($p < .05$) on every scale of the RMHI and on two neuropsychological measures. Within the peyote group, total lifetime peyote use was not significantly associated with neuropsychological performance. Since there is no evidence of psychological or cognitive deficits among Native Americans using peyote regularly in a religious setting, these findings may not generalize to illicit hallucinogen users. Halpern, J.H., Sherwood, A.R., Hudson, J.I., Yurgelun-Todd. D. and Pope, H.G. Biological Psychiatry. 58(8), pp. 624-631, 2005.

Smokers Have Increased fMRI Activation to Smoking-Related Pictorial Cues in the Ventral Striatum / Nucleus Accumbens

Sean David and colleagues recruited smokers and non-smokers to view smoking-related or neutral images while undergoing continuous 3 Tesla fMRI. Three clusters of bilateral activation were observed in smokers for smoking related cues: anterior cingulate/orbitofrontal cortex, superior frontal gyrus, and occipital cortex. Importantly, in secondary analysis (a priori hypothesis) of the ventral striatum/nucleus accumbens region, smokers had significantly greater activation than non-smokers. The authors stipulate that this is the first demonstration of greater activation of this area in addicted smokers than non-smokers presented with smoking-related cues using fMRI. David, S.P., Munaf˜, Johansen-Berg, H., Smith, S.M., Rogers, R.D., Matthews, P.M. and Walton, R.T. Biological Psychiatry, 58, pp. 488-494, 2005.

COMT SNPs and Haplotypes Differentially Associated with European and African American, Male and Female Smokers

Li and colleagues studied 5 SNPs and associated haplotypes in over 600 nuclear families. Results showed the Val/Met polymorphism (rs4680) was associated with three different (but related) measures of smoking. Haplotype analysis revealed one SNP trio was a protective factor for European Americans; another

three-SNP haplotype was protective for African Americans while a third was high-risk. However, further analysis showed the protective factors were only for the African American females and the European American males. Both SNPs and haplotypes had different frequencies in the two ethnic groups. These data suggest that COMT variants are related to nicotine dependence but that the effects are both sex and ethnic specific. Other studies have shown the val/met polymorphism to be related to low extraversion and high neuroticism usually in females. Beuten, J., Payne, T.J., Ma, J.Z. and Li, M.D. Neuropsychopharmacology, 31, pp. 675-684, 2006.

Association Between the DOPA Decarboxylase (DDC) Gene and Nicotine Dependence

Based on a suggestive link in previous research, Li and associates studied eight SNPs within the DDC gene in search of an association with nicotine dependence assessed by several measures of smoking severity. It was found in 2037 smokers in 602 nuclear families that one SNP was associated with two of the smoking measures in a European American sample. Haplotype association analysis revealed a risk haplotype. However, a protective haplotype (a different combination of SNPs) was found in the African American sample associated with all smoking measures. These results not only show the involvement of DDC in nicotine dependence but demonstrate a racial specificity. Ma, J.Z., Beuten, J., Payne, T.J., Dupont, R.T., Elson, R.C. and Li, M.D. Human Molecular Genetics, 14(12), pp. 1691-1698, 2005.

Sex Differences in Smoking Initiation and Consumption and in Linkage Analysis

Madden and her colleagues queried their sample of Australian twins with regard to smoking onset and continuation as a "smoker" in both males and females. Results demonstrated the presence of sex differences in the magnitude of genetic and genetic and environmental influences. Heritability was higher for men; shared environment was important only for women in a group where self-described non-smokers were excluded. For smoking initiation, the strongest linkage peak was at 20p13; for cigarette consumption where non-smokers were included, the highest peak was at 11q23 with secondary peaks at4q35 and 6p34. The peaks were similar but not the same when non-smokers were excluded. Also males tended to have the stronger peaks. These results support some recent studies and add to the growing list of possible susceptibility genes for smoking. Morley, K.I., Medland, S.E., Ferreira, M.A.R., Lynsky, M.T., Montgomery, G.W., Heath, A.C., Madden, P.A.F. and Martin, N.G. Behavior Genetics, ONLINE, pp. 1-13, Dec 20, 2005.

Association of the Mu Opioid Receptor Gene (OPRM1) for Drug or Alcohol Dependence

Gelernter and colleagues examined 13 single nucleotide polymorphisms in introns spanning the coding region of the mu opioid receptor gene. In analyses that identified associated haplotypes in European Americans, two blocks were found—one in which a combination of the minor alleles were more common in cases; the other in which they were more common in controls, suggesting a protective factor. These data were repeated in a secondary sample collected in Russia. The association in the first block is close to the much-studied exon (118A/Gˆ asn40 to asp40) gene variant lending support to the affirmative results reported. In summary, the results showed that multiple intronic SNPs in OPRM1 might increase risk for substance dependence. The data are consistent with an interpretation that there are at least two bi-allelic risk variants at the OPRM1 locus mapping to different haplotypes. Zhang, H., Luo, X., Kranzler, H.R., Lappalainen, J., Yang, B.-Z., Krupitsky, E., Zvartau, E. and Gelernter, J.

Human Molecular Genetics 15, pp. 807-819, 2006.

Genes Associated with Opioid Dependence Subtypes Determined by Genome-Wide Scan

Gelernter and associates recruited 393 families each with at least one opioid dependent individual and performed a genome-wide scan for phenotypes determined a priori by cluster analysis. Two of the clusters were significantly associated with a location on chromosome 17. There was a LOD score of 3.06 for a "heavy-opioid-use" cluster for all subjects (European American and African American groups combined). A slightly larger LOD score of 3.46 was found for "non-opioid-use" in European Americans only. (These individuals were largely dependent or addicted to other drugs primarily cocaine.) These results are a suggestive step for association to specific subtypes of opioid (or non-opioid) dependent subjects. Gelernter, J., Panhuysen, C., Wilcox, M., Hesselbrock, V., Rounsaville, B., Poling, J., Weiss, R., Sonne, S., Zhao, H., Farrer, L. and Kranzler, H.R. American Journal of Human Genetics, 78, pp. 759-769, May 2006.

Low Socialization Is Correlated with Increased Activity in the Medial Prefrontal Cortex in Cocaine-Dependent Women

Rajita Sinha, T. R. Kosten and C-S. R. Li assessed antisocial personality using the California Psychological Inventory socialization scale and compared it to brain activation during a script-guided induction of stress. Three (right inferior frontal cortex, right anterior cingulate and medial prefrontal cortex (MDFC)) of eight brain regions which showed greater activation during stress imagery than at baseline and which were within the corticolimbic circuitry were correlated with the socialization score separately for males and females. The scores were all correlated but only the MPFC in females was (negatively) significant. A low socialization score means a lower arousal to stress and has been previously related to physiological measurements such as skin conductance and heart rate. In other words, females seemed to be underaroused during stress imagery (a suggestion of antisocial pathology) which is shown to be related to increased brain activity in the MDFC. Li, C-S. R., Kosten, T.R. and Sinha, R. NeuroReport, 17(3), pp. 243-247, 2006.

The Alpha-4 Subunit of the Nicotinic Acetylcholine Receptor Is Ethnically-Specific and Gender-Specific Associated with Nicotine Dependence

M.D. Li and associates assessed over 2,000 European or African American subjects from over 600 families. Two (different) single nucleotide polymorphisms are associated with measures of smoking in each of the two ethnic origin groups. After correction, one SNP and a haplotype remained significant in African American females. There were no associations with the beta-2 subunit of the receptor. These data suggest that there is involvement of the alpha 4 subunit of the nicotinic acetylcholine receptor in nicotine addiction. Li, M.D., Beuten, J, Ma, J.Z., Payne, T.J., Lou, X-Y., Garcia, V., Duenes, A.R., Crews, K.M. and Elston, R.C. Human Molecular Genetics, 14(9), pp. 1211-1219, 2005.

Sleep Quality Deteriorates in Abstinent Cocaine Dependent Individuals

Hobson, Stickgold and associates studied sleep in non-treatment-seeking cocaine dependent individuals on an inpatient basis during a binge-smoking followed by two-week abstinent session. Several measures of sleep quality including duration, efficiency, and onset latency all deteriorated during the

abstinent period. By contrast, subjectively the subjects reported no loss of sleep quality. That is, they felt that they were consistently rested across the two-week period while objective measures showed decline. The speculation of this dissociation between objective and subjective sleep quality is a consequence of disruption of the sleep homeostat. How cocaine affects the neurobiology underlying these phenomena and how that relates to relapse is the next stage of this research. Pace-Schott, E.F., Stickgold, R., Muzur, A., Wigren, P.E., Ward, A.S., Hart, C.L., Clarke, D., Morgan, A. and Hobson, J.A. Psychopharmacology, 179, pp. 873-883, 2005.

Methamphetamine Abusers with Low CD4 Lymphocyte Counts Demonstrate an Additive Effect on Neuropsychological Deficits Associated with HIV Infection

Methamphetamine (MA) dependence and HIV infection are independently associated with cerebral dysfunction, especially within frontal-basal ganglia circuits. Recent evidence indicates that MA dependence has an additive effect on neuropsychological (NP) deficits associated with HIV infection. This study by Igor Grant and colleagues extends prior findings by examining the combined effects of MA dependence (MA+) and immuno-suppression (i.e., CD4 lymphocyte count <200) on NP functioning in 284 HIV+ individuals. Prevalence of NP impairment was examined in four demographically comparable groups: (1) MA+/CD4 < 200; (2) MA+/CD4 >/= 200; (3) MA-/CD4 < 200; and (4) MA-/CD4 >/= 200. Results revealed that both MA dependence and immuno-suppression were significant predictors of NP impairment. More importantly, additive effects were evident whereby the MA+/CD4 < 200 group exhibited the highest rate of NP impairment. Findings indicate that MA dependence conveys an additive deleterious impact on NP status in immunosuppressed persons with HIV infection, perhaps reflecting the combined effects of neuropathophysiological mechanisms in fronto-striatal circuits. Carey, C.L., Woods, S.P., Rippeth, J.D., Gonzalez, R., Heaton, R.K. and Grant, I. AIDS Behavior, 10, pp. 1-6, 2006.

Study of Ecstasy in a Naturalistic Environment

Johns Hopkins researcher, Dr. Una McCann, conducted a study in humans to determine whether MDMA (ecstasy), when used in the naturalistic setting of dance parties ("raves"), leads to plasma levels that have been associated with the toxicity to 5-HT neurons seen in animals. A variety of measures were obtained prior to, and hours after, individuals attended a rave where they had taken ecstasy. After the rave, subjects were without clinical complaints, had measurable amounts of residual MDMA in plasma, and nearly half of the subjects also tested positive for methamphetamine, another amphetamine analog that has been shown to have 5-HT neurotoxic potential in animals. Plasma concentrations of MDMA did not correlate with self-reported use of ecstasy and, in some subjects, levels overlapped with those that have been associated with 5-HT neurotoxicity in non-human primates. Others were believed to have had similar concentrations while at the dance party, when one considers the reported time of drug ingestion and the plasma half-life of MDMA in humans. Hematological and biochemical analyses were generally unremarkable. Moderate increases in blood pressure, heart rate and body temperature were observed in the subjects with the highest MDMA plasma concentrations. These findings are consistent with epidemiological findings that most people who use MDMA at dance parties do not develop serious clinical complications. Irvine, R.J., Keane, M., Felgate, P., McCann, U.D., Callaghan, P.D. and White, J.M. Neuropsychopharmacology. 31, pp. 424-430, 2006.

Increased Acoustic Noise During Working Memory May Have A Greater Impact In HIV+ Patients

Linda Chang and colleagues compared HIV- patients to those who were HIV+. HIV+ patients showed reduced acoustic noise (AN) activation and lower neuronal marker N-acetylaspartate in prefrontal and parietal cortices. Competing use of the working memory network between AN and cognitive load showed lower dynamic range of the hemodynamic responses in prefrontal and parietal cortices in HIV patients. These findings suggest that reduced reserve capacity of the working memory network in HIV patients and additional stress (eg, AN) might exhaust the impaired network for more demanding tasks. Tomasi, D., Chang, L., de Castro Caparelli, E., Telang, F. and Ernst, T. The Human Immunodeficiency Virus Reduces Network Capacity: Acoustic Noise Effect. Annals of Neurology, 59, pp. 419 - 423, 2006.

Common Deactivation Patterns During Working Memory And Visual Attention Tasks

Linda Chang and colleagues conducted a parametric functional magnetic resonance imaging (fMRI) study to investigate the balance of negative and positive fMRI signals in the brain. A set of visual attention (VA) and working memory (WM) tasks with graded levels of difficulty was used to deactivate separate but overlapping networks that include the frontal, temporal, occipital, and limbic lobes; regions commonly associated with auditory and emotional processing. Brain activation (% signal change and volume) was larger for VA tasks than for WM tasks, but deactivation was larger for WM tasks. Load-related increases of blood oxygenation level-dependent (BOLD) responses for different levels of task difficulty cross-correlated strongly in the deactivated network during VA but less so during WM. The variability of the deactivated network across different cognitive tasks supports the hypothesis that global cerebral blood flow vary across different tasks, but not between different levels of task difficulty of the same task. The task-dependent balance of activation and deactivation might allow maximization of resources for the activated network. Tomasi, D., Ernst, T., Carpelli, L.C. and Chang, L. Common Deactivation Patterns During Working Memory and Visual Attention Tasks: An Intra-subject fMRI Study at 4 Tesla. Human Brain Mapping, On-Line, January 10, 2006.

Director's Report to the National Advisory Council on Drug Abuse - May, 2006

Research Findings - Epidemiology and Etiology Research

Epidemiology of Smoking Behaviors in a National Young Adult Sample

This study describes the epidemiology of smoking behaviors in a national young adult sample and identifies common and unique demographic, social, and psychological correlates of daily smoking and lifetime and current nicotine dependence by race/ethnicity. Data are from the National Longitudinal Survey of Adolescent Health, wave III. Hispanic ethnicity, low education, parental and peer smoking, novelty seeking, early age of smoking onset, and pleasurable initial smoking experiences are significantly correlated with daily smoking and lifetime nicotine dependence. Depressive symptoms are uniquely associated with lifetime and current dependence. Few factors are highly associated with current dependence. Initial sensitivity to smoking has a significantly greater impact on daily smoking than on dependence. Correlates of smoking behaviors are mostly common across racial/ethnic groups, although parental and peer smoking are significant for Whites and Hispanics but not for African Americans. There are more common than unique correlates of each smoking stage and across racial/ethnic groups. Primary prevention and interventions addressing the factors tested could be uniform for most chronic smokers irrespective of dependence status and race/ethnicity. Hu, M., Davies, M., and Kandel, D. Epidemiology and Correlates of Daily Smoking and Nicotine Dependence Among Young Adults in the United States. Am J Public Health, 96(2), pp. 299-308, 2006.

Cigarette Smoking in Two American Indian Reservation Populations

This study describes the prevalence and correlates of cigarette smoking in two American Indian reservation populations using multinomial logistic regression on data from a population-based, cross-sectional study of Southwest and Northern Plains American Indians aged 15-54. 19% of Southwest men, 10% of Southwest women, 49% of Northern Plains men and 51% of Northern Plains women were current smokers. Male gender and younger age were associated with higher odds of smoking in the Southwest tribe, whereas current or former marriage and less time spent on a reservation were associated with higher odds of smoking in the Northern Plains population. Alcohol consumption was strongly associated with higher odds of smoking in both groups. Nez Henderson, P., Jacobsen, C., Beals, J. and the AI-SUPERPFP Team. Correlates of Cigarette Smoking Among Selected Southwest and Northern Plains Tribal Groups: The AI-SUPERPFP Study. Am J Public Health, 95, pp. 867-872, May 2005.

Exposure to Trauma Among Two American Indian Tribes

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This study examined the prevalence of trauma in 2 large American Indian communities in an attempt to describe demographic correlates and to compare findings with a representative sample of the US population. The researchers determined differences in exposure to each of 16 types of trauma among 3084 tribal members aged 15 to 57 years through structured interviews. The researchers compared prevalence rates of trauma, by gender, across the 2 tribes and with a sample of the US general population. The researchers used logistic regression analyses to examine the relationships of demographic correlates to trauma exposure. Lifetime exposure rates to at least 1 trauma (62.4%-67.2% among male participants, 66.2%-69.8% among female participants) fell at the upper limits of the range reported by other researchers. Unlike the US general population, female and male American Indians exhibited equivalent levels of overall trauma exposure. Members of both tribes more often witnessed traumatic events, experienced traumas to loved ones, and were victims of physical attacks than their counterparts in the overall US population. Many American Indians live in adverse environments that place them at high risk for exposure to trauma and harmful health sequelae. Manson, S., Beals, J., Klein, S., Croy, C., and Croy, C. Social Epidemiology of Trauma Among 2 American Indian Reservation Populations. Am J Public Health, 95(5), pp. 851-859, 2005.

Psychosocial Adjustment Among Drug Using Suburban Adolescents

Despite ongoing concern about substance use during adolescence, very little is known about alcohol and drug use among teens living in affluent social settings. In this longitudinal study, cluster analysis was used to characterize patterns of substance use and change in other dimensions of psychosocial adjustment within a cohort of 292 high school students (54% girls) living in an affluent, suburban community. When compared with a cluster of students reporting minimal use, clusters reporting escalating, declining, and persistently high use consistently demonstrated relatively poorer psychosocial adjustment. Moreover, other dimensions of psychosocial adjustment remained relatively stable despite changes in substance use, and there were relations involving substance use and other aspects of psychosocial adjustment that may be specific to this social setting. McMahon, T. and Luthar, S. Patterns and Correlates of Substance Use Among Affluent, Suburban High School Students. J Clin Child Adolesc Psychol, 35(1), pp. 72-89, 2006.

Late Onset Antisocial Behavior and Risk for SUD

This study compared late onset antisocial behavior with the more commonly recognized two courses, persisting (beginning by early adolescence and continuing through late adolescence) and desisting (stopping by mid-adolescence) antisocial behavior, in terms of risk for later substance dependence and background risk factors (gender, IQ, socioeconomic status, parental antisocial behavior, and parental divorce). A population-based sample of 500 twins from the Minnesota Twin Family Study, evaluated at ages 17 and 20, was used. The results indicated that youths with late onsets were similar to those with persisting antisocial behavior and that both groups were at higher risk of later nicotine, alcohol, and cannabis dependence than controls; both also had similarly high levels of background risk factors. The late-onset group included a significant overrepresentation of females, whereas the persisting and desisting groups included more males. The authors conclude that late-onset antisocial behavior has many of the same negative correlates of persisting antisocial behavior but includes significantly more females. Clinical implications include the need to recognize this pathway, particularly for vulnerable young women, even though they do not meet criteria for the

diagnosis of antisocial personality disorder, for both etiologic studies and preventive interventions. Marmorstein, N. and Iacono, W. Longitudinal Follow-Up of Adolescents with Late-Onset Antisocial Behavior: A Pathological Yet Overlooked Group. J Am Acad Child Adolesc Psychiatry, 44(12), pp. 1284-1291, 2005.

Familial and Peer Influences on Adolescent Substance Use

Parental, peer, and older siblings' contributions to adolescents' substance use were investigated with 2 waves of panel data from 225 African American families. Structural equation modeling showed that older siblings' behavioral willingness (BW) to use substances at Time 1 (T1) predicted target adolescents' Time 2 (T2) use, controlling for other T1 variables. Regression analyses revealed an interaction between targets and siblings' BW, such that targets were more likely to use at T2 if both they and their siblings reported BW at T1. This interaction was stronger for families living in high-risk neighborhoods. Finally, siblings' willingness buffered the impact of peer use on targets' later use: Low sibling BW was associated with less evidence of peer influence. Pomery, E., Gibbons, F., Gerrard, M., Cleveland, M., Brody, G. and Wills, T. Families and Risk: Prospective Analyses of Familial and Social Influences on Adolescent Substance Use. J Fam Psychol, 19(4), pp. 560-570, 2005.

Social Competence Among Children of Alcoholics

In the current study, the authors tested the hypothesis that children of alcoholic parents (COAs) show deficits in social competence that begin in early childhood and escalate through middle adolescence. A community sample of families with high levels of alcohol use disorder and control families was used (n=110 COAs and 263 controls). Teachers, parents, and children reported on the social competence of COAs and matched controls assessed from ages 6 to 15. Hierarchical linear growth models revealed different patterns of change in social competence across development as a function of the reporter of various indicators of competence. Moreover, female COAs showed deficits in social competence in early childhood that receded in adolescence and that varied across subtypes of parent alcoholism. Implications of these findings for understanding the development of social competence in children, and at-risk children in particular, are discussed. Hussong, A., Zucker, R., Wong, M., Fitzgerald, H., and Puttler, L. Social Competence in Children of Alcoholic Parents Over Time. Dev Psychol, 41(5), pp. 747-759, 2005.

Behavior Problems Among Maltreated Children

Maltreated children are at increased risk for behavior problems. This study examines a model in which shame mediates the potential relation between maltreatment and anger, and anger mediates the potential relation between shame and behavior problems. Participants were 177 children (ages 3 to 7 years) and their mothers, 90 of whom had histories of perpetrating neglect and/or physical abuse. Physical abuse, but not neglect, was related to increased shame during an evaluative task; shame was related to increased anger; and anger to teacher ratings of total behavior problems and externalizing problems. Age moderated the relation between physical abuse and adjustment, as abuse was related to more total problems only among the younger children. Anger was a significant mediator of shame and both behavior problems and externalizing problems. Shame, anger, age, and type of maltreatment appear to be important factors in explaining variance in behavioral adjustment following a history of maltreatment. Bennett, D., Sullivan, M., and Lewis, M. Young Children's Adjustment as a Function of Maltreatment, Shame, and Anger. Child Maltreat, 10(4), pp. 311-323, 2005.

Illicit Drug Use and HIV-1 Disease Progression: A Longitudinal Study in the Era of Highly Active Antiretroviral Therapy

This study assessed the association between longitudinal patterns of illicit drug use and clinical progression of HIV disease. Confidential computer-based interviews, which addressed illicit drug use and other factors, were completed by HIV-infected participants in Baltimore, Maryland, at 6-month intervals from 1998 onward. To assess this association, the authors used a random-effects model in which clinically defined opportunistic conditions were linked to self-reported periods of drug use, enabling four categories of drug use to be distinguished: nonusers, intermittent users during abstinent periods, intermittent users during active periods, and persistent users. Included in the analysis were 1,851 participants who completed > or = 1 survey. For participants who used drugs intermittently over time, the risk of developing new opportunistic conditions during periods of abstinence was similar to that for those who never used drugs (odds ratio = 1.2, 95% confidence interval: 0.9, 1.7). In contrast, compared with that for nonusers, the risk of opportunistic infection was significantly higher for intermittent drug users during periods of active use (odds ratio = 2.2, 95% confidence interval: 1.4, 2.9) and for persistent drug users (odds ratio = 1.9, 95% confidence interval: 1.2, 2.8). Active drug use is temporally linked to HIV disease progression and mortality. Effectively targeting and treating active substance abuse in HIV treatment settings may provide a mechanism to improve clinical outcomes. Lucas, G., Griswold, M., Gebo, K., Keruly, J., Chaisson, R and Moore, R. Illicit Drug Use and HIV-1 Disease Progression: A Longitudinal Study in the Era of Highly Active Antiretroviral Therapy. Am J Epidemiol, 163(5), pp. 412-420, 2006.

HIV/AIDS and Injection Drug Use in the Neighborhoods of Dar es Salaam, Tanzania

This study examines the intersection between needle-sharing practices and HIV recovered from used syringes collected from 73 heroin injection drug users (IDUs) in Dar es Salaam, Tanzania, between October 2003 and January 2004. To extract blood residue, syringes were flushed and 10 micro liters of solution mixed with 120 micro liters of a latex solution was placed on a Capillus HIV-1/2 slide. Thirty-five(57%) of the useable syringes tested positive for HIV antibodies. Results varied significantly: 90% of syringes tested HIV positive in a mixed-income neighborhood 2 kilometers from the city center; 0% of syringes tested HIV positive in the outlying areas. In addition, semi structured interviews were conducted with 51 IDUs. The interviews were content coded, and codes were collapsed into emergent themes regarding syringe-use practices. Injecting is a recent practice, particularly among heroin users in neighborhoods far from the city center. Sharing syringes has resulted in a high proportion of used syringes containing HIV-positive blood residue. Geographic distance is an indicator of recent adoption of IDU in neighborhoods and correlates strongly with the distribution of syringes containing HIV-positive blood residue. McCurdy, S.A., Ross, M.W., Kilonzo, G.P., Leshabari, M.T. and Williams, M.L. HIV/AIDS and Injection Drug Use in the Neighborhoods of Dar es Salaam, Tanzania. Drug Alcohol Depend, 82(1), pp. S23-S27, 2006.

Reductions in Hepatitis C Virus and HIV Infections Among Injecting Drug Users in New York City, 1990-2001

Researchers assessed trends in HIV, hepatitis C virus (HCV) and HIV/HCV infection among injecting drug users (IDU) from 1990 to 2001 in New York City. The 1990-2001-time period included a very large expansion of syringe exchange in New York City, from 250,000 to 3,000,000 syringes exchanged annually. Cross-sectional seroprevalence surveys were conducted of IDU

entering drug abuse treatment in New York City, with sample sizes for HCV of 72 in 1990-1991 and 412 in 2000-2001. A structured risk behavior questionnaire was administered, and HIV and HCV testing were conducted. HCV testing was performed on de-linked stored serum samples. Findings showed that, over the 1990-2001 period, HIV prevalence declined from 54 to 13%. HCV prevalence declined from 80 to 59% among HIV-seronegative individuals, and from 90 to 63% overall. The estimated HCV incidence in 2000-2001 among new injectors was 18 per 100 person-years at risk. These results indicate that the large-scale expansion of syringe exchange was temporally associated with large reductions in both HIV and HCV prevalence. The prevalence and incidence of HCV, however, still remain at high levels among IDU in New York City. Des Jarlais, D., Perlis, T., Arasteh, K., Torian, L., Hagan, H., Beatrice, S., Smith, L., Wethers, J., Milliken, J., Mildvan, D., Yancovitz, S. and Friedman, S. Reductions in Hepatitis C Virus and HIV Infections Among Injecting Drug Users in New York City, 1990-2001. AIDS, 19(3), pp. S20-S25, 2005.

Behavioral Risk Exposure and Host Genetics of Susceptibility to HIV-1 Infection

Some individuals are readily infected with low HIV-1 exposure, whereas others appear less susceptible, suggesting that host genetics plays a role in the viral entry pathway. The matched case-control study design with measured risk exposures provides an avenue for discovering genes involved in susceptibility to infection. Researchers conducted a nested case-control study of African Americans (266 HIV-1 seroconverter cases and 532 seronegative controls from the AIDS Link to Intravenous Experience cohort), to examine the association between 50 single-nucleotide polymorphisms (SNPs) in 9 candidate genes (CCR5, CCR2, RANTES, MIP1A, MCP2, IL10, IFNG, MCSF, and IL2) and susceptibility to HIV-1 infection. To account for differential exposure propensities, risk behavior self-reported during semiannual visits was used to estimate a standardized cumulative risk exposure (SCRE). Individual SNPs were evaluated using conditional logistic-regression models, and the inferred haplotypes were assessed in the haplotype trend regression analyses after adjusting for age and SCRE. Four SNPs (CCR2-V64I, CCR5-2459, MIP1A+954, and IL2+3896) and specific haplotypes in the IL2 and CCR2/CCR5 regions were found to be significantly associated with HIV-1 infection susceptibility in different genetic models. These results suggest that genetic variants in associated host genes may play an important role in susceptibility to HIV-1 infection. Shrestha, S., Strathdee, S., Galai, N., Oleksyk, T., Fallin, M., Mehta, S., Schaid, D., Vlahov, D., O 'Brien, S., and Smith, M. Behavioral Risk Exposure and Host Genetics of Susceptibility to HIV-1 Infection. J Infect Dis, 193(1), pp. 16-26, 2006.

Longitudinal Predictors of Injection Cessation and Subsequent Relapse among a Cohort of Injection Drug Users in Baltimore, MD, 1988-2000

Researchers sought to determine predictors of injection drug use cessation and subsequent relapse among a cohort of injection drug users (IDUs). IDUs in Baltimore, MD were recruited through community outreach in 1988-1989. Among IDUs with at least three follow-up visits, parametric survival models for time to injection cessation (>/=6 months) and subsequent relapse were constructed. Of 1327 IDUs, 94.8% were African American, 77.2% were male, median age was 34 years, and 37.7% were HIV-infected. Among 936 (70.5%) subjects who ceased injection, median time from baseline to cessation was 4.0 years. Three-quarters subsequently resumed injection drug use, among whom median time to relapse was 1.0 year. Factors independently associated with a shorter time to cessation were: age <30 years, stable housing, HIV seropositivity, methadone maintenance treatment, detoxification, abstinence

from cigarettes and alcohol, injecting less than daily, not injecting heroin and cocaine together, and not having an IDU sex partner. Factors independently associated with shorter time to injection relapse were male gender, homelessness, HIV seropositivity, use of alcohol, cigarettes, non-injection cocaine, sexual abstinence and having a longer time to the first cessation. These findings show how important it is to target cessation efforts among young IDUs and severely dependent, unstably housed, and HIV-infected individuals. Shah, N.G., Galai, N., Celentano, D., Vlahov, D. and Strathdee, S. Longitudinal Predictors of Injection Cessation and Subsequent Relapse among a Cohort of Injection Drug Users in Baltimore, MD, 1988-2000. Drug Alcohol Depend, available online 20 December 2005.

High Prevalence of Alcohol Use among Hepatitis C Virus Antibody Positive IDUs in 3 US Cities

IDUs acquire the majority of new hepatitis C virus (HCV) infections and frequently use alcohol. Alcohol abuse accelerates liver disease among HCV-infected persons, can reduce the effectiveness of treatment for HCV infection and may be a contradiction for HCV treatment. HCV seropositive, HIV-negative IDUs aged 28-35 years in Baltimore, New York City, and Seattle who were enrolled in a behavioral risk-reduction intervention trial underwent computerized self-interviews to assess baseline alcohol use and dependence and medical history. Researchers measured problem alcohol use using the 10-item Alcohol Use Disorders Identification Test (AUDIT) scale. Of 598 participants, 84% responded "false" to "it is safe for a person with HCV to drink alcohol." Problem drinking, defined as a score of 8 or higher on AUDIT, was identified in 37%. Correlates of scoring 8 or higher on AUDIT included homelessness, male gender, primarily injecting speedballs, having injected with used needles, prior alcohol treatment, and depression. Although most HCV positive IDUs appeared to be informed about their increased risk of liver disease from alcohol, 40% screened positive for problem alcohol use. These findings indicate how important it is to refer HCV-positive persons to effective alcohol treatment programs to reduce foture liver damage and improve eligibility for and treatment of HCV. Campbell, J.V., Hagan, H., Latka, M.H., Garfein, R.S., Golub, E.T., Coady, M.H., Thomas, D.L., and Strathdee, S.A. High Prevalence of Alcohol Use Among Hepatitis C Virus Antibody Positive IDUs in 3 US Cities. Drug Alcohol Depend, 81, pp. 259-265, 2006.

The Impact of Sex Partners' HIV Status on HIV Seroconversion in a Prospective Cohort of Injection Drug Users

The identification of individuals at highest risk of HIV infection is critical for targeting prevention strategies. This study evaluated the HIV status of the sex partners of IDUs and rates of subsequent HIV seroconversion among a prospective cohort study of IDUs. Researchers performed an analysis of the time to HIV infection among baseline HIV-negative IDUs enrolled in the Vancouver Injection Drug Users Study. IDUs were stratified based on whether or not they reported having an HIV-positive sex partner. Kaplan-Meier methods were used to estimate cumulative HIV incidence rates, and Cox regression was used to determine adjusted relative hazards (RHs) for HIV seroconversion. Of 1013 initially HIV-negative IDUs, 4.8% had an HIV-positive partner at baseline. After 18 months, the cumulative HIV incidence rate was significantly elevated among those who reported having an HIV-positive sex partner (23.4% vs. 8.1%; log-rank $P < 0.001$). In a Cox regression model adjusting for all variables that were associated with the time to HIV infection in univariate analyses, including drug use characteristics, having an HIV-positive sex partner (RH = 2.42 [95% confidence interval: 1.30 to 4.60]; $P = 0.005$) remained independently associated with time to HIV seroconversion. These findings indicate that having an HIV-positive sex partner was strongly and independently associated with seroconversion after adjustment for risk factors

related to drug use. The findings may aid public health workers in their efforts to identify IDUs who should be targeted with education and prevention efforts and indicate the need for ongoing development of prevention interventions for IDU sex partners who are HIV discordant. Kerr, T., Stoltz, J., Strathdee, S., Li, K., Hogg, R., Montaner, J., and Wood, E. The Impact of Sex Partners' HIV Status on HIV Seroconversion in a Prospective Cohort of Injection Drug Users. J Acquir Immune Defic Syndr, 41(1), pp. 119-123, 2006.

Predictors of Early Initiation of Vaginal and Oral Sex Among Urban Young Adults in Baltimore, Maryland

Over the past three decades, most research on adolescent sexual behavior has focused on vaginal intercourse and related behaviors, including contraception and unintended pregnancy. In this study, researchers describe the prevalence and correlates of vaginal, oral, and anal sex in an epidemiologically defined population in Baltimore, Maryland. Young adults (ages 18-24), who had been enrolled in a behavioral intervention trial during elementary school, were interviewed by telephone between 1998 and 2002 to assess their sexual behavior. Of 1679 respondents interviewed, 70.8% were Black and 55% were women. Overall, 93% of the young adults reported vaginal intercourse, 78% reported receiving oral sex, 57% reported performing oral sex, and 10% reported receptive anal intercourse. Among men, 27% reported insertive anal intercourse. Blacks initiated vaginal intercourse at an earlier age than Whites; White women performed oral sex earlier than Black women. Significant interactions were observed between age of first vaginal partner and both gender and race/ethnicity. Blacks with older partners initiated sex at an earlier age than both Blacks with a partner the same age or younger and Whites. A relationship between older female sex partners and earlier vaginal sex initiation among men was observed. These findings indicate that older sex partners play an important role in sexual initiation among young adults. In light of the rates of oral and anal sex, sexual education and intervention programs should address the risk for unintended consequences of these behaviors. Ompad, D., Strathdee, S., Celentano, D. and Latkin, C. Predictors of Early Initiation of Vaginal and Oral Sex Among Urban Young Adults in Baltimore, Maryland. Arch Sex Behav, 35(1), pp. 53-65, 2006.

The Impact of Emotional Distress on HIV Risk Reduction among Women

This study evaluated whether 333 seronegative African American female drug users (aged 18-59 years) participating in an HIV intervention and with higher levels of emotional distress, specifically symptoms of depression and anxiety, reduced HIV risk behaviors to a lesser extent than those with lower levels of emotional distress. Participants were recruited between June 1998 and January 2001 from inner-city Atlanta (Georgia, U.S.) neighborhoods and were randomly assigned to one of two enhanced gender-specific and culturally specific HIV intervention conditions or to the NIDA standard condition. Participants were interviewed at baseline, post-intervention and at 6-month follow-up with a structured questionnaire including information on sociodemographics, sexual and drug-using behavior, and psychosocial characteristics. Despite a significant decline in symptoms of emotional distress during the study period, the women in this sample reported high levels of depressive and anxiety symptoms at baseline and 6-month follow-up. Higher levels of emotional distress were positively associated with post-intervention sexual and drug-taking risk. Women in both enhanced intervention conditions reduced their sexual and drug-taking risks more than women in the standard intervention. Those in the motivation intervention arm experienced a greater reduction in depressive symptoms, accompanied by a greater reduction in sexual risk behavior. Findings suggest the need for effective interventions and mental health resources among subgroups of high-risk women who may be most resistant to

behavioral change. Sterk, C., Theall, K. and Elifson, K. The Impact of Emotional Distress on HIV Risk Reduction Among Women. Subst Use Misuse, 41(2), pp. 157-173, 2006.

Drug Treatment Disparities among Hispanic Drug-Using Women in Puerto Rico and New York City

This paper reports findings on 334 out-of-treatment drug users in Puerto Rico and 617 in New York City, at the 6-month follow-up interview of a longitudinal survey. Main outcomes were health care and drug treatment utilization since baseline, assessed by asking participants if they had received physical or mental health services (including HIV medications), and if they had been in methadone maintenance, inpatient or outpatient drug treatment, or drug treatment while incarcerated. Chi-square tests were used to evaluate associations between gender and other correlates. Logistic regression was used to calculate the contribution of each variable in predicting use of drug treatment. The analysis suggests that women in both sites were likely to suffer from disparities in health care and drug treatment utilization when compared with men, although women in New York utilized more drug treatment resources and were more embedded in the immediate family than their female peers in Puerto Rico. Further research to specify the impact of contextual factors at the organizational and community levels, among members of the same ethnic group residing in different sites, may prove valuable in identifying the health needs and factors that impede or facilitate drug-using women in obtaining the most appropriate treatment. Findings from these studies can help in developing appropriate public health policy and science-based drug treatment programs to eliminate such disparities as those identified in this study. Robles, R., Matos, T., Deren, S., Col—n, H., Sahai, H., Marrero, C., Reyes, J., And'a, J., and Shepard, E. Drug Treatment Disparities among Hispanic Drug-Using Women in Puerto Rico and New York City. Health Policy, 75(2), pp. 159-169, 2006.

Correlates of Unsafe Syringe Acquisition and Disposal among Injection Drug Users in Baltimore, Maryland

Because multi-person syringe use is the most common vehicle for HIV and hepatitis C virus transmission among IDUs, safe sources of sterile syringes and safe methods of disposal are necessary to curb these epidemics. This study examined syringe acquisition and disposal in a cohort of IDUs in Baltimore. Between January 1, 1998 and December 31, 2001, 1034 participants reported on syringe acquisition at 3492 visits, and 953 reported on disposal at 2569 visits. Participants were 69.9% male, 93.9% African-American, and median age was 44. Syringes were acquired exclusively from unsafe sources at 32.3% of visits, while exclusively unsafe disposal was reported at 59.3% of visits. Significant correlates of unsafe acquisition were: attending shooting galleries, anonymous sex, sharing needles, smoking crack, and emergency room visits. Significant correlates of unsafe disposal were: injecting speedball, no methadone treatment, acquiring safely, and frequent injection. Having a primary source of medical care was associated with safe acquisition, but unsafe disposal. IDUs continue to acquire safely but dispose unsafely, especially among those with a primary source of care; this suggests that messages about safe disposal are not being disseminated as widely as those about acquisition. These data suggest the need for a more active program involving pharmacists, an expanded syringe access program, and better efforts to enhance safe disposal. Golub, E., Bareta, J., Mehta, S., McCall, L., Vlahov, D., and Strathdee, S. Correlates of Unsafe Syringe Acquisition and Disposal among Injection Drug Users in Baltimore, Maryland. Subst Use Misuse, 40(12), pp. 1751-1764, 2005.

Binge Drug Use Independently Predicts HIV Seroconversion among Injection Drug Users: Implications for Public Health

Strategies

Several studies have highlighted risk factors that cause HIV vulnerability among IDUs; these studies in turn have prompted public health officials to take action to minimize these risks. In this study, researchers sought to evaluate the potential association between binge drug use and HIV seroconversion and, subsequently, risk factors associated with binge drug use among a cohort of IDUs. To do this, they performed analyses of (1) associations with HIV seroconversion and (2) associations with binge drug use among participants enrolled in the Vancouver Injection Drug Users Study (VIDUS), a prospective cohort of IDU. Because serial measures for each individual were available, a time-updated Cox regression analysis was used to detect associations with HIV incidence and variables potentially associated with binge drug use were evaluated by using generalized estimating equations (GEE). Overall, 1548 IDU were enrolled into the VIDUS cohort between May 1996 and May 2003. There were 1013 individuals who were HIV seronegative at enrollment and had at least one follow-up visit; 125 (12%) became HIV positive during the study period for a cumulative incidence rate of 14% at 64 months after enrollment. In the final multivariate model, binge drug use [Adjusted Hazards Ratio: 1.61 (CI: 1.12, 2.31)] was independently associated with HIV seroconversion. In sub analyses, when associations with binge drug use were evaluated in GEE analyses, borrowing [Odds Ratio (OR): 153 (CI: 1.33-1.76)] and lending [OR: 1.73 (CI: 1.50-1.98)] syringes, sex trade work [OR: 1.14 (CI: 1.01-1.29)], frequent cocaine [OR: 2.34 (CI: 2.11-2.60)] and heroin [OR: 1.29 (CI: 1.17-1.43)] injection were independently associated with binge drug use and methadone [OR: 0.80 (CI: 0.71-0.89)] was protective against binge drug use. This study identified an independent association between binge drug use and HIV incidence and demonstrated several high-risk drug practices associated with bingeing. Given the unaddressed public health risks associated with bingeing, a public health response protocol must be developed to minimize the personal and public health risks associated with the binge use of drugs. Miller, C., Kerr, T., Frankish, J., Spittal, P., Li, K., Schechter, M., and Wood, E. Binge Drug Use Independently Predicts HIV Seroconversion among Injection Drug Users: Implications for Public Health Strategies. Subst Use Misuse, 41(2), pp. 199-210, 2006.

The Protective Role of Racial and Ethnic Identity and Africentricity in Drug Abuse by African-American Young Adults

In this study, the authors examined (a) the protective potential of multiple components of ethnic and racial identity and (b) the aspects of an Africentric orientation for moderating psycho behavioral risk and protective factors for drug use among a sample of 333 urban low-income African American young adults. Ethnic and racial identity and Africentric variables moderated the relationship between psycho behavioral variables and drug stage in 32.5% of the cases. Ethnic and racial identity and Africentric values for African American young adults seemed to be important as moderators of the association between psycho behavioral factors and young adult drug use. The authors suggested implications for future research and interventions. Brook, J., and Pahl, K. The Protective Role of Ethnic and Racial Identity and Aspects of an Africentric Orientation Against Drug Use Among African American Young Adults. J Genet Psychol, 166(3), pp. 329-345, 2005.

Physical Victimization Related to Alcohol and Cigarette Use

This study examined associations between two forms of peer victimization, physical and relational, and externalizing behaviors including drug use, aggression, and delinquent behaviors among a sample of 276 predominantly African American eighth graders attending middle school in an urban public

school system. Regression analyses indicated that physical victimization was significantly related to cigarette and alcohol use but not to advanced alcohol and marijuana use; relational victimization contributed uniquely to all categories of drug use after controlling for physical victimization. Physical victimization was also significantly related to physical and relational aggression and delinquent behaviors, and relational victimization made a unique contribution in the concurrent prediction of these behaviors. Physical victimization was more strongly related to both categories of alcohol use, aggression, and to delinquent behaviors among boys than among girls. In contrast, relational victimization was more strongly related to physical aggression and marijuana use among girls than among boys, but more strongly related to relational aggression among boys than among girls. These findings provide information about the generalizability of prior research and have important implications for intervention efforts. This research was supported by Cooperative Agreement U81/CCU309966 from the Centers for Disease Control and Prevention (CDC). Sullivan, T., Farrell, A., and Kliewer, W. Peer Victimization in Early Adolescence: Association Between Physical and Relational Victimization and Drug Use, Aggression, and Delinquent Behaviors Among Urban Middle School Students. Dev Psychopathol, 18(1), pp. 119-137, 2006.

School Tobacco Policies and Student Smoking

This study examines the association between school policies regarding monitoring student behavior, severity of action taken for infraction of policies, and tobacco use by staff, and student smoking behavior and attitudes. Data on students' smoking behavior and attitudes were obtained from the 1999 and 2000 Monitoring the Future surveys of nationally representative samples of 8th-, 10th-, and 12th-grade students. Data on school policies and practices were obtained from administrators in those same schools. Hierarchical analyses using HLM5 were conducted. Strictness of monitoring was significantly negatively associated with daily cigarette use by middle school students. Permitting staff to smoke was significantly positively associated with students' daily cigarette use and negatively with their disapproval of cigarette use. This study's findings suggest that a multipronged approach to the prevention of student smoking should be implemented including clear written policies that regulate both student and staff behavior, monitoring of student behavior for compliance with policies, and the provision of prevention education and smoking cessation programs in supportive environments that discourage tobacco use by both students and staff. Kumar, R., O 'Malley, P., and Johnston, L. School Tobacco Control Policies Related to Students' Smoking and Attitudes Toward Smoking: National Survey Results, 1999-2000. Health Educ Behav, 32(6), pp. 780-794, 2005.

Psychiatric and Drug Use Disorders in Children of Antisocial Parents

The authors examined the prevalence of common externalizing and internalizing disorders in the pre-adolescent and late adolescent offspring of antisocial parents. Lifetime diagnoses for a sample of 11-year-old twins (958 males, 1042 females) and a sample of 17-year-old twins (1332 males, 1434 females) from the Minnesota Twin Family Study, as well as their parents, were obtained through in-person interviews. Odds ratios were calculated for the effect of the parent's diagnosis on the child's diagnosis, controlling for the effect of the co-parent's diagnosis. For the 11 year olds, antisocial behavior in either parent was associated with increased odds of a variety of externalizing disorders. For the 17 year olds, parental antisociality was associated with increased risk for a range of externalizing and internalizing disorders, including paternal antisociality with abuse and dependence on nicotine, alcohol, and drugs. This study extends the previous literature by using a population-based sample and looking at gender of both parents and offspring, finding that each

parent has an effect net any effects of the co-parent. Herndon, R., and Iacono, W. Psychiatric Disorder in the Children of Antisocial Parents. Psychol Med, 35(12), pp. 1815-1824, 2005.

Relationships of Deterrence and Law Enforcement to Drug-Related Harms among Drug Injectors in US Metropolitan Areas

This study sought to understand associations of punitive policies to the population prevalence of injection drug users and to HIV seroprevalence among injectors. A lagged-cross-sectional analysis of metropolitan statistical area data was used to estimate drug injectors per capita and HIV seroprevalence among injectors in 89 large US metropolitan areas. Regressions were run on three measures of legal repressiveness (hard drug arrests per capita; police employees per capita; and corrections expenditures per capita) controlling for other metropolitan area characteristics. The study found no legal repressiveness measures were associated with injectors per capita; but all three measures of legal repressiveness were positively associated with HIV prevalence among injectors. These findings suggest that legal repressiveness may have little deterrent effect on drug injection and may have a high cost in terms of HIV and perhaps other diseases among injectors and their partners--and that alternative methods of maintaining social order should be investigated. Friedman, S., Cooper, H., Tempalski, B., Keem, M., Friedman, R., Flom, P. and Des Jarlais, D. Relationships of Deterrence and Law Enforcement to Drug-Related Harms among Drug Injectors in US Metropolitan Areas. AIDS, 20(1), pp. 93-99, 2006.

Marginalized and Socially Integrated Groups of IDUs in Hungary: Potential Bridges of HIV Infection

The discrepancy in HIV rates among Eastern and central European injecting drug users (IDUs) suggests that, in addition to risk behaviors, social contact patterns also play an important role. This study identifies two groups of IDUs in Budapest, Hungary, marginalized IDUs (M-IDUs) and socially integrated IDUs (SI-IDUs) and compares their HIV/hepatitis B virus (HBV)/hepatitis C virus (HCV) social and risk network characteristics, risk behaviors, and travel patterns. Between May 2003 and January 2004, 29 nontreatment-recruited young IDUs in Budapest participated in ethnographic interviews and focus groups. The mean age was 23.6 years (SD=3.6); eight were female and two Roma/Gypsy. Most injected heroin (n=23) and/or amphetamines (n=10) in the past 30 days. M-IDUs had no legal employment, injected heroin and sniffed glue, and stopped using drugs in treatment/prison. SI-IDUs had regular jobs or were students, injected heroin and sniffed cocaine, and stopped using drugs before exams/tests. Both M-IDUs and SI-IDUs shared injecting equipment on occasion and used condoms rarely. M-IDUs had a large social network of "buddies" and a small risk network of "friends". SI-IDUs had two separate large social networks of "buddies": a M-IDU and a non-IDU network; and a small risk network of "friends". Both groups reported monogamous sexual relationships. M-IDUs traveled within Hungary, whereas SI-IDUs traveled to Western Europe. If an HIV epidemic among IDUs in Hungary is not prevented, SI-IDUs may form a potential "bridge" of HIV infection between high-risk IDU populations and the low-risk general population, whereas M-IDUs may become cores of infection. These findings suggest that different approaches may be appropriate for M-IDUs and SI-IDUs to prevent HIV. Gyarmathy, V. and Neaigus, A. Marginalized and Socially Integrated Groups of IDUs in Hungary: Potential Bridges of HIV Infection. J Urban Health, 82(3-4), pp. iv101-iv112, 2005.

Hospitalizations for Metabolic Conditions, Opportunistic Infections, and Injection Drug Use among HIV Patients: Trends Between 1996 and 2000 in 12 States

Rapid changes in HIV epidemiology and highly active antiretroviral therapy (HAART) may have resulted in recent changes in patterns of inpatient utilization. This study examined trends in inpatient diagnoses and mortality in HIV patients. Serial cross-sectional analyses were conducted of HIV patients hospitalized in 1996, 1998, and 2000, using hospital discharge data from the Healthcare Costs and Utilization Project for 12 states. Each hospitalization was classified as an opportunistic illness, complication of injection drug use (IDU), liver-related complication, ischemic heart disease, cerebrovascular disease, non-Pneumocystis carinii pneumonia (PCP), diabetes, or chronic hepatitis C virus (HCV). Outcome measures were the number of hospital admissions and inpatient mortality. The study evaluated 316,963 admissions that occurred between 1996 and 2000, with an overall mortality of 7%. Hospitalizations for opportunistic infections significantly decreased from 40% to 27% of all HIV-related admissions. The overall proportion of IDU complications remained relatively stable (6%) each year. Hospitalizations increased for liver-related complications from 8% to 13% and for chronic HCV from 1% to 5% in this period. The number of hospitalizations for cerebrovascular disease and for ischemic heart disease was relatively negligible in all years. Overall, inpatient mortality decreased between 1996 and 2000. Relatively higher mortality was observed among African Americans, Hispanics, those with Medicaid, those with Medicare, and the uninsured, however. Opportunistic infections and liver-related complications were associated with greater inpatient mortality. Results do not show a significant recent rise in HIV-related inpatient utilization. Admissions to treat opportunistic infections have declined precipitously, consistent with the effects of HAART. Although not dramatic, liver-related disease is an increasing cause of hospitalization in HIV+ patients. Gebo, K., Fleishman, J., and Moore, R. Hospitalizations for Metabolic Conditions, Opportunistic Infections, and Injection Drug Use among HIV Patients: Trends Between 1996 and 2000 in 12 States. J Acquir Immune Defic Syndr, 40(5), pp. 609-616, 2005.

HIV, HBV, and HCV Infections Among Drug-Involved, Inner-City, Street Sex Workers in Miami, Florida

This study describes the rates of HIV, HBV, and HCV seropositivity among drug-involved, female street sex workers in low-income, inner-city sections of Miami, Florida; further, their sociodemographic characteristics, drug use, and sexual risk behaviors were assessed; and predictors of infection were reported. A sample of 586 sex workers was recruited through targeted sampling methods, interviewed, and counseled and tested for the presence of antibody to HIV, HBV, and HCV. Respondents' median age was 38 years, median time in sex work was 14 years, all were heavily involved in the use of alcohol and drugs, and 42% were homeless. More than half (51.0%) had engaged in unprotected vaginal sex in the past month. Prevalences were HIV, 22.4%; HBV, 53.4%; HCV, 29.7%. A multidimensional public health program must address not only issues related to unsafe sex, but also the problems of drug abuse, homelessness, and other lifestyle factors that contribute to risk behaviors. Inciardi, J., Surratt, H.L., and Kurtz, S.P. HIV, HBV, and HCV Infections Among Drug-Involved, Inner-City, Street Sex Workers in Miami, Florida. AIDS Behav, 10(2), pp. 139-147, March 2006.

HIV Risk Behavior among Amphetamine Injectors at U.S. Syringe Exchange Programs

The goal of this study was to compare HIV risk behaviors of amphetamine and non-amphetamine injectors at syringe exchange programs (SEP) in the United States and to identify factors associated with injection risk. The analysis is based on data from a random cross-section of participants at 13 SEPs in different parts of the country. All interviews were done using Audio Computer-

Assisted Personal Interviewing technology. Amphetamine injectors differ from other SEP participants in that they are younger and more likely to be White, to have had a recent same sex partner, and to be homeless. Rates of injection risk behavior are higher among amphetamine injectors than other SEP participants, but rates of condom use are similar. Factors associated with injection risk behavior are amphetamine injection, homelessness, depression, and having a recent same-gender sexual partner (for both men and women). SEPs have been repeatedly demonstrated to reduce injection risk behavior, but some groups of program participants continue to be at elevated risk. These findings suggest that SEPs need to develop new approaches to outreach and education to address the needs of amphetamine injectors and other populations at persistent risk. Braine, N., Des Jarlais, D., Goldblatt, C., Zadoretzky, C., and Turner, C. HIV Risk Behavior among Amphetamine Injectors at U.S. Syringe Exchange Programs. AIDS Educ Prev, 17(6), pp. 515-524, 2005.

Sex, Touch, and HIV Risk Among Ecstasy Users

This study examined HIV risk among heavy and non-heavy ecstasy users, focusing specifically on touch and sexual behavior as part of the ecstasy experience. Structured interviews were conducted with 268 young adult (age 18-25) ecstasy users in Atlanta, Georgia. Heavy ecstasy users were more likely to have been tested for HIV than non-heavy users (79 vs. 68%). However, they also were more likely to perceive no chance of contracting HIV (36 vs. 26%). Touch, both sensual and sexual, was a significant part of the ecstasy experience. In addition, ecstasy use seemed to increase the sexual desire, however, not the ability to achieve an orgasm. Heavy users reported more sexual risk-taking than their non-heavy using counterparts. Results suggest that the setting of ecstasy use also may influence involvement in risk behaviors. Future longitudinal studies are needed on the relationship between ecstasy use, touch, sexual arousal and ability, and risk behavior. Theall, K.P., Elifson, K.W. and Sterk, C.E. Sex, Touch, and HIV Risk Among Ecstasy Users. AIDS Behav, 10(2), pp. 169-178, March 2006.

HIV/Hepatitis C Virus Co-infection in Drug Users: Risk Behavior and Prevention

Studies of HIV-positive patients have consistently shown that drug users, in particular injection drug users (IDU), are far more likely to have hepatitis C virus (HCV) infection than other patient groups. HIV incidence and prevalence in IDU has declined in recent years, but HCV remains endemic in this population. HCV antibody prevalence among non-injection users of drugs such as heroin and cocaine is between 5 and 30%, although there are scant data on specific transmission risk behavior. The control of HIV/HCV co-infection must address HCV prevention. Epidemiological studies have suggested that HCV prevalence in IDU is subject to various influences, some of which may be modifiable by interventions. However, studies have not shown consistent effects of various prevention strategies on HCV transmission, including studies of HCV screening and education, drug treatment or needle exchange. Although some large cross-sectional studies in regions where needle exchange is available to a large number of drug injectors have reported declining HCV prevalence, the scale of services needed is a matter of considerable debate and has not been systematically quantified. Priorities for research related to the prevention of HIV/HCV co-infection should include estimating the effect on disease occurrence of eliminating specific risk factors, and specifying the level of resources needed to alter HCV incidence. Hagan, H., Thiede, H., and Des Jarlais, D. HIV/Hepatitis C Virus Co-infection in Drug Users: Risk Behavior and Prevention. AIDS, 19(3), pp. S199-S207, 2005.

Stigmatization of Newly Emerging Infectious Diseases: AIDS and SARS

This study assessed relationships between sociodemographic characteristics and mental health status and knowledge of, being worried about, and stigmatization of 2 emerging infectious diseases: AIDS and SARS. A random-digit-dialed survey of 928 residents of the New York City metropolitan area was conducted as part of a study of the effects of the September 11, 2001, terrorist attacks. Questions added for this study concerned respondents' knowledge of, worry about, and support of stigmatizing actions to control AIDS and SARS. In general, respondents with greater personal resources (income, education, social support) and better mental health status had more knowledge, were less worried, and were less likely to stigmatize. This pattern held for both AIDS and SARS. The findings suggest that personal resources and mental health factors are likely to influence the public's ability to learn about, rationally appraise the threat of, and minimize stigmatization of emerging infectious diseases such as AIDS and SARS. Des Jarlais, D., Galea, S., Tracy, M., Tross, S., and Vlahov, D. Stigmatization of Newly Emerging Infectious Diseases: AIDS and SARS. Am J Public Health, 96(3), pp. 561-567, 2006.

Social Support and HIV-Related Injection Risk among Puerto Rican Migrant and Nonmigrant IDUs Recruited in New York City

This study compared associations between social support and HIV injection risk among Puerto Rican migrant (n=221) and nonmigrant (n=340) injection drug users in New York City. Practical and emotional support scales were developed from 8 items and examined by migrant status as predictors of risk. Bivariate and regression analysis were conducted with drug shooting gallery use, sharing needles, paraphernalia, and number of monthly injections as dependent variables. Migrants had lower emotional (2.82 vs 3.19, p=.002) and practical (1.87 vs 2.05, p=.051) support than nonmigrants. Controlling for age, sex, and homelessness, emotional support was negatively associated with injection frequency (standardized coefficient = -168, p=.020) and gallery use (AOR = .76, CI = .62-.94, p = .011) among migrants and with an almost 2-fold increase in sharing syringes (AOR=1.87, CI = 1.02-3.43, p=.041) among nonmigrants. These findings suggest that migrants have less support than nonmigrants do, but their support reduces risk and thus their likelihood of injection-related HIV infection. Mino, M., Deren, S., and Yeon-Kang, S. Social Support and HIV-Related Injection Risk among Puerto Rican Migrant and Nonmigrant IDUs Recruited in New York City. AIDS Educ Prev, 18(1), pp. 81-90, 2006.

Psychological Resilience after Disaster

Research on adult reactions to potentially traumatic events has focused almost exclusively on posttraumatic stress disorder (PTSD). Although there has been relatively little research on the absence of trauma symptoms, the available evidence suggests that resilience following such events may be more prevalent than previously believed. This study examined the prevalence of resilience, defined as having either no PTSD symptoms or one symptom, among a large (n= 2,752) probability sample of New York area residents during the 6 months following the September 11th terrorist attack. Although many respondents met criteria for PTSD, particularly when exposure was high, resilience was observed in 65.1% of the sample. Resilience was less prevalent among more highly exposed individuals, but the frequency of resilience never fell below one third even among the exposure groups with the most dramatic elevations in PTSD. Bonanno, G., Galea, S., Bucciarelli, A., and Vlahov, D. Psychological Resilience After Disaster. Psychol Sci, 17(3), pp. 181-186, 2006.

The Relationship Between Self-Reported Sexual Orientation and Behavior In a

Data are sparse on injection drug using (IDU) men who have sex with men (MSM). Previous literature suggests perceived taboos can result in an underreporting of atypical sexual orientation (i.e., bisexuality, homosexuality). As a result, HIV prevention programs have been difficult to mount, particularly programs for IDU-MSM. The association between self-reported sexual orientation and sexual behavior at semi-annual study visits was longitudinally assessed in a population of 1300 male IDUs in Baltimore during the period 1993 to 1998. Overall, a small minority (5%) of the male IDUs inconsistently reported their sexual orientation over time. Logistic regression analyses were performed, which yielded five significant predictors. These men tended to be older, to have been incarcerated, to have attended shooting galleries during follow-up, and were more than twice as likely to be HIV-seropositive (OR, 2.66; 95% CI, 1.62-4.36) compared with those who consistently reported their sexual orientation. Furthermore, men reporting inconsistent sexual orientation tended to engage in higher risk behaviors, suggesting that these men should be especially targeted for interventions. Washington, T., Galai, N., Cohn, S., Celentano, D., Vlahov, D., and Strathdee, S. The Relationship Between Self-Reported Sexual Orientation and Behavior In a Sample of Middle-Aged Male IDU. Arch Sex Behav, 35(1), pp. 67-74, 2006.

Needle-Sharing among Young IV Drug Users and Their Social Network Members: The Influence of the Injection Partner's Characteristics on HIV Risk Behavior

Injection drug use is a risk factor for HIV among adolescents and young adults, yet the interpersonal dynamics of needle-sharing among young injectors remain poorly understood. Research has focused on identifying the characteristics of injecting drug users (IDUs) that increase their risk of needle-sharing. Most studies have not taken into consideration IDUs' decisions to share needles with certain partners but not with other partners. This study examined partner characteristics associated with needle-sharing among 96 male and 77 female young adult IDUs who had shared needles previously. Men were most likely to share needles with partners who gave them emotional support, partners who they injected or who injected them, and partners with whom they had had sex. Women were most likely to share needles with partners who they injected or who injected them, partners with whom they had discussed HIV risk, and partners with whom they had had sex. Results indicate that needle-sharing occurs within the context of mutual injection rituals and close emotional and sexual relationships. These findings point to the need for targeted interventions to help young IDUs avoid needle-sharing with intimate partners. Unger, J.B., Kipke, M.D., De Rosa, C.J., Hyde, J., Ritt-Olson, A., and Montgomery, S. Needle-Sharing Among Young IV Drug Users and Their Social Network Members: The Influence of the Injection Partner's Characteristics on HIV Risk Behavior. Addict Behav, available online 3 February 2006.

Do Street Youths' Perceptions of Their Caregivers Predict HIV-Risk Behavior

This study examined street youths' perceptions of their caregivers and the association between these perceptions and HIV-risk behavior in a random probability sample of 715 12- to 23-year-old street youths from Los Angeles and San Diego, CA (mean age, 18.7 years). All participants had been homeless at some point during the past 12 months, with 70% recruited from nonshelter sites. Although youths reported high rates of hostility, unavailability, substance use, and legal problems among their caregivers, 86% reported that their caregivers had at least one attribute associated with support. Caregiver

problems were associated with youth having had more sexual partners in the past 30 days and having higher risk drug use. High caregiver support was associated with more sexual partners and lower use of condoms with steady partners. Caregiver attributes did not predict condom use with transient partners. Darling, N., Palmer, R. and Kipke, M. Do Street Youths' Perceptions of Their Caregivers Predict HIV-Risk Behavior? J Fam Psychol, 19(3), pp. 456-464, 2005.

Alcohol and Other Drug Use in the US and Australia

Although youth drug and alcohol harm minimization policies in Australia are often contrasted with the abstinence and zero tolerance policies adopted in the United States, there has been little research directly comparing youth substance use behaviour in the two countries. Three state representative samples in Victoria, Australia (n = 7898) and in the US states of Oregon (n = 15,224) and Maine (n = 16,245) completed a common cross-sectional student survey. Rates of alcohol use (lifetime alcohol use, recent use in the past 30 days), alcohol use exceeding recommended consumption limits (binge drinking: five or more drinks in a session), other licit drug use (tobacco use), and norm-violating substance use (substance use at school, use in the past 30 days of marijuana or other illicit drug use) were compared for males and females at ages 12-17. Rates were lower (odds ratios 0.5-0.8) for youth in Maine and Oregon compared to Victoria for lifetime and recent alcohol use, binge drinking and daily cigarette smoking. However, rates of recent marijuana use and recent use of other illicit drugs were higher in Maine and Oregon, as were reports of being drunk or high at school. In contradiction of harm minimization objectives, Victoria, relative to the US states of Oregon and Maine, demonstrated higher rates of alcohol use exceeding recommended consumption limits and daily tobacco use. However, findings suggested that aspects of norm-violating substance use (substance use at school, marijuana use and other illicit drug use) were higher in the US states compared to Victoria. Toumbourou, J., Beyers, J., Catalano, R., Hawkins, J., Arthur, M., Evans-Whipp, T., Bond, L., and Patton, G. Youth Alcohol and Other Drug Use in the United States and Australia: A Cross-National Comparison of Three State-Wide Samples. Drug Alcohol Rev, 24(6), pp. 515-523, 2005.

Adverse Outcomes for Community Sample of Adolescents and Young Adults with Personality Disorder Not Otherwise Specified

This study investigated whether adolescents and young adults diagnosed with personality disorder not otherwise specified are at elevated risk for adverse outcomes, and whether this elevation in risk is comparable with that associated with the DSM-IV cluster A, B, and C personality disorders. A community-based sample of 693 mothers and their offspring were interviewed during the offspring's childhood, adolescence, and early adulthood. Offspring psychopathology, aggressive behavior, educational and interpersonal difficulties, and suicidal behavior were assessed. Individuals who met DSM-IV criteria for personality disorder not otherwise specified were significantly more likely than those without personality disorders to have concurrent axis I disorders and behavioral, educational, or interpersonal problems during adolescence and early adulthood. In addition, adolescents with personality disorder not otherwise specified were at significantly elevated risk for subsequent educational failure, numerous interpersonal difficulties, psychiatric disorders, and serious acts of physical aggression by early adulthood. Adolescents with personality disorder not otherwise specified were as likely to have these adverse outcomes as those with cluster A, B, or C personality disorders or those with axis I disorders. Adolescents and young adults in the general population diagnosed with personality disorder not otherwise specified may be as likely as those with DSM-IV cluster A, B, or C personality disorders to have axis I psychopathology and to have behavioral, educational, or

interpersonal problems that are not attributable to co-occurring psychiatric disorders. Individuals with personality disorder not otherwise specified and individuals with DSM-IV cluster A, B, or C personality disorders are likely to be at substantially elevated risk for a wide range of adverse outcomes. Johnson, J., First, M., Cohen, P., Skodol, A., Kasen, S., and Brook, J. Adverse Outcomes Associated with Personality Disorder Not Otherwise Specified in a Community Sample. Am J Psychiatry, 162(10), pp. 1926-1932, 2005.

Dissociative Disorder in Adults with Impaired Functioning and Co-Occurring Axis I and Personality Disorders

The purpose of this study was to investigate the association of dissociative disorder (DD) with impaired functioning and co-occurring Axis I and personality disorders among adults. Psychiatric interviews were administered to a sample of 658 adult participants in a community-based longitudinal study. Depersonalization disorder (prevalence: 0.8%), dissociative amnesia (prevalence: 1.8%), dissociative identity disorder (prevalence: 1.5%), and dissociative disorder not otherwise specified (prevalence: 4.4%), evident within the past year, were each associated with impaired functioning, as assessed by the clinician-administered Global Assessment of Functioning Scale. These associations remained significant after controlling for age, sex, and co-occurring disorders. Individuals with anxiety, mood, and personality disorders were significantly more likely than individuals without these disorders to have DD, after the covariates were controlled. Individuals with Cluster A (DD prevalence: 58%), B (DD prevalence: 68%), and C (DD prevalence: 37%) personality disorders were substantially more likely than those without personality disorders to have DD. The authors concluded that DD is associated with clinically significant impairment among adults in the community. DD may be particularly prevalent among individuals with personality disorders. Johnson, J., Cohen, P., Kasen, S. and Brook, J. Dissociative Disorders Among Adults in the Community, Impaired Functioning, and Axis I and II Co-morbidity. J Psychiatr Res, 40(2), pp. 131-140, 2006.

Substance Using Peers Remain Important Predictor of Adult Abuse and Dependence

This study explores three avenues in early young adulthood through which adolescent problems may be linked to later substance use problems: problematic substance use, failure to assume adult roles and responsibilities, and exposure to pro-drug social influences. Participants (N = 1,986; 49% female) filled out surveys at ages 18, 23 and 29. Participants were 67% white, 9% black, 10% Hispanic and 8% Asian. Deviance, poor mental health, substance use, alcohol and other drug (AOD) problems, and school dropout were measured at age 18. AOD problems were also measured at age 23, as were role changes (e.g., marriage) and pro-drug social influences (e.g., friends use drugs). Indicators of substance abuse and dependence were measured at age 29. Demographics and family history of AOD were covariates. Reporting more deviant behavior and heavier drinking at age 18 was associated with a higher likelihood of abuse and dependence at age 29. Alcohol use and pro-drug social influences at age 23 appeared to mediate the effects of adolescent substance use; lack of role assumption did not. The effect of poor mental health at age 18 was not mediated by any set of variables but instead appeared to directly predict dependence at age 29. Findings highlight the importance of early young adult drinking and substance-using peers in continuing patterns of heavy substance use developed during adolescence and also underscore the long-term impact of poor mental health during adolescence on substance use problems in late young adulthood. D 'Amico, E., Ellickson, P., Collins, R., Martino, S., and Klein, D. Processes Linking Adolescent Problems to Substance-Use Problems in Late Young Adulthood. J Stud Alcohol, 66(6), pp. 766-775, 2005.

For Females, Marriage at Any Age is Protective from Alcohol Use

Previous research shows that marriage leads to reductions in alcohol use, especially for women. Because marriage prior to age 20 (early marriage) is a marker for deviance, the protective effects of marriage may not extend to those who marry in adolescence. This study compared the effects of marriage in adolescence versus young adulthood on alcohol consumption, negative alcohol-related consequences and heavy episodic drinking at age 29. They analyzed data from 1,138 women in a longitudinal cohort followed from ages 18 to 29. The original sample was recruited from 30 California and Oregon middle schools and first surveyed at age 13. Women who had not married, had married early or had married between ages 20 and 29 did not differ on alcohol use at age 18. Women who married as young adults were less likely than singles to engage in any alcohol use, heavy episodic drinking or experience negative consequences and reported less alcohol use at age 29. Women who married in adolescence reported fewer negative consequences at age 29 than did singles and (if they had not divorced) were less likely to engage in heavy episodic drinking or experience any negative consequences, reported fewer consequences and consumed less alcohol. The protective effects of marriage in young adulthood were observed whether or not women divorced. Parenthood and college attendance before age 23 did not explain the marriage effect. Results support role theory, which posits that individuals who marry are socialized into conventional adult roles that discourage deviant behavior. Bogart, L., Collins, R., Ellickson, P., Martino, S., and Klein, D. Effects of Early and Later Marriage on Women's Alcohol Use in Young Adulthood: A Prospective Analysis. J Stud Alcohol, 66(6), pp. 729-737, 2005.

Trajectories of Young Adult Concurrent Alcohol and Tobacco Use

This study examines the concurrent course of heavy alcohol use and tobacco use during early adulthood (ages 19-26). Panel data were drawn from the Monitoring the Future Project young adult sample (N=32,087). The authors applied growth mixture modeling to 4 waves of data to disentangle the effect of cohort and developmental stage on heavy drinking and smoking. The influence of covariates (sex, race, alcohol expectancies, delinquency, religiosity, and parent education) on the course of alcohol-tobacco co-morbidity was examined. Seven co-occuring trajectories of alcohol and tobacco use, controlling for secular changes occurring over 2 decades were identified. Associations between trajectory classes and risk factors were relatively unique to the substance being predicted. The association of smoking with alcohol expectancies and delinquency appeared to exist by virtue of smoking's co-morbidity with drinking. Although recent work characterizes drinking and smoking trajectories, this study is novel in exploring the course of concurrent drinking and smoking and establishes the feasibility of modeling co-morbidity and course with in a person-centered approach to data analysis. Jackson, K., Sher, K., and Schulenberg, J. Conjoint Developmental Trajectories of Young Adult Alcohol and Tobacco Use. J Abnorm Psychol, 114(4), pp. 612-626, 2005.

Personality Traits and Externalizing Disorders in Adolescence

The authors examined personality profiles among children who differed in their co-morbidity of externalizing disorders: attention-deficit/hyperactivity disorder (ADHD) and conduct disorder (CD). 11- and 17-year-old male and female twins from a community sample of 2876 twin pairs in the Minnesota Twin Family Study were categorized as ADHD only, CD only, co-morbid CD-ADHD, and controls (no ADHD or CD) based on threshold and subthreshold CD and ADHD diagnoses assessed with structured interviews. Multivariate analyses were used to identify patterns of personality that differentiate these four diagnostic

groups. The authors found that the co-morbid group had a pattern of personality marked by higher Negative Emotionality and lower Constraint than the other diagnostic groups. This pattern was evidenced across gender and age cohort. They concluded that an extreme personality profile may represent a liability toward the occurrence of ADHD and CD with more extreme profiles contributing to the occurrence of both disorders among boys and girls. The significance of this study lies in prediction and understanding of risk based on childhood psychiatric diagnosis and personality traits, given the findings from other groups that co morbid ADHD and CD represent a particularly strong risk group for substance use disorders. Significance is further strengthened by the use of a large, population-based sample and the extension of findings across ages and gender. Cukrowicz, K., Taylor, J., Schatschneider, C., and Iacono, W. Personality Differences in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder, Conduct Disorder, and Controls. J Child Psychol Psychiatry, 47(2), pp. 151-159, 2006.

Measuring Violence Risk and Outcomes among Mexican American Adolescent Females

Central to the development of culturally competent violence prevention programs for Hispanic youth is the development of psychometrically sound violence risk and outcome measures for this population. A study was conducted to determine the psychometric properties of two commonly used violence measures, in this case for Mexican American adolescent females. The Conflict Tactics Scales (CTS2) and the Past Feelings and Acts of Violence Scale (PFAV) were analyzed to examine their interitem reliability, criterion validity, and discriminant validity. A sample of 150 low-risk and 150 high-risk adolescent females was studied. Discriminant validity was indicated by the perpetrator negotiation scale and by the victim psychological aggression and sexual coercion scales of the CTS2 and the PFAV. Analysis indicates that the CTS2 scales and the PFAV demonstrate adequate reliability, whereas strong criterion validity was evidenced by eight of the CTS2 scales and the PFAV. Cervantes, R., Duenas, N., Valdez, A., and Kaplan, C. Measuring Violence Risk and Outcomes among Mexican American Adolescent Females. J Interpers Violence, 21(1), pp. 24-41, 2006.

Mexican American Youth and Adult Prison Gangs in a Changing Heroin Market

This article focuses on the interaction between the larger community's drug markets and youth and adult prison gangs, and the process that leads to specific adverse consequences both to the youth gangs as organizations and to individual members. Described is the emergence of a restructured heroin market dominated by an adult prison gang. A major consequence of this was the increasing use of heroin among Mexican American gang members and their transformation from autonomous youth gangs to extensions of the adult prison gangs or their demise. Data were collected from 160 members of 26 Mexican American youth gangs and key informants in San Antonio. Findings focus on organizational rules, drug market transformations, consequences on members, and the impact of heroin on the gang's organization. Discussed is how the dominance of prison gangs is related to the increased incarceration and recidivism rates of Mexican Americans and declining economic opportunities for urban minorities. Valdez, A. Mexican American Youth and Adult Prison Gangs in a Changing Heroin Market. Journal of Drug Issues, Fall pp. 843-867, 2005.

Reported Condom Use and Condom Use Difficulties in Street Outreach Samples of Men of Four Racial and Ethnic Backgrounds

The epidemiology of the HIV/AIDS epidemic in the United States has focused

research attention on lesbian, gay, bisexual and transgendered communities as well as on racial and ethnic minorities. Much of that attention has, however, been focused on specific racial and ethnic groups, and specific sexual minorities. This paper reports on the results of a study that examined the association between condom use and partnership types among drug-using men from four major racial/ethnic groups. Self-reported data on sexual identity (homosexual, bisexual, and heterosexual) and condom use in the past three months were collected from 806 African Americans, Hispanic, Asian, and white men intercepted in public places in Houston, TX. Data indicated that condom use was lowest in African Americans and Hispanic men, bisexual men reported the highest levels of use, with heterosexual men reporting the lowest use. African Americans and Hispanic men reported generally that it was very difficult to use a condom during sexual contact, although the patterns for self-identified homosexual, heterosexual, and bisexual men varied across race/ethnicity. Homosexual African American men reported the least difficulty, and white homosexual men the most difficulty compared with heterosexual and bisexual peers. For homosexually identified men, there were considerable differences across race/ethnicity in the proportion of partners who never or rarely disagreed to use condoms, with Asians disagreeing least, and African Americans most. Within racial/ethnic groups, the levels of condom use and difficulty were similar for male and female partners, suggesting that it is sexual identity, rather than partner gender, that has impacted condom-use messages. These data suggest that racial/ethnic targeting of condom use is likely to be most efficacious in increasing condom use in men. Essien, E., Ross, M., Fern‡ndez-Esquer, M. and Williams, M. Reported Condom Use and Condom Use Difficulties in Street Outreach Samples of Men of Four Racial and Ethnic Backgrounds. Int J STD AIDS, 16(11), pp. 739-743, 2005.

Using Standardized Methods for Research on HIV and Injecting Drug Use in Developing/Transitional Countries: Case Study from the WHO Drug Injection Study

Successful cross-national research requires methods that are both standardized across sites and adaptable to local conditions. This study reports on the development and implementation of the methodology underlying the survey component of the WHO Drug Injection Study Phase II - a multi-site study of risk behavior and HIV seroprevalence among Injecting Drug Users (IDUs). Standardized operational guidelines were developed by the Survey Coordinating Center in collaboration with the WHO Project Officer and participating site Investigators. Throughout the duration of the study, survey implementation at the local level was monitored by the Coordinating Center. Surveys were conducted in 12 different cities. Prior rapid assessment conducted in 10 cities provided insight into local context and guided survey implementation. Where possible, subjects were recruited both from drug abuse treatment centers and via street outreach. While emphasis was on IDUs, non-injectors were also recruited in cities with substantial non-injecting use of injectable drugs. A structured interview and HIV counseling/testing were administered. Over 5,000 subjects were recruited. Subjects were recruited from both drug treatment and street outreach in 10 cities. Non-injectors were recruited in nine cities. Prior rapid assessment identified suitable recruitment areas, reduced drug users' distrust of survey staff, and revealed site-specific risk behaviors. Centralized survey coordination facilitated local questionnaire modification within a core structure, standardized data collection protocols, uniform database structure, and cross-site analyses. Major site-specific problems included: questionnaire translation difficulties; locating affordable HIV-testing facilities; recruitment from drug treatment due to limited/selective treatment infrastructure; access to specific sub-groups of drug users in the community, particularly females or higher income groups; security problems for users and interviewers, hostility from local drug dealers; and interference by local service providers. This study found that rapid assessment was helpful

in paving the way for the survey. Central coordination of data collection was also crucial. While fully standardized methods may be a research ideal, local circumstances may require substantial adaptation of the methods to achieve meaningful local representation. Allowance for understanding of local context may increase rather than decrease the generalizability of the data. Des Jarlais, Perlis, Stimson, and Poznyak. Using Standardized Methods for Research on HIV and Injecting Drug Use in Developing/Transitional Countries: Case Study from the WHO Drug Injection Study. BMC Public Health, 6(1), pp. 54-87, 2006.

Assessing Parenting Behaviors Among Mothers with a History of Maltreatment

Parenting assessments (the Parent-Child Conflict Tactics Scale, CTSPC; and a mother-child observation) were examined for their ability to identify mothers with a history of physically abusing or neglecting their child. Participants were mothers of 139 children (age 3 to 6 years; 58 with a history of maltreatment). Mothers with a history of maltreatment reported higher scores on the Neglect, Nonviolent Discipline, and Psychological Aggression subscales of the CTSPC. These group differences, however, were limited to mothers who acknowledged a history of maltreatment, as mothers who concealed their maltreatment history rated themselves similar to controls. Observation of parental behaviors during a brief, non-stressful task did not discriminate mothers who maltreated from mothers who did not maltreat. The findings suggest that parental report using the CTSPC may be useful in assessing parenting behaviors among mothers with a history of maltreatment, although socially desirable responding is a significant problem. Bennett, D., Sullivan, M., and Lewis, M. Relations of Parental Report and Observation of Parenting to Maltreatment History. Child Maltreat, 11(1), pp. 63-75, 2006.

Sibling Contact is Source of Social Contagion for Smoking and Drinking

Prior research on sibling contagion for substance use has not attended to individual differences in the sibling relationship that may be influenced by genetic similarity. The authors utilizing data on a sample of twin and nontwin siblings participating in the National Longitudinal Study of Adolescent Health (Add Health). Although monozygotic twins had the highest levels of sibling contact and mutual friendships, the pattern of results for other sibling types were not consistent with genetic models, and biometric analysis indicated that shared environmental factors influenced these sibling relationship features. Application of DeFries-Fulker regression models provided evidence that sibling contact and mutual friendships represent a source of social contagion for adolescent smoking and drinking independent of genetic relatedness. The results are interpreted using a social contagion framework and contrasted with other competing models such as those focused on the equal environments assumption and niche selection. Rende, R., Slomkowski, C., Lloyd-Richardson, E., and Niaura, R. Sibling Effects on Substance Use in Adolescence: Social Contagion and Genetic Relatedness. J Fam Psychol, 19(4), pp. 611-618, 2005.

Serum Albumin as a Prognostic Indicator for HIV Disease Progression

Low albumin levels have been associated with HIV progression. The objective of this analysis was to confirm this association and to further examine the effect of albumin before and after HIV seroconversion on disease progression. The association was first examined among individuals already infected with HIV at entry into a community-based cohort (n = 453) and further assessed among HIV seroconverters with albumin concentrations measured after (n = 219) and before seroconversion (n = 138). The prognostic effect of albumin on AIDS,

AIDS mortality, and all-cause mortality was examined using Cox regression. Among 453 HIV-infected individuals, albumin <35 g/liter was associated with faster progression to AIDS [adjusted relative hazard (ARH), 1.8; 95% confidence interval (CI), 1.2-2.8], AIDS mortality (ARH, 2.2; 95% CI, 1.3-3.8), and all-cause mortality (ARH, 2.4; 95% CI, 1.6-3.5). Analyses restricted to HIV seroconverters were similar. Preseroconversion levels of albumin did not predict outcomes, but HIV seroconversion appeared to lower albumin levels. These data show that albumin <35 g/liter after HIV seroconversion is associated with faster HIV disease progression and suggest that low albumin levels are probably a consequence of HIV infection rather than merely reflective of some individuals inherently having low albumin levels. Mehta, S., Astemborski, J., Sterling, T., Thomas, D., and Vlahov, D. Serum Albumin as a Prognostic Indicator for HIV Disease Progression. AIDS Res Hum Retroviruses, 22(1), pp. 14-21, 2006.

Facilitating Entry into Drug Treatment among Injection Drug Users Referred from a Needle Exchange Program: Results from a Community-Based Behavioral Intervention Trial

Researchers evaluated a case management intervention to increase treatment entry among injecting drug users referred from a needle exchange program (NEP). A randomized trial of a strengths based case management (intervention) vs passive referral (control) was conducted among NEP attenders requesting and receiving referrals to subsidized, publicly funded opiate agonist treatment programs in Baltimore, MD. Logistic regression identified predictors of treatment entry within 7 days, confirmed through treatment program records. Of 247 potential subjects, 245 (99%) participated. HIV prevalence was 19%. Overall, 34% entered treatment within 7 days (intervention: 40% vs control: 26%, p=0.03). In a multivariate "intention to treat'' model (i.e., ignoring the amount of case management actually received), those randomized to case management were more likely to enter treatment within 7 days. Additional ''as treated '' analyses revealed that participants who received 30min or more of case management within 7 days were 33% more likely to enter treatment and the active ingredient of case management activities was provision of transportation. These findings demonstrate the combined value of offering dedicated treatment referrals from NEP, case management and transportation in facilitating entry into drug abuse treatment. Such initiatives could be implemented at more than 140 needle exchange programs currently operating in the United States. These data also demonstrate the importance of more accessible programs such as mobile or office-based drug abuse treatment. Strathdee, S.A., Ricketts, E.P., Huettner, S., Cornelius, L. et al.,. Facilitating Entry into Drug Treatment among Injection Drug Users Referred from a Needle Exchange Program: Results from a Community-Based Behavioral Intervention Trial. Drug Alcohol Depend, available online 20 December 2005.

Elevated Rates of HIV infection among Young Aboriginal Injection Drug Users in a Canadian Setting

Recent reports have suggested that Aboriginal and American Indian people are at elevated risk of HIV infection. The present study compared socio-demographic and risk variables between Aboriginal and non-Aboriginal young (aged 13 - 24 years) IDUs and characterized the burden of HIV infection among young Aboriginal IDUs. Socio-demographic and risk variables were compared between Aboriginal and non-Aboriginal young IDUs. Data were collected through the Vancouver Injection Drug Users Study (VIDUS). Semi-annually, participants have completed an interviewer-administered questionnaire and have undergone serologic testing for HIV and Hepatitis C (HCV). To date over 1500 Vancouver IDU have been enrolled and followed, among whom 291 were aged 24 years and younger. Of the 291 young

injectors, 80 (27%) were Aboriginal. In comparison to non-Aboriginal youth, Aboriginal youth were more likely to test seropositive for either HIV (20% vs 7%, p=>0.001) or Hepatitis C virus (HCV) (66% vs 38%, p=>0.001), be involved in sex work and live in the city Ôs IDU epi-centre at baseline. After 48 months of follow-up, Aboriginal youth experienced significantly higher HIV seroconversion rates than non-Aboriginal youth, 27.8 per ppy (95% CI: 13.4-42.2) vs. 7.0 per ppy (95% CI: 2.3-11.8) respectively (log-rank p=0.005) and the incidence density over the entire follow-up period was 12.6 per 100 pyrs (CI: 6.49-21.96) and 3.9 per 100 pyrs (CI: 1.8-7.3) respectively. These findings demonstrate that culturally relevant, evidence based prevention programs are urgently required to prevent HIV infection among Aboriginal youth. Miller, Strathdee, S., et al., Elevated Rates of HIV infection Among Young Aboriginal Injection Drug Users in a Canadian Setting. Harm Reduct J, 3(1), pp. 1-9, 2006.

Trends in GHB Abuse 1999 to 2003

This study examined California Poison Control System (CPCS) data to analyze changes in gamma-hydroxybutyrate (GHB) case reporting and compare the findings to other data sets including the data from the American Association of Poison Control Centers (AAPCC), Drug Abuse Warning Network (DAWN) and Monitoring the Future Study data on students and young adults. The investigators identified cases from the CPCS computerized database using standardized codes and key terms for GHB and congener drugs ("gamma butyrolactone," "1,4-butanediol," "gamma valerolactone"), and noted CPCS date, caller and exposure site, patient age and sex, reported coingestions, and outcomes. The CPCS data were compared to case incidence data from AAPCC and DAWN data and drug use prevalence from the Monitoring the Future survey data. A total of 1,331 patients identified from CPCS were included over the 5-year period (1999-2003). California Poison Control System-reported GHB exposures decreased by 76% from baseline (n=426) to the final study year (n=101). The absolute decrease was present across all case types, although there was a significant proportional decrease in routine drug abuse cases and an increase in malicious events, including GHB-facilitated sexual assault (P=.002). AAPCC data showed a similar decrease from 2001 to 2003. DAWN incidence flattened from 2001 to 2002. Monitoring the Future survey time trends were inconsistent across age groups. A precipitous decrease in case incidence for GHB for the CPCS was observed. In comparison with other data sources, the authors conclude that a true decrease in case incidence is likely. This could be due to decreased abuse rates or because fewer abusers seek emergency medical care. Case reporting may account for part of the decrease in the incidence of poison center contacts involving GHB. Anderson, I., Kim, S., Dyer, J., Burkhardt, C., Iknoian, J., Walsh, M., and Blanc, P. Trends in Gamma-Hydroxybutyrate (GHB) and Related Drug Intoxication: 1999 to 2003. Ann Emerg Med, 47(2), pp. 177-183, 2006.

Was There Unmet Mental Health Need after the September 11, 2001 Terrorist Attacks

This study examined the use of professionals for mental health problems among New York City residents who were directly affected by the September 11, 2001 terrorist attacks on the World Trade Center (WTC) or had a probable diagnosis of post-traumatic stress disorder (PTSD) or depression in its aftermath. Correlates of help seeking from professionals for mental health problems after the attacks and barriers to care were also assessed. Data were from a random digit dial telephone survey of 2,752 adults representative of the Greater New York Metropolitan area conducted 6 months after the September 11 terrorist attacks. Fifteen percent of those directly affected and 36% of those with probable PTSD or depression sought help from a professional for a mental health problem after the attacks. There was little new utilization of

professionals for mental health problems after the attacks among persons who were not already receiving care prior to September 11. Barriers that prevented people from seeking help for mental health problems 6 months after the September 11 attacks included traditional barriers to care (e.g., cost) and barriers that are unique to the post-disaster context (e.g., the belief that others need the services more than oneself). This study suggests that there was potential unmet mental health need in New York City 6 months after the September 11 attacks on the WTC, but these findings should be tempered by research showing an apparent decrease in population-rates of PTSD. In the aftermath of a disaster, interventions should target persons with mental health needs who were not previously seeking help from a professional for a mental health problem. Stuber, Galea, Boscarino, and Schlesinger. Was There Unmet Mental Health Need After the September 11, 2001 Terrorist Attacks? Soc Psychiatry Psychiatr Epidemiol, pp. 1-11, 2006.

Director's Report to the National Advisory Council on Drug Abuse - May, 2006

Research Findings - Prevention Ressearch

Effect of Combined School and Community Communication Campaign on Youth Alcohol, Tobacco and Marijuana Use

This study tested the impact of an in-school mediated communication campaign based on social marketing principles, in combination with a participatory, community-based media effort, on marijuana, alcohol and tobacco uptake among middle-school students. Eight media treatment and eight control communities throughout the US were randomly assigned to condition. Within both media treatment and media control communities, one school received a research-based prevention curriculum and one school did not, resulting in a crossed, split-plot design. Four waves of longitudinal data were collected over 2 years in each school and were analyzed using generalized linear mixed models to account for clustering effects. Youth in intervention communities (N = 4216) showed fewer users at final post-test for marijuana [odds ratio (OR) = 0.50, P = 0.019], alcohol (OR = 0.40, P = 0.009) and cigarettes (OR = 0.49, P = 0.039). Growth trajectory results were significant for marijuana (P = 0.040), marginal for alcohol (P = 0.051) and non-significant for cigarettes (P = 0.114). Results suggest that an appropriately designed in-school and community-based media effort can reduce youth substance uptake. Effectiveness does not depend on the presence of an in-school prevention curriculum. Slater, M.D., Kelly, K.J., Edwards, R.W., Thurman, P.J., Plested, B.A., Keefe, T.J., Lawrence, F.R., and Henry, K.L. Combining In-School and Community-Based Media Efforts: Reducing Marijuana and Alcohol Uptake Among Younger Adolescents. Health Education Research, 21(1), pp. 157-167, 2006.

Definition and Outcome of the ATHENA Program to Prevent Disordered Eating and Body-Shaping Drug Use in Female Athletes

This study examined the outcomes of the Athlete Targeting Healthy Exercise and Nutrition Alternatives (ATHENA) intervention in female high school athletes. The ATHENA program is based on the Athletes Training and Learning to Avoid Steroids (ATLAS) curriculum, a sport team-centered drug-use prevention program for male high school athletes, which has been shown to reduce alcohol and illicit drug use. Just as anabolic steroid use is associated with male athletes, female sport participants may be at a greater risk for disordered eating and body-shaping drug use. Extending sport team-centered programs to young women athletes required defining and ranking factors related to developing those harmful behaviors. Survey results from a cross-sectional cohort of female middle and high school student athletes were used to identify and prioritize potential curriculum components, including mood and self-esteem, norms of behavior, perceptions of healthy body weight, effects of media depictions of women, and societal pressures to be thin. The derived

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sport team-centered program was prospectively assessed among a second group of female student athletes from 18 high schools, randomized to receive the intervention or the usual care control condition. The ATHENA intervention is a scripted, coach-facilitated, peer-led 8-session program, which was incorporated into a team's usual training activities. The ATHENA program significantly altered the targeted risk factors and reduced ongoing and new use of diet pills and body-shaping substances (amphetamines, anabolic steroids, and sport supplements). These findings illustrate the utility of a structured process to define curriculum content, and the program's positive results also confirm the sport team's potential as a vehicle to effectively deter health-harming behaviors. Elliot, D., Moe, E., Goldberg, L., Defrancesco, C., Durham, M., and Hix-Small, H. Definition and Outcome of a Curriculum to Prevent Disordered Eating and Body-Shaping Drug Use. J Sch Health, 76(2), pp. 67-73, 2006.

Prevention Study Confirms Positive Impact on Rate of Substance Use

This study reports findings on a combined family and school-based competency-training intervention involving two intervention programs, the Life Skills Training school-based program and the Strengthening Families Program 10-14. Thirty-six rural schools were randomly assigned to (a) a combined family and school intervention condition, (b) a school-only condition, or (c) a control condition. A previous study showed a significant reduction of substance initiation for both the combined intervention and the school-only intervention at the 1-year follow-up as measured by a combined index of lifetime alcohol, cigarette, and marijuana use. The current study extends this work by examining effects from 2.5 years past baseline using multilevel growth curve analysis in a addition to point-in-time analysis. In addition, the authors introduce analysis of problematic alcohol use (i.e., regular alcohol use and weekly drunkenness). The earlier significant outcome was replicated, such that growth in substance initiation for both the combined and school-only conditions was slower than for the control group. Furthermore, positive point-in-time results for weekly drunkenness were observed for the combined intervention as compared to the control intervention. However, there were no statistically significant outcomes for tests of intervention impact on regular alcohol use. Spoth, R., Randall, G., Shin, C., and Redmond, C. Randomized Study of Combined Universal Family and School Preventive Interventions: Patterns of Long-term Effects on Initiation, Regular use, and Weekly Drunkenness. Psychol Addict Behav, 19(4), pp. 372-381, 2005.

Effects of Age and Sensation Seeking on Processing PSAs

This article investigates how sensation seeking and age influence television viewers' online information processing of substance-abuse public service announcements (PSAs). College students and adolescents viewed 30 PSAs that varied in terms of arousing content and production pacing. The experiment used a mixed Arousing Content (2) x Production Pacing (3) x Message (5) x Order of Presentation (3) x Sensation Seeking (2) x Age (2) factorial design. Fifty-nine undergraduate college students (aged 18-27) and eighty-six adolescent high school students (aged 12 to 17) participated in the study. Dependent variables included substance use, self-reported emotional responses (valence and arousal), physiological responses (heart rate and skin conductance response), and recognition. Results show that high-sensation seekers prefer all messages, remember more, and exhibit lower arousal compared to low-sensation seekers. Adolescents remember more information from the PSAs than college students. However, all participants exhibited cognitive overload at the same point in time. Specifically, the combination of arousing content and fast pace overloaded the cognitive system and resulted in

decreases in recognition memory for both adolescents and college students and sensation seeking had no effect on this interaction. Lang, A., Chang, Y., Lee, S., Schwartz, N., and Shin, M. It's an Arousing, Fast-Paced Kind of World: The Effects of Age and Sensation Seeking on The Information Processing of Substance-Abuse PSAs. Media Psychology, 7(4), pp. 421-454, 2005.

Written Personal Feedback Profile as Effective as Brief Motivational Interview

This study evaluated two brief personal feedback substance-use interventions for students mandated to the Rutgers University Alcohol and Drug Assistance Program for Students (ADAPS). One intervention was a brief motivational interview (BMI) and the other intervention involved written feedback-only (WF). A key question addressed was whether there is a need for face-to-face feedback in the context of motivational interviewing to affect changes in substance-use behaviors or whether a written personal feedback profile is enough to motivate students to change their substance use. The participants included 222 students who were mandated to ADAPS. Eligible students completed a baseline assessment from which a personal feedback profile was created. They were then randomly assigned to the BMI or WF condition. Students were reassessed 3 months later. Students in both interventions reduced their alcohol consumption, prevalence of cigarette and marijuana use, and problems related to alcohol and drug use between baseline and follow-up. There were no differences between the two intervention conditions in terms of substance-use outcomes. These results suggest that assessment and WF students changed similarly to those who had an assessment and WF within the context of a BMI. Given the fact that the former is less costly in terms of time and personnel, written profiles may be found to be a cost-effective means of reducing alcohol and drug use and related problems among low- to moderate-risk mandated college students. White, H.R., Morgan, T.J., Pugh, L.A., Celinska, K., Labouvie, E.W., and Pandina, R.J. Evaluating Two Brief Substance-Use Interventions for Mandated College Students. Journal of Studies on Alcohol, 67(2), pp. 309-317, 2006.

Intensity of Contact with Preventive Intervention is Associated with Improved Intervention Outcomes

The ATP intervention is a school-based, family-focused intervention to reduce risk of substance use and other problem behaviors. A family resource center (FRC), staffed by a professionally-trained parent consultant, is created within the participating school. A menu of family-centered intervention services, ranging from brief supportive contacts such as email reports of behavior, attendance, and homework completion to family therapy, are available to families. The goal of this study was to test whether dosage of FRC contacts would predict teacher perception of risk behavior. Four middle schools were involved in the three-year study where contacts with family teachers and youth were tracked and recorded. Five hundred eighty-four youth enrolled in the study and data from all three measurement periods were available for 394 students. Overall 59% of the total contacts were in person, 27% were phone contacts, and 14% were letter or email contacts. Greater student reported substance use, antisocial behavior, deviant peer affiliations, and low academic achievement in 6th grade lead to more family contact with the FRC during 8th grade. Furthermore, larger numbers of FRC contacts predicted a stronger rate of decline in teacher-rated student risk. Stormshak, E., Dishion, T., Light, J., and Yasui, M. Implementing Family-Centered Interventions Within the Public Middle School: Linking Service Delivery to Change in Student Problem Behavior. J Abnorm Child Psychol, 33(6), pp. 723-733, 2005.

Intervention Outcomes for Girls Referred From Juvenile Justice:

Effects on Delinquency

An increasing number of girls are entering the juvenile justice system. However, intervention programs for delinquent girls have not been examined empirically. The authors examined the 12-month outcomes of a randomized intervention trial for girls with chronic delinquency (N = 81). Girls were randomly assigned into an experimental condition (Multidimensional Treatment Foster Care; MTFC) or a control condition (group care; GC). Analysis of covariance indicated that MTFC youth had a significantly greater reduction in the number of days spent in locked settings and in caregiver-reported delinquency and had 42% fewer criminal referrals than GC youth (a trend) at the 12-month follow-up. Implications for reducing girls' chronic delinquency are discussed. Leve, L., Chamberlain, P., and Reid, J. Intervention Outcomes for Girls Referred From Juvenile Justice: Effects on Delinquency. J Consult Clin Psychol, 73(6), pp. 1181-1185, 2005.

Effects of Culturally Adapted Parent Management Training

A randomized experimental test of the implementation feasibility and the efficacy of a culturally adapted Parent Management Training intervention was conducted with a sample of 73 Spanish-speaking Latino parents with middle-school-aged youth at risk for problem behaviors. Intervention feasibility was evaluated through weekly parent satisfaction ratings, intervention participation and attendance, and overall program satisfaction. Intervention effects were evaluated by examining changes in parenting and youth adjustment for the intervention and control groups between baseline and intervention termination approximately 5 months later. Findings provided strong evidence for the feasibility of delivering the intervention in a larger community context. The intervention produced benefits in both parenting outcomes (i.e., general parenting, skill encouragement, overall effective parenting) and youth outcomes (i.e., aggression, externalizing, likelihood of smoking and use of alcohol, marijuana, and other drugs). Differential effects of the intervention were found related to youth nativity status such that parents of U.S.-born youth benefited more from participation in the intervention than parents of foreign-born youth. Martinez, C., and Eddy, J. Effects of Culturally Adapted Parent Management Training on Latino Youth Behavioral Health Outcomes. J Consult Clin Psychol, 73(5), pp. 841-851, 2005.

Skills That Are Foci of Drug Prevention Predict Academic Achievement

This study assessed whether characteristics of individuals that are predictors of youth problem behavior such as substance use, delinquency, and violence also predict academic achievement. Longitudinal data from 576 suburban students participating in the Raising Healthy Children (RHC) project were analyzed. Tenth-grade academic achievement was measured by scores on a standardized test administered to students in Washington State and by student self-report of grades. Measures of social and behavioral characteristics at seventh grade were based on data from student, parent, and teacher surveys. Researchers assessed overall correlations between 7th-grade predictors and 10th-grade academic achievement as well as partial correlations adjusted for demographic characteristics and scores on an earlier achievement test, the Comprehensive Test of Basic Skills, in 4th grade. Results indicated that higher levels of school bonding and better social, emotional, and decision-making skills were related to higher test scores and higher grades. Lower test scores and lower grades were predicted by elevated levels of attention problems, negative behavior of peers, and disruptive and aggressive behavior. Lower test scores also were predicted by early use of alcohol and cigarettes. These findings support the premise that school-based social development interventions that address

specific risk factors, curb early manifestations of antisocial behavior, and promote school bonding and social and emotional skills are likely to improve student academic achievement. Fleming, C., Haggerty, K., Catalano, R., Harachi, T., Mazza, J., and Gruman, D. Do Social and Behavioral Characteristics Targeted by Preventive Interventions Predict Standardized Test Scores and Grades? J Sch Health, 75(9), pp. 342-349, 2005.

The Building Resiliency and Vocational Excellence (BRAVE) Program: A Violence-Prevention and Role Model Program for Young, African American Males

There are sharp disparities between non-Hispanic Whites and African Americans in mortality and years of potential life lost for numerous health-related conditions, including HIV/AIDS. The Building Resiliency and Vocational Excellence (BRAVE) Program is an intervention using Resiliency Networking designed for use with African American young men to help offset these disparities. Resiliency Networking incorporates coaching, career planning, and re-definition of gender roles to help young men develop a sense of purpose and future and to manage their lifestyles effectively. In addition to fostering a strong link with an older mentor, the program fosters healthy peer-to-peer relationships. This paper reports on preliminary use of the intervention and recommends future applications. Griffin, J. The Building Resiliency and Vocational Excellence (BRAVE) Program: A Violence-Prevention and Role Model Program for Young, African American Males. J Health Care Poor Underserved, 16(4 Suppl B), pp. 78-88, 2005.

Inattention Associated With Early-Onset Smoking

This research examines the covariation of attention processes in childhood and adolescence with tobacco use in middle adolescence, controlling for both comorbid antisocial behavior and psychosocial risk. Study participants originated from a sample of 672 6th grade children enrolled in an prevention study. Attention and behavior problems were assessed during T1 via parent report on the Child Behavior Checklist (CBCL). In 11th grade, 501 of these youth completed the Attention Network Test (ANT), a test of the efficiency of alerting, orienting, and executive function systems. Parent ratings of childhood inattention increased the risk of early-onset smoking (odds ratio= 4.12). During adolescence, high performance on an attention task was associated with increased risk (odds ratio=2.07) for patterned tobacco use after controlling for antisocial behavior and known psychosocial risk factors. These analyses suggest a possible regulatory dynamic linking patterned tobacco use and inattention. Gardner, T., Dishion, T., Posner, M., and Posner, M. Attention and Adolescent Tobacco Use: A Potential Self-Regulatory Dynamic Underlying Nicotine Addiction. Addict Behav, 31(3), pp. 531-536, 2006.

Cost-Effectiveness of a Behavioral Intervention for Seropositive Youth

An intervention for young people living with HIV (YPLH) was effective in reducing the number of partners of unknown serostatus and the number of unprotected sexual risk acts. New methods are outlined to assess the cost-effectiveness of this intervention. Over a period of 3 months, the intervention would avert an estimated 2.02 new infections per 1,000 YPLH. The cost of mounting the intervention was estimated at US 522 dollars/YPLH, with the cost-effectiveness over a 1-year period being US 103,366 dollars/infection averted. Based on standardized estimates of the cost of treating HIV-positive persons and the adjusted quality of life years lost (10.23 for partners of a mean age of 29 years), the cost utility estimate shows that the treatment costs averted exceed the cost of the intervention. Both the methodology of

calculating cost-effectiveness and the cost utility of interventions are important for focusing policy makers, clinicians, community providers, and researchers on prevention for persons living with HIV. Lee, M., Leibowitz, A., and Rotheram-Borus, M. Cost-effectiveness of a Behavioral Intervention for Seropositive Youth. AIDS Educ Prev, 17(2), pp. 105-118, 2005.

Screening High School Students for Suicide: Challenges and Opportunities

This study evaluated the feasibility of a population-based approach to preventing adolescent suicide, through screening for suicide risk. A total of 930 high risk students in 10 high schools that were participating in a randomized controlled trial testing the effectiveness of the Reconnecting Youth intervention for improving school performance, decreasing substance use and improving mood management, and 393 low-risk, "typical," students completed the Suicide Risk Screen (SRS). Screening results, student follow-up, staff feedback, and school responses were assessed. Overall, 29% of the participants were rated as at risk of suicide. As a result of this overwhelming percentage, school staffs chose to discontinue the screening after 2 semesters. In further analysis, about half of the students identified through the SRS were deemed at high risk for suicide on the basis of high levels of depression, suicidal ideation, or suicidal behavior. And students with high risk for suicide also were more likely to have other related problems, including more drug use, less family support, more feelings of hopelessness, and less connection to school. A simpler, more specific screening instrument than the SRS would identify approximately 11% of urban high school youths for assessment, offering high school officials an important opportunity to identify young people at the greatest levels of need and to target scarce health resources. This study shows that a lack of feasibility testing greatly contributes to the gap between science and practice. Hallfors, D., Brodish, P., Khatapoush, S., Sanchez, V., Cho, H., and Steckler, A. Feasibility of Screening Adolescents For Suicide Risk in. Am J Public Health, 96(2), pp. 282-287, 2006.

Religiosity and Drug Use Among Mexican and Mexican American Youth

Among a predominately Mexican and Mexican American sample of pre-adolescents, religiosity protected against lifetime alcohol, cigarette, and marijuana use and recent alcohol and cigarette use when religious affiliation was controlled. When religiosity was controlled, however, adolescents with no religious affiliation and adolescents who were religiously affiliated reported similar substance use outcomes. Interaction effects demonstrated that the protective effect of greater religiosity operated more strongly in some religions than in others for selected outcomes. Overall, the impact of religiosity on reported drug use did not differ significantly for more and less acculturated Latino youth. Marsiglia, F., Kulis, S., Nieri, T., and Parsai, M. God Forbid! Substance Use Among Religious and Nonreligious Youth. Am J Orthopsychiatry, 75(4), pp. 585-598, 2005.

Ethnic and Gender-specific Substance Use Patterns in Adolescence

This article documents the prevalence of self-reported substance use among White and American Indian adolescents enrolled in seventh grade (ages 12 through 13) in 1997 in a Northern Plains state. Data were collected by self-administered questionnaire preceding adolescents' participation in a randomized field trial of Project Alert, a seventh and eighth grade substance use prevention curriculum. Rates of lifetime and past-month use of cigarettes and marijuana were higher among American Indians than among Whites of the same gender. American Indian girls exceeded American Indian boys as well as

White girls and White boys on lifetime and past-month use of cigarettes and marijuana as well as alcohol and inhalants; differences on cigarette and inhalant use reached statistical significance. These findings add to the sparse literature on substance use among adolescents as young as 12 through 13 years old and underscore the importance of examining gender-specific substance use patterns early in adolescence. Spear, S., Longshore, D., McCaffrey, D., and Ellickson, P. Prevalence of Substance Use Among White and American Indian Young Adolescents in a Northern Plains State. J Psychoactive Drugs, 37(1), pp. 1-6, 2005.

Externalizing Behavior & Gender Predict Drug Initiation Trajectories

The purpose of the current study was to investigate the influence of externalizing behaviors on substance initiation trajectories among rural adolescents over a 42-month period. Data were obtained from 198 rural adolescents who were participating in a longitudinal study. At the baseline assessment, subjects were on average 12.3 years old. Controlling for gender, higher baseline levels of externalizing were associated with a greater number of substances initiated over time. The initiation trajectory was curvilinear. Girls, compared with boys, reported a lower number of substances initiated at baseline, a greater linear growth trajectory, and a deceleration of growth over time. Lillehoj, C., Trudeau, L., Spoth, R., and Madon, S. Externalizing Behaviors as Predictors of Substance Initiation Trajectories Among Rural Adolescents. J Adolesc Health, 37(6), pp. 493-501, 2005.

Identifying High School Students At Risk for Substance Use and Related Problems

Attendance and grade point average (GPA) data are universally maintained in school records and can potentially aid in identifying students with concealed behavioral problems, such as substance use. Researchers evaluated attendance (truancy) and GPA as a means to identify high school students at risk for substance use, suicide behaviors, and delinquency in 10 high schools in San Antonio, Texas, and San Francisco, California, during the spring and fall of 2002. These schools were involved in a randomized controlled trial testing the effectiveness of the Reconnecting Youth Program, an indicated prevention program designed to improve school performance, decrease substance use, and improve mood management in high risk students. A screening protocol identified students as "high risk" if (1) in the top quartile for absences and below the median GPA or (2) teacher referred. Survey responses of 930 high-risk students were compared with those from a random sample of 393 "typical" students not meeting the protocol. Bivariate and multivariate analyses assessed associations between the screening protocol variables and demographics, risk and protective factors, and problem outcomes. The individual contribution of each of the variables was also assessed. Students identified as high risk were significantly more likely than typical students to use cigarettes, alcohol, and marijuana, evidence suicide risk factors, and engage in delinquent behavior. Norms varied between the two districts; nevertheless, high-risk students showed consistent differences in risk and protective factors, as well as problem behaviors, compared with typical students. Because of site differences in data collection and teacher participation, the comprehensive protocol is recommended, rather than individual indicators alone (e.g., truancy). Strengths of the screening protocol are the ready availability of school record data, the ease of use of the adapted protocol, and the option of including teacher referral. More research is recommended to test the generalizability of the protocol and to ensure that there are no unintended negative effects associated with identification of students as high risk. Hallfors, D., Cho, H., Brodish, P., Flewelling, R., and Khatapoush, S. Identifying High School Students "At Risk" for Substance Use and Other Behavioral Problems:

Implications for Prevention. Subst Use Misuse, 41(1), pp. 1-15, 2006.

Association with Delinquent Peers: Intervention Effects for Youth in the Juvenile Justice System

Although association with delinquent peers is a recognized precursor to ongoing delinquency problems, youth in the juvenile justice system are commonly prescribed intervention services that aggregate delinquent youth. However, little is known about the process variables that mediate the relationship between aggregating youth in intervention settings and poor subsequent outcomes. The researchers examined data from two randomized intervention trials (one male sample and one female sample) with delinquent adolescents placed either in Multidimensional Treatment Foster Care (MTFC) or in group care. Path analysis suggested that the MTFC youth had fewer associations with delinquent peers at 12 months than did the group care youth. Further, associating with delinquent peers during the course of the intervention mediated the relationship between group condition and 12-month delinquent peer association. Implications for the development of interventions with delinquent youth are discussed. Leve, L., and Chamberlain, P. Association with Delinquent Peers: Intervention Effects for Youth in the Juvenile Justice System. J Abnorm Child Psychol, 33(3), pp. 339-347, 2005.

Female Caregivers' Experiences With Intimate Partner Violence Are Related to Child Functioning

This study examined the relationship between women's experiences with intimate partner violence and their reports of child behavior problems. Data were from the National Survey of Child and Adolescent Well-Being, a national probability study of children who were the subjects of child abuse and neglect investigations. The sample consisted of 2020 female caregivers of children between the ages of 4 and 14 years who were interviewed about demographic characteristics, child behavior problems, female caregiver mental health, parenting behaviors, experiences with intimate partner violence, and community characteristics. Information on child abuse and neglect was obtained in interviews with child protective services workers. Multiple-regression analyses were used to investigate the association between caregiver victimization and child behavior problems while controlling for the effects of child, family, and environmental characteristics. The potential moderating effects of caregiver depression and parenting practices on the relation between intimate partner violence and child behavior problems were examined also. Severe intimate partner violence was associated with both externalizing and internalizing behavior problems when other risk factors were controlled. Use of corporal punishment and psychological aggression were significant moderators, but maternal depression did not moderate the relation between intimate partner violence and behavior problems. This study adds to the evidence that maternal caregivers' experiences with intimate partner violence are related to child functioning. The findings suggest that systematic efforts are needed to ensure that mental health needs are identified and addressed appropriately in children exposed to this violence. Hazen, A., Connelly, C., Kelleher, K., Barth, R., and Landsverk, J. Female Caregivers' Experiences With Intimate Partner Violence and Behavior Problems in Children Investigated as Victims of Maltreatment. Pediatrics, 117(1), pp. 99-109, 2006.

Differences Among Sexually Abused and Nonabused Youth Living with HIV

Risk behaviors were compared between sexually abused and non-abused youth living with HIV (YLH). Abused YLH were significantly more likely to have attempted suicide, to have been admitted into an alcohol and/or drug

treatment program, and to have engaged in crack cocaine use than were non-abused YLH and had a greater number of sexual partners. A significantly higher proportion of abused YLH had been incarcerated in contrast to non-abused youth. There were also significantly greater conduct problems among abused YLH. Finally, abused YLH had significantly higher scores on positive action and social-support coping styles than non-abused youth. Consistent with previous research, abused youth are at higher risk for a variety of negative outcomes and are also similar in many respects to sexually abused youth who are not HIV-positive. The high frequencies of two positive styles of coping among abused YLH were also observed. Anaya, H.D., Swendeman, D., and Rotheram-Borus, M.J. Differences Among Sexually Abused and Nonabused Youth Living with HIV. J Interpers Violence, 20(12), pp. 1547-1559, 2005.

Predictors of Serostatus Disclosures to Partners Among Young People Living with HIV in the Pre- and Post-HAART Eras

Predictors of serostatus disclosure were identified among youth living with HIV pre- and post-introduction of highly active antiretroviral therapy (HAART). Two cohorts of HIV-positive youth, aged 13-24, in 1994-1996 (n = 351) and 1999-2000 (n = 253) in Los Angeles, New York, San Francisco, and Miami were sampled through medical providers and a variety of social service agencies. Data were collected on demographic, social, medical, and behavioral topics. Men who had sex with men were more likely to disclose serostatus to their partners. Moreover, a positive association with length of time since diagnosis and the likelihood of disclosure exists; across time, youth were less likely to disclose serostatus to casual partners or HIV-negative partners. Post-HAART, number of sex acts with a partner was associated with increased likelihood of disclosure. Interventions for HIV-positive youth must improve disclosure to casual and serodiscordant sexual partners. Batterham, P., Rice, E., and Rotheram-Borus, M. Predictors of Serostatus Disclosure to Partners Among Young People Living with HIV in the Pre- and Post-HAART Era. AIDS Behav, 9(3), pp. 281-287, 2005.

Correlates of HIV Status among Injection Drug Users in a Border Region of Southern China and Northern Vietnam

This article presents an analysis of the correlates of HIV status among samples of injection drug users (IDUs) in Lang Son Province, Vietnam (n=348), and Ning Ming County, Guangxi Province, China (n=294), who were interviewed and tested for HIV antibody just before the start of a peer-based HIV prevention intervention in this border region. Participants were largely male, in their 20s, and single. Logistic regression analysis suggests that among Chinese IDUs, border-related factors (eg, living closer to the border, buying drugs across the border more frequently) and younger age are the best predictors of HIV positivity. In Vietnam, HIV status seems to drive behavior (eg, some risk reduction practices are predictive of HIV positivity). These differing patterns may reflect the fact that the intertwined epidemics of heroin injection and HIV began earlier and HIV prevalence has reached significantly higher levels in Lang Son than across the border in Ning Ming. Although border-related factors emerge as predictors in Ning Ming, more IDUs in Lang Son are HIV-positive and may be reacting behaviorally to that status. Their greater likelihood of engaging in risk reduction measures may reflect some combination of a belief that risk reduction can slow disease progression and an altruistic desire to avoid infecting others. Hammett, T., Johnston, P., Kling, R., Liu, W., Ngu, D., Tung, N., Binh, K., Dong, H., Hoang, T., Van, L., Donghua, M., Chen, Y., and Des Jarlais, D. Correlates of HIV Status Among Injection Drug Users in a Border Region of Southern China and Northern Vietnam. J Acquir Immune Defic Syndr, 38(2), pp. 228-235, 2005.

Self-Perceived Social Acceptance and Peer Social Standing in Children with Aggressive-Disruptive Behaviors

Examining children's perceptions of their social acceptance in conjunction with others' ratings of their peer social standing can enhance our understanding of the heterogeneity in children exhibiting disruptive behavior problems. Using a sample of 213 youth rated in the top 31 percent of their class on aggressive-disruptive behaviors, the current study examined the interaction between children's perceptions of their social acceptance and their peer-rated social standing in predicting emotional and behavioral problems. Overall, lower peer-rated social standing was associated with higher levels of antisocial behavior, academic problems, and hyperactivity/inattention. On the other hand, higher self-perceived social acceptance was associated with increased levels of peer-rated fighting at school. For children who were rated as having high social standing among their peers, poorer self-perceived social acceptance was associated with increased oppositional behaviors and conduct problems at home. In addition, children who reported lower self-perceived social acceptance exhibited increased levels of depressive symptoms, even when they were relatively well liked by their peers. The potential implications for working with subgroups of children with aggressive-disruptive behaviors are discussed. Pardini, D.A., Barry, T.D., Barth, J.M., Lochman, J.E., and Wells, K.C. Self-Perceived Social Acceptance and Peer Social Standing in Children with Aggressive-Disruptive Behaviors. Social Development, 15(1), pp. 46-64, 2006.

Adverse School Context Moderates the Outcomes of Selective Interventions for Aggressive Children

Drawing on social ecological theory and empirical studies on the role of school context in aggression, the authors argue that school adversity is an important consideration in choosing selective interventions for aggressive children. The moderating role of school adversity on intervention effectiveness is illustrated with data from a randomized clinical trial study investigating 2 selective interventions administered to 86 aggressive 2nd and 3rd graders. The authors expected that PrimeTime, an intervention targeting child competencies, would be more effective in low-adversity schools, whereas Lunch Buddy, an intervention targeting peer ecology, would be more effective in high-adversity schools. Hierarchical linear regression analysis showed significant post-treatment effects on composite measures of aggression and achievement for the interaction between the level of school adversity and treatment condition. Hughes, J., Cavell, T., Meehan, B., Zhang, D., and Collie, C. Adverse School Context Moderates the Outcomes of Selective Interventions for Aggressive Children. J Consult Clin Psychol, 73(4), pp. 731-736, 2005.

Measuring Adolescents' Smoking Expectancies

Outcome expectancies have been related to smoking behavior among adults, but less attention has been given to expectancies about smoking among adolescents at differing levels of smoking experience. The present study reports the psychometric properties and predictive validity of a brief expectancy scale across two samples of adolescents. Sample 1 (N = 349) consisted of high school students (54% female) who were regular smokers enrolled in a cessation program. Sample 2 (N = 273) consisted of 8th- and 10th-grade early experimenters (54% female) involved in a natural history study of smoking trajectories. In both samples, a principal component analysis of a 13-item expectancy scale yielded four factors (taste, weight control, boredom relief, and negative affect management), each with high internal consistency (coefficient alphas >.77) and accounting for 73% and 80% of the total variance for each sample, respectively. Expectancies were significantly higher among current smokers than among early initiators. In Sample 1,

boredom relief and weight management expectancies predicted smoking status 6 months later. In Sample 2, students whose smoking increased over 18 months had higher overall expectancies at baseline compared with those who tried smoking and did not escalate. These findings support the predictive validity of expectancies in predicting escalation and cessation. Wahl, S., Turner, L., Mermelstein, R., and Flay, B. Adolescents ' Smoking Expectancies: Psychometric Properties and Prediction of Behavior Change. Nicotine Tob Res, 7(4), pp. 613-623, 2005.

Psychometric Examination of English and Spanish Versions of Scales

The psychometric properties of the Revised Conflict Tactics Scales (CTS2) are examined for English-speaking (n = 211) and Spanish-speaking (n = 194) Latino women. Internal consistency of total scale scores is satisfactory (Cronbach's alpha of .70 to .84). However, subscale alphas range from .46 to .80. Confirmatory factor analysis supported five factors of negotiation, minor and severe psychological aggression, and minor and severe physical assault. In unconstrained two-group models, loadings are of similar magnitude across language of administration, with the exception of the Physical Assault scales. Unconstrained and constrained model comparisons show scale structure varied by language group for physical assault. Although results of this study show some comparability for English-speaking and Spanish-speaking Latinas, simply combining results across language groups may obscure important differences in rates of endorsement and patterns of responses reflecting cultural, educational, and economic differences. Connelly, C., Newton, R., and Aarons, G. A Psychometric Examination of English and Spanish Versions of the Revised Conflict Tactics Scales. J Interpers Violence, 20(12), pp. 1560-1579, 2005.

Measurement Properties of the Communities That Care Youth Survey Across Demographic Groups

Prevention science has produced information about risk and protective factors that predict adolescent use and related problem behaviors. This paper investigates the Communities That Care Youth survey that measures multiple risk and protective factors. Using a sample of 172,628 students who participated in surveys administered in seven states in 1998, analyses were conducted to test the factor structure of these risk and protective factors and to test the equivalence of the factor models across five racial/ethnic groups (African Americans, Asians or Pacific Islanders, Caucasians, Hispanic Americans, and Native Americans), four grade levels (6th, 8th, 10th and 12th), and both gender groups. Results support the construct validity of the survey's risk and protective factor scales and indicate that the measures are equally reliable across males and females and five racial/ethnic groups. Implications of these findings for science-based prevention planning are discussed. Glaser, R.R., Van Horn, M.L., Arthur, M.W., Hawkins, J.D., and Catalano, R.F. Measurement Properties of the Communities That Care Youth Survey Across Demographic Groups. J Quantitative Crim, 21(1), pp. 73-101, 2005.

Tobacco Industry Successfully Prevented Tobacco Control Legislation in Argentina

This study evaluates how transnational tobacco companies, working through their local affiliates, influenced tobacco control policymaking in Argentina between 1966 and 2005. Analysis of internal tobacco industry documents, local newspapers and magazines, internet resources, bills from the Argentinean National Congress Library, and interviews with key individuals in Argentina. Transnational tobacco companies (Philip Morris International, British American Tobacco, Lorillard, and RJ Reynolds International) have been actively

influencing public health policymaking in Argentina since the early 1970s. As in other countries, in 1977 the tobacco industry created a weak voluntary self-regulating code to avoid strong legislated restrictions on advertising. In addition to direct lobbying by the tobacco companies, these efforts involved use of third party allies, public relations campaigns, and scientific and medical consultants. During the 1980s and 1990s efforts to pass comprehensive tobacco control legislation intensified, but the organized tobacco industry prevented its enactment. There has been no national activity to decrease exposure to secondhand smoke. The tobacco industry, working through its local subsidiaries, has subverted meaningful tobacco control legislation in Argentina using the same strategies as in the USA and other countries. As a result, tobacco control in Argentina remains governed by a national law that is weak and restricted in its scope. SebriŽ, E., Barnoya, J., PŽrez-Stable, E., and Glantz, S. Tobacco Industry Successfully Prevented Tobacco Control Legislation in Argentina. Tob Control, 14(5), pp. e2-e22, 2005.

Reframing

Federal HIV prevention strategy seeks to increase efforts by health care providers to identify and reduce their HIV-positive patients transmission-related behaviors. Implementation of these recommendations will be hindered if providers perceive these efforts have the potential to harm their relationships with patients. Because transmission-related behaviors (unsafe sex and sharing needles) and the related issues of drug and alcohol use also jeopardize the health of HIV-positive patients, providers can use patient-centered counseling when addressing those behaviors. The researchers suggest efforts to increase provider-delivered transmission-prevention counseling be reframed so that "prevention with positives" includes the goal of protecting HIV-positive patients health. The researchers review the specific consequences of these risky behaviors on HIV-positive patient's health and review brief counseling strategies appropriate for HIV care providers. Gerbert, B., Danley, D., Herzig, K., Clanon, K., Ciccarone, D., Gilbert, P., Allerton, M., and Allerton, M. Reframing "Prevention with Positives": Incorporating Counseling Techniques that Improve the Health of HIV-Postitive Patients. AIDS Patient Care STDS, 20(1), pp. 19-29, 2006.

Director's Report to the National Advisory Council on Drug Abuse - May, 2006

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

Prize-based Contingency Management Does Not Increase Gambling Behavior

Dr. Petry and colleagues at the University of Connecticut Health Center have shown that a treatment which awards chances to draw for prizes in exchange for treatment relevant behaviors such as providing drug free urines or attendance is efficacious (Prize-based CM). However this intervention has been criticized because of concerns that participating in this type of raffle or lottery like program might increase gambling behavior. Dr Petry randomly enrolled stimulant users in a multi-site trial to twelve weeks of either usual care or usual care plus Prize-based CM. People with prior gambling problems were not admitted to the study. She found that during the study period, 26% of people in the traditional outpatient programs and 37% of people in the methadone maintenance programs engaged in gambling. However, participation in the con- tingency management intervention did not significantly alter rates of gambling behavior, indicating that increasing gambling is likely not a risk for stimulant users without a prior gambling problem. This is significant because the possibility of increasing gambling risk, is no longer a barrier to adoption of this procedure by community providers. Petry, N.M., Kolodner, K.B., Li, R., Peirce, J.M., Roll, J.M., Stitzer, M.L. and Hamilton, J.A. Drug and Alcohol Dependence, available online 10 January 2006.

Voucher-Based Reinforcement Therapy (VBRT) Better than Control Treatments

Dr. Higgins and others at University of Vermont examined thirty studies of Voucher Based Reinforcement Therapy in a meta-analysis. Of these, twenty studies provided clients with vouchers redeemable for goods and services in exchange for client provided drug abstinent urine tests, six provided them in exchange for treatment attendance and four provided them in exchange for medication compliance. Control treatments included Effect sizes were d=.32, d=.15, and d=.32, respectively suggesting that VBRT is effective particularly for increasing abstinence and medication taking behaviors. The study showed that effects were enhanced by increasing the speed of voucher delivery and by increasing the magnitude of voucher delivery. Studies offering on average greater than $5.00 per day were associated with a moderate effect size. Studies delivering immediate vouchers had double the effect of studies in which the participants had to wait to receive their voucher. This is the first meta-analysis showing that VBRT is robust with myriad outcome measures and in numerous populations, and suggesting that the effect can be improved by following certain guidelines with respect to voucher magnitude and delivery. Lussier, J.P., Heil, S.H., Mongeon, J.A., Badger G.J. and Higgins, S.T. Addiction,

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Staff Highlights

Grantee Honors

pp. 192-203, February 2006.

Cognitive Deficits Predict Low Treatment Retention in Cocaine Dependent Patients

Dr. Aharonovich and colleagues at Columbia University conducted this study to investigate the association between cognitive abilities at treatment entry and retention and outcome in treatment seeking cocaine dependent patients. Fifty-six cocaine dependent patients receiving CBT in outpatient clinical trials were assessed for cognitive performance at treatment entry with the computerized MicroCog (MC) and the Wisconsin Card Sort Test (WCST). Treatment completion was defined as 12 or more weeks. Results demonstrated that treatment dropouts had significantly lower MC scores than completers, indicating poorer cognitive functioning. Significant differences were found in the following domains: attention, memory, spatial ability, speed, accuracy, global cognitive functioning and global proficiency. Mental reasoning demonstrated a trend toward significance. In contrast, performance on the WCST was at average or near average range, and completers and dropouts did not differ significantly on any measures. The authors speculate that the tasks on the WCST may not have been complex enough to tap into deficits in executive functioning. The findings from this study show that general level of cognitive functioning and specific cognitive deficits at treatment entry predict retention in outpatient CBT treatment for cocaine dependent patients. Knowledge of the presence of cognitive impairments at treatment entry may help tailor psychological and pharmacological interventions for cognitively impaired patients. Aharonovich, A., Hasin, D.S., Brooks, A.C., Liu, X., Bisaga, A. and Nunes, E.V. Drug and Alcohol Dependence, 81, pp. 313-322, 2006.

Predicting Smoking Stage of Change among Emergency Department Patients and Visitors

Dr. Boudreaux and colleagues from the Robert Wood Johnson Medical School conducted this study to determine if emergency department (ED) patients or their visitors are interested in smoking cessation. Patients and visitors aged 18 years and older presenting to four Boston EDs over two 24-hour periods, were interviewed. Twenty-three percent of those screened were current smokers. The interview showed some heterogeneity in stage of change of the smokers: 57% were in precontemplation stage, 31% in contemplation, and 12% in preparation. The variables most strongly associated with stage of change were self-efficacy, anticipated cessation-related health improvement, and having a smoking-related health problem. The authors conclude that the ED is a major source of health care in the U.S., especially among the uninsured and economically disadvantaged, and increased attention to smoking in the ED setting holds tremendous public health potential. The heterogeneity of smokers suggests that different strategies should be used to assist smokers on the basis of their stage. More research is needed to assess the efficacy and feasibility of different strategies of cessation promotion within the ED setting. Boudreaux, E.D., Hunter, G.C., Bos, K., Clark, S., Camargo Jr., C.A. Academic Emergency Medicine, 13, pp. 39-34, 2006.

Experimental Evidence for a Causal Relationship between Smoking Lapse and Relapse

This study evaluated the impact of smoking lapse on relapse probability. Smokers (N=87) who were not seeking cessation treatment participated in a 10-day study that involved a temporary quit attempt during which a smoking-lapse episode was experimentally manipulated. Participants who demonstrated abstinence until day four were randomly assigned to one of three experimental manipulations: (a) smoke five nicotine-containing cigarettes; (b) smoke five

denicontinized-containing cigarettes; (c) or remain abstinent (no lapse) during a four-hour period. Subsequently, smokers were asked to remain abstinent for the remaining six days. The percentage of participants abstinent at the end of the 6-day follow-up period was 70% for the no-lapse group, relative to 45% and 40% among those who smoked nicotine-containing and denicotinized cigarettes, respectively. That is, those receiving the lapse exposure manipulation, returned to smoking more rapidly than those who remained abstinent. Smoking outcomes did not differ between nicotine-containing and denicotinized cigarettes. This data suggests that stimulus factors may play an important role in the lapse to relapse processes. In summary, this study demonstrates under controlled conditions that smoking lapse has a direct detrimental effect on subsequent abstinence outcomes. Juliano, L.M., Donny, E.C., Houtsmuller, E.J. and Stitzer, M.L. Journal of Abnormal Psychology, 115(1), pp. 166-173, 2006.

Tobacco Cessation in Dental Settings: Research Findings and Future Directions

Dr. Judith Gordon and colleagues at the Oregon Research Institute reviewed the literature on smoking cessation interventions conducted in dental office-based settings. The dental office visit represents a clinical opportunity during which patients may be receptive to cessation advice and assistance. Data from seven randomized clinical trials indicate there is ample evidence for the efficacy of dental office-based interventions, but adoption of tobacco cessation activities into practice has been slow. Currently, there are several studies underway that may help to increase the effectiveness of dental office-based tobacco cessation programs, and to further efforts to encourage adoption of empirically proven interventions into routine dental care. The public health impact would be enormous if dental practitioners provided cessation assistance routinely to their patients. The authors suggest that researchers and clinicians continue to work together towards universal adoption of effective tobacco cessation interventions at each clinical encounter. Gordon, J.S., Lichtenstein, E., Severson, H.H. and Andrews, J.A. Drug and Alcohol Review, 25, pp. 27-37, 2006.

Cardiovascular Risk Behavior Among Sedentary Female Smokers and Smoking Cessation Outcomes

Researchers from the Harvard School of Dental Medicine conducted this study to determine if female sedentary smokers with additional cardiovascular disease (CVD) health risk behaviors, like diet and alcohol use, predict abstinence from tobacco use. This study was part of a randomized controlled trial testing the effectiveness of exercise and nicotine gum in smoking cessation. Included in the analysis were 148 participates. This study suggested that high alcohol consumption alone and accumulation of two added risk behaviors predicted poorer smoking cessation outcome in a quit attempt. Dietary behavior alone was not related to cessation outcome. However, the high-fat diet interacted with depression, suggesting that depressed women engaging in high-fat diet are significantly more likely to relapse in their quit attempt compared to other subgroups. The authors conclude that non-moderate alcohol use alone and accumulation of multiple CVD risk behaviors seem to be associated with lower success in smoking cessation. Korhonen, T., Kinnunen, T., Quiles, Z., Leeman, R.F., Terwal, D.M. and Garvey, A.J. Tobacco Induced Diseases, 3, pp. 7-26, 2005.

Clinical Trial of Abstinence-Based Vouchers and Cognitive-Behavioral Therapy for Cannabis Dependence

Dr. Budney and colleagues at the University of Vermont conducted a study to

test behavioral treatments for marijuana dependent persons. Ninety adults seeking treatment for marijuana dependence were randomly assigned to receive cognitive-behavioral therapy, abstinence-based voucher incentives, or their combination. Treatment duration was 14 weeks, and outcomes were assessed for 12 months post-treatment. Findings suggest that (a) abstinence-based vouchers were effective for engendering extended periods of continuous marijuana abstinence during treatment, (b) cognitive-behavioral therapy did not add to this during-treatment effect, and (c) cognitive-behavioral therapy enhanced the post-treatment maintenance of the initial positive effect of vouchers on abstinence. This study extends the literature on cannabis dependence indicating that abstinence-based vouchers is a potent treatment option. Budney, A.J., Moore, B.A., Rocha, H.L. and Higgins, S.T. Journal of Consulting and Clinical Psychology, 74(2), pp. 307-316, 2006.

A Controlled Trial of Naltrexone Augmentation of Nicotine Replacement Therapy for Smoking Cessation

Dr. O'Malley and colleagues at Yale University conducted this study to evaluate whether naltrexone hydrochloride augmentation of nicotine patch therapy improves smoking abstinence and reduces postcessation weight gain more than nicotine patch therapy alone. In an outpatient research center, four hundred individuals who smoked more than 20 cigarettes per day participated in a six-week, double-blind, placebo-controlled trial. The patients were randomly assigned to a treatment of a 21-mg nicotine patch and various doses of naltrexone hydrochloride (0, 25, 50, or 100 mg/d). All patients received behavioral counseling. Among the 295 treatment completers, the 100-mg/d was associated with higher continuous abstinence rates (71.6%) compared with the placebo (48%). Also, the 25-mg/d naltrexone hydrochloride group gained significantly less weight than the placebo group. The authors conclude that the 100-mg dose of naltrexone hydrochloride shows the most potential to enhance the efficacy of nicotine patch therapy for smoking cessation outcomes and the low-dose naltrexone hydrochloride may help control weight gain in weight-concerned smokers, however further research is required. O'Malley, S., Cooney, J.L., Krishnan-Sarin, S., Dubin, J.A., McKee, S., Cooney, N.L., Blakeslee, A., Meandzija, B., Romano-Dahlgard, D., Wu, R., Makuch, R. and Jatlow, M.D.P. Arch Intern Med, 166, pp. 667-674, 2006.

Comprehensive Treatment Including Provision of Housing Reduced Drug Use for Homeless, Dually-Diagnosed Cocaine Abusers

Drs. Jesse Milby and Joseph Schumacher and colleagues at the University of Alabama delivered a cognitive behaviorally-based day treatment and work therapy platform to 196 homeless cocaine abusers, along with one of 3 randomly-assigned housing conditions: 1) provision of housing contingent upon abstinence from drugs; 2) provision of housing without an abstinence contingency; and 3) no provision of housing. Treatment occurred in phases, beginning with a skills-based day treatment and free housing for those receiving housing (months 1 - 2), followed by work therapy, group treatment, and low-cost rent for those receiving housing (months 3 - 6), and finally less intensive support group meetings (months 7 - 12). Participants who were provided housing had significantly better abstinence rates and retention rates than did those who were not provided housing, and there were few significant differences in outcomes between the two housing groups. However, among participants who were engaged into the day-treatment phase, those with abstinent-contingent housing had better abstinence than the other groups. Also, all housing recipients were successful in earning and paying rent during the work therapy phase of treatment. Sex/gender did not appear to moderate the relationships between interventions and outcomes. This study contributes to a line of related research highlight the value of housing in recovery, and

suggests several methods for successfully integrating provisions of housing and work skills into substance abuse treatment. Milby, J.B., Schumacher, J.E., Wallace, D., Freedman, M.J. and Vuchinich, R.E. To House or Not to House: The Effects of Providing Housing to Homeless Substance Abusers in Treatment. American Journal of Public Health, 95, pp. 1259-1265, July 2005.

Director's Report to the National Advisory Council on Drug Abuse - May, 2006

Research Findings - Research on Pharmacotherapies for Drug Abuse

Pharmacokinetics and Pharmacodynamics of Multiple Sublingual Buprenorphine Tablets in Dose-Escalation Trials

In this investigation, the pharmacokinetic and pharmacodynamic properties were determined of multiple doses of sublingual tablets containing either buprenorphine alone or buprenorphine and naloxone. Subjects were experienced opiate users who received escalating doses (4-24 mg) of buprenorphine either alone or in combination with naloxone. Peak concentration (Cmax) and area under the concentration-time curves (AUCs) increased for both buprenorphine and naloxone with escalating doses. Significant differences were found across the range of doses administered for dose-adjusted Cmax for both tablet formulations and for the dose-adjusted AUCs for the buprenorphine-naloxone tablets. For both formulations, the maximal buprenorphine-induced decreases in respiratory rate and pupil diameter did not vary significantly across doses. Several of the subjective effects of buprenorphine did not increase as the dose of buprenorphine administered was increased. These findings are consistent with the ceiling effect associated with the partial agonist actions of buprenorphine. They also indicate a lack of dose proportionality for buprenorphine sublingual tablets, at least during the times at which levels of this agent are highest. Ciraulo, D.A., Hitzemann, R.J., Somoza, E., Knapp, C.M., Rotrosen, J., Sarid-Segal, O., Ciraulo, A.M., Greenblatt, D.J. and Chiang, C.N. J Clin Pharmacol. 46(2), pp. 179-192, February 2006.

Gender Effects Following Repeated Administration of Cocaine and Alcohol in Humans

Use of cocaine, alcohol, and the two drugs simultaneously is common and the risk of morbidity and mortality associated with these drugs is widely reported. This double-blind, placebo-controlled, randomized study examined gender differences in response to administration of these drugs alone and in combination. Current users of cocaine and alcohol (n = 17) who met diagnostic criteria (DSM-IV) for cocaine dependence and alcohol abuse or dependence (not physiologically dependent on alcohol) and who were not seeking treatment for substance use disorders gave voluntary, written, informed consent to participate in three drug administration sessions:1) four doses of intranasal cocaine (1 mg/kg every 30 min) with oral alcohol (1 g/kg following the initial cocaine dose and a second drink at +60 min (120 mg/kg) calculated to maintain a plasma alcohol concentration of approximately 100 mg/dL; 2)four doses of cocaine and alcohol placebo; 3) cocaine placebo and alcohol. Pharmacokinetics were obtained by serial blood sampling, physiological measurements (heart rate and blood pressure) were obtained with automated

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equipment, and subjective effects were assessed using visual analog scales over 480 min. Responses to cocaine, alcohol, and cocaine-alcohol were equivalent by gender for most measurements. Women had higher heart rates following alcohol administration (p =.02). Women consistently reported higher ratings for "Feel Good" a measure of overall mental/physical well-being, for all study conditions, reaching statistical significance for cocaine (p = .05) and approaching significance for alcohol administration (p = .1). Women showed equivalent responses to drug administration with the exception of perception of well-being, which was significantly increased for women. These findings may have implications for differential risk for acute and chronic toxicity in women. McCance-Katz, E.F., Hart, C.L., Boyarsky, B., Kosten, T. and Jatlow, P. Subst Use Misuse. 40(4), pp. 511-528, 2005.

Clinical Pharmacodynamics of HIV-1 Protease Inhibitors: Use of Inhibitory Quotients to Optimize Pharmacotherapy

The introduction of HIV-1 protease inhibitors and non-nucleoside reverse transcriptase inhibitors in 1996 began an era described as that of highly active antiretroviral therapy. In addition, the more recent development and availability of HIV-1 genotypic and phenotypic resistance tests and advances in pharmacological assays that support therapeutic drug monitoring (TDM) have created tools that may help clinicians to provide more individualized treatment with HIV-1 protease inhibitors. All current treatment guidelines provide fixed doses of protease inhibitors with vague recommendations for the use of TDM in selected clinical situations. In patients with resistance to protease inhibitors, the combined use of resistance tests with TDM provide a mechanism for individualising the clinical pharmaco-dynamics of protease inhibitors. Current therapeutic approaches seek to include the monitoring of protease-inhibitor concentrations as part of a TDM programme with phenotypic assays to calculate an inhibitory quotient, virtual inhibitory quotient, or normalised inhibitory quotient, whereas genotypic tests are used with TDM to calculate a genotypic inhibitory quotient. Current investigation is focused on examining the predictive value of this approach for clinical monitoring. Morse, G.D., Catanzaro, L.M. and Acosta, E.P. Lancet Infect Dis. 6(4), pp. 215-225, April 2006.

Update on the Pharmacokinetic Aspects of Antiretroviral Agents: Implications in Therapeutic Drug Monitoring

The observed inter-individual variation in antiretroviral pharmacokinetics (PK) that results in a wide range of drug exposures from fixed-dose regimens has led to increasing interest in the clinical use of therapeutic drug monitoring (TDM) to individualize dosing of antiretroviral therapy (ART). The focus of this review is to provide an overview of literature available to support therapeutic drug monitoring among the current classes of antiretrovirals, suggest patient populations that may benefit from TDM and bring forth some of the limitations that may exist for widespread use of TDM in a traditional clinical setting. Slish, J.C., Catanzaro, L.M., Ma, Q., Okusanya, O.O., Demeter, L., Albrecht, M. and Morse, G.D. Curr Pharm Des. 12(9), pp. 1129-1145, 2006.

A Low Dose of Aripiprazole Attenuates the Subject-rated Effects of d-Amphetamine

In a previous published study, 20 mg aripiprazole, an atypical antipsychotic that has partial D2 agonist activity, attenuated many of the behavioral effects of d-amphetamine., but also impaired performance on a computerized version of the DSSTY when administered alone. A study was conducted in six subjects to determine if a lower dose of aripiprazole (10 mg) could acutely attenuate the discriminative and physiological effects of 2.5-15 mg d-amphetamine without

impairing performance as measured with a computerized version of the DSST. The results indicated that 10 mg aripiprazole attenuated some abuse-related behavioral effects, and that this dose would be a reasonable starting dose for the treatment of stimulant abuse and dependence. Stoops, W.W., Lile, J.A., Glaser, P.E. and Rush, C.R. Drug Alcohol Depend. (E-publication) 2006.

Memantine Increases Cardiovascular but not Behavioral Effects of Cocaine in Methadone-maintained Humans

Previous work has suggested that maintenance on the noncompetitive N-methyl-d-aspartate (NMDA) antagonist, memantine, increased the subjective effects of smoked cocaine in experienced cocaine users. To determine whether this phenomenon occurs in opioid-dependent individuals, eight (seven male, one female) methadone-maintained cocaine smokers participated in a 47-day inpatient and outpatient study to assess the effects of memantine on smoked cocaine self-administration, subjective effects, and cardiovascular responses. The participants were maintained on memantine (0 mg and 20 mg daily) for 7-10 days prior to laboratory testing, using a double-blind crossover design. Under each medication condition during inpatient phases, participants smoked a sample dose of cocaine base (0, 12, 25, and 50 mg) once, and were subsequently given five choice opportunities, 14 min apart, to self-administer that dose of cocaine or receive a merchandise voucher (US $5.00). Each cocaine dose was tested twice under each medication condition, and the order of medication condition and cocaine dose were varied systematically. Memantine maintenance did not alter the subjective or reinforcing effects of cocaine. Several cardiovascular responses, however, including peak and initial diastolic pressures following cocaine, were significantly greater during memantine maintenance, although these elevations were not clinically significant. Taken together, these findings corroborate earlier data suggesting that this dose of memantine will not be helpful in the pharmacotherapy of cocaine abuse. Collins, E.D., Vosburg, S.K., Ward, A.S., Haney, M. and Foltin, R.W. Pharmacol.Biochem.Behav., 83, pp. 47-55, 2006.

Injectable, Sustained-release Naltrexone for the Treatment of Opioid Dependence: a Randomized, Placebo-controlled Trial

Oral naltrexone can completely antagonize the effects produced by opioid agonists. However, poor compliance with naltrexone has been a major obstacle to the effective treatment of opioid dependence. The purpose of this study was to evaluate the safety and efficacy of a sustained-release depot formulation of naltrexone in treating opioid dependence in a randomized, double-blind, placebo-controlled, 8-week trial conducted at 2 medical centers, in 60 heroin-dependent adults. Participants were stratified by sex and years of heroin use (> or = 5 vs < 5) and then were randomized to receive placebo or 192 or 384 mg of depot naltrexone. Doses were administered at the beginning of weeks 1 and 5. All participants received twice-weekly relapse prevention therapy, provided observed urine samples, and completed other assessments at each visit. Retention in treatment was dose related, with 39%, 60%, and 68% of patients in the placebo, 192 mg of naltrexone, and 384 mg of naltrexone groups, respectively, remaining in treatment at the end of 2 months. Time to dropout had a significant main effect of dose, with mean time to dropout of 27, 36, and 48 days for the placebo, 192 mg of naltrexone, and 384 mg of naltrexone groups, respectively. The percentage of urine samples negative for opioids, methadone, cocaine, benzodiazepines, and amphetamine varied significantly as a function of dose. When the data were recalculated without the assumption that missing urine samples were positive, a main effect of group was not found for any drugs tested except cocaine, where the percentage of cocaine-negative urine samples was lower in the placebo group. Adverse events were minimal and generally mild. This formulation of naltrexone was well tolerated and produced a robust, dose-related increase in treatment

retention. These data provide new evidence of the feasibility, efficacy, and tolerability of long-lasting antagonist treatments for opioid dependence. Comer, S.D., Sullivan, M.A., Yu, E., Rothenberg, J.L., Kleber, H.D., Kampman, K. et al. Arch.Gen.Psychiatry, 63, pp. 210-218, 2006.

Early Impact of Methadone Induction for Heroin Dependence: Differential Effects of Two Dose Sequences in a Randomized Controlled Study

The pharmacodynamic and pharmacokinetic effects of 2 methadone (METH) induction dose sequences were evaluated in this 15-day outpatient experimental protocol. Heroin-dependent, non-treatment-seeking volunteers were randomly assigned (stratified for gender, race, and route of heroin use) to 2 groups. In 1 sequence, METH doses ascended (28, 56, then 84 mg/day; stepwise, n = 18), whereas in the other sequence doses escalated, then tapered (28-84 mg on Days 1-6 to 56 mg/day; rapid, n = 16). A contingency-management intervention was common to both groups. Drug use and heroin craving and opioid withdrawal symptoms decreased, whereas agonist symptoms and positive mood increased overall across days for both groups. Plasma concentrations and the acute reinforcing effects of METH paralleled each dose sequence. Stepwise relative to rapid METH induction significantly decreased heroin craving and opioid withdrawal symptoms and increased agonist symptoms and positive mood but did not significantly improve drug use or retention. Although these specific dosing procedures would not necessarily be used in clinical settings, they provide a procedural template that might be applied safely and effectively with a broader range of treatment-seeking individuals. Greenwald, M.K. Exp.Clin.Psychopharmacol., 14, pp. 52-67, 2006.

Severity of Dependence and Motivation for Treatment Comparison of Marijuana- and Cocaine-Dependent Treatment Seekers

Most individuals with marijuana dependence do not seek treatment, and there are few data characterizing treatment seeking marijuana dependent patients compared to patients presenting for treatment of other drugs. In this study, 42 marijuana-dependent individuals were compared to 58 cocaine-dependent individuals seeking treatment. Compared to cocaine-dependent individuals, those with marijuana dependence were younger and less likely to be dependent on alcohol or other drugs. Both groups had similar rates of comorbid anxiety and affective disorders. Marijuana-dependent individuals had lower total number of dependence symptoms but a higher percentage of individuals endorsing withdrawal symptoms. Comparison with two different assessment scales suggests that treatment seeking marijuana-dependent individuals have substantial withdrawal dependence symptomatology although it is less clear if they are as motivated to seek out treatment as cocaine-dependent treatment seekers. Levin, F.R., Brooks, D.J., Bisaga, A., Raby, W., Rubin, E., Aharonovich, E., and Nunes, E.V. J. Addict Dis, 25(1), pp. 33-41, 2006.

Effects of Baclofen on Cocaine Self-Administration: Opioid- and Nonopioid-Dependent Volunteers

Preclinical and clinical studies suggest that GABA(B) receptor agonists selectively decrease cocaine use. The behavioral mechanism for the interaction between baclofen and cocaine in humans is not known, nor have its effects been characterized in individuals dependent on both cocaine and methadone. The objective of this study was to determine how maintenance on baclofen influences smoked cocaine's reinforcing and subjective effects, mood and cocaine craving prior to and after the initiation of cocaine use in cocaine-dependent volunteers with and without concurrent opioid dependence. Nontreatment-seeking volunteers (10 nonopioid dependent; seven methadone

maintained), residing on an in-patient research unit for 21 days, were maintained on each baclofen dose (0, 30, 60 mg po) for 7 days. A smoked cocaine dose-response curve (0, 12, 25, 50 mg) was determined twice: on days 3-4 and days 6-7 of each baclofen maintenance condition. Cocaine sessions began with a sample trial, when participants smoked the cocaine dose available that session, and five choice trials, when participants chose between smoking the available cocaine dose or receiving one $5 merchandise voucher. The results show that in the nonmethadone group, baclofen (60 mg) decreased self-administration of a low cocaine dose (12 mg). In the methadone group, baclofen decreased craving for cocaine. In both groups, baclofen decreased cocaine's effects on heart rate. Baclofen did not alter cocaine's robust subjective effects (eg 'High,' 'Stimulated') for either group. The results from this laboratory study appear consistent with clinical evidence showing that baclofen decreases cocaine use in nonopioid-dependent patients seeking treatment for cocaine dependence. The distinct pattern of effects in methadone-maintained participants suggests baclofen may not be effective in opioid-dependent cocaine users. Haney, M., Hart, C. L. and Foltin, R.W. Neuropsychopharmacology, January 11, 2006 (e-pub ahead of print).

Effect of Bupropion on Physiological Measures of Stress in Smokers During Nicotine Withdrawal

Studies suggest that among cigarette smokers trying to quit, stress undermines abstinence. Little research has assessed if therapies that increase smoking cessation rates impact physiological measures of stress response. Forty-three subjects completed this repeated-measures study in which a laboratory assessment was completed at baseline and after 17 days of treatment with either placebo (n=15), bupropion sustained release (150mg twice daily) (n=14) or bupropion with stress reduction counseling (n=14). All subjects quit smoking 3 days prior to the second laboratory assessment. At each laboratory assessment physiological measures of stress (i.e. blood pressure, heart rate, plasma epinephrine, norepinephrine and cortisol concentrations) were measured during rest periods and in response to a speech, a math and a cold pressor task. Among subjects taking placebo, physiological measures of stress were generally lower at rest and during the stressors after smoking cessation. In those taking bupropion these measures were equivalent at the two assessments. Additionally, compared to placebo, those on bupropion had a greater diastolic blood pressure response to the speech stressor and greater systolic blood pressure response to the math stressor during the second laboratory session. This study suggests that bupropion may be maintaining physiological measures of stress during the nicotine withdrawal period. Kotlyar, M., Brauer, L.H., al'Absi, M., Adson, D.E., Robiner, W., Thuras, P. et al. Pharmacol. Biochem. Behav., March 6, 2006 (e-pub ahead of print).

Six-month Trial of Bupropion with Contingency Management for Cocaine Dependence in a Methadone-maintained Population

The purpose of this study was to compare the efficacy of bupropion hydrochloride and CM for reducing cocaine use in methadone hydrochloride-maintained individuals. This 25-week, placebo-controlled, double-blind trial randomly assigned participants to 1 of 4 treatment conditions: CM and placebo (CMP), CM and 300 mg/d of bupropion hydrochloride (CMB), voucher control and placebo (VCP), or voucher control and bupropion (VCB). All study participants received methadone hydrochloride (range, 60-120 mg). Participants receiving bupropion hydrochloride were given 300 mg/d beginning at week 3. In the CM conditions, each urine sample negative for both opioids and cocaine resulted in a monetary-based voucher that increased for consecutively drug-free urine samples during weeks 1 to 13. Completion of abstinence-related activities also resulted in a voucher. During weeks 14 to 25,

only completion of activities was reinforced in the CM group, regardless of sample results. The voucher control groups received vouchers for submitting urine samples, regardless of results, throughout the study. Groups did not differ in baseline characteristics or retention rates. Opiate use decreased significantly, with all treatment groups attaining equivalent amounts of opiate use at the end of the study. In the CMB group, the proportion of cocaine-positive samples significantly decreased during weeks 3 to 13 (P<.001) relative to week 3 and remained low during weeks 14 to 25. In the CMP group, cocaine use significantly increased during weeks 3 to 13 (P<.001) relative to week 3, but then cocaine use significantly decreased relative to the initial slope during weeks 14 to 25 (P<.001). In contrast, by treatment end, the VCB and VCP groups showed no significant improvement in cocaine use. These findings suggest that combining CM with bupropion for the treatment of cocaine addiction may significantly improve outcomes relative to bupropion alone. Poling, J., Oliveto, A., Petry, N., Sofuoglu, M., Gonsai, K., Gonzalez, G. et al. Arch. Gen. Psychiatry, 63, pp. 219-228, 2006.

Temperament Characteristics, as Assessed by the Tridimensional Personality Questionnaire, Moderate the Response to Sertraline in Depressed Opiate-dependent Methadone Patients

During a randomized, double-blind, placebo controlled study of the effects of sertraline in depressed methadone-maintained patients, 82 completed the tri-dimensional personality questionnaire (TPQ) to assess whether temperament dimensions can affect treatment-related changes in mood and drug use. Mood outcome significantly differed according to scores on the reward dependence scale (RD). Low RD participants displayed a significantly better mood response to sertraline than high RD participants. Participants with high harm avoidance (HA) scores were more likely to be abstinent at the end of the 12 week trial of sertraline than low HA participants. High persistence (P) participants were less likely to be abstinent at the end of the 12-week trial. These results suggest that temperament dimensions may be important for identifying substance dependent patients more likely to benefit from pharmaco-logical interventions for comorbid depressive disorders. Raby, W.N., Carpenter, K.M., Aharonovich, E., Rubin, E., Bisaga, A., Levin, F. et al. Drug Alc Depend. 81, pp. 283-292, 2006.

Emerging Pharmacological Strategies in the Fight Against Cocaine Addiction

Cocaine addiction continues to be an important public health problem worldwide. At present, there are no proven pharmacotherapies for cocaine addiction. The studies reviewed here revealed a number of emerging targets for cocaine pharmacotherapy. First, disulfiram, a medication with dopaminergic effects, reduced cocaine use in a number of clinical trials. Second, GABA medications, tiagabine and topiramate, were found promising in clinical trials. Third, a beta-adrenergic blocker, propranolol, may be effective especially among cocaine-addicted individuals with high withdrawal severity. Fourth, treatment with a stimulant medication, modafinil, has reduced cocaine use. Last, a cocaine vaccine that slows entry of cocaine into the brain holds promise. These promising findings need to be further tested in controlled clinical trials. Sofuoglu, M. and Kosten, T.R. Expert. Opin. Emerg. Drugs, 11, pp. 91-98, 2006.

Effects of Topiramate in Combination with Intravenous Nicotine in Overnight Abstinent Smokers

Topiramate, an anticonvulsant medication, may be effective as a treatment for alcohol and cocaine addiction. While a recent clinical study has demonstrated

the potential utility of topiramate for smoking cessation in alcohol-dependent smokers, the effects of topiramate on tobacco addiction have not been systematically examined in humans. The purpose of this study is to determine topiramate's effects on acute physiological and subjective responses to intravenous (IV) nicotine in overnight abstinent smokers. Seven male and five female smokers participated in a double-blind, placebo-controlled, crossover study, which consisted of one adaptation and three experimental sessions. Before each session, participants were treated orally with either a single 25 or 50 mg topiramate dose or with placebo. Starting 2 h following the medication treatment, participants received an IV saline injection, followed by 0.5 and 1.0 mg/70 kg IV nicotine. Topiramate treatment at 50 mg, compared to 25 mg or placebo, attenuated heart rate increases induced by nicotine. Topiramate, compared to placebo, enhanced the ratings of subjective effects from nicotine including "drug strength," "good effects," "head rush," and "drug liking." Topiramate treatment did not affect performance on the Stroop test. These results suggest that topiramate may enhance the subjective effects of nicotine and attenuate the heart rate response to nicotine. While the exact mechanisms are unclear, enhancement of the dopaminergic system and attenuation of the noradrenergic system may mediate topiramate's effects on the subjective and cardiovascular responses to nicotine, respectively. The utility of topiramate for smoking cessation needs to be examined further in controlled clinical trials. Sofuoglu, M., Poling, J., Mouratidis, M. and Kosten, T. Psychopharmacology (Berl), 184, pp. 645-651, 2006.

Director's Report to the National Advisory Council on Drug Abuse - May, 2006

Research Findings - Research on Medical Consequences of Drug Abuse and Infections

Drugs of Abuse and HIV/AIDS

Effect of Long-term Cocaine Use on Regional Left Ventricular Function as Determined by Magnetic Resonance Imaging

Current knowledge about the cardiovascular effects of long-term cocaine use in humans is quite limited. The present study compared the left ventricular (LV) regional mid-wall circumferential strain (Ecc) in long-term cocaine users (the Coc+ group) and controls with no history of cocaine use (the Coc- group). Cardiac tagged magnetic resonance images (MRI) were obtained from 32 study participants in the Coc+ group (average cocaine use: 12.7 ± 8.2 years) and 14 participants in the Coc- group. Regional myocardial Ecc for the standard LV segmentations were obtained through analyzing tagged cardiac images using a harmonic phase MRI processing method. The average systolic or diastolic Ecc measurements of LV segmentations were compared between the Coc- and Coc+ groups with the use of the Student's t test. Compared with their respective counterparts in the Coc- group, the majority of the LV segmentations in the Coc+ group had lower average Ecc measurements: 11 of the 16 ventricular segmentations in the systolic phase, and 15 of the 16 ventricular segmentations in the diastolic phase. Among them, five diastolic average Ecc measurements were significantly lower in the Coc+ group ($p < 0.05$). The ventricular segmentations with low systolic or diastolic Ecc measurements in the Coc+ group were scattered in LV walls and did not appear to fit into any anatomic pattern. In conclusion, long-term cocaine use may be associated with abnormal cardiac myocardial functions, most prominently in the diastolic phase. The abnormal myocardial segmentations scattering around LV in long-term cocaine users indicate the focal nature of the cocaine-induced myocardial damage. Ren, S., Tong, W., Lai, H., Osman, N.F., Pannu, H. and Lai, S. Am J. Cardiol. 97(7), pp. 1085-1088, April 1, 2006.

Unprotected Sex with Multiple Partners: Implications for HIV Prevention Among Young Men with a History of Incarceration

The objectives of this study were to describe preincarceration risk behaviors of young men and identify correlates of unprotected sex with multiple partners during the 3 months before incarceration. Data on preincarceration risk behaviors were obtained from 550 men, aged 18 to 29 years, in state prisons in California, Mississippi, Rhode Island, and Wisconsin. Correlates of unprotected sex with multiple partners were determined by logistic regression. Of 550 participants, 71% had multiple sex partners, 65.1% had sex with a partner they perceived as risky, and 45.3% engaged in unprotected sex with multiple partners. Men who drank heavily (odds ratio [OR], 1.68; 95%

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confidence interval [CI], 1.11-2.54) or who had a risky partner (OR, 3.90; 95% CI, 2.60-5.85) were more likely to report unprotected sex with multiple partners. Men who attended religious gatherings (OR, 0.66; 95% CI, 0.46-0.96) or lived in stable housing (OR, 0.69; 95% CI, 0.48-1.00) were less likely to report unprotected sex with multiple partners. Most participants engaged in behaviors that could result in a sexually transmitted disease, including HIV. Prevention programs should address the relationship between heavy alcohol use and risky sexual behavior. Discharge planning should address housing needs. Faith-based community organizations may play an important role for some young men in their transition to the community. Margolis, A.D., MacGowan, R.J., Grinstead, O., Sosman, J., Kashif, I. and Flanigan, T.P. Project START Study Group. Sex Transm Dis. 33(3), pp. 175-180, March 2006.

Commercial Sex Work and Risk of HIV Infection Among Young Drug-Injecting Men Who Have Sex With Men in San Francisco

The objective of this study was to investigate the relationship between sex work and HIV infection among young injection drug-using men who have sex with men (MSM-IDU). This study was a cross-sectional analysis of behavioral and serologic data collected from 227 street-recruited MSM-IDU in San Francisco, California, between January 2000 and November 2001. Sixty-eight percent of participants reported being paid by another man for sex. HIV prevalence was 12% (95% confidence interval, 8-16%); 42% of seropositive participants were unaware of their infection. HIV was independently associated with higher number of paying male partners and history of gonorrhea and inversely associated with number of female partners, education, and syringe-sharing. Consistent condom use overall was 41%, but varied significantly by type of partner. Among MSM-IDU in San Francisco, sex work with men is strongly associated with HIV infection and the prevalence of condom use is low. HIV prevention among MSM-IDU must be tailored to address the excess risk associated with sex work. Bacon, O., Lum, P., Hahn, J., Evans, J., Davidson, P., Moss, A. and Page-Shafer, K. Sex Transm Dis. 33(4), pp. 228-234, April 2006.

HIV-related Wasting in HIV-infected Drug Users in the Era of Highly Active Antiretroviral Therapy

A decrease in the rate of human immunodeficiency virus (HIV) infection-related wasting has been reported in the era of highly active antiretroviral therapy (HAART). Authors investigated this concern in a hard-to-reach population of HIV-infected drug users in Miami, Florida. After informed consent was obtained, 119 HIV-infected drug users were administered questionnaires involving demographic, medical history, and food-security information. Blood samples were drawn for immunological and viral studies. HIV-related wasting over a period of >6 months was defined as a body mass index of <18.5 kg/m2, unintentional weight loss of >10% over 6 months, or a weight of <90% of the ideal body weight. The prevalence of HIV-related wasting was 17.6%. A significantly higher proportion of those who experienced wasting (81%) reported that there were periods during the previous month when they went for > or =1 day without eating (i.e., food insecurity), compared with those who did not experience wasting (57%). Although a greater percentage of patients who experienced wasting were receiving HAART, their HIV RNA levels were more than twice as high (mean+/-standard deviation [SD], 166,689+/-238,002 copies/mL; median log HIV RNA level +/- SD, 10.2+/-2.7 log10 copies/mL) as those for the group that did not experience wasting (mean+/-SD, 72,156 +/- 149,080; median log HIV RNA level+/-SD, 9.2+/-2.3 log10 copies/mL). Participants who experienced wasting were more likely to be heavy alcohol drinkers and users of cocaine. In multivariate analysis that included age, sex, food security, alcohol use, cocaine use, viral load, and receipt of antiretroviral therapy, the only significant predictors of wasting were

>1 day without eating during the previous month (odds ratio [OR], 1.96; 95% confidence interval [CI], 1.18-3.26; P=.01) and viral load (OR, 1.64; 95% CI, 1.00-2.69; P=.05). HIV-related wasting continues to be common among HIV-infected drug users, even among HAART recipients. Food insecurity and viral load were the only independent predictors of wasting. The social and economic conditions affecting the lifestyle of HIV-infected drug users constitute a challenge for prevention and treatment of wasting. Campa, A., Yang, Z., Lai, S., Xue, L., Phillips, J.C., Sales, S., Page, J.B. and Baum, M.K. Clin Infect Dis. 41(8), pp. 1179-1185, October 2005.

Drugs of Abuse and the Endocrine System

Cortisol Levels and Depression in Men and Women Using Heroin and Cocaine

Abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis are well documented in men using illicit drugs and/or infected with HIV; however, less is known about HPA function, or the health consequence of HPA dysfunction, in their female counterparts. People with depression exhibit hypercortisolemia, and depression is common in people with HIV or substance use problems. The current study investigated cortisol secretion in 209 demographically matched men and women, stratified by their HIV and drug use status. Self-reported depressive symptoms were evaluated using a standardized, validated questionnaire (CES-D). Women reported more depressive symptoms than men (p=.01). Male and female drug users exhibited higher cortisol concentrations (p=.03), and were more likely to report depressive symptoms (p=.04), than non-users. Depression was related to elevated cortisol concentrations for the study population (p=.03), and women with elevated cortisol concentrations were significantly more depressed than all other participants (p=.05). While it is unknown whether high cortisol concentrations precede depressive symptoms or vice versa, these data indicate that higher cortisol concentrations are associated with depressive symptoms in heroin and cocaine users, and that this association is more pronounced in women than men. HIV status did not act in an additive or synergistic way with drug use for either cortisol or CES-D measures in the current study. Unique therapies to treat the endocrine and mental health consequences of illicit drug use in men and women deserve consideration as depressive symptoms, and high cortisol concentrations associated with depressive symptoms, differ by gender. Wisniewski, A.B., Brown, T.T., John, M., Cofranceso, J.Jr., Golub, E.T., Ricketts, E.P., Wand, G. and Dobs, A.S. Psychoneuroendocrinology. 31(2), pp. 250-255, February 2006.

RNAi-directed Inhibition of DC-SIGN by Dendritic Cells: Prospects for HIV-1 Therapy

Drug-resistant human immunodeficiency virus (HIV) infections are increasing globally, especially in North America. Therefore, it is logical to develop new therapies directed against HIV binding molecules on susceptible host cells in addition to current treatment modalities against virus functions. Inhibition of the viral genome can be achieved by degrading or silencing posttranslational genes using small interfering (si) ribonucleic acids (RNAs) consisting of double-stranded forms of RNA. These siRNAs usually contain 21-23 base pairs (bp) and are highly specific for the nucleotide sequence of the target messenger RNA (mRNA). These siRNAs form a complex with helicase and nuclease enzymes known as "RNA-induced silencing complex"; (RISC) that leads to target RNA degradation. Thus, siRNA has become a method of selective destruction of HIV now used by various investigators around the globe. However, given the sequence diversity of the HIV genomes of infected subjects, it is difficult to target a specific HIV sequence. Therefore, targeting nonvariable HIV binding receptors on susceptible cells or other molecules of

host cells that are directly or indirectly involved in HIV infections may be an interesting alternative to targeting the virus itself. Thus, the simultaneous use of siRNAs specific for HIV and host cells may be a unique, new approach to the therapy of HIV infections. In this article, authors present evidence that siRNA directed at the CD4 independent attachment receptor (DC-SIGN) significantly inhibits HIV infection of dendritic cells (DCs). This effect may be mediated by modulation of p38 mitogen activated protein kinase (MAPK). Nair, M.P., Reynolds, J.L., Mahajan, S.D., Schwartz, S.A., Aalinkeel, R., Bindukumar, B. and Sykes, D. AAPS J. 7(3)pp. E572-E578, October 19, 2005.

Drugs of Abuse and Hepatitis C Infection

Treatment Algorithm for the Management of Hepatitis C in HIV-coinfected Persons

In the era of highly effective antiretroviral therapy (ART), HCV-related liver disease has emerged as a significant cause of morbidity and mortality. Accordingly, expert panels have recommended that coinfected patients undergo medical evaluation for HCV-related liver disease, consideration for HCV treatment and, if indicated, orthotopic liver transplantation. While the treatment of such patients is complicated by medical, and psychiatric comorbidities, HIV disease, and concurrent antiretroviral therapy, randomized controlled trials support the safety, tolerability and efficacy of HCV treatment with peginterferon alfa (PEG-IFN) plus ribavirin (RBV) in HIV-infected persons. Although, the available data has led to consensus among experts regarding the need to medically manage HCV disease in HIV-infected persons, uncertainty remains regarding the best treatment algorithm for coinfected patients. Sulkowski, M.S. J Hepatol. 44(1 Suppl), pp. S49-55, 2006.

Progression of Liver Fibrosis Among Injection Drug Users with Chronic Hepatitis C

Although most hepatitis C virus (HCV) infections are acquired by injection drug use, prospective data on the progression of liver fibrosis are sparse. Baseline liver biopsies were obtained (1996-1998) on a random sample of 210 out of 1667 HCV-positive injection drug users (IDUs). Subjects were followed biannually, with a second biopsy offered to those eligible. Paired biopsies were scored 0 to 6 (modified Ishak score), significant fibrosis was defined as score 3 or greater, and progression of fibrosis was defined as an increase 2 or more units or clinical evidence of end-stage liver disease. Predictive values of blood markers [FibroSURE, aspartate aminotransferase-to-platelet-ratio index (APRI) and alanine aminotransferase (ALT)] were assessed for detection of contemporaneous and future liver fibrosis. Among 119 prospectively followed IDUs, 96% were African American; 97% HCV genotype 1a/b; 27% HIV-infected, and median age was 42 years. Most (90.7%) did not have significant liver fibrosis at first biopsy. Although predictive value for detecting insignificant fibrosis at first biopsy was greater than 95% for FibroSURE, APRI, and ALT, specificities were 88.9%, 72.7%, and 72.7%, respectively. After 4.2 years median follow-up, 21% had progression of fibrosis, which was significantly associated with serum level of HCV RNA and ALT. No serological test had predictive value greater than 40% for contemporaneous or future significant fibrosis. Even initial biopsy result had only a 30.4% value for predicting future significant fibrosis. In conclusion, significant liver fibrosis and progression were detected in some, but not most, IDUs in this cohort. In this setting with low fibrosis prevalence, FibroSURE, ALT, and APRI tests predict insignificant fibrosis; however, further work is needed to find noninvasive markers of significant liver fibrosis. Wilson, L.E., Torbenson, M., Astemborski, J., Faruki, H., Spoler, C., Rai, R., Mehta, S., Kirk, G.D., Nelson, K., Afdhal, N. and Thomas, D.L. Hepatology. 43(4), pp. 788-795, April 2006.

Drug-Drug Interactions

Effect of Buprenorphine and Antiretroviral Agents on the QT Interval in Opioid-Dependent Patients

Cardiac arrhythmias have been linked to treatment with methadone and levacetylmethadol. HIV-positive patients often have conditions that place them at risk for QT interval prolongation including HIV-associated dilated cardiomyopathy, coronary artery disease as a consequence of highly active antiretroviral (ARV) therapy-associated metabolic syndrome, and uncorrected electrolyte abnormalities. As of February 14, 2006, no cases of adverse events related to QT interval prolongation have been reported in patients receiving buprenorphine, an opioid partial agonist and the newest drug approved for the treatment of opioid dependence. The objective of this study was to evaluate the effects of buprenorphine/naloxone alone and in combination with 1 of 5 ARV agents (efavirenz, nelfinavir, delavirdine, ritonavir, lopinavir/ritonavir) on the QT interval. This study was prospective, open-label, and within-subject in design, with subjects serving as their own controls. In 50 HIV-negative, opioid-dependent subjects, electrocardiogram recordings were obtained at baseline, after receiving buprenorphine/naloxone for 2 weeks, and then following buprenorphine/naloxone plus ARV administration for 5-15 days at steady-state. QTc interval measurements were compared using mixed-model, repeated-measures ANOVA. Recent cocaine use and gender were considered covariates. Buprenorphine/naloxone alone and often in the presence of evidence for recent use of cocaine did not significantly alter the QT interval ($p = 0.612$). Buprenorphine/naloxone in combination with ARVs caused a statistically, but not clinically, significant increase ($p = 0.005$) in the QT interval. Subjects receiving buprenorphine/naloxone in combination with either delavirdine or ritonavir had the greatest increase in QTc intervals. Prolonged QT intervals were not observed in opioid-dependent subjects receiving buprenorphine/naloxone alone. QT interval increases were observed with buprenorphine/naloxone in combination with either delavirdine or ritonavir, which inhibit CYP3A4. Baker, J.R., Best, A.M., Pade, P.A. and McCance-Katz, E.F. Ann Pharmacother. 40(3), pp. 392-396, April 2006.

Drug Interactions Between Opioids and Antiretroviral Medications: Interaction Between Methadone, LAAM, and Delavirdine

Understanding the drug interactions between antiretrovirals and opioid therapies may decrease toxicities and enhance adherence with improved HIV outcomes in opioid-dependent individuals. The authors report the results of a clinical pharmacology study designed to determine whether significant pharmacokinetic and/or pharmacodynamic interactions occur between the non-nucleoside reverse transcriptase inhibitor, delavirdine (DLV), and either methadone or levo-alpha acetyl methadol (LAAM) ($n = 40$). DLV significantly decreased methadone clearance ($p = .018$) and increased the methadone elimination half-life ($p<.001$) with a resultant increase in AUC of 19% and C(min)of 29%. The combined effect of DLV on the total concentration of LAAM and its active metabolites, norLAAM and dinorLAAM, was to significantly increase AUC by 43% ($p<.001$), C(max) by 30% ($p = .013$), and C(min) by 59% ($p = .004$) while decreasing T(max) ($p = .05$). Cognitive deficits over the seven-day study period as measured by the Mini-Mental State Examination, opioid withdrawal symptoms as measured by the Objective Opioid Withdrawal Scale, or complaints of adverse symptoms were not observed. Methadone and LAAM did not affect DLV concentrations. The findings from this study show that DLV treatment in methadone- or LAAM-maintained individuals results in altered opioid pharmacokinetics with an increased exposure and potential risk for opioid toxicity with methadone or LAAM treatment and an increased risk of

cardiac toxicity with concomitant LAAM and DLV administration. McCance-Katz, E.F., Rainey, P.M., Smith, P., Morse, G.D., Friedland, G., Boyarsky, B., Gourevitch, M. and Jatlow, P. Am J Addict. 5(1), pp. 23-34, Jan-Feb 2006.

Novel Metabolites of Buprenorphine Detected in Human Liver Microsomes and Human Urine

The in vitro metabolism of buprenorphine was investigated to explore new metabolic pathways and identify the cytochromes P450 (P450s) responsible for the formation of these metabolites. The resulting metabolites were identified by liquid chromatography-electrospray ionization-tandem mass spectrometry. In addition to norbuprenorphine, two hydroxylated buprenorphine (M1 and M2) and three hydroxylated norbuprenorphine (M3, M4, and M5) metabolites were produced by human liver microsomes (HLMs), with hydroxylation ccurring at the tert-butyl group (M1 and M3) and at unspecified site(s) on the ring moieties (M2, M4, and M5). Time course and other data suggest that buprenorphine is N-dealkylated to form norbuprenorphine, followed by hydroxylation to form M3; buprenorphine is hydroxylated to form M1 and M2, followed by N-dealkylation to form M3 and M4 or M5. The involvement of selected P450s was investigated using cDNA-expressed P450s coupled with scaling models, chemical inhibition, monoclonal antibody (MAb) analysis, and correlation studies. The major enzymes involved in buprenorphine elimination and norbuprenorphine and M1 formation were P450s 3A4, 3A5, 3A7, and 2C8, whereas 3A4, 3A5, and 3A7 produced M3 and M5. Based on Mab analysis and chemical inhibition, the contribution of 2C8 was higher in HLMs with higher 2C8 activity, whereas 3A4/5 played a more important role in HLMs with higher 3A4/5 activity. Examination of human urine from subjects taking buprenorphine showed the presence of M1 and M3; most of M1 was conjugated, whereas 60 to 70% of M3 was unconjugated. Chang, Y., Moody, D.E. and McCance-Katz, E.F. Drug Metab Dispos. 34(3), pp. 440-448, March 2006.

Medical Illness and Comorbidities in Drug Users: Implications for Addiction Pharmacotherapy Treatment

Providing effective medical care to those with substance use disorders can be a challenge to clinicians. In this article, the authors briefly summarize issues that occur frequently in the medical treatment of substance users. The focus of this article is twofold. The first is to briefly summarize common co-occurring medical illnesses in those manifesting substance use disorders with an emphasis on issues related to providing effective treatment for these diseases in this population. Using specific examples of frequently occurring comorbid medical illness in substance users, including infectious diseases (hepatitis C and HIV disease), sexually transmitted diseases, and pregnancy as examples, the complexities of medical care for this population is demonstrated. Second, this article addresses some of the difficulties encountered in pharmacotherapy aimed specifically at treatment of substance use disorders. For example, difficulties in managing concomitant opiate therapy in those requiring medications for medical illness that may have strong and adverse interactions with opiates are addressed. Adverse events reported for some substance use disorder pharmacotherapies are also highlighted. The authors conclude with a brief review of models of care that have been effective in addressing the needs of this challenging population that can provide additional means for enhancing the clinical care of substance users. Draper, J.C. and McCance-Katz, E.F. Subst Use Misuse. 40(13), pp. 1899-1921, 2005.

Treatment of Opioid Dependence and Coinfection with HIV and Hepatitis C Virus in Opioid-dependent Patients

The occurrence of human immunodeficiency virus (HIV) disease and hepatitis C is common in injection drug users, most of whom are opioid dependent. Methadone pharmacotherapy has been the most widely used treatment for opioid addiction in this population. Methadone has significant, adverse drug-drug interactions with many antiretroviral therapeutic agents that can contribute to nonadherence and poor clinical outcomes in this high-risk population. The present article summarizes current knowledge about interactions between methadone and antiretroviral medications. Buprenorphine is the newest agent available for the treatment of opioid dependence and may have fewer adverse interactions with antiretroviral agents. Buprenorphine has a significant pharmacokinetic interaction with efavirenz but no pharmacodynamic interaction; therefore, simultaneous administration of these drugs is not associated with opioid withdrawal, as has been observed with methadone. This promising finding may simplify the treatment of opioid-dependent patients with HIV disease and should also improve clinical outcomes for persons coinfected with HIV and hepatitis C virus. McCance-Katz, E.F. Clin Infect Dis. 41 Suppl 1, pp. S89-95, July 1, 2005.

Efficacy of Dose and Contingency Management Procedures in LAAM-maintained Cocaine-dependent Patients

Opioid- and cocaine-dependent participants (N=140) were randomly assigned to one of the following in a 12-week clinical trial: LAAM (30, 30, 39 mg/MWF) with contingency management (CM) procedures (LC); LAAM (30, 30, 39 mg/MWF) without CM (LY); LAAM (100, 100, 130 mg/MWF) with CM (HC); LAAM (100, 100, 130 mg/MWF) without CM (HY). Urine samples were collected thrice-weekly. In CM, each urine negative for both opioids and cocaine resulted in a voucher worth a certain monetary value that increased for consecutively drug-free urines. Subjects not assigned to CM received vouchers according to a yoked schedule. Vouchers were exchanged for mutually agreed upon goods and services. Groups generally did not differ on retention and baseline characteristics. Overall opioid use was least in the HC and HY groups; opioid use decreased most rapidly over time in the HC group relative to the HY, LC and LY groups. Overall cocaine use was least in the HC group relative to the HY, LC, and LY groups; cocaine use decreased over time most rapidly in the HC and LY groups. Abstinence from both was greatest in the HC group. Opioid withdrawal symptoms decreased most rapidly in the high-dose groups relative to the low-dose groups. These results suggest that an efficacious maintenance dose is necessary for contingencies to be effective in facilitating both opioid and cocaine abstinence. Oliveto, A., Poling, J., Sevarino, K.A., Gonsai, K.R., McCance-Katz, E.F., Stine, S.M. and Kosten, T.R. Drug Alc Depend. 79(2), pp. 157-165, August 1, 2005.

Effect of Extended Exposure to Grapefruit Juice on Cytochrome P450 3A Activity in Humans: Comparison with Ritonavir

Acute ingestion of usual quantities of grapefruit juice produces inhibition of enteric cytochrome P450 (CYP) 3A enzymes, causing pharmacokinetic interactions with a number of drugs. However, the effect of extended exposure to grapefruit juice on CYP3A activity is not established. Triazolam, a CYP3A index compound, was administered to 3 cohorts of volunteers (n = 6-7 per group) on 4 occasions (trials 1-4), as follows: 1 day prior to cotreatment initiation, at the beginning and end of cotreatment, and 3 days after cotreatment discontinuation. The 3 cotreatments (daily administration for 10 consecutive days) were: 300 mL grapefruit juice, 400 mg ritonavir, or 300 mL water. Grapefruit juice cotreatment (trial 2) increased the triazolam area under the plasma concentration curve by 50% compared to the trial 1 control (15.1 +/- 7.6 ng/mL.h versus 10.0 +/- 3.5 ng/mL.h, $p<.05$), but the half-life was not changed. Effects of acute and extended exposure to grapefruit juice (trials 2 and 3) were similar, and produced augmentation in benzodiazepines agonist

effects measured by the Digit Symbol Substitution Test and electroencephalographic beta amplitude. Kinetic and dynamic effects reverted to baseline (trial 1) values at 3 days after grapefruit juice discontinuation (trial 4). Ritonavir caused a more than 20-fold increase in the triazolam area under the plasma concentration curve during trial 2 (553 +/- 422 ng/mL.h) and trial 3 (287 +/- 299 ng/mL.h) compared to the trial 1 control (13.3 +/- 16.3 ng/mL.h) ($p<.05$ for both comparisons); Digit Symbol Substitution Test and electroencephalographic pharmacodynamics increased in parallel. During trial 4, triazolam kinetics reverted close to trial 1 values, with no evidence of induction. Triazolam kinetics were not altered by water cotreatment. Acute and extended exposure to grapefruit juice produces quantitatively similar inhibition of enteric, but not hepatic, CYP3A. Recovery is complete within 3 days after grapefruit juice discontinuation. Ritonavir greatly inhibits both enteric and hepatic CYP3A. With extended exposure to ritonavir, inhibition is the predominant effect, and recovery to baseline is nearly complete 3 days after ritonavir dis-continuation. Culm-Merdek, K.E., von Moltke, L.L., Gan, L., Horan, K.A., et al., Clin Pharmacol Ther. 79(3), pp. 243-254, March 2006.

Director's Report to the National Advisory Council on Drug Abuse - May, 2006

Research Findings - Services Research

Pathways in the Relapse, Treatment, Recovery Cycle

For many individuals, substance use leads to a chronic cycle of relapse, treatment reentry, and recovery, often lasting for decades. This study replicates earlier work, documents the transition patterns within the cycle during a 3-year period, and identifies variables that predict these transitions. Data are from 1,326 adults recruited from sequential admissions to 12 substance abuse treatment facilities in Chicago, IL, between 1996 and 1998. Participants were predominantly female (60%) and African American (88%) adults. Participants were interviewed at intake, and at 6, 24, and 36 months post-intake. Follow-up rates ranged from 94% to 98% per wave. At each observation, participants' current status in the cycle was classified as (1) in the community using, (2) incarcerated, (3) in treatment, or (4) in the community not using. The transitional probabilities and correlates of pathways between these states were estimated. Over 83% of the participants transitioned from one point in the cycle to another during the 3 years (including 36% two times, 14% three times). For the people in the community, about half remained in the same status (either using or abstinent) and just under half transitioned to incarceration or treatment. The majority of people whose beginning status was incarceration or in-treatment also transitioned to in the community by the end of the observation period. While there was some overlap, predictors typically varied by pathway and direction (e.g., using to not using vs. not using to using). These results help demonstrate the need to adopt a chronic vs. acute care model for substance use. While exploratory and observational, several of the predictors are time-dependent and identify promising targets for interventions designed to shorten the cycle and increase the long-term effectiveness of treatment. Scott, C., Foss, M. and Dennis, M. Pathways in the Relapse--Treatment--Recovery Cycle Over 3 Years. J Subst Abuse Treat, 28(1), pp. S63-S72, 2005

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Matching Offenders to Treatment and Services

This study examined the effectiveness of matching offenders with substance abuse problems to levels of treatment, services, and criminal justice supervision based on risk for recidivism and need. Building on the "risk, need, and responsivity" principle from criminology literature and the treatment matching concept from services research literature, this randomized clinical trial investigated the extent to which providing offenders identified as "high" risk (n=144) with more intense treatment and services than those identified as "moderate" risk (n=128) improved outcomes including drug use and criminal activity. Using a blocked random assignment procedure offenders were

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assessed for risk and treatment need and randomly assigned to receive either an enhanced regiment of treatment and supervision (seamless system) or standard probation services. The enhanced system consisted of intensive drug treatment, drug testing on a routine basis, use of graduated sanctions, and ensuring offenders participated in treatment for at least 6 months. Study results found that the seamless system model improved treatment participation, with greater gains experienced by offenders with high risk. However no main effects were observed for drug use or criminal behavior outcomes, although effect sizes illustrated that small effects were observed for high risk offenders. Investigators hypothesize failure to observe main effects may be attributable to instrumentation problems and the fact that substance abusers in the study reported low-severity substance abuse problems. They suggest that measurement of risk and need factors for offenders with substance abuse factors might benefit from a life course perspective regarding issues of onset and persistence of drug abuse and criminal activity. They state the importance of considering static (past) and dynamic (variable, temporal) risk and need factors when matching offenders to treatment, services, and criminal justice supervision. Taxman, F.S. and Thanner, M. Risk, Need, and Responsivity (RNR): It All Depends. Crime & Delinquency, 52(1), pp. 28-51, 2006.

HIV Intervention for Indigent Women Substance Abusers in the US Virgin Islands

As the HIV/AIDS epidemic continues to expand and penetrate new communities around the globe, risk reduction intervention initiatives must continue to evolve and adapt to new challenges and populations. This is especially true in the Caribbean Basin, where the feminization of the HIV epidemic is tied to a cultural milieu characterized by pervasive gender inequality. HIV intervention programs in the Caribbean must treat women's risks as a function of the social context, standards, and meanings of sexual behaviors and practices in the local community. As such, this article describes an initiative to develop an HIV prevention-intervention protocol for the cultural context of substance abusing women in the US Virgin Islands. Through street-based survey research combined with focus groups and in-depth interviews with such "cultural insiders" as members of the substance-abusing target population, members of the local public health and social services system, and community leaders, a culturally sensitive HIV/AIDS protocol was developed which addresses the supports and barriers to risk reduction faced by substance abusing women in the Virgin Islands. The intervention, which is delivered in three sessions, was pilot tested with 20 active or former substance abusing women. Results from the pilot test revealed that the women were engaged and found the material relevant to their lifestyles and concerns. Surratt, H., and Inciardi, J. Developing an HIV Intervention for Indigent Women Substance Abusers in the United States Virgin Islands. J Urban Health, 82(3-4), pp. iv74-iv83, 2005.

Substance Use, Sexual Risk, and Violence: HIV Prevention Intervention with Sex Workers in Pretoria

This paper describes an HIV prevention intervention designed in the US that was adapted and implemented in South Africa. Using an experimental design, 93 women who reported recent substance use and sex trading were randomly assigned to a modified Standard HIV intervention or to a Woman-Focused HIV prevention intervention. Eighty women completed the one-month follow-up interview. Participants reported high rates of sexual risk and violence at baseline. At follow-up, findings showed decreases in the proportion of women reporting unprotected sex and the daily use of alcohol and cocaine. Daily alcohol and cocaine use decreased more for women receiving the Woman-Focused intervention. Although violence continued to be a problem, at follow-

up Woman-Focused participants reported being victimized less often than women receiving the Standard intervention. This study demonstrates the feasibility of implementing cross-cultural behavioral HIV prevention interventions, and supports the need for future studies of women's contextual issues and the effectiveness of targeted interventions. Wechsberg, W.M., Luseno, W.K., Lam, W.K., Parry, C.D. and Morojele, N.K. Substance Use, Sexual Risk, and Violence: HIV Prevention Intervention with Sex Workers in Pretoria. AIDS & Behavior, pp. 1-5, 2006.

The Effects of Providing Housing to Homeless Substance Abusers in Treatment

Housing typically is not provided to homeless persons during drug abuse treatment. This study examined how treatment outcomes were affected under three different housing provision conditions to which the sample was randomly assigned. One hundred and ninety six (196) cocaine-dependent participants received day treatment and no housing (NH), housing contingent on drug abstinence (ACH), or housing not contingent on abstinence (NACH). Drug use was monitored with urine testing. The ACH group had a higher prevalence of drug abstinence than the NACH group (after control for treatment attendance), which in turn had a higher prevalence than the NH group. All 3 groups showed significant improvement in maintaining employment and housing. The results of this and previous trials indicate that providing abstinence-contingent housing to homeless substance abusers in treatment is an efficacious, effective, and practical intervention. Programs to provide such housing should be considered in policy initiatives. Milby, J.B., Schumacher, J.E., Wallace, D., Freedman, M.J., and Vuchinich, R.E. To House or Not to House: The Effects of Providing Housing to Homeless Substance Abusers in Treatment. Am J Public Health, 95(7), pp. 1259-1265, 2005.

Trial of Interim Methadone Maintenance

Effective alternatives to long waiting lists for entry into methadone hydrochloride maintenance treatment are needed to reduce the complications of continuing heroin dependence and to increase methadone treatment entry. The researchers compare the effectiveness of interim methadone maintenance with that of the usual waiting list condition in facilitating methadone treatment entry and reducing heroin and cocaine use and criminal behavior. The researchers followed 319 patients who participated in a randomized, controlled, clinical trial using 2 conditions, with treatment assignment on a 3:2 basis to interim maintenance-waiting list control within a methadone treatment program in Baltimore. The intervention consisted of Interim methadone maintenance, consisting of an individually determined methadone dose and emergency counseling only for up to 120 days, or the comparison control referral to community-based methadone treatment programs. Significantly more participants assigned to the interim methadone maintenance condition entered comprehensive methadone maintenance treatment by the 120th day from baseline (75.9%) than those assigned to the waiting list control condition (20.8%) ($P<.001$). Overall, in the past 30 days at follow-up, interim participants reported significantly fewer days of heroin use ($P<.001$), had a significant reduction in heroin-positive drug test results ($P<.001$), reported spending less money on drugs ($P<.001$), and received less illegal income ($P<.02$) than the waiting list participants. Thus, according to this study's findings, interim methadone maintenance results in a substantial increase in the likelihood of entry into comprehensive treatment, and is an effective means of reducing heroin use and criminal behavior among opioid-dependent individuals awaiting entry into a comprehensive methadone treatment program. Schwartz, R., Highfield, D., Jaffe, J., Brady, J., Butler, C., Rouse, C., Callaman, J., O 'Grady, K. and Battjes, R. Trial of Interim Methadone Maintenance. Arch Gen Psychiatry, 63(1), pp. 102-109, 2006.

Trends of HIV Risk Behaviors in a Cohort of Injecting Drug Users and Their Sex Partners

A cohort of 111 injection drug users (IDUs) and their sex partners was assessed in 1988 concerning risk behaviors for HIV and knowledge of HIV/AIDS. Ten years later, in 1998, the cohort was reassessed using the same instrument. All who were HIV negative in 1988 were retested by blood draw for antibodies to HIV. A paired analysis was utilized to determine individual changes in risk behaviors for three serostatus groups--those who remained HIV negative (long-term HIV negatives), seroconverters, and those positive in 1988 (long-term HIV positives). Incidence was twice as high for sex partners (37.5%) as for IDUs (18.0%). Drug and needle use risk behaviors, except crack use, showed decreases; sexual risk behaviors were less amenable to change. Knowledge significantly increased among the long-term HIV negatives and seroconverters but not among those HIV positive in 1988. This analysis demonstrates the need for continued intervention among IDUs and their sex partners. McCoy, C., Metsch, L., Comerford, M., Zhao, W., Coltes, A., and Messiah, S. Trends of HIV Risk Behaviors in a Cohort of Injecting Drug Users and Their Sex Partners in Miami, Florida, 1988-1998. AIDS Behav, 9(2), pp. 187-199, 2005.

Psychosocial and Behavioral Differences Among Drug Injectors Who Use and Do Not Use Syringe Exchange Programs

Most research on the benefits of syringe exchange programs (SEPs) has focused on assessing program effectiveness and identifying risk profiles of SEP customers. To the researchers' knowledge, no empirical studies have considered the psychosocial characteristics of IDUs who do and do not use SEPs. To determine whether IDUs who do and do not use SEPs differ along demographic, psychosocial, and HIV risk characteristics and behaviors, data were analyzed from a three-city (Chicago, IL; Hartford, CT; Oakland, CA) observational study of how HIV prevention messages and supplies diffuse from SEPs. The study sample consisted of 350 participants with no reported history of HIV, hepatitis B or C virus infection. Self-efficacy was the only psychosocial factor to differentiate SEP customers from all non-customers groups; injecting others and pre-injection cleaning of the injection site differentiated some non-customers from customers. Implications for Future Interventions are discussed. Grau, L., Bluthenthal, R., Marshall, P., Singer, M., and Heimer, R. Psychosocial and Behavioral Differences Among Drug Injectors Who Use and Do Not Use Syringe Exchange Programs. AIDS Behav, 9(4), pp. 495-504, 2005.

Assessing Criminal Thinking as part of Drug Abuse Treatment for Offenders

Risk assessments used by the criminal justice system have focused on recidivism and generally relied on actuarial measures of criminal history. The research described in this paper seeks to expand measures of risk for offenders with substance abuse problems and measure dynamic factors of risk that may change as a result of intervention and participation in drug treatment. The instrument developed by this group of researchers, TCU Criminal Thinking Scales (TCU CTS), is intended to measure criminal thinking, a dynamic type of cognitive risk that has been correlated with static risk factors such as prior incarceration. Criminal thinking constructs, including antisocial attitudes, can be the target of intervention for treatment programs, including drug abuse treatment, seeking to change behavior and improve outcomes for offenders. The TCU CTS was developed in an effort to provide criminal justice treatment providers with a brief and cost-effective criminal thinking instrument. This instrument was designed initially to be used in a prison-based residential drug

abuse treatment program using a cognitive-based curriculum targeting drug use and criminal activity. The 37-item instrument includes scales to measure Entitlement, Justification, Personal Irresponsibility, Power Orientation, Cold Heartedness, and Criminal Rationalization. For each scale, items are rated using a 5-poing Likert-type scale (1=disagree strongly, 2=disagree, 3=uncertain, 4=agree, 5=agree strongly). Five research centers, funded as part of NIDA' s Criminal Justice Drug Abuse Treatment Studies Research Cooperative participated in the study. Data was collected from a cross-sectional sample of 3,266 offenders participating in 26 prison-based drug treatment programs across the country. Results indicate that the TCU CTS has good psychometric properties and offers the correctional treatment field a quick and reliable self-report assessment of criminal thinking. All 6 criminal thinking scales had sound factor structures and respectable response distributions. All maintained acceptable reliability and goodness-of-fit coefficients across the split-half samples. The investigators suggest that this instrument could be used as part of a larger measurement system designed to examine treatment progress and program effectiveness. When repeatedly administered over the course of treatment, the instrument provides programs with a method to document the impact of interventions and change in offender thinking and attitudes that have been associated with drug use and criminal activity. Knight, K., Garner, B.R., Simpson, D.D., Morey, J.T., and Flynn, P.M. An Assessment for Criminal Thinking. Crime & Delinquency, 52(1), pp. 159-177, 2006.

HIV and HCV Testing for Young Drug Users in Rhode Island

Young injection drug users (IDU) are at risk for both human immunonodeficiency virus (HIV) and Hepatitis C infections (HCV). Rates of HIV testing have been widely documented, but limited information exists regarding HCV screening rates. Among a community sample of 86 IDUs, aged 18-25 years in Rhode Island, 87.2% reported having ever been tested for HIV, versus 51.2% for HCV ($p < .001$). Young IDUs were under-screened for HCV compared with the far less prevalent HIV infection. Pugatch, D., Anderson, B., O'Connell, J., Elson, L., and Stein, M. HIV and HCV Testing for Young Drug Users in Rhode Island. J Adolesc Health, 38(3), pp. 302-304, 2006.

Mechanisms that Link Addiction Treatment Patients to Primary Care Influence Subsequent Utilization of Emergency and Hospital Care

Patients with drug use disorders are heavy users of emergency department (ED) and inpatient hospital care. This study examines whether formal mechanisms to link addiction treatment patients to primary medical care, either directly on site, or by off-site referral-when compared with an absence of these mechanisms-might reduce these patients use of ED and hospital services after substance abuse treatment. The authors used longitudinal data from 6 methadone maintenance programs with 232 patients, 24 outpatient nonmethadone programs with 1202 patients, and 14 long-term residential programs with 679 patients in the National Treatment Improvement Evaluation Study. Multivariate logistic models controlling for health status and medical service utilization before treatment examined whether provision of medical services on- or off-site during treatment linkage led to reduced use of ED and hospital services in the year after treatment compared with no such provision. This study shows that the on-site delivery of primary care reduced subsequent ED and hospital use among patients in methadone maintenance and long-term residential compared with the non-linkage condition but not in outpatient nonmethadone programs. Off-site referral for medical care reduced subsequent ED visits but not hospitalizations in long-term residential programs. These findings suggest that for some treatment modalities, stronger primary care linkage mechanisms decrease subsequent utilization of expensive ED and hospital services. Future study should examine the cost implications of these

strong linkage mechanisms and ways to strengthen linkages to off-site medical care. Friedmann, P., Hendrickson, J., Gerstein, D., Zhang, Z., and Stein, M. Do Mechanisms that Link Addiction Treatment Patients to Primary Care Influence Subsequent Utilization of Emergency and Hospital Care? Med Care, 44(1), pp. 8-15, 2006.

A Risk-Taking Among Adolescents with Serious Conduct and Substance Problems

Adolescent patients' conduct disorder and substance use disorder symptoms are "risky behaviors" with unpredictable rewards and punishments. The authors studied whether such youths also take excessive risks in new situations without prior learning, peer pressure, or intoxication. Subjects were 20 adolescent patients in a program treating conduct disorder and substance use disorder and 20 controls. All were substance free > or =7 days; underwent substance-related, psychological, and social assessments; and performed the Balloon Analogue Risk Task: mouse presses inflated a computerized "balloon" image, each press earning 1 cent. The 30 balloons "popped" at unpredictable sizes; earnings from popped balloons were lost. A "Collect" response saved current earnings and advanced to the next balloon. It was found that the mean number of inflating presses was 1021in patients, and 705 ($p = .001$) in controls, group differences were stable from the task's beginning. Mean inflating presses before a "collect" response: was 38.6 in patients, and 24.0 ($p = .0005$) in controls, Mean balloons popped were 9.8 in patients, and 6.3 ($p = .001$) in controls. Patients (versus controls) reported more aggressiveness and substance use and perceived less risk from substances. Patients' responses were significantly slower than those of controls. This study shows that from the beginning of this novel task, conduct disorder and substance use disorder patients (compared with controls) took more risks, indicating an initial risk-taking propensity, although patients' slower responses argued against "impulsive, thoughtless" behavior. Crowley, T., Raymond, K., Mikulich-Gilbertson, S., Thompson, L., and Lejuez, C. A Risk-Taking "Set" in a Novel Task Among Adolescents with Serious Conduct and Substance Problems. J Am Acad Child Adolesc Psychiatry, 45(2), pp. 175-183, 2006.

Medicaid Eligibility and Access to Mental Health Services Among Adolescents in Substance Abuse Treatment

The co-occurrence of a mental disorder is common among adolescents who present for substance abuse treatment. This study was conducted to determine whether Medicaid eligibility was associated with greater use of mental health services. The study used administrative data for 25,813 adolescents in Oregon. Propensity score analysis was used to assess the likelihood that the adolescents would use mental health services, with group differences and mental health needs as control variables. The study found that Medicaid-eligible youths were nearly five times as likely to receive mental health services in the year they entered substance abuse treatment compared with non-Medicaid-eligible youths. In both groups, there was evidence of racial disparities as well as factors such as foster care that may facilitate access. The fact that Medicaid-eligible youths have greater access to mental health services should be considered in both policy and research design. Funding bodies considering ways to better serve adolescents with co-occurring disorders should consider examining ways to promote Medicaid enrollment or expand eligibility. Deck, D., and Ley, K. Medicaid Eligibility and Access to Mental Health Services Among Adolescents in Substance Abuse Treatment. Psychiatr Serv, 57(2), pp. 263-265, 2006.

Associations Between Phenylthiocarbamide Gene Polymorphisms (Bitter Taste Sensation) and Cigarette Smoking

Phenotypic evidence indicates that the ability to taste the bitter compounds phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP) may protect against cigarette smoking. In this study, PTC gene haplotypes were found to be associated with both the odds of being a smoker and the importance of cigarette taste as a smoking motive. Smokers (n = 384) and nonsmokers (n = 183) were genotyped for polymorphisms that affect taste sensitivity to PTC and PROP. The "taster" PAV haplotype, relative to the "nontaster" AVI haplotype, was predicted to be associated with reduced odds of being a smoker and lower taste motivation as measured by the Wisconsin Inventory of Smoking Dependence Motives-68 taste/sensory processes scale. The results did not support the predicted association between the PAV and AVI haplotypes and smoker odds, but the AAV haplotype, which confers intermediate PTC/PROP taste sensitivity, was associated with reduced smoker prevalence (49% vs. 70%), chi(2)(1, N = 567) = 10.392, p = .001. The predicted relationship between PAV and AVI and taste motivation was found, F (2, 348) = 3.303, p = .038. The results encourage further exploration of the role of taste/sensory processes in tobacco dependence, and their role in specific smoking cessation treatments. Cannon, D., Baker, T., Piper, M., Scholand, M., Lawrence, D., Drayna, D., McMahon, W., Villegas, G., Caton, T., Coon, H., and Leppert, M. Associations Between Phenylthiocarbamide Gene Polymorphisms and Cigarette Smoking. Nicotine Tob Res, 7(6), pp. 853-858, 2005.

Matching Judicial Supervision to Client Risk in Drug Courts

This article reports outcomes from a program of experimental research evaluating the risk principle in drug courts which posits that the level of criminal justice supervision and services should match the level of risk an individual poses to the community. Prior studies revealed that participants who were determined to be high risk and had (a) antisocial personality disorder or (b) a prior history of drug abuse treatment performed better in drug court when scheduled to attend biweekly judicial status hearings in court. In contrast, participants who were low risk performed equivalently regardless of the court hearings schedule. This study prospectively matches drug court clients (n=274) to the optimal schedule of court hearings based on an assessment of their risk status and compares outcomes to clients randomly assigned to the standard hearings schedule. Results confirmed that participants who were high risk and matched to biweekly hearings had better during-treatment outcomes than participants assigned to status hearings as usual. These findings provide confirmation of the risk principle in drug courts and yield practical information for enhancing the efficacy and cost-efficiency of drug courts. Marlowe, D.B., Festinger, D.S., Lee, P.A., Dugosh, K.L., and Benasutti, K.M. Matching Judicial Supervision to Clients' Risk Status in Drug Court. Crime & Delinquency, 52(1), pp. 52-76, 2006.

Secondary Prevention Services in Drug Court: A Conceptual Model

This article presents a conceptual framework for developing and administering secondary prevention services in drug courts and proposes a platform of prevention techniques that can be tailored in a clinically relevant manner for the sizeable population of drug court clients who are low risk. The drug court model assumes that most drug offenders are addicts, and that drug use fuels other criminal activity. As a result, drug court clients must satisfy an intensive regimen of treatment and supervisory obligations. However, research suggests that roughly one third of drug court clients do not have a clinically significant substance use disorder. For these clients, standard drug court services may be ineffective or even contraindicated. Instead, these clients may be best suited for a secondary prevention approach directed at interrupting the acquisition of addictive behaviors. DeMatteo, D.S., Marlowe, D.B., and Festinger, D.S. Secondary Prevention Services for Clients who are Low Risk in Drug Court: A

Conceptual Model. Crime & Delinquency, 52(1), pp. 114-134, 2006.

The Role of Health Insurance in Getting a Physical Exam

One component of social work' s endeavors on behalf of drug users and other populations- at-risk has been advocating for increased access to health care. This article examines the role that having health insurance plays in obtaining the most basic of all health care-getting a physical examination. Featuring a sample of 1,271 chronic and injecting street drug users and comparison group non-users, the analysis demonstrates that having health insurance enhances access and utilization of health care among this at-risk population. Subjects who had health insurance for even one month of the past twelve were twice as likely to participate in basic health care by having a physical exam. McBride, D., Drumm, R., Terry-McElrath, Y. and Chitwood, D. Back to Basics: The Role of Health Insurance in Getting a Physical Exam. Soc Work Health Care, 42(51), pp. 93-106, 2005.

Sexual Risk Behavior and Substance Use Among a Sample of Asian Pacific Islander Transgendered Women

This study examined the prevalence and correlates of HIV-related sexual risk and substance use behaviors among Asian Pacific Islander (API) male-to-female (MTF) transgendered individuals, referred to here as API transgendered women. As part of a larger study on HIV risk among transgendered women of color (Nemoto, Operario, Keatley, Han, & Soma, 2004), a sample of 110 API transgendered women in San Francisco completed individual interviews, of which 13% reported being HIV-positive. In the past 30 days, one fifth of the sample engaged in unprotected receptive anal intercourse (URAI) with any male partner, nearly one half had sex while under the influence of substances, and over half used illicit drugs. In multivariate models, URAI was associated with commercial sex work (odds ratio [OR] = 4.23, 95% confidence interval [CI] = 1.10, 16.25) and previous attempted suicide (OR = 5.83, 95% CI = 1.02, 33.44). Sex under the influence of substances was associated with commercial sex work (OR = 3.35, 95% CI = 1.11, 10.13) and having a college degree (OR = 5.32, 95% CI = 1.34, 21.18). Illicit drug use was associated with commercial sex work (OR = 7.15, 95% = 2.26, 22.63). Findings suggest that API MTF transgenders are on the front line of HIV risk for the API community, and provide insight into factors within this group that might contribute to unsafe sex and substance use. Operario, D., and Nemoto, T. Sexual Risk Behavior and Substance Use Among a Sample of Asian Pacific Islander Transgendered Women. AIDS Educ Prev, 17(5), pp. 430-443, 2005.

Addiction Treatment Utilization among Homeless and Housed

Research on addiction treatment utilization in indigent samples mainly has been retrospective, without the measures of three factors: addictive consequences, social network influences, and motivation. In this prospective study, the researchers focus upon these three factors as they are associated with utilization of addiction treatment and mutual help groups among substance-dependent persons with high rates of homelessness. Patients detoxified from alcohol or drugs at baseline were followed for 2 years in a randomized clinical trial of linkage to primary care (n = 274). Outcomes included utilization of Inpatient/Residential, Outpatient, Any Treatment, and Mutual Help Groups. Predictor variables in longitudinal regression analyses came from the literature and clinical experience, organized according to theoretical categories of Need, and non-Need (e.g., Predisposing and Enabling). Many subjects used Inpatient/Residential (72%), Outpatient (62%), Any Treatment (88%) or Mutual Help Groups (93%) at least once. In multivariable analyses, addictive consequences (odds ratio [OR] 1.38, 95%

confidence interval [CI] 1.12-1.71), motivation (OR 1.32, 95% CI 1.09-1.60), and female gender (OR 1.80, 95% CI 1.13-2.86) were associated with most treatment types. Homelessness was associated with Residential/Inpatient (for Chronically Homeless vs. Housed, OR 1.75, 95% CI 1.04-2.94). Living with one's children (OR 0.51, 95% CI 0.31-0.84) and substance-abusing social environment (OR 0.65, 95% CI 0.43-0.98) were negatively associated with Any Treatment. Addictive consequences, social network variables, and motivation were associated with treatment utilization in this sample. Non-need factors, including living with one's children and gender, also were found to be significant influences on treatment utilization. Kertesz, S., Larson, M., Cheng, D., Tucker, J., Winter, M., Mullins, A., Saitz, R., and Samet, J. Need and Non-Need Factors Associated with Addiction Treatment Utilization in a Cohort of Homeless and Housed Urban Poor. Med Care, 44(3), pp. 225-233, 2006.

Club Drug Use and Risky Sexual Practices Among Hispanic MSM

This study measured use of club drugs among 262 Hispanic men who have sex with men (MSM) recruited at community venues in Miami-Dade County, Florida in 2001. More than 50% of men used club drugs, and 36% used them in the last 3 months. Lifetime and 3-month rates were: ecstasy (36% and 20%), cocaine (34% and 12%), amyl nitrates (28% and 9%), and crystal methamphetamine (20% and 15%). Thirty-six percent had used two or more drugs (polydrug use) in their lifetime and 20% reported polydrug use in the last 3 months. Club drug users had significantly more sex partners in the last 12 months than nonclub drug users. High rates (35%) of unprotected anal sex in the last 3 months were reported by both groups. Men who reported polydrug use in the last 3 months were significantly more likely than men who used a single club drug to have had sex under the influence of club drugs (83% vs. 57%; X2=7.4, p=0.006). At the multivariate level, a significant association between preference for use of English and lifetime club drug use emerged. Effective interventions to reduce club drug use and risky sex for Hispanic MSM are needed. Fern‡ndez, M., Bowen, G., Varga, L., Collazo, J., Hernandez, N., Perrino, T., and Rehbein, A. High Rates of Club Drug Use and Risky Sexual Practices Among Hispanic Men Who Have Sex With Men in Miami, Florida. Subst Use Misuse, 40(9-10), pp. 1347-1362, 2005.

Sexual Minoirites Seeking Substance Abuse Treatment Show Relatively Higher Symptom Severity

Previous research has suggested that lesbian, gay, bisexual, and transgender (LGBT) individuals enter treatment for substance abuse with more severe problems than heterosexual individuals. However, methodological difficulties, particularly the difficulty of obtaining a representative sample, have limited the ability to draw conclusions. This study examined a representative sample of openly LGBT clients receiving publicly funded substance abuse treatment by using data gathered by treatment providers in Washington State. Baseline differences between 610 openly LGBT and 15,705 heterosexual clients admitted for treatment at any of 212 agencies during an 18-month period ending in 2002, were compared in a variety of domains. Results demonstrated that openly LGBT clients enter treatment with more severe substance abuse problems, greater psychopathology, and greater medical service utilization when compared with heterosexual clients. Cochran, B.N. and Cauce, A. Characteristics of Lesbian, Gay, Bisexual, and Transgender Individuals Entering Substance Abuse Treatment. J Subst Abuse Treat, 30, pp. 135-146, 2006.

Gender Differences in the Prediction of Condom use Among Incarcerated Juveniles

This research study applied the Information-Motivation-Behavioral skills (IMB)

model in predicting condom-protected vaginal intercourse among incarcerated youth. The IMB model is a three-factor conceptualization of HIV preventive behavior. According to the IMB Model, there are three fundamental determinants of AIDS risk reduction including: information on HIV/AIDS transmission and information on specific prevention methods, motivation to act on the knowledge and change risky behavior, and behavioral skills in performing the specific prevention acts. Self-report measures of AIDS knowledge, pro-condom peer influence, risk perception, condom attitudes, condom use self-efficacy, frequency of vaginal intercourse, and frequency of condom-protected vaginal intercourse were collected from predominately African-American adolescent juvenile detainees (N=523). Study results found that for males and females combined condom use was significantly predicted by being male, peer influence, positive condom attitudes, and condom self-efficacy. In separate gender analyses, condom use among adolescent males was predicted by peer influence and positive condom attitudes, whereas condom use among females was predicted by peer influence, self-efficacy, and influence, higher perceived risk for infection, more positive condom attitudes, and more self-efficacy, but females also reported less condom use. The investigators conclude that girls may find it more difficult to consistently use condoms despite awareness of their efficacy. Power imbalances or other dynamics operating in their relationships with boys need further exploration. Robertson, A.A., Stein, J.A., and Baird-Thomas, C. Gender Differences in the Prediction of Condom Use Among Incarcerated Juvenile Offenders: Testing the Information-Motivation-Behaviors Skills (IMB) Model. Journal of Adolescent Health, 38, pp. 18-25, 2006.

Motivational Interviewing for Improving Adherence to Antiretroviral Medications

Many interventions have been developed to address barriers to antiretroviral medication adherence, but few have focused on motivation, a fundamental component of behavior change. Research on other health behavior changes and a few pilot studies investigating motivational interviewing (MI) for adherence to antiretroviral medication suggests that MI may be highly beneficial by helping to motivate patients with HIV to adhere to their medications. Existing research, although limited, suggests that MI combined with other interventions is feasible and efficacious for improving adherence to antiretroviral medications. With continued development and refinement of antiretroviral adherence interventions that incorporate MI, more persons with HIV infection can be expected to choose to make the difficult changes necessary for them to benefit from antiretroviral therapy. Cooperman, N., and Arnsten, J. Motivational Interviewing for Improving Adherence to Antiretroviral Medications. Curr HIV/AIDS Rep, 2(4), pp. 159-164, 2005.

Stakeholders in Recovery: Demands, Expectations, and Research Opportunities

A broad array of agencies, institutions, and individuals interact with community-based substance abuse treatment programs, providing resources or services and asserting demands and expectations in return. These relationships shape the environment in which treatment and community-based research take place, and themselves raise issues worthy of research attention. This article enumerates the stakeholders in one well-established program and describes the scope of the program's efforts to accommodate these stakeholders, along with some of the complications and difficulties programs confront in their attempts to satisfy stakeholders, especially when their demands are unrealistic or their interests conflict. The article concludes by identifying research areas that could facilitate these relationships, enhancing their benefits for patients. McCarty, D., Zammarelli, L., Wylie, H., and Greenlick, M.R. NIDA Science & Practice Perspectives, 3(1), pp. 34-37, 2005.

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Director's Report to the National Advisory Council on Drug Abuse - May, 2006

Research Findings - Intramural Research

Development and Plasticity Section, Cellular Neurobiology Research Branch

GABAergic Lineage Differentiation of AF5 Neural Progenitor Cells In Vitro IRP scientists have previously described an immortal rat central-nervous-system progenitor cell line, AF5, which is able to exit the cell cycle and assume a differentiated state with neuronal properties. The phenotypic specification of differentiated AF5 cells, however, is not known. In the present study, when induced to differentiate by serum starvation in Neurobasal medium, AF5 cells down-regulate glial fibrillary acidic protein and up-regulate expression of beta-III-tubulin, medium-molecular-weight neurofilament protein, and neuronal growth-associated protein 43. Expression of the gamma-aminobutyric acid (GABA) lineage marker, glutamic acid decarboxylase 67 (GAD67), increases during differentiation, suggesting that AF5 cells adopt a GABAergic lineage. Time-course analysis of the GABAergic neuron specification transcription factor, Pitx2, by reverse transcription/polymerase chain reaction, has shown an increase in the Pitx2 transcript 48 h after initiation of differentiation. In differentiated AF5 cells, expression of the Pitx2 target gene products GAD65 and GABA transporter-1 increases. Cellular GABA levels in differentiated AF5 cells increase by about 26-fold, and GABA release into the medium is 150-fold higher compared with that of undifferentiated cells. Therefore, AF5 cells can be induced to differentiate to a neuronal phenotype with a GABAergic lineage. Sanchez, J.F., Crooks, D.R., Lee, C.T., Schoen, C.J., Amable, R., Zeng, X., Florival-Victor, T., Morales, N., Truckenmiller, M.E., Smith, D.R. and Freed, W.J. Cell Tissue Research, 324, pp. 1-8, 2006.

Assessing Self-Renewal and Differentiation in Human Embryonic Stem Cell Lines Like other cell populations, undifferentiated human embryonic stem cells (hESCs) express a characteristic set of proteins and mRNA that is unique to the cells regardless of culture conditions, number of passages, and methods of propagation. IRP researchers sought to identify a small set of markers that would serve as a reliable indicator of the balance of undifferentiated and differentiated cells in hESC populations. Markers of undifferentiated cells should be rapidly downregulated as the cells differentiate to form embryoid bodies (EBs), whereas markers that are absent or low during the undifferentiated state but that are induced as hESCs differentiate could be used to assess the presence of differentiated cells in the cultures. In this paper, authors describe a list of markers that reliably distinguish undifferentiated and differentiated cells. An initial list of approximately 150 genes was generated by scanning published massively parallel signature sequencing, expressed sequence tag scan, and microarray datasets. From this list, a subset of 109 genes was selected that included 55 candidate markers of undifferentiated cells, 46 markers of hESC derivatives, four germ cell markers, and four trophoblast markers. Expression

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of these candidate marker genes was analyzed in undifferentiated hESCs and differentiating EB populations in four different lines by immunocytochemistry, reverse transcription-polymer-ase chain reaction (RT-PCR), microarray analysis, and quantitative RT-PCR (qPCR). Authors show that qPCR, with as few as 12 selected genes, can reliably distinguish differentiated cells from undifferentiated hESC populations. Cai, J., Chen, J., Liu, Y., Miura, T., Luo, Y., Loring, J.F., Freed, W.J., Rao, M.S., and Zeng, X. Stem Cells, 24, pp. 516-530, 2006.

Characterization of a New NIH-Registered Variant Human Embryonic Stem Cell Line, BG01V: A Tool for Human Embryonic Stem Cell Research Human embryonic stem cells (hESCs) offer a renewable source of a wide range of cell types for use in research and cell-based therapies. Characterizing these cells provides important information about their current state and affords relevant details for subsequent manipulations. For example, identifying genes expressed during culture, as well as their temporal expression order after passaging and conditions influencing the formation of all three germ layers may be helpful for the production of functional beta islet cells used in treating type I diabetes. Although several hESC lines have demonstrated karyotypic instability during extended time in culture, select variant lines exhibit characteristics similar to their normal parental lines. Such variant lines may be excellent tools and abundant sources of cells for pilot studies and in vitro differentiation research in which chromosome number is not a concern, similar to the role currently played by embryonal carcinoma cell lines. It is crucial that the cells be surveyed at a genetic and proteomic level during extensive propagation, expansion, and manipulation in vitro. Here IRP scientists describe a comprehensive characterization of the variant hESC line BG01V, which was derived from the karyotypically normal, parental hESC line BG01. Authors characterization process employs cytogenetic analysis, short tandem repeat and HLA typing, mitochondrial DNA sequencing, gene expression analysis using quantitative reverse transcription-polymerase chain reaction and microarray, assessment of telomerase activity, methylation analysis, and immunophenotyping and teratoma formation, in addition to screening for bacterial, fungal, mycoplasma, and human pathogen contamination. Plaia, T.W., Josephson, R., Liu, Y., Zeng, X., Ording, C., Toumadje, A., Brimble, S.N., Sherrer, E.S., Uhl, E.W., Freed, W.J., Schulz, T.C., Maitra, A., Rao, M.S. and Auerbach, J.M. Stem Cells, 24, pp. 531-546, 2006.

Electrophysiology Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Visualizing Cannabinoid Effects Using Brain Slice Imaging and Electrophysiological Approaches The use of electrophysiological recordings in brain slices is now routinely used to assess the actions of cannabinoid ligands within various central nervous system nuclei. In this chapter authors describe common protocols involving both intracellular and extracellular recording techniques in the hippocampus, where the presynaptic modulatory effects of cannabinoid receptor activation have been studied in detail. In addition to describing the basic electrophysiological setup needed for these recordings, we will address common technical problems and limitations involved in working with highly lipophilic compounds, such as the cannabinoid ligands, in brain slices. Hoffman, A.F., and Lupica, C.R. Methods in Molecular Medicine, 123, pp. 105-112, 2006.

Receptor-Independent Effects of Endocannabinoids on Ion Channels Endogenous cannabinoids (endocannabinoids), produced from membrane-bound precursors via calcium and/or G-protein dependent processes, mimic the effects of cannabinoids by activating cannabinoid CB(1) and/or CB(2) receptors. Several reports however, also indicate that endocannabinoids can

produce effects that are independent of cannabinoid receptors. Thus, in pharmacologically relevant concentrations, endocannabinoids have been demonstrated to modulate the functional properties of voltage-gated ion channels including Ca(2+) channels, Na(+) channels and various types of K(+) channels, and ligand-gated ion channels such as 5-HT(3), and nicotinic ACh receptors. In addition, the functional modulations by endocannabinoids of other ion-transporting membrane proteins such as transient potential receptor-class channels, gap junctions, and neurotransmitter transporters have also been reported. These findings indicate that additional molecular targets for endocannabinoids exist and that these targets may represent important sites for cannabinoids to alter either the excitability of the neurons or the response of the neuronal systems. This review focuses on the results of recent studies indicating that beyond their receptor-mediated effects, endocannabinoids alter the function of ion channels directly. Oz, M. Current Pharmaceutical Design, 12, pp. 227-239, 2006.

Proteomics Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Decoy Peptides that Bind Dynorphin Noncovalently Prevent NMDA Receptor-Mediated Neurotoxicity Prodynorphin-derived peptides elicit various pathological effects including neurological dysfunction and cell death. These actions are reduced by N-methyl-d-aspartate receptor (NMDAR) but not opioid receptor antagonists suggesting NMDAR-mediation. Here, IRP researchers show that a conserved epitope (KVNSEEEEEDA) of the NR1 subunit of the NMDAR binds dynorphin peptides (DYNp) noncovalently. Synthetic peptides containing this epitope form stable complexes with DYNp and prevent the potentiation of NMDAR-gated currents produced by DYNp. They attenuate DYNp-evoked cell death in spinal cord and prevent, as well as reverse, DYNp-induced paralysis and allodynia. The data reveal a novel mechanism whereby prodynorphin-derived peptides facilitate NMDAR function and produce neurotoxicity. Furthermore, they suggest that synthetic peptides that bind DYNp, thus preventing their interaction with NMDAR, may be novel therapeutic agents for the treatment of spinal cord injury. Woods, A.S., Kaminski, R., Oz, M., Wang, Y., Hauser, K., Goody, R., Wang, H.Y., Jackson, S.N., Zeitz, P., Zeitz, K.P., Zolkowska, D., Schepers, R., Nold, M., Danielson, J., Graslund, A., Vukojevic, V., Bakalkin, G., Basbaum, A., and Shippenberg, T. Journal of Proteome Research, 5, pp. 1017-1023, 2006.

Phosphate Stabilization of Intermolecular Interactions Receptor heteromerization is an important phenomenon that results from the interaction of epitopes on two receptors. Previous studies have suggested the possibility of Dopamine D2-NMDA receptors' interaction. IRP scientists believe that the interaction is through an acidic epitope of the NMDA NR1 subunit (KVNSEEEEEDA) and a basic epitope of the D2 third intracellular loop (VLRRRRKRVN), which was shown to also interact with the Adenosine A2A receptor. In previous work, authors highlighted the role of certain amino acid residues, mainly two or more adjacent arginine on one peptide and two or more adjacent glutamate, or aspartate, or a phosphorylated residue on the other in the formation of noncovalent complexes (NCX) between epitopes. In the present work, they use the phosphorylated (KVNSpEEEEEDA), nonphosphorylated (KVNSEEEEEDA) and modified (KVNpSAAAAAAA) forms of the NMDA epitope that possibly interact with the D2 epitope to investigate the gas-phase stability of the NCXs as a function of the nominal energy given to the NCX ion as it enters the collision cell. In addition to theoretical calculations, the experimental data was used to calculate the stability of each electrostatic complex versus that of the dimer of KVNSpEEEEEDA. Our results demonstrate the importance of the phosphate group in stabilizing molecular interactions and that appreciably higher collision energies are required to completely dissociate any of the three different NCX ions that are formed through electrostatic

interaction in comparison to the energy required to dissociate the KVNpSEEEEEDA dimer ion, which is mainly kept together by hydrogen bonding. This study emphasizes ionic bonds stability and their importance to protein structure as their potent electrostatic attractions can in the gas-phase surpass the strength of covalent bonds. Jackson, S.N., Wang, H.Y., Yergey, A., and Woods, A.S. Journal of Proteome Research, 5, pp. 122-126, 2006.

Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Effect of Methamphetamine Self-Administration on Tyrosine Hydroxylase and Dopamine Transporter Levels in Mesolimbic and Nigrostriatal Dopamine Pathways of the Rat Many studies have examined the effect of experimenter-delivered methamphetamine on the mesolimbic and nigrostriatal dopamine pathways. In contrast, little is known about the effect of methamphetamine self-administration on these neuronal pathways. IRP researchers studied the effect of methamphetamine self-administration on two key regulators of dopamine transmission, tyrosine hydroxylase (TH), and dopamine transporter (DAT), in components of the mesolimbic and nigrostriatal dopamine pathways. Rats self-administered methamphetamine (0.1 mg/kg per infusion, fixed-ratio-1 reinforcement schedule) or saline (control condition) for 9 h/day over 10 days. The brains of these rats were collected after 1 or 30 days of forced abstinence and the expression levels of TH and DAT were assayed by in situ, hybridization and western blot. TH mRNA and protein levels were increased in the ventral tegmental area (VTA, the cell body region of the mesolimbic dopamine system) and the substantia nigra pars compacta (SNC, the cell body region of the nigrostriatal dopamine system) after 1 day, but not 30 days, of forced abstinence from methamphetamine. In contrast, methamphetamine self-administration had no effect on TH protein levels in dopaminergic terminals located in the nucleus accumbens and caudate-putamen. In addition, methamphetamine self-administration had no effect on DAT mRNA levels in the VTA. Results suggest that extended daily access to self-administered methamphetamine results in a transient, short-lasting effect on mesolimbic and nigrostriatal dopamine neurons of the rat brain. Shepard, J.D., Chuang, D.T., Shaham, Y. and Morales, M. Psychopharmacology, 185, pp. 505-513, 2006.

Morphometric Study on Cytoskeletal Components of Neuronal and Astroglial Cells after Chronic CB1 Agonist Treatment One of the major goals for the use of digital image analysis systems in neuroanatomy is to visualize structures, cells, or other tissue components in order to compare various populations. In addition, digital image analysis allows semi-quantification of cell labeling because it is capable of measuring simultaneously the staining intensity, location, size, and shape of labeled profiles. In the present work, the morphological changes in the CB1 hippocampal area and corpus striatum induced by chronic treatment with the synthetic CB1-receptor agonist WIN55,212-2 were analyzed as an example of digital image analysis application. Twice-daily treatment for 14 d with the CB1-receptor agonist demonstrated significant changes in the expression of neuronal cytoskeletal proteins and in neuronal morphology, as evidenced by immunocytochemical and digital analysis studies. However, changes in the expression of astroglial cytoskeletal proteins were not found. Tagliaferro, P., Ramos, A.J., Onaivi, E.S., Evrard, S.G., Vega, M.D., and Brusco, A. Methods in Molecular Medicine, 123, pp. 91-104, 2006.

Molecular Neuropsychiatry Research Branch

Neurological Assessments of Marijuana Users This chapter summarizes the neurological approaches used to assess the potential long-term effects of drugs on the nervous system of drug abusers. These include the use of

neuropsychological assessments, transcranial Doppler (TCD) sonography, and electroencephalographic (EEG) recordings. Neuropsychological procedures are used in an effort to provide an unbiased estimate of the individual's cognitive capacity, and included tests of language skills, attention, memory, and motor skills. TCD allows for the measurements of blood flow in the anterior cerebral and middle cerebral arteries, which supply blood to the cortex. An EEG recording was included in our assessment on marijuana abusers using a sound-attenuated, electronically shielded chamber. These neurological approaches have allowed the detection of various neurological and neurovascular deficits that are associated with the abuse of marijuana. Cadet, J.L., Bolla, K. and Herning, R. Methods of Molecular Medicine, 123, pp. 255-268, 2006.

Molecular Neurobiology Research Branch

Association Genome Scanning for Human Addiction Vulnerability Branch scientists validated pooled genome scanning using "10k" Affymetrix microarrays. They then used these arrays to provide millions of person/genotype equivalents for the DNAs that they have collected from NIDA IRP research volunteers who are dependent on illegal substances and volunteers who report no significant lifetime use of addictive substances. The genes identified using this genome scanning approach fall into several classes, and provide markers to help separate those with greater and lesser addiction vulnerabilities. Liu, Q.R., Drgon, T., Walther, D., Johnson, C., Poleskaya, O., Hess, J. and Uhl GR. Proceedings of the National Acadamy of Sciences, USA, 102, pp 11864-11869, 2005.

Fine Mapping Studies for Human Addiction Vulnerability Identify the Cell Adhesion Molecule NrCAM Branch scientists followed up on pooled genome scanning using Affymetrix microarrays and data from drug-regulated gene expression to positionally clone NrCAM as a gene whose 5' regulatory variants 1) lead to differences in levels of NrCAM expression and 2) contribute to differential vulnerability to addiction. Mouse models impressively replicated this effect: altering NrCAM expression dramatically changed place preferences for cocaine and for morphine. Ishiguro, H., Liu, Q.R., Gong, J.P., Hall, F.S., Ujike, H., Morales, M., Sakurai, T., Grumet, M. and Uhl GR. Neuropsychopharmacology, 31, pp. 572-584, 2006.

Behavioral Neuroscience Section, Behavioral Neuroscience Research Branch

Reinforcing Effects of Nicotine are Triggered from Regions Inside and Outside the Ventral Tegmental Area Nicotine is thought to be the key substance responsible for tobacco-smoking habits and appears to trigger reinforcement via the ventral tegmental area (VTA). Recently, multiple anatomical substrates for drug reinforcement have been identified in the vicinity of the ventral midbrain. In addition to the posterior portion of the VTA, the central linear nucleus raphe and the supramammillary nucleus of the posterior hypothalamus mediate drug reinforcement. Using intracranial self-administration procedures, IRP researchers examined whether these regions mediate the reinforcing effects of nicotine. Rats learned to lever press for self-administration of nicotine into the posterior VTA, central linear nucleus, and supramammillary nucleus, suggesting a reinforcing action of nicotine in these regions. The rats did not self-administer nicotine into surrounding regions including the anterior VTA, substantia nigra, the region just dorsal to the posterior VTA, interpeduncular nucleus, or medial mammillary nucleus. The reinforcing effects of nicotine into the three brain regions were further confirmed by a two-lever discrimination procedure, in which rats learned to selectively respond between active and inactive levers. The reinforcing effects of nicotine administration into the posterior VTA, central linear nucleus, and supramammillary nucleus were blocked by coadministration of the nicotine

receptor antagonist mecamylamine. The reinforcing effects of nicotine into the posterior VTA or central linear nucleus were attenuated by coadministration of the D2 receptor agonist quinpirole. These findings demonstrate that nicotine reinforcement involves multiple regions both inside and outside the VTA. Ikemoto, S., Qin, M., Liu Z-H. Journal of Neuroscience, 26, pp. 723-730, 2006.

A New Peptide Input to Learning and Addiction In this issue of Neuron, Borgland et al. report that the arousal-associated peptide orexin enhances LTP-like changes in glutamatergic excitability of ventral tegmental dopamine neurons. This parallels a similar effect of corticotropin-releasing factor and suggests a form of neuroadaptation that increases the likelihood of addiction relapse. Wise, R.A. Neuron, 49, 483-484, 2006.

Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch

The Dopamine D3 Receptor: A Therapeutic Target for the Treatment of Neuropsychiatric Disorders The role of the D(3) receptor has remained largely elusive before the development of selective research tools, such as selective radioligands, antibodies, various highly specific pharmacological agents and knock-out mice. The data collected so far with these tools have removed some of the uncertainties regarding the functions mediated by the D(3) receptor. The D(3) receptor is an autoreceptor that controls the phasic, but not tonic activity of dopamine neurons. The D(3) receptor, via regulation of its expression by the brain-derived neurotrophic factor (BDNF), mediates sensitization to dopamine indirect agonists. This process seems responsible for side-effects of levodopa (dyskinesia) in the treatment of Parkinson's disease (PD), as well as for some aspects of conditioning to drugs of abuse. The D(3) receptor mediates behavioral abnormalities elicited by glutamate/NMDA receptor blockade, which suggests D(3) receptor-selective antagonists as novel antipsychotic drugs. These data allow us to propose novel treatment options in PD, schizophrenia and drug addiction, which are awaiting evaluation in clinical trials. Sokoloff, P., Diaz, J., Le Foll, B., Guillin, O., Leriche, L., Bezard, E. and Gross, C. CNS Neurological Disorders Drug Targets, 5, pp. 25-43, 2006.

A Comparison of Drug-seeking Behavior Maintained by d-Amphetamine, l-Deprenyl (selegiline), and d-Deprenyl under a Second-order Schedule in Squirrel Monkeys L-Deprenyl (selegiline) is used in the treatment of Parkinson's disease and has been proposed as an aid for cigarette smoking cessation and a treatment for psychostimulant abuse. L-Deprenyl is metabolized in the body to L-methamphetamine and L-amphetamine, suggesting that it may have abuse potential. The current study assessed whether L-deprenyl or its isomer would maintain drug-seeking behavior on a second-order schedule and whether L-deprenyl would alter drug-seeking behavior maintained by D-amphetamine if given as a pretreatment. Squirrel monkeys learned to respond on a second-order schedule of reinforcement, where every tenth response was followed by a brief light flash, and the first brief light flash after 30 min was paired with intravenous (i.v.) injection of D-amphetamine (0.56 mg/kg), administered over a 2-min period at the end of the session. When responding was stable, saline or different i.v. doses of D-amphetamine (0.3-1.0 mg/kg), L-deprenyl (0.1-10.0 mg/kg), and D-deprenyl (0.1-3.0 mg/kg) were substituted for 10 days each. Subsequently, monkeys were pretreated with 0.3 or 1.0 mg/kg L-deprenyl intramuscularly 30 min prior to D-amphetamine baseline sessions. D-Amphetamine maintained high rates of drug-seeking behavior on the second-order schedule. D-Deprenyl maintained high rates of drug-seeking behavior similar to D-amphetamine. L-Deprenyl maintained lower rates of responding that were not significantly above saline substitution levels. Pretreatment with L-deprenyl failed to alter drug-seeking behavior maintained by D-amphetamine. These results indicate that D-deprenyl, but not L-deprenyl, may have abuse potential. Under conditions

where drug-seeking and drug-taking behaviors are actively maintained by D-amphetamine, L-deprenyl, at doses that specifically inhibit type B monoamine oxidase, may not be effective as a treatment. Yasar, S., Gaal, J., Panlilio, L.V., Justinova, Z., Molnar, S.V., Redhi, G.H. and Schindler, C.W. Psychopharmacology, 183, pp. 413-421, 2006.

The "Two-state Dimer Receptor Model": A General Model for Receptor Dimers Non-linear Scatchard plots are often found for agonist binding to G-protein-coupled receptors. Since there are clear evidences of receptor dimerization these non-linear Scatchard plots can reflect cooperativity on agonist binding to the two binding sites in the dimer. According to this, the "two-state dimer receptor model" has been recently derived. In this paper the performance of the model has been analyzed in fitting data from A1 adenosine receptors agonist binding, which is an example of receptor displaying concave downward Scatchard plots. Analysis of agonist/antagonist competition data for dopamine D1 receptors using the "two-state dimer receptor model" has also been performed. Although fitting to the "two-state dimer receptor model" is similarly good than the fitting to the "two-independent-site receptor model", the former is simpler and a discrimination test selects the "two-state dimer receptor model" as the best. This model was also very robust in fitting data of estrogen binding to the estrogen receptor, which display concave upward Scatchard plots. On the one hand, the model would predict the already demonstrated existence of estrogen receptor dimers. On the other hand, the model would predict that concave upward Scatchard plots reflect positive cooperativity, which cannot be neither predicted nor explained by assuming the existence of two different affinity states. In summary the "two-state dimer receptor model" is good for fitting data of binding to dimeric receptors displaying either linear, concave upward or concave downward Scatchard plots. Franco, R., Casado, V., Mallol, J., Ferrada, C., Ferre, S., Fuxe, K., Cortes, A., Ciruela, F., Lluis, C. and Canela, E.I. Molecular Pharmacology, February 24, 2006, Epubmed ahead of print, PMID 16501032.

Nicotine Pre-exposure Does Not Potentiate the Locomotor or Rewarding Effects of delta-9-tetrahydrocannabinol in Rats This study assessed the effects of nicotine pre-exposure on subsequent locomotor and rewarding effects of repeated Delta-9-tetrahydrocannabinol administration in Sprague-Dawley rats. Repeated administration of the same dose of Delta-9-tetrahydrocannabinol (0.01-2 mg/kg) did not produce significant tolerance or behavioral sensitization to Delta-9-tetrahydrocannabinol's locomotor effects. An unbiased place conditioning paradigm was then used to obtain a measure of the rewarding effects of Delta-9-tetrahydrocannabinol. Rats received an injection of either Delta-9-tetrahydrocannabinol (0.01-2 mg/kg) before being placed in one compartment (three trials) or saline before being placed in the other compartment (three trials) of a two-compartment apparatus. Control rats received saline injections associated with both compartments. Significant conditioned place preferences developed with 0.1 mg/kg Delta-9-tetrahydrocannabinol in control rats, but not in nicotine pre-exposed rats. Surprisingly, significant place aversions developed at higher 1 and 2 mg/kg doses of Delta-9-tetrahydrocannabinol in nicotine pre-exposed rats. To the extent that behavioral sensitization may reflect reward processes in drug dependence, the lack of behavioral sensitization on repeated Delta-9-tetrahydrocannabinol administration is consistent with the difficulties usually encountered in demonstrating rewarding or reinforcing effects of Delta-9-tetrahydrocannabinol in rats. The present findings suggest, moreover, that nicotine pre-exposure alters the qualitative nature of rewarding effects and accentuates aversive effects of Delta-9-tetrahydrocannabinol. Le Foll, B., Wiggins, M. and Goldberg, S.R. Behavioral Pharmacology, 17, pp. 195-199, 2006.,/p>

Presynaptic Control of Striatal Glutamatergic Neurotransmission by Adenosine A1-A2A Receptor Heteromers The functional role of heteromers

of G-protein-coupled receptors is a matter of debate. In the present study, IRP researchers demonstrate that heteromerization of adenosine A1 receptors (A1Rs) and A2A receptors (A2ARs) allows adenosine to exert a fine-tuning modulation of glutamatergic neurotransmission. By means of coimmunoprecipitation, bioluminescence and time-resolved fluorescence resonance energy transfer techniques, authors showed the existence of A1R-A2AR heteromers in the cell surface of cotransfected cells. Immunogold detection and coimmunoprecipitation experiments indicated that A1R and A2AR are colocalized in the same striatal glutamatergic nerve terminals. Radioligand-binding experiments in cotransfected cells and rat striatum showed that a main biochemical characteristic of the A1R-A2AR heteromer is the ability of A2AR activation to reduce the affinity of the A1R for agonists. This provides a switch mechanism by which low and high concentrations of adenosine inhibit and stimulate, respectively, glutamate release. Furthermore, it is also shown that A1R-A2AR heteromers constitute a unique target for caffeine and that chronic caffeine treatment leads to modifications in the function of the A1R-A2AR heteromer that could underlie the strong tolerance to the psychomotor effects of caffeine. Ciruela, F., Casado, V., Rodrigues, R.J., Lujan, R., Burgueno, J., Canals, M., Borycz, J., Rebola, N., Goldberg, S.R., Mallol, J., Cortes, A., Canela, E.I., Lopez-Gimenez, J.F., Milligan, G., Lluis, C., Cunha, R.A., Ferre, S. and Franco, R. Journal of Neuroscience, 26, pp. 2080-2087, 2006.

Stimulation of Adenosine Receptors Selectively Activates Gene Expression in Striatal Enkephalinergic Neurons In the striatum, adenosine A(2A) and dopamine D(2) receptors exert reciprocal antagonistic interactions that modulate the function of GABAergic enkephalinergic neurons. We have previously shown that stimulation of adenosine A(1) receptors allows the stimulation of A(2A) receptors to overcome a tonic inhibitory effect of D(2) receptors and induce striatal expression of c-fos. In the present work, by studying co-localization of c-Fos immunoreactivity and preproenkephalin and preprodynorphin transcripts, IRP scientists show that co-administration of the A(1) receptor agonist CPA and the A(2A) receptor agonist CGS 21680 increases the striatal expression of c-fos in GABAergic enkephalinergic but not in GABAergic dynorphinergic neurons. Co-administration of CPA and CGS 21680 also induced a significant increase in the striatal expression of preproenkephalin. The results underscore the role of adenosine in the activation of gene expression in the GABAergic enkephalinergic neuron. Karcz-Kubica, M., Ferre, S., Diaz-Ruiz, O., Quiroz-Molina, C., Goldberg, S.R., Hope, B.T. and Morales, M. Neuropsychopharmacology, February 1, 2006, Epubmed ahead of print, PMID 16452987.

Role of Adenosine in the Control of Homosynaptic Plasticity in Striatal Excitatory Synapses Long-lasting, activity-dependent changes in synaptic efficacy at excitatory synapses are critical for experience-dependent synaptic plasticity. Synaptic plasticity at excitatory synapses is determined both presynaptically by changes in the probability of neurotransmitter release, and postsynaptically by changes in the availability of functional postsynaptic glutamate receptors. Two kinds of synaptic plasticity have been described. In homosynaptic or Hebbian plasticity, the events responsible for synaptic strengthening occur at the same synapse as is being strengthened. Homosynaptic plasticity is activity-dependent and associative, because it associates the firing of a postsynaptic neuron with that of the presynaptic neuron. Heterosynaptic plasticity, on the other hand, is activity-independent and the synaptic strength is modified as a result of the firing of a third, modulatory neuron. It has been suggested that long-term changes in synaptic strength, which are associated with gene transcription, can only be induced with the involvement of heterosynaptic plasticity. The neuromodulator adenosine plays an elaborated pre- and postsynaptic control of glutamatergic neurotransmission. This paper reviews the evidence suggesting that in some striatal excitatory synapses, adenosine can provide the heterosynaptic-like modulation essential for stabilizing homosynaptic plasticity without the need of

a "third, modulatory neuron". Ferre, S., Borycz, J., Goldberg, S.R., Hope, B.T., Morales, M., Lluis, C., Franco, R., Ciruela, F. and Cunha, R. J Journal of Integrative Neuroscience, 4, pp. 445-464, 2005.

Antidepressant-like Activity and Modulation of Brain Monoaminergic Transmission by Blockade of Anandamide Hydrolysis Although anecdotal reports suggest that cannabis may be used to alleviate symptoms of depression, the psychotropic effects and abuse liability of this drug prevent its therapeutic application. The active constituent of cannabis, delta9-tetrahydrocannabinol, acts by binding to brain CB1 cannabinoid receptors, but an alternative approach might be to develop agents that amplify the actions of endogenous cannabinoids by blocking their deactivation. Here, IRP researchers show that URB597, a selective inhibitor of the enzyme fatty-acid amide hydrolase, which catalyzes the intracellular hydrolysis of the endocannabinoid anandamide, exerts potent antidepressant-like effects in the mouse tail-suspension test and the rat forced-swim test. Moreover, URB597 increases firing activity of serotonergic neurons in the dorsal raphe nucleus and noradrenergic neurons in the nucleus locus ceruleus. These actions are prevented by the CB1 antagonist rimonabant; are accompanied by increased brain anandamide levels; and are maintained upon repeated URB597 administration. Unlike direct CB1 agonists, URB597 does not exert rewarding effects in the conditioned place preference test or produce generalization to the discriminative effects of delta9-tetrahydrocannabinol in rats. The findings support a role for anandamide in mood regulation and point to fatty-acid amide hydrolase as a previously uncharacterized target for antidepressant drugs. Proceedings of the National Adademy of Sciences USA, 102, pp. 18620-18625, 2005.

Metabolic Transformation Plays a Primary Role in the Psychostimulant-like Discriminative-stimulus Effects of Selegiline l-Deprenyl [selegiline, (R)-(-)-deprenyl] is a selective inhibitor of monoamine oxidase B (MAO-B) used in the treatment of Parkinson's disease and proposed as an antidepressant and an aid for cigarette-smoking cessation and treatment of psychostimulant abuse. Beneficial therapeutic effects of (R)-(-)-deprenyl may also result from indirect actions. Brain levels of dopamine and beta-phenylethylamine (beta-PEA), a behaviorally active endogenous trace amine, increase after (R)-(-)-deprenyl treatment due to MAO-B blockade and (R)-(-)-deprenyl is metabolized to (R)-(-)-methamphetamine and (R)-(-)-amphetamine, suggesting that (R)-(-)-deprenyl may have psychostimulant-like behavioral effects. Indeed, (R)-(-)-deprenyl produces psychostimulant-like discriminative-stimulus effects in experimental animals. Here, IRP scientists tested the hypothesis that psychostimulant-like behavioral effects of (R)-(-)-deprenyl are mainly mediated by its metabolites. Male Fisher F344 rats were trained to discriminate i.p. injection of 1.0 mg/kg (S)-(+)-methamphetamine or 10.0 mg/kg cocaine from injection of saline using two-lever choice schedules of food delivery or stimulus shock termination. When (R)-(-)-deprenyl was tested by substitution, it had (S)-(+)-methamphetamine- and cocaine-like discriminative-stimulus effects, but only at doses of 10 to 30 mg/kg, doses 10 to 20 times higher than those selective for MAO-B inhibition. Ro 16-6491 [N-(2-aminoethyl)-4-chlorobenzamide hydrochloride], a selective inhibitor of MAO-B enzyme activity without psychoactive metabolites, had no psychostimulant-like discriminative effects. In addition, blockade of (R)-(-)-deprenyl's metabolism with SKF 525A (beta-DEAE-diphenylpropylacetate hydrochloride; 50 mg/kg i.p.) reduced or eliminated (R)-(-)-deprenyl's psychostimulant-like discriminative effects. When beta-PEA synthesis was blocked by NSD 1015 (m-hydroxy-benzyl-hydrazine; 30 mg/kg i.p.), there was a modest reversal of (R)-(-)-deprenyl's psychostimulant-like discriminative effects under some conditions, indicating a facilitatory modulation of the psychostimulant-like discriminative effects of (R)-(-)-deprenyl metabolites by elevated levels of beta-PEA under certain conditions. Yasar, S., Justinova, Z., Lee, S.H., Stefanski, R., Goldberg, S.R. and Tanda, G. Journal of Pharmacology and Experimental Therapeutics, 317, pp.

387-394, 2006.

Treatment Section, Clinical Pharmacology and Therapeutics Research Branch

Assessment of Cannabis Craving Using the Marijuana Craving Questionnaire Cannabis is the most widely used illicit drug in the United States with 14.6 million current users. Cannabis-dependent individuals presenting for treatment typically report cannabis craving; however, the phenomenon has received little research attention. In the absence of a valid, multidimensional questionnaire to assess cannabis craving, IRP scientists developed the Marijuana Craving Questionnaire (MCQ). The MCQ consists of four constructs or factors that characterize cannabis craving: compulsivity, emotionality, expectancy, and purposefulness. A separate score is calculated for each factor. The MCQ can be used to measure cue-elicited craving in a research setting or natural craving in cannabis-dependent individuals presenting for treatment. Either the 47-item or 12-item version can be used, and standardized instructions for completion of the MCQ should be given. The MCQ can be administered using a paper and pencil form or a computerized version. In a research setting, the MCQ should be administered immediately after cue presentation and repeated frequently to capture the full time course. In a treatment setting, the MCQ should be administered at intake and during and at the end of treatment. Heishman, S.J. and Singleton, E.G. Methods in Molecular Medicine: Marijuana and Cannabinoid Research: Methods and Protocols, pp. 209-216. Totowa, NJ: Humana Press, 2006.

Methods for Clinical Research Involving Cannabis Administration Better scientific understanding of cannabis effects and the development of treatments for cannabis dependence require clinical studies involving cannabis administration. Cannabis can be administered by smoking a plant-derived cigarette or by oral or intravenous administration of D9-tetrahydrocannabinol (THC), the primary psychoactive chemical in cannabis. The smoked route is most commonly used outside the laboratory, but is subject to wide variation in absorbed dose. Oral synthetic THC is a legally marketed medication (dronabinol) also subject to wide pharmacokinetic variation, but offering a greater safety margin because of slower onset of action and lower potency. Intravenous THC offers precise investigator control of dose and timing. Acute adverse effects of cannabis administration include tachycardia, orthostatic hypotension, pulmonary irritation (if smoked), motor incoordination, cognitive impairment, anxiety, paranoia, and psychosis. Screening of research subjects should identify and exclude those with risk factors for such events, e.g., a history of significant cardiovascular, pulmonary, or psychiatric disorders. Monitoring of subjects during cannabis administration should include heart rate, blood pressure, and mental status. Subjects should not be discharged from research participation until reevaluation has shown that they have returned to baseline status. Gorelick, D.A. and Heishman, S.J. Methods in Molecular Medicine: Marijuana and Cannabinoid Research: Methods and Protocols, pp. 235-254. Totowa, NJ: Humana Press, 2006.

Chemistry and Drug Metabolism Section, Clinical Pharmacology and Therapeutics Research Branch

Smoking Rates and Topography Predict Adolescent Smoking Cessation Following Treatment with Nicotine Replacement Therapy Smoking puff topography predicts adolescent tobacco cessation outcome. IRP scientists examined the predictive value of pre-treatment smoking rates and puff topography variables for abstinence outcomes among 66 adolescents enrolled in a three-month smoking-cessation trial using nicotine replacement and cognitive-behavioral therapy. Pre-treatment variables included cigarettes per day, puff volume, puff duration, and several youth-adapted Fagerstršm-derived

questionnaire scores. Outcome measures included prolonged abstinence at end of treatment and point-prevalent abstinence three months after the end of the trial. Logistic regression controlling for treatment group showed that increases in baseline cigarettes per day (OR=1.438, 95% CI 1.051-1.967) and average puff volume (OR=1.168, 95% CI 1.030-1.326) predicted continued smoking at the end of treatment. Baseline puff volume (p=0.013), but not CPD, predicted abstinence at the three-month follow-up. None of the youth-adapted Fagerstršm dependence questionnaires predicted outcome with either abstinence measure. Franken, F.H., Pickworth, W.B., Epstein, D.H. and Moolchan, E.T. Cancer Epidemiology, Biomarkers and Prevention, 15, pp. 154-157, 2006.

Director's Report to the National Advisory Council on Drug Abuse - May, 2006

Program Activities

New NIDA PAs and RFAs

On March 8, 2006, NIDA issued a Program Announcement (PA) entitled **Cutting-Edge Basic Research Awards (CEBRA) (R21) (PAR-06-209)**. The NIDA CEBRA award is designed to foster highly innovative or conceptually creative research related to drug abuse and addiction and how to prevent and treat them, and to support research that is high risk and potentially high impact that is underrepresented or not included in NIDA's current portfolio.

On March 31, 2006, NIDA issued a Program Announcement (PA) entitled **Drug Abuse Aspects of HIV/AIDS and Other Infections (R21) (PA-06-309)**. This PA is intended to support Exploratory/Developmental research projects that address drug abuse aspects of HIV/AIDS, other blood-borne and sexually transmitted infections, and TB in men and women, adolescents and adults, and in majority and minority populations.

On March 31, 2006, NIDA issued a Program Announcement (PA) entitled **Drug Abuse Aspects of HIV/AIDS and Other Infections (R03) (PA-06-310)**. This PA is intended to support small research projects that address drug abuse aspects of HIV/AIDS, other blood-borne and sexually transmitted infections, and TB in men and women, adolescents and adults, and in majority and minority populations.

On March 30, 2006, NIDA issued a Program Announcement entitled **Behavioral Science Track Award for Rapid Transition (B/START) (R03) (PA-06-300)**. This PA seeks to facilitate the entry of beginning investigators into the field of behavioral science research related to drug abuse. To be appropriate for a B/START award, research must be primarily focused on behavioral processes and research questions.

On March 31, 2006, NIDA issued a Program Announcement entitled **Imaging-Science Track Award for Rapid Transition (I/START) (R03) (PA-06-311)**. This PA seeks to facilitate the entry of investigators to the area of neuroimaging, including both new investigators and established investigators seeking to adopt neuroimaging methodologies in their research programs.

On April 5, 2006, NIDA issued a Program Announcement (PA) entitled **Drug Abuse Prevention Intervention Research (R21) (PA-06-317)**. The goals of this PA are to encourage exploratory/developmental research projects of cognitive, behavioral and social processes as they relate to: 1) the development of novel drug abuse prevention approaches; 2) the efficacy and effectiveness of newly developed and/or modified prevention programs; 3) the processes associated with the selection, adoption, adaptation, implementation, sustainability, and financing of empirically validated interventions; and 4) methodologies appropriate for studying complex aspects of prevention science.

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Staff Highlights

Grantee Honors

On April 5, 2006, NIDA issued a Program Announcement (PA) entitled **Drug Abuse Prevention Intervention Research (R03) (PA-06-318)**. The goals of this PA are to encourage pilot/feasibility research projects of cognitive, behavioral and social processes as they relate to: 1) the development of novel drug abuse prevention approaches; 2) the efficacy and effectiveness of newly developed and/or modified prevention programs; 3) the processes associated with the selection, adoption, adaptation, implementation, sustainability, and financing of empirically validated interventions; and 4) methodologies appropriate for studying complex aspects of prevention science.

On April 5, 2006, NIDA issued a Program Announcement (PA) entitled **Inhalant Abuse: Supporting Broad-Based Research Approaches (R21) (PA-06-327)**. The goal of this PA is to encourage research on all aspects of inhalant abuse (i.e., epidemiology; prevention, treatment and service delivery; antecedents, consequences and neurobiological mechanisms).

On April 5, 2006, NIDA issued a Program Announcement (PA) entitled **Inhalant Abuse: Supporting Broad-Based Research Approaches (R03) (PA-06-328)**. The goal of this PA is to encourage research on all aspects of inhalant abuse (i.e., epidemiology; prevention, treatment and service delivery; antecedents, consequences and neurobiological mechanisms).

On April 6, 2006, NIDA issued a Program Announcement (PA) entitled **Women, Sex/Gender Differences and Drug Abuse (R21) (PA-06-331)**. The purpose of this PA is to encourage sex/gender-based drug abuse research that focuses on the mechanisms, origins and consequences of drug abuse, as well as prevention and treatment interventions and services. It also encourages the study of female-specific issues in all areas of drug abuse.

On April 6, 2006, NIDA issued a Program Announcement (PA) entitled **Women, Sex/Gender Differences and Drug Abuse (R03) (PA-06-332)**. The purpose of this PA is to encourage sex/gender-based drug abuse research that focuses on the mechanisms, origins and consequences of drug abuse, as well as prevention and treatment interventions and services. It also encourages the study of female-specific issues in all areas of drug abuse.

On April 7, 2006, NIDA issued a Program Announcement (PA) entitled **Epidemiology of Drug Abuse (R21) (PA-06-329)**. This PA is intended to support exploratory/developmental research projects that address: 1) drug use patterns and trends within and across populations; 2) interplay of social interactions, social environment, structural context with individual behavioral characteristics and genetic vulnerability; 3) the phenotypic heterogeneity of drug abuse; 4) causal mechanisms leading to onset, maintenance, and remittance of drug abuse, as well as protective mechanisms that reduce the risk of drug abuse; and 5) drug abuse over the life course, including developmental processes that influence drug use trajectories and behavioral, health and social consequences of drug abuse.

On April 7, 2006, NIDA issued a Program Announcement (PA) entitled **Epidemiology of Drug Abuse (R03) (PA-06-330)**. This PA is intended to support small research projects that address: 1) drug use patterns and trends within and across populations; 2) interplay of social interactions, social environment, structural context with individual behavioral characteristics and genetic vulnerability; 3) the phenotypic heterogeneity of drug abuse; 4) causal mechanisms leading to onset, maintenance, and remittance of drug abuse, as well as protective mechanisms that reduce the risk of drug abuse; and 5) drug abuse over the life course, including developmental processes that influence drug use trajectories and behavioral, health and social consequences of drug abuse.

On April 10, 2006, NIDA issued a Program Announcement (PA) entitled

Prescription Drug Abuse (R21) (PA-06-339). The purpose of this PA is to encourage research aimed at reducing prescription drug abuse while supporting appropriate medical use of therapeutic agents with abuse liability. A range of research is needed to combat prescription drug abuse—from specifying the extent and nature of the problem (including health and social consequences) and identifying their determinants, to discovering effective clinical practices that identify those at risk and designing and disseminating prevention and treatment interventions.

On April 10, 2006, NIDA issued a Program Announcement (PA) entitled **Prescription Drug Abuse (R03) (PA-06-340)**. The purpose of this PA is to encourage research aimed at reducing prescription drug abuse while supporting appropriate medical use of therapeutic agents with abuse liability. A range of research is needed to combat prescription drug abuse—from specifying the extent and nature of the problem (including health and social consequences) and identifying their determinants, to discovering effective clinical practices that identify those at risk and designing and disseminating prevention and treatment interventions.

PAs and RFAs Issued With Other NIH Components/Agencies

On February 16, 2006, NIDA, in collaboration with NIMH and NINDS, issued a Program Announcement (PA) entitled **Preclinical Therapeutics Development for NeuroAIDS (R21) (PA-06-139)**. The purpose of this PA is to invite applications proposing novel models of HIV-related central or peripheral nervous system damage that can be used to screen for compounds showing promise as treatments in the patient population. This PA will use the NIH Exploratory/Developmental Grant (R21) award mechanism.

On February 16, 2006, NIDA, in collaboration with NIMH and NINDS, issued a Program Announcement (PA) entitled **Preclinical Therapeutics Development for NeuroAIDS (R03). (PA-06-140)**. The purpose of this PA is to invite applications proposing novel models of HIV-related central or peripheral nervous system damage that can be used to screen for compounds showing promise as treatments in the patient population. This PA will use the NIH Small Research Grant (R03) award mechanism.

On March 2, 2006, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement (PA) entitled **NIH Small Research Grant Program (Parent R03) (PA-06-180)**. The NIH Investigator-Initiated Small Grant (R03) funding opportunity supports small research projects that can be carried out in a short period of time with limited resources. 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.

On March 2, 2006, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement (PA) entitled **NIH Exploratory/Developmental Research Grant Program (Parent R21) (PA-06-181)**. The Exploratory/Developmental Grant (R21) mechanism is intended to encourage exploratory and developmental research projects by providing support for the early and conceptual stages of these projects. These studies may involve considerable risk but may lead to a breakthrough in a particular area, or the development of novel techniques, agents, methodologies, models, or applications that could have a major impact on a field of biomedical, behavioral or clinical research.

On March 3, 2006, NIDA, in collaboration with a number of other NIH components, issued a Program Announcement (PA) entitled **Characterization, Behavior and Plasticity of Pluripotent Stem Cells (R21) (PA-06-198)**.

This PA invites applications for studies on the characterization, behavior and plasticity of human and non-human stem cells, regulation of their replication, differentiation, integration and function in the nervous system, and the identification and characterization of normal and tumor stem cells.

On March 2, 2006, NIDA, in collaboration with a number of other NIH components, issued a Program Announcement (PA) entitled **Health Research with Diverse Populations (R01) (PA-06-218)**. The purpose of this PA is to invite grant applications for biological, behavioral, social, mental health and drug and alcohol abuse research bearing on the health of the lesbian, gay, bisexual, transgender, intersex and related populations. Proposed research should be appropriate for the missions of one or more of the participating Institutes.

On March 8, 2006, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement (PA) entitled **Exploratory Collaborations with National Centers for Biomedical Computing (R21) (PAR-06-223)**. This PA is for projects from individual investigators or small groups to collaborate with the recently-formed NIH Roadmap for Medical Research National Centers for Biomedical Computing (NCBCs).

On March 8, 2006, NIDA, in collaboration with several other NIH Institutes, issued a Program Announcement (PA) entitled **Gene Discovery for Complex Neurological and Neurobehavioral Disorders (R21) (PAS-06-204)**. The goal of this funding opportunity announcment (FOA) is to promote the identification of susceptibility genes for complex neurological and neurobehavioral disorders.

On March 9, 2006, NIDA, in collaboration with a number of other NIH Institutes, issued a Program Announcement (PA) entitled **Interactions Between Stem and Progenitor Cells and the Microenvironment (R03) (PAS-06-207)**. Through this PA, the sponsoring Institutes invite applications for studies on the molecular and cellular signaling between the local environment within organisms and stem and progenitor cells that are either introduced as transplants or are normally resident within host tissues and organs. The objective of this initiative is to promote a thorough exploration and characterization of the bi-directional communication between multipotent cells and the three-dimensional local milieu or niche that they encounter in vivo under normal and compromised states, such as with aging or following injury, disease or drug exposure.

On March 9, 2006, NIDA, in collaboration with a number of other NIH Institutes, issued a Program Announcement (PA) entitled **Interactions Between Stem and Progenitor Cells and the Microenvironment (R21) (PAS-06-208)**. Through this PA, the sponsoring Institutes invite applications for studies on the molecular and cellular signaling between the local environment within organisms and stem and progenitor cells that are either introduced as transplants or are normally resident within host tissues and organs. The objective of this initiative is to promote a thorough exploration and characterization of the bi-directional communication between multipotent cells and the three-dimensional local milieu or niche that they encounter in vivo under normal and compromised states, such as with aging or following injury, disease or drug exposure.

On March 9, 2006, NIDA, in conjunction with several other NIH Institutes, issued a Program Announcement (PA) entitled **International Neuroscience Fellowship (F05) (PAR-06-227)**. The goal of this International Neuroscience Fellowship Program is to provide a unique opportunity to qualified foreign neuroscientists, at junior or mid-career level, to receive one to two years of research training in the United States.

On March 10, 2006, NIDA, in collaboration with numerous other NIH

components, issued a Program Announcement (PA) entitled **Research on Social Work Practice and Concepts in Health (R03) (PA-06-233)**. This funding opportunity announcement (FOA) issued by the Office of Behavioral and Social Sciences Research solicits Small Research Grant (R03) applications from organizations/institutions that propose to develop empirical research on social work practice, concepts, and theory as they relate to the NIH public health goal of improving health outcomes for persons with medical and behavioral disorders and conditions.

On March 10, 2006, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement (PA) entitled **Research on Social Work Practice and Concepts in Health (R21) (PA-06-234)**. This funding opportunity announcement (FOA) issued by the Office of Behavioral and Social Sciences Research solicits Exploratory/Developmental Research Grant (R21) applications from organizations/institutions that propose to develop empirical research on social work practice, concepts, and theory as they relate to the NIH public health goal of improving health outcomes for persons with medical and behavioral disorders and conditions.

On March 16, 2006, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement (PA) entitled **Research on Sleep and Sleep Disorders (R21) (PA-06-238)**. This PA invites submission of grant applications proposing research to advance biomedical knowledge related to sleep or sleep disorders, improve understanding of the neurobiology or functions of sleep over the lifespan, enhance timely diagnosis and effective treatment for individuals affected by sleep-related disorders, or implement and evaluate innovative community-based public health education and intervention programs.

On March 17, 2006, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement (PA) entitled **Community Participation in Research (R21) (PA-06-247)**. The ultimate goal of this PA is to support research on health promotion, disease prevention, and health disparities that is jointly conducted by communities and researchers.

On March 17, 2006, NIDA, in collaboration with NIMH and NIAAA, issued a **Program Announcement entitled Mechanism for Time-Sensitive Research Opportunities (R03) (PAR-06-249)**. This PA is intended to support mental health and/or substance abuse services research, as well as broader based alcohol or drug abuse research in rapidly evolving areas (e.g., changes in service systems, health care financing, policy, etc.) where opportunities for empirical study are, by their very natures, only available through expedited award of support.

On March 24, 2006, NIDA, in collaboration with a number of other NIH Institutes, issued a Program Announcement (PA) entitled **Neurotechnology Research, Development, and Enhancement (R21) (PA-06-278)**. This funding opportunity announcement (FOA) for Exploratory/Developmental (R21) grant applications seeks to enable neuroscience and behavioral research by soliciting research and development of novel, or significant enhancement of existing, tools and approaches to be used in brain and behavioral research.

On March 24, 2006, NIDA, in collaboration with a number of other NIH Institutes, issued a Program Announcement (PA) entitled **Neurotechnology Research, Development, and Enhancement (R01) (PA-06-279)**. This PA seeks to enable neuroscience and behavioral research by soliciting research and development of novel, or significant enhancement of existing, tools and approaches to be used in brain and behavioral research.

On March 24, 2006, NIDA, in collaboration with NINDS and NIMH, issued a Program Announcement entitled **Non-Human Lentiviral Models of the Neurological Complications of AIDS (R03) (PAS-06-275)**. This PA invites

research grant applications aimed at developing non-human lentiviral in-vivo model systems for study of the neurologic complications of AIDS, without without a history of drug use.

On March 24, 2006, NIDA, in collaboration with NINDS and NIMH, issued a Program Announcement entitled **Non-Human Lentiviral Models of the Neurological Complications of AIDS (R21) (PAS-06-276)**. This PA invites research grant applications aimed at developing non-human lentiviral in-vivo model systems for study of the neurologic complications of AIDS, without without a history of drug use.

On March 29, 2006, NIDA, in conjunction with a number of other NIH components, issued a Program Announcement (PA) entitled **Understanding Mechanisms of Health Risk Behavior Change in Children and Adolescents (R21) (PA-06-298)**. This PA invites research grant applications that will enhance our understanding of the factors and mechanisms that determine changes in health risk behaviors during childhood and adolescence. Interdisciplinary research is sought to explore the biological, genetic, physiological, psychological, and social/environmental factors and mechanisms that influence health risk behavior change in children and adolescents.

On March 29, 2006, NIDA, in conjunction with a number of other NIH components, issued a Program Announcement (PA) entitled **Centers for AIDS Research: D-FAR, C-FAR (P30) (PAR-06-291)**. This PA solicits applications for the Centers for AIDS Research (CFAR) program to provide administrative and shared research support to enhance AIDS research. CFARs provide core facilities, expertise, resources, and services not readily obtained otherwise through more traditional funding mechanisms.

On March 31, 2006, NIDA, in collaboration with a number of other NIH components, issued a Program Announcement (PA) entitled **The Effect of Racial and Ethnic Discrimination/Bias on Health Care Delivery (R21) (PA-06-306)**. The purposes of this PA are 1) to improve the measurement of racial/ethnic discrimination in health care delivery systems through improved instrumentation, data collection, and statistical/analytical techniques; 2) to enhance understanding of the influence of racial/ethnic discrimination in health care delivery and its association with disparities in disease incidence, treatment and outcomes among disadvantaged racial/ethnic minority groups; and 3) to reduce the prevalence of racial/ethnic health disparities through the development of interventions to reduce the influence of racial/ethnic discrimination of health care delivery systems in the United States.

On March 31, 2006, NIDA, in collaboration with a number of other NIH components, issued a Program Announcement (PA) entitled **The Effect of Racial and Ethnic Discrimination/Bias on Health Care Delivery (R03) (PA-06-348)**. The purposes of this PA are 1) to improve the measurement of racial/ethnic discrimination in health care delivery systems through improved instrumentation, data collection, and statistical/analytical techniques; 2) to enhance understanding of the influence of racial/ethnic discrimination in health care delivery and its association with disparities in disease incidence, treatment and outcomes among disadvantaged racial/ethnic minority groups; and 3) to reduce the prevalence of racial/ethnic health disparities through the development of interventions to reduce the influence of racial/ethnic discrimination of health care delivery systems in the United States.

On March 31, 2006, NIDA and NIAAA issued a joint Program Announcement entitled **Health Services Research on the Prevention and Treatment of Drug and Alcohol Abuse (R21) (PA-06-307)**. This PA solicits health services research on the prevention and treatment of drug and alcohol abuse. Proposed research might emphasize any of the following subjects: 1) Factors that affect the delivery of drug and alcohol abuse intervention and related services, such as social factors, personal behaviors and attributes, financing,

organization, management and health technologies; 2) Dimension of drug and alcohol abuse intervention and related services, such as accessibility, utilization, quality, effectiveness and costs; 3) Processes of blending science-based practices into community-based provision of drug and alcohol abuse prevention services; and 4) Research tools to facilitate higher quality health services research on drug and alcohol abuse.

On March 31, 2006, NIDA and NIAAA issued a joint Program Announcement entitled **Health Services Research on the Prevention and Treatment of Drug and Alcohol Abuse (R03) (PA-06-308)**. This PA solicits health services research on the prevention and treatment of drug and alcohol abuse. Proposed research might emphasize any of the following subjects: 1) Factors that affect the delivery of drug and alcohol abuse intervention and related services, such as social factors, personal behaviors and attributes, financing, organization, management and health technologies; 2) Dimension of drug and alcohol abuse intervention and related services, such as accessibility, utilization, quality, effectiveness and costs; 3) Processes of blending science-based practices into community-based provision of drug and alcohol abuse prevention services; and 4) Research tools to facilitate higher quality health services research on drug and alcohol abuse.

On April 5, 2006, NIDA and NIAAA issued a joint Program Announcement (PA) entitled **Economics of Prevention and Treatment Services for Drug and Alcohol Abuse (R21) (PA-06-319)**. This PA solicits research projects 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, including health insurance and/or payment mechanisms; 2) alternative delivery systems and managed care; 3) cost-benefit, cost-effectiveness, or cost-utility analyses; 4) service costs and production; and 5) methodological research.

On April 5, 2006, NIDA and NIAAA issued a joint Program Announcement (PA) entitled **Economics of Prevention and Treatment Services for Drug and Alcohol Abuse (R03) (PA-06-320)**. This PA solicits research projects 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, including health insurance and/or payment mechanisms; 2) alternative delivery systems and managed care; 3) cost-benefit, cost-effectiveness, or cost-utility analyses; 4) service costs and production; and 5) methodological research.

On April 5, 2006, NIDA, in collaboration with NCI, issued a Program Announcement (PA) entitled **Cross-Disciplinary Translational Research at NIH (R21) (PA-06-321)**. The purpose of this PA is to foster research that furthers the translation of existing knowledge into treatment and treatment practice, or research that, in and of itself, will readily translate to clinical research or practice. This PA is intended to encourage projects that provide tools and resources that serve as platforms for the development of effective prevention and treatment strategies.

On April 5, 2006, NIDA, in collaboration with NCI, issued a Program Announcement (PA) entitled **Cross-Disciplinary Translational Research at NIH (R03) (PA-06-322)**. The purpose of this PA is to foster research that furthers the translation of existing knowledge into treatment and treatment practice, or research that, in and of itself, will readily translate to clinical research or practice. This PA is intended to encourage projects that provide tools and resources that serve as platforms for the development of effective prevention and treatment strategies.

On April 5, 2006, NIDA, in collaboration with NIMH and the NIH Office of Dietary Supplements (ODS), issued a Program Announcement (PA) entitled **Psychopharmacology of Widely Available Psychoactive Nature Products**

(R03) (PA-06-323). This PA will support research grant applications that characterize the chemistry, psychopharmacology, and/or toxicology of acute and chronic exposure to psychoactive natural products, as well as the transition in the use of these products to licit or illicit drugs of abuse.

On April 7, 2006, NIDA, in collaboration with NCI and NIAAA, issued a Program Announcement (PA) entitled **Decision Making in Health: Behavior Maintenance (R21) (PA-06-337)**. The purpose of this initiative is to invite applications for research projects that will expand our knowledge of basic decision-making processes underlying initiation and long-term maintenance of healthy lifestyle behaviors that may reduce one's risk of cancer and other chronic diseases, such as cardiovascular disease, diabetes, and addiction.

On April 12, 2006, NIDA, in collaboration with NICHD, issued a Program Announcement (PA) entitled **The Science and Ecology of Early Development (SEED) (R03) (PA-06-345)**. This PA invites research grant applications that seek to develop a comprehensive program of research focused on the mechanisms through which social, economic, cultural and community-level factors, and their interactions, impact the early cognitive, neurobiological, socio-emotional, and physical development of children.

On April 13, 2006, NIDA, in collaboration with NIMH and NIAAA, issued a Program Announcement (PA) entitled **Building Translational Research in Integrative Behavioral Science (R21) (PAR-06-355)**. This PA is intended to encourage the development of translational research partnerships between scientists who study basic behavioral processes and those who study the etiology, diagnosis, treatment, and prevention of mental and behavioral disorders (including alcohol and drug use disorders) and the delivery of services to those suffering from those disorders.

On April 13, 2006, NIDA, in collaboration with NIMH and NIAAA, issued a Program Announcement (PA) entitled **Building Translational Research in Integrative Behavioral Science (R01) (PAR-06-356)**. This PA is intended to encourage the development of translational research partnerships between scientists who study basic behavioral processes and those who study the etiology, diagnosis, treatment, and prevention of mental and behavioral disorders (including alcohol and drug use disorders) and the delivery of services to those suffering from those disorders.

On April 13, 2006, NIDA, in collaboration with NIMH and NIAAA, issued a Program Announcement (PA) entitled **Building Translational Research in Integrative Behavioral Science (R24) (PAR-06-357).** This PA is intended to encourage the development of translational research partnerships between scientists who study basic behavioral processes and those who study the etiology, diagnosis, treatment, and prevention of mental and behavioral disorders (including alcohol and drug use disorders) and the delivery of services to those suffering from those disorders.

On April 14, 2006, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement (PA) entitled **Methodology and Measurement in the Behavioral and Social Sciences (R21) (PA-06-343)**. The goal of this PA 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.

On April 14, 2006, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement (PA) entitled **Methodology and Measurement in the Behavioral and Social Sciences (R031) (PA-06-344)**. The goal of this PA 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.

On April 18, 2006, NIDA, in collaboration with NCI, issued a Program Announcement (PA) entitled **Testing Tobacco Products Promoted to Reduce Harm (R21) (PA-06-361)**. The purpose of this PA is to stimulate multidisciplinary research on potential reduced-exposure tobacco products, both smoked and smokeless, through the interplay of basic, biological, behavioral, surveillance, and epidemiology research.

On April 21, 2006, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement (PA) entitled **NIH Clinical Trial Planning Grant Program (R34) (PA-06-363)**. The purpose of this PA is to provide support for the development of a Phase III clinical trial. This includes the establishment of the research team, the development of tools for data management and oversight of the research, the definition of recruitment strategies, and the finalization of the protocol and other essential elements of the study included in a manual of operations/procedures.

On April 25, 2006, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement (PA) entitled **Research on Ethical Issues In Human Subjects Research (R03)(PA-06-367)**. Through this PA the NIH invites research grant applications to investigate ethical issues in human subjects research.

On April 25, 2006, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement (PA) entitled **Research on Ethical Issues In Human Subjects Research (R21)(PA-06-368)**. Through this PA the NIH invites research grant applications to investigate ethical issues in human subjects research.

On April 25, 2006, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement (PA) entitled **Research on Ethical Issues In Human Subjects Research (R01)(PA-06-369)**. Through this PA the NIH invites research grant applications to investigate ethical issues in human subjects research.

On March 3, 2006, NIDA, in collaboration with NIMH and NINDS, issued an RFA entitled **Institutional Research Training Programs: Increasing Diversity (T32) (RFA-MH-07-030)**. Through this RFA, sponsoring Institutes request competing renewal applications from the current grant recipients of RFA-MH-01-009, Institutional Training Programs: Increaing Diversity which were funded in FY 2002. The goal of the Increasing Diversity T32 program is to help ensure that a diverse pool of highly trained scientists is available in adequate numbers and in appropriate research areas to address the Nation's biomedical, behavioral, and clinical research needs in research areas relevant to NIMH, and/or NIDA, and/or NINDS.

Other Program Activities

The Division of Pharmacotherapies and Medical Consequences of Drug Abuse, with support from the NIDA OSPC, arranged for the participation of NIDA as an exhibitor at both the joint meeting of Screening Europe and MedChem Europe in Prague (February 20-22, 2006) and at the PharmaDiscovery meeting in Rockville (May 10-12, 2006). These meetings provided opportunities for NIDA/pharmaceutical company discussions at the NIDA booth related to ongoing and future collaborations.

CTN Update

A total of 26 protocols and surveys have been initiated since 2001. A total of 11,585 participants were screened and 7,056 enrolled in studies as of April 7, 2006. Of these studies, 12 have completed enrollment and locked the data; seven completed enrollment and are in the follow-up phase; four are currently enrolling; two will begin enrollment within the next month, and one is in the

protocol development phase.

Twelve protocols have locked the data:
Protocol CTN 0001, Buprenorphine/Naloxone versus Clonidine for Inpatient Opiate Detoxification

Protocol CTN 0002, Buprenorphine/Naloxone versus Clonidine for Outpatient Opiate Detoxification

Protocol CTN 0003, Bup/Nx: Comparison of Two Taper Schedules

Protocol CTN 0004, MET (Motivational Enhancement Treatment) To Improve Treatment Engagement and Outcome in Subjects Seeking Treatment for Substance Abuse

Protocol CTN 0005, MI (Motivational Interviewing) To Improve Treatment Engagement and Outcome in Subjects Seeking Treatment for Substance Abuse

Protocol CTN 0006, Motivational Incentives for Enhanced Drug Abuse Recovery: Drug Free Clinics

Protocol CTN 0007, Motivational Incentives for Enhanced Drug Abuse Recovery: Methadone Clinics

Protocol CTN 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 0016, Patient Feedback: A Performance Improvement Study in Outpatient Addiction Treatment

Seven protocols have ended enrollment and are in the follow-up phase:
Protocol CTN 0010 (Buprenorphine/Naloxone Facilitated Rehabilitation for Opioid Dependent Adolescents/Young Adults) began enrollment in July 2003. Recruitment ended January 31, 2006.

Protocol CTN 0015 (Women's Treatment for Trauma and Substance Use Disorder: A Randomized Clinical Trial) began in March 2004. The study reached its enrollment target in October 2005, and follow-up continues until fall 2006.

Protocol CTN 0017 (HIV and HCV Intervention in Drug Treatment Settings). The study began enrollment in November 2004 and enrolled at eight community treatment sites across five Nodes. Enrollment ended in February 2006; follow-up will be complete in summer 2006.

Protocol CTN 0018 (Reducing HIV/STD Risk Behaviors: A Research Study for Men in Drug Abuse Treatment) began enrolling in April 2004 and reached its target enrollment in September 2005. Follow-up will be complete in summer 2006.

Protocol CTN 0019 (Reducing HIV/STD Risk Behaviors: A Research Study for Women in Drug Abuse Treatment) began enrollment in May 2004 and reached its target in October 2005. Follow-up will continue until fall 2006.

Protocol CTN 0020 (Job Seekers Training for Substance Abusers). The protocol began enrollment in October 2004 and reached its enrollment target in February 2006. This study is also being conducted in a Navajo American Indian

site, the Na'nizhoozhi Center, Inc. in Gallup, New Mexico, the first CTN study to be conducted there. Follow-up will continue through August 2006.

Protocol CTN 0021 (Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome for Spanish-Speaking Individuals Seeking Treatment for Substance Abuse) began enrollment in November 2003 and reached its target goal in October 2005, and will complete the follow-up phase this spring. This is the first Spanish-only protocol in the CTN.

Four protocols are currently enrolling:
Protocol CTN 0013 (Motivational Enhancement Therapy to Improve Treatment Utilization and Outcome In Pregnant Substance Abusers) began enrollment in November 2003 and has enrolled 96% of the projected target enrollment with 193 randomized participants.

Protocol CTN 0014, Brief Strategic Family Therapy for Adolescent Drug Abusers (BSFT), has been implemented at eight sites. The study has reached 63% enrollment. There currently are a total of 301 randomized participants.

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). Enrollment began March 17, 2006 in three sites; eight more sites should begin enrollment in June 2006.

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). This study is being carried out at six community treatment sites across five Nodes. Enrollment began at three sites in November 2005. There are a total of 22 randomized participants. Two participants have completed the active treatment phase and are currently in follow-up.

Two protocols will begin enrollment spring 2006:
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). Implementation is planned for April 2006 and will include nine sites. The National Protocol Training was held in Gaithersburg, MD on March 27-28, 2006. The first randomization is anticipated to take place on April 24, 2006. A genetics component was included in this study.

Protocol CTN 0030, Prescription Opioid Addiction Treatment Study (POATS) is a randomized 2-phase, open-label, multi-center study in outpatient treatment settings. Implementation is planned for May 2006 and will be carried out in 12 sites. The National Protocol Training Meeting was held in Gaithersburg, MD on March 29-31, 2006.

One protocol is in the development phase:
Protocol CTN 0031, Twelve-Step Facilitation: Evaluation of an Intervention to Improve Substance Abuse Treatment Outcomes by Increasing 12-Step Involvement.

In addition to the primary CTN trials, there are currently 11 funded studies supported by independent grants that use CTN studies as a platform.

NIDA's New and Competing Continuation Grants Awarded Since May 2006

Abrams, Donald I. -- University of California San Francisco
Opioid and Cannabinoid Pharmacokinetic Interactions

Altice, Frederick L. -- Yale University
Improving Health Outcomes for Released HIV+ Prisoners

Anand, Rene -- Louisiana State University Health Science Center, New Orleans
Proteomics of Nicotinic Receptor Complexes

Anderson, Kristen G. -- University of California, San Diego
Cognitions in Youth Substance Use Relapse Contexts

Angulo, Jesus A. -- Hunter College
Methamphetamine and the Striatal Nk-1 Receptors

Barker, Eric L. -- Purdue University West Lafayette
Psychostimulant Recognition by Serotonin Transporters

Beckham, Jean C. -- Duke University
The Effect of Smoking on Startle & PPI In PTSD

Blendy, Julie A. -- University of Pennsylvania
Molecular Genetic Analysis of Drug Addiction

Bouhamdan, Mohamad -- Wayne State University
Rgs9-2 Protein: Novel Partners and Functional Roles

Boutros, Nashaat N. -- Wayne State University
Cortical Excitability In Cocaine-Dependent Subjects

Buch, Shilpa J. -- University of Kansas Medical Center
HIV-Encephalitis and Cocaine Abuse: Mechanism of Synergy and Therapy

Burdzovic-Andreas, Jasmina -- Harvard University Medical School
Substance Use In Adolescents From High-Risk Neighborhoods: Risk and Protection

Chamberlain, Patricia -- Oregon Social Learning Center, Inc.
Preventing Behavior and Health Problems In Foster Teens

Chang, Sulie L. -- Seton Hall University
Opiate's Effects on the Inflammation and Cytotoxicity In HIV-1 Transgenic Rat

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Development of the Basal Telencephalic Limbic System

Cravatt, Benjamin F. -- Scripps Research Institute
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Davies, Robert D. -- University of Colorado Denver/Health Science Center, Aurora
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Deleo, Joyce A. -- Dartmouth College
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Epperson, Cynthia N. -- Yale University
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Evans, Suzette M. -- New York State Psychiatric Institute
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Effects of Self-Administered MDMA on Brain and Behavior In Rhesus Monkeys

Feelisch, Martin -- Boston University Medical Campus
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Fendrich, Michael -- University of Wisconsin Milwaukee
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Filizola, Marta -- Weill Medical College of Cornell University
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Gewirtz, Jonathan C. -- University of Minnesota Twin Cities
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Gordon, Judith S. -- Oregon Research Institute
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Greengard, Paul -- Rockefeller University
Drugs of Abuse -- Role of Protein Phosphorylation

Grigson, Patricia S. -- Pennsylvania State University Hershey Medical Center
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Rogers, Thomas J. -- Temple University
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Roman, Paul M. -- University of Georgia
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Rotrosen, John P. -- New York University School of Medicine
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Rowe, Cynthia L. -- University of Miami-Medical
Family-Based Drug Services For Young Disaster Victims

Rutherford, Megan J. -- University of Washington
Factors Related To Juvenile Drug Court Completion

Ryan, Andrea K. -- Pennsylvania State University, University Park
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Samet, Jeffrey H. -- Boston Medical Center
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Scheiffele, Peter -- Columbia University Health Sciences
Regulation of Growth and Pruning of Neuronal Arbors

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Schneider, Jay S. -- Thomas Jefferson University
Nicotine and Cognition In Parkinsonism

Schrott, Lisa M. -- Louisiana State University Health Sciences Center, Shreveport
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Traynor, John R. -- University of Michigan at Ann Arbor
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Wu, Z. Helen -- University of Texas Medical Branch, Galveston
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Yamamoto, Bryan K. -- Boston University Medical Campus
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Zald, David H. -- Vanderbilt University
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Director's Report to the National Advisory Council on Drug Abuse - May, 2006

Extramural Policy and Review Activities

Receipt, Referral, and Review

NIDA received 1594 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 934 applications.

OEA arranged and managed 17 grant review meetings in which 386 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 14 contract proposal reviews and 2 concept reviews and 144 applications to the Loan Repayment Program.

NIDA's chartered committees consist of NIDA-E (Treatment Review Committee), NIDA-F (Health Services Review Committee), NIDA-L (Medications Development Committee), and NIDA-K (Training Committee). In addition to meetings of each of these committees, OEA staff held 13 Special Emphasis Panels for a variety of reasons:

Conflicts with the chartered committees
Center Grant Applications
The Minority Institutions' Drug Abuse Research Development Program (MIDARP)
Program Project Grant applications
Mechanism For Time-Sensitive Research Opportunities
Behavioral Science Track Award for Rapid Transition (B/START)
Cutting Edge Basic Research Awards (CEBRA)
Imaging Science Track Awards for Research Transition (I/START)
Conference Grants (R13)
Loan Repayment Programs
1 Special Emphasis Panel that reviewed RFA submissions

OEA managed the following RFA reviews:

- DA06-001: Enhancing Practice Improvement In Community-Based Care for Prevention and Treatment of Drug Abuse or Co-Occurring Drug Abuse and Mental Disorders

Completed Contract Reviews from the Contracts Review Branch since the last Council are as follows:

Contract Reviews (R&D and non-R&D)

Phase I SBIR Reviews

Staff Highlights

Grantee Honors

- N43DA-6-7758 (Topic 064): Nanoscience-based Design of Therapies for Substance Abuse Treatment
- N43DA-6-1127 (Topic 076): Development of Science Literacy Materials or Programs
- N43DA-6-4404 (Topic 077): Development of Serious Games for Neuro-Rehabilitation of Drug-Induced Cognitive Deficiencies
- N43DA-6-4405 (Topic 078): E-Health Applications of Empirically Supported Therapies in English and/or Spanish
- N43DA-6-5533 (Topic 079): Development of State-of-the-Art Mechanisms for Epidemiological Research
- N43DA-6-5534 (Topic 080): Training and Infrastructure Development for Community Coalitions
- N43DA-6-8862 (Topic 082): Development of Novel Drug Delivery Systems for Treatment of Drug Addictions
- N43DA-6-1128 (Topic 084): Develop Methods for Stimulating International Collaborations

Phase II SBIR Reviews

- N44DA-6-5531 (Topic 028): Dissemination of an Evidence-based Drug Prevention Program for High School Health Providers (NHPA)
- N44DA-6-1121 (Topic 029): Simulations for Drug Related Science Education
- N44DA-6-5530 (Topic 073): Online Buprenorphine Practice Manager for Physicians
- N44DA-6-1124 (Topic 070): International DA Research E-Learning
- N44DA-6-1126 (Topic 029): Science Education for Deaf High School Students
- N44DA-6-7754 (Topic 075): Wearable Wireless PDA Peripheral

R&D Concept Reviews

- N01DA-6- 8867: Pharmacokinetic and Pharmacodynamic Studies for Medication Development
- N01DA-6-8859: Preclinical Medication Discovery and Abuse Liability Testing for NIDA

Certificates of Confidentiality

Dr. Paul Coulis manages the processing of Certificates of Confidentiality. Between December 13, 2005 and April 27, 2006, 119 new certificates, 41 extensions, and 17 amendments were processed.

Extramural Outreach

Dr. Eliane Lazar-Wesley, OEA, presented "The Grant Application Enterprise at the NIH" to the NIDA INVEST Drug Abuse Research Fellows (NIDA International Program) on March 3, 2005.

Dr. Meenaxi Hiremath, OEA, participated in several NIH-wide meetings dealing with the use of public/consumer members participating on peer review activities.

Dr. Levitin, Director, OEA, continues to serve as the NIDA liaison to the NIH Director's Pioneer Award Implementation Committee, one of the NIH Roadmap activities.

In March 2006, Dr. Levitin co-chaired two discussion hours at the biennial

meeting of the Society for Research on Adolescence: 1) Get Schooled: NIDA Funding for Adolescent Research and 2) NIH Research Grants 101: A Survival Guide for Application, Referral, and Review.

Dr. Levitin has accepted an appointment to the Society for Research on Adolescence Social Policy Committee.

Dr. Levitin continues to serve on various committees related to her membership on the NIH-wide Extramural Program Management Committee (EPMC). For example, she is currently assisting in the development of a plan to evaluate the CSR pilot study on shortening the review cycle for new investigators and is on the Multiple-Principal Investigator Initiative evaluation committee.

Dr. Gerald McLaughlin, OEA, serves as the NIDA Liaison to the NIH-wide committee dealing with all aspects of the transition to electronic grant submission. He presented a talk on this topic to the 2006 HMO Research Network Conference. He is also a member of the trans-NIH workgroup tasked with implementing the electronic transition of the R01 and U01 grant mechanisms.

Dr. Gerald McLaughlin is a member of the trans-NIH workgroup that addresses issues related to public or community members in peer review meetings, and attended a COPR meeting in which related issues were discussed with the NIH OD.

Dr. Gerald McLaughlin is a member of the trans-NIH workgroup to improve technologies and SOP's associated with contract-provided reviewer lodging and review meeting room arrangements. He is also the NIDA representative to this group's parent trans-NIH PSA Review User Group transition team.

Ms. Loretta Beuchert, OEA, serves on a trans-NIH workgroup responsible for implementing the time line for electronic receipt of applications and working out procedures for converting existing grant mechanisms into the electronic 424 format.

Dr. Mark Green, OEA, serves on the NIH-wide Contingency Planning Workgroup dealing with electronic submission of grant applications.

Dr. Mark Green serves on the NIH-wide workgroup developing the transition of the R18 and R25 grant mechanisms to electronic submission format.

Dr. Mark Green presented an overview of the grant receipt, referral and review process as well as issues in electronic submission of grant applications, on April 19, 2006 at the NIDA Research Training Institute, in Bethesda, Maryland.

Staff Training and Development

The OEA Symposium Series, a forum for staff training and sharing of ideas and information, continued through the winter and spring. Topics addressed have included presentations on the new Pathway to Independence Awards and the NIH initiative to have multiple principal investigators on grants.

Other Activities

Dr. Gerald McLaughlin participates in the D.C. area Iowa Alumni Club. In 2006 he represented the University of Iowa at two College Fairs in the greater Washington DC area.

The Data and Safety Monitoring Board (DSMB) conducted a review on February 3, 2006 via teleconference. The board reviewed the performance of two study protocols: Protocol CTN 0013 (Motivational Enhancement Therapy to Improve

Treatment Utilization and Outcome In Pregnant Substance Abusers) and Protocol CTN 0014 (Brief Strategic Family Therapy for Adolescent Drug Abusers -BSFT).

Director's Report to the National Advisory Council on Drug Abuse - May, 2006

Congressional Affairs (Prepared May 8, 2006)

BUDGET FY 2007

The FY 2007 program level for the NIH is $28.587 million, the same as the FY 2006 program level. The President's Budget Request for NIDA for FY 2007 is $994,829,000, a **decrease** of $5.2 million, or .5%, from the FY 2006 enacted level.

HEARINGS, BRIEFINGS, AND EVENTS OF INTEREST

House Hearing on Drug Abuse Treatment in the Criminal Justice System

On February 8, 2006, the House Judiciary Subcommittee on Crime, Terrorism, and Homeland Security held a hearing titled **"An Examination of Drug Treatment Programs Needed to Ensure Successful Re-Entry."** This hearing was designed in part to assist the committee as it considers legislation such as H.R. 1704, the Second Chance Act, which focuses on the need for addiction treatment services for individuals in correctional facilities and in the community.

Witness testimony was provided to the Subcommittee by NIDA Director Dr. Nora Volkow; Ken Batten, Director of the Office of Substance Abuse Services at the Virginia Department of Mental Health, Mental Retardation & Substance Abuse Services; Pamela Rodriguez, Executive Vice President of Treatment Alternatives for Safe Communities (TASC, Inc); and Lorna Hogan, Associate Director of Sacred Authority at The Rebecca Project for Human Rights.

Dr. Volkow spoke to the Subcommittee about addiction as a disease of the brain and how drug addiction affects the decision-making process. Noting the extremely high prevalence of incarcerated individuals in need of drug addiction treatment, Dr. Volkow framed in-prison treatment and aftercare as providing a tremendous opportunity to help individuals to become healthy. Dr. Volkow spoke about the importance of providing aftercare to individuals once they leave incarceration and about how effective drug treatment is in reducing the likelihood that the individual will recidivate.

Prescription Drug Abuse Congressional Briefing Sponsored by the Friends of NIDA

On February 23, 2006, The Friends of NIDA Coalition sponsored a Congressional briefing titled, **"Prescription Drug Abuse - An Emerging Public Health Threat."** The briefing was very well attended by Congressional staff and constituent group representatives, and featured as speakers NIDA Director Dr. Nora Volkow; Dr. Carol Boyd, Director, Institute for Research on

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Staff Highlights

Grantee Honors

Women and Gender, University of Michigan; and Nick, a young man in recovery from prescription drug abuse.

Dr. Volkow reviewed the extent of the prescription drug abuse problem in the United States; the impact nonmedical use of prescription drugs has on the brain; and NIDA's agenda to further research and understand all of these issues to help develop prevention and treatment approaches. Dr. Volkow's presentation is available at http://www2.apa.org/ppo/volkow22306.ppt.

Dr. Boyd focused her presentation on surveys regarding the nonmedical use of prescription drugs by secondary and college students. Her presentation is available at http://www2.apa.org/ppo/boyd22306.ppt.

Nick, a young man in recovery from prescription drug abuse, courageously told his compelling story of becoming addicted to Vicodin and OxyContin. He noted that over time, he also became addicted to heroin and found that he no longer recognized his life. Nick also spent time in the criminal justice system and was at one point pronounced dead in an emergency room. At that point, Nick said that he chose to muster his strength to dedicate himself to a treatment regimen that included the medication buprenorphine as an adjunct to counseling. Since then, Nick said that he is growing stronger every day and is appreciative of the opportunity to be an active and important part of society.

Nick was asked to review for the audience core "take home messages." Nick called on a strong investment in prevention programming - from the elementary grades through high school. In addition, he explained that addiction "does not discriminate" and noted that the treatment protocols made possible through the research at NIDA literally saved his life.

Senate Hearing on Methamphetamine in Indian Country

On April 5, 2006, the Senate Indian Affairs Committee held a hearing titled **"The Problem of Methamphetamine in Indian Country."** The hearing focused on the widespread problem of methamphetamine use and addiction in Tribal communities, and featured as witnesses: William Ragsdale, Director of the Bureau of Indian Affairs at the U.S. Department of the Interior; Robert McSwain, Deputy Director of the Indian Health Service; Matthew H. Mead, U.S. Attorney's Office District of Wyoming; Kathleen W. Kitcheyan, Chairwoman of the San Carlos Apache Tribe; Jefferson Keel, First Vice President of the National Congress of American Indians; Gary L. Edwards, Chief Executive Office of the National Native American Law Enforcement Association; and Karrie Azure, Grant Coordinator of the United Tribes Multi-Tribal Indian Drug and Alcohol Initiative.

Witness testimony focused on the severe problem of methamphetamine use and addiction among young people and adults in Tribal communities, and the need for additional support for education, prevention and treatment services. In offering recommendations to the Committee, a number of witnesses spoke in favor of increasing funds for drug use prevention and addiction treatment programs through the Indian Health Service and the Substance Abuse and Mental Health Services Administration, increasing the number of culturally competent programs for Tribal members, and improving the collaboration and coordination among the various Tribal, state and federal agencies.

Senate Hearing on Methamphetamine and Child Welfare System Issues

On April 25, 2006, the Senate Finance Committee held a hearing titled **"The Social and Economic Effects of the Methamphetamine Epidemic on America's Child Welfare System."** The Senate Finance Committee has jurisdiction over Medicaid, Medicare, child welfare financing and the Temporary Assistance to Needy Families (TANF) program.

Witnesses providing testimony to the Committee included: Allison Bruno, a

mother in recovery from addiction to methamphetamine; Aaronette and Darren Noble, parents in recovery from addiction to methamphetamine and their son, Joey Binkley; Kevin T. Frank, Regional Administrator for the Department of Public Health and Human Services, Child and Family Services Division in South Central Montana; Nancy K. Young, Ph.D., Director of Children and Family Futures, Inc. at the National Center on Substance Abuse and Child Welfare; and Reverend Frederick Aigner, Ph.D., President/CEO of Lutheran Social Services of Illinois.

Ms. Bruno and Mr. and Mrs. Noble all spoke about their successful experiences in drug addiction treatment. Each of these panelists noted that the ability for their children to also receive services, and the presence of a comprehensive array of services for all of their family members, were key to their recovery process. Mr. Binkley spoke about his parents becoming healthy through addiction treatment services that were offered to his entire family. In response to a question by Senator Grassley on availability of treatment, Ms. Bruno spoke about waiting lists and particularly the number of women with families who are trying to get into treatment programs that also provide comprehensive services to their family members. Ms. Noble spoke about the importance of services to support individuals in recovery. Mr. Noble spoke about the need for treatment to be more accessible, and about the need to educate parents about addiction so that they can see the signs and help their children. In response to a question by Senator Baucus about the importance of prevention programming, Ms. Bruno emphasized that school-based prevention programs are critical to educating young people about how drugs affect and harm the body.

Dr. Young spoke about how, although emphasis has been placed on fighting methamphetamine, the problems with addiction in the United States are not a single-drug issue. In discussing the need for drug treatment services, Dr. Young cited the extremely high number of people who need such services but are not able to receive them. In response to a question from Senator Grassley about the large number of women who use and become addicted to methamphetamine, Dr. Young spoke about the need to understand that trauma, abuse and domestic violence are often significant factors and that addressing these needs with addiction treatment and mental health services is critical. In his comments, Mr. Frank emphasized that addiction to methamphetamine and other drugs affects people across socio-economic lines. Mr. Frank also spoke of the importance of education and awareness efforts about the dangers of methamphetamine and other drugs, and of the importance of collaboration between community agencies and groups. Reverend Aigner spoke about the need for additional resources to support drug addiction treatment programs, particularly in rural parts of his state of Illinois, so that individuals receiving treatment services could remain in treatment for longer periods of time where appropriate. Discussing the child welfare system and the role of methamphetamine, Reverend Aigner spoke about the need for addiction counselors to work on child welfare services teams and for more training money to be provided to assist children of people with addiction histories.

Materials from this hearing, including webcast and full witness testimony and Committee member statements, can be found at: http://finance.senate.gov/hearings/hearing/?id=4a8416cc-bdb9-86e6-ffa4-96fbcf5236a2.

PASSED BILLS OF INTEREST — 109th Congress

H.R. 3 - This law was originally introduced by Representative Young (R-AK) as the "Transportation Equity Act: A Legacy for Users," a bill to authorize funds for federal aid for highways, highway safety programs, and transit programs. The original House version of this bill included language (Section 2013 "Drug Impaired Driving Research and Prevention Act") that would require the

development of a model statute for States relating to drug impaired driving. The model would include threshold levels of impairment for a controlled substance; methods for detecting the presence of controlled substances; and penalties for drug impaired driving. It would be based on recommendations contained in a report to be developed by NIH and submitted to Congress not later than 18 months after the date of enactment. The final version of the law maintains the requirements for model statute development, and for a report to be developed on the problem of drug-impaired driving. The Secretary of Transportation will develop the report, "in cooperation with the National Institutes of Health." The President signed the bill into law (109-59) on August 10, 2005.

H.R. 2520/S. 1317 - On December 20, 2005 the President signed into law, as Public Law 109-129, the Stem Cell Therapeutic and Research Act of 2005. H.R. 2520 passed the House on May 24, 2005. An amended version passed the Senate on December 16, 2005 and the House on December 17, 2005. The bill does not have a direct impact on NIH. It would require the Secretary of HHS, acting through the Director of the Health Resources and Services Administration, to establish the C.W. Bill Young Cell Transplantation Program, a network of cord blood banks to facilitate the use of cord blood for transplantation purposes. Cord blood units that are collected, but not appropriate for clinical use, would be required to be made available for peer-reviewed research.

H.R. 3199 - On March 2, 2006, the full Senate approved the conference report for H.R. 3199, the USA PATRIOT and Terrorism Prevention Reauthorization Act of 2005. The House of Representatives approved the final legislative package on March 8, 2006. Provisions from the "Combat Meth Act," the "Drug Courts Improvement Act," and "The Meth Epidemic Elimination Act" were included in the legislation, which was signed into law (P.L. 109-177) by the President on March 9, 2006.

This law imposes federal regulations on the sale of products containing pseudoephedrine by requiring stores to keep medications with pseudoephedrine behind the counter and by requiring purchasers of the medication to show photo identification and sign a log. In addition, individuals are restricted from buying more than 3.6 grams per day and 9 grams per month of pseudoephedrine. The law does not preclude states from adopting or enforcing regulations or penalties more strict than those in the federal law.

The law also creates a sentencing enhancement for individuals convicted of manufacturing, distributing, or possessing with the intent to manufacture or distribute, methamphetamine on a premises where children reside. Under this provision, in addition to any other sentence imposed, another sentence of imprisonment for a period up 20 years, a fine or both would be applied. The Attorney General is authorized under the bill to award grants to States, territories, and American Indian tribes to address use of methamphetamine among pregnant and parenting women in the criminal justice system by facilitating or enhancing collaboration between the criminal justice, child welfare and State substance abuse systems.

S. 45/H.R. 869 - Senator Carl Levin (D-MI) in the Senate and Representative Mark Souder (R-IN) in the House introduced identical bills to amend the Controlled Substances Act to lift the patient limitation on prescribing drug addiction treatments by medical practitioners in group practices, and for other purposes. Both the House and Senate passed their bills and the President signed it into law (P.L. 109-56) on August 2, 2005. This law will impact practices that prescribe buprenorphine products for treatment of opiate addiction, making the medication available to more patients across the country.

S. 518/H.R. 1132 - Senator Sessions (R-AL) in the Senate and Representative Whitfield (R-KY) in the House introduced identical bills, the

"National All Schedules Prescription Electronic Reporting Act of 2005." This law (P.L. 109-60) will provide for the establishment of a controlled substance monitoring program in each State; it was signed by the President on August 11, 2005.

H.R. 2829 - On March 9, 2006, the House passed this bill, legislation to reauthorize the Office of National Drug Control Policy (ONDCP). The bill enhances certain current ONDCP functions, and does not address the banning and testing for anabolic steroids in professional sports. A number of amendments to the legislation were offered during consideration on the House floor. Successful amendments to the original bill text will:

- Require the ONDCP Director to complete an assessment of report materials, studies, and statistics to determine the extent to which children who are 12 to 17 years of age (a) experiment with and regularly use marijuana, alcohol, cigarettes, prescription drugs without a prescription, designer drugs such as ecstasy, other illicit drugs such as cocaine, and (b) have access to intervention services or programs, including drug testing, counseling, rehabilitation, legal representation and other services or programs associated with prevention, treatment and punishment of substance abuse.
- Require the ONDCP Director to submit to Congress a comprehensive strategy that addresses the increased threat from methamphetamine.
- Require the ONDCP Director to provide for a corporation to (a) advise States on establishing laws and policies to address alcohol and other drug issues, based on the model State drug laws developed by the President's Commission on Model State Drug Laws in 1993, and (b) revise such model State drug laws and draft supplementary model State laws to take into consideration changes in the alcohol and drug abuse problems in the State involved.
- Require the ONDCP Director to request the Institute of Medicine to conduct a study to examine certain aspects of addiction to prescription drugs such as OxyContin.
- Require the ONDCP Director to conduct a study on drug court programs that conduct hearings in nontraditional public places such as schools.
- Direct the ONDCP Director, in consultation with the Secretary of State, the Attorney General, the Secretary of Homeland Security, the Secretary of Health and Human Services, and the United States Trade Representative, to seek to convene an international summit on the threat of methamphetamine and synthetic drug precursors.

H. Res. 556 - On April 6, 2006, the House passed a resolution stating that (1) a National Methamphetamine Prevention Week should be established to increase awareness of methamphetamine and educate the public on effective ways to help prevent methamphetamine use at the international, Federal, State, and local levels; and (2) the people of the United States and interested groups should be encouraged to observe National Methamphetamine Prevention Week with appropriate ceremonies and activities.

BILLS OF INTEREST - SENATE

[For the full text and additional information about any bill, go to the Library of Congress website at http://thomas.loc.gov]

S. 103 - Senator Talent (R-MO) introduced on January 24, 2005 the "Combat Meth Act of 2005," a bill to respond to the illegal production, distribution, and use of methamphetamine in the United States, and for other purposes. See above, H.R. 3199, for final disposition.

S. 259 - Senator Johnson (D-SD) introduced on February 2, 2005 a bill to require that federal forfeiture funds be used, in part, to clean up

methamphetamine laboratories. Committee: Judiciary.

S. 399 - Senators Coleman (R-MN) and Feinstein (D-CA) introduced on February 16, 2005 the Internet Pharmacy Consumer Protection Act, to amend the Federal Food, Drug, and Cosmetic Act with respect to the sale of prescription drugs through the Internet, and for other purposes. Committee: Health, Education, Labor, and Pensions.

S. 408 - Senator DeWine (R-OH) introduced on February 16, 2005 the "STOP Underage Drinking Act." In part, the bill would authorize the Director of ONDCP to award "enhancement grants" to eligible entities to design, test, evaluate and disseminate strategies to maximize the effectiveness of community-wide approaches to preventing and reducing underage drinking. Committee: Health, Education, Labor and Pensions. Related Bills: See H.R. 864.

S. 521 - Senator Hutchison (R-TX) introduced on March 3, 2005 the "Hepatitis C Epidemic Control and Prevention Act," a bill to amend the Public Health Service Act to direct the Secretary HHS to establish, promote, and support a comprehensive prevention, research, and medical management referral program for hepatitis C virus infection. Committee: Health, Education, Labor and Pensions. Related Bills: See H.R. 1290.

S. 537 - Senator Bingaman (D-NM) introduced on March 7, 2005 the "Child Healthcare Crisis Relief Act" a bill to increase the number of well-trained mental health service professionals (including those based in schools) providing clinical mental health care to children and adolescents, and for other purposes. Committee: Health, Education, Labor and Pensions. Related Bills: See H.R. 1106.

S. 538 - Senator Biden (D-DE) introduced on March 7, 2005 the "Health Professionals Substance Abuse Education Act." In introductory remarks, he explained that the bill would do three things for each of the fiscal years 2006 thru 2010: (1) authorize $9 million in grants to train medical generalists to recognize substance abuse and know properly how to refer patients and their families for treatment; (2) authorize $6 million to fund a faculty fellowship program at educational institutions to teach courses on substance abuse, incorporate substance abuse issues into required courses, and educate health professionals about matters involving non-therapeutic uses of prescription medications; and (3) authorize $6 million to establish centers of excellence at medical centers or universities to initiate and implement training, research and clinical activities related to special focal areas of substance abuse, and provide opportunities for interdisciplinary collaboration in curriculum development, clinical practice, research and policy analysis. Committee: Health, Education, Labor and Pensions.

S. 550 - On September 21, 2005, former Senator John Corzine (D-NJ) introduced S. 550, the Microbicide Development Act, to facilitate the development of microbicides for preventing transmission of HIV and other diseases, and for other purposes. Research provisions would require the Director of the NIH Office of AIDS Research to: 1) expedite implementation of a Federal microbicide research and development strategic plan, 2) expand, intensify and coordinate the relevant activities of appropriate NIH research components, and 3) prepare and submit, within six months of enactment and annually thereafter, a report to Congress on Federal microbicide research implementation strategies. The bill would also require the Director of NIAID to establish a microbicide development unit within its Division of AIDS. The measure also contains provisions for relevant activities at the CDC and the U.S. Agency for International Development. Committee: Health, Education, Labor and Pensions. Related bill: H.R. 3854.

S. 666 - Senator DeWine (R-OH) introduced on March 17, 2005 the "Family Smoking Prevention and Tobacco Control Act," a bill to protect the public health

by providing the FDA with certain authority to regulate tobacco products. Committee: Health, Education, Labor and Pensions.

S. 803 - Senators Norm Coleman (R-MN) and Hillary Rodham Clinton (D-NY) introduced on April 14, 2005 the "Help Expand Access to Recovery and Treatment Act of 2005," to provide parity with respect to substance abuse treatment benefits under group health plans and health insurance coverage. Committee: Health, Education, Labor and Pensions. Related Bills, see H.R. 1258.

S. 884 - Senator Cantwell (D-WA) introduced on April 25, 2005 the "Methamphetamine and Identity Theft Study Act of 2005," instructing the Attorney General to conduct a study evaluating whether there is a connection between the commission of crimes involving methamphetamine and the commission of identity theft crimes. Committee: Judiciary.

S. 927 - Former Senator Corzine (D-NJ) introduced on April 27, 2005 the "Medicare Mental Health Modernization Act of 2005," which would amend Title XVIII of the Social Security Act to expand and improve coverage of mental health services under the Medicare program. Committee: Finance. Related Bills: See H.R. 1946.

S. 1051 - Senator Dodd (D-CT) introduced on May 17, 2005 the "Children and Family HIV/AIDS Research and Care Act of 2005," to amend the Public Health Service Act to reauthorize and extend certain programs to provide coordinated services and research with respect to children and families with HIV/AIDS. Committee: Health, Education, Labor, and Pensions.

S. 1332 - On June 29, 2005, Senator Arlen Specter (R-PA) introduced S. 1332, the Personal Data Privacy and Security Act of 2005. Of specific interest to NIH, the measure would prohibit the display, sale or purchase of Social Security numbers (SSNs) to third parties without an individual's informed consent. Exemptions are included for public health and research conducted for the purpose of advancing public knowledge. Researchers would be required to provide adequate assurances that the SSNs will not be used inappropriately, and that there are safeguards to protect the privacy and confidentiality of any information about individuals. S. 1332, which has two cosponsors, was placed on the Senate Legislative Calendar under General Orders.

S. 1334 - On June 29, 2005, Senator Bunning (R-KY) introduced the "Professional Sports Integrity and Accountability Act," to provide for integrity and accountability in professional sports. In late September, the Commerce, Science and Transportation Committee held a hearing to discuss the bill. Committees: Finance; Commerce, Science and Transportation.

S. 1436 - On July 20, 2005, Senator Mike DeWine (R-OH) introduced S. 1436, the Campus-Based Underage Alcohol Use Reduction Act. The bill would require the Secretary of Education to award grants to reduce the rate of underage alcohol use and binge drinking among students at institutions of higher education. Committee: Health, Education, Labor, and Pensions.

S. 1722 - On September 19, 2005, Senator Lisa Murkowski (R-AK) introduced S. 1722, the "Advancing FASD Research, Prevention, and Services Act." This legislation would amend the Public Health Service Act to reauthorize and extend the Fetal Alcohol Syndrome prevention and services program. S. 1722 would require the Secretary of Health and Human Services, acting through the Director of the National Institutes of Health and in coordination with the Interagency Coordinating Committee on Fetal Alcohol Syndrome to establish a research agenda for Fetal Alcohol Spectrum Disorders (FASD) and award grants, contracts, or cooperative agreements to public or private nonprofit entities to pay all or part of carrying out research under such agenda. Committee: Health, Education, Labor, and Pensions. Related bill HR 4272.

S. 1934 - On October 27, 2005, several cosponsoring Senators introduced the "Second Chance Act of 2005: Community Safety Through Recidivism Prevention." of 2005," which would reauthorize the grant program of the Department of Justice for reentry of offenders into the community, to establish a task force on Federal programs and activities relating to the reentry of offenders into the community, and for other purposes. Committee: Judiciary. Related bill: see H.R.1704.

S. 1960 - On November 3, 2005, Senator Jim Bunning (R-KY) introduced S. 1960, the Integrity in Professional Sports Act, to protect the health and safety of all athletes, to promote the integrity of professional sports by establishing minimum standards for the testing of steroids and other performance-enhancing substances and methods by professional sports leagues, and for other purposes. Status: Placed on Senate legislative calendar under general orders.

S. 1974 - On November 8, 2005, Senator Bill Nelson (D-FL) introduced S. 1974, the Drug Free Varsity Sports Act of 2005. The bill would provide states with the resources needed to rid our schools of performance enhancing drug use. Committee: Health, Education, Labor, and Pensions.

S. 2046 - On November 17, 2005, Senator Mike DeWine (R-OH) introduced S. 2046, the National Methamphetamine Information Clearinghouse Act of 2005, to establish a National Methamphetamine Information Clearinghouse to promote sharing information regarding successful law enforcement, treatment, environmental, social services, and other programs related to the production, use, or effects of methamphetamine and grants available for such programs, and for other purposes. Committee: Judiciary.

S. 2104 - On December 14, 2005, Senator Joseph Lieberman (D-CT) introduced the "American Center for Cures Act of 2005," to amend the Public Health Service Act to establish the American Center for Cures to accelerate the development of public and private research efforts towards tools and therapies for human diseases with the goal of early disease detection, prevention, and cures. Specific aims of this proposed legislation are to: 1) expedite translational research and 2) implement some recommendations from the 2003 NAS study entitled "Enhancing the Vitality of the National Institutes of Health: Organizational Change to Meet New Challenges." Committee: Health, Education, Labor, and Pensions.

S. 2315 - On February 16, 2006, Senator Burns (R-MT) introduced the "Methamphetamine Awareness and Prevention Act of 2006," to amend the Public Health Service Act to establish a federally-supported education and awareness campaign for the prevention of methamphetamine use. Committee: Health, Education, Labor, and Pensions.

S. 2560 - On April 6, 2006, Senator Specter (R-PA) introduced the "Office of National Drug Control Policy Reauthorization Act of 2006" to authorize and enhance the operations of the Office of National Drug Control Policy. The bill as introduced differs significantly from its related House bill (H.R. 2829). Committee: Judiciary.

S. 2643 - On April 25, 2006, Senator Bingaman (D-NM) introduced the "Native American Methamphetamine Enforcement and Treatment Act of 2006," To amend the Omnibus Crime Control and Safe Streets Act of 1968 to clarify that Indian tribes are eligible to receive grants for confronting the use of methamphetamine. Committee: Judiciary.

S. 2695 - On May 2, 2006, Senators Cornyn (R-TX) and Lieberman (D-CT) introduced the "Federal Research Public Access Act of 2006," which would require every Federal agency with an annual extramural research budget of $100 million or more to implement a public access policy that is consistent with

and advances purposes of the Federal agency. The bill requires that articles resulting from Federally funded research be deposited in a public archive and made available no later than six months after publication in a peer-reviewed journal. Committee: Homeland Security and Governmental Affairs.

S. Res. 313 - On November 15, 2005, Senator Cantwell (D-WA) introduced a resolution expressing the sense of the Senate that a National Methamphetamine Prevention Week should be established to increase awareness of methamphetamine and to educate the public on ways to help prevent the use of that damaging drug. Committee: Judiciary. Related bill: H.Res. 556 (passed the House April 6)

S. Res. 462 - On May 3, 2006, Senator Grassley (R-IA) introduced a resolution "designating June 6, 2006 as the day of a National Vigil for Lost Promise, to call public attention to the tremendous promise which has been lost with the deaths of those affected by drugs.

BILLS OF INTEREST - HOUSE

H.R. 240 - Representative Pryce (R-OH) introduced on January 4, 2005 the "Personal Responsibility, Work, and Family Promotion Act of 2005." The bill, which would extend welfare legislation, was approved by the Ways and Means Committee's Human Resources Subcommittee on March 15, 2005. The subcommittee amended the bill to cut federal welfare funding to any state that does not drug test those applying for or receiving welfare benefits. No state currently drug tests welfare recipients. In fact, a 2003 ruling by a federal appeals court that covers the states of Kentucky, Michigan, Ohio, and Tennessee ruled that states cannot drug test welfare recipients because it is unconstitutional. Those states, and many others, could lose federal funding if the drug testing provision makes it into law. Status: pending at House Financial Services.

H.R. 314 - Representative Blunt (R-MO) introduced on January 25, 2005 the "Combat Meth Act of 2005," a bill to respond to the illegal production, distribution, and use of methamphetamine in the United States, and for other purposes. See H.R. 3199 above, under "Passed Bills of Interest."

H.R. 370 - Representative Bilirakis (R-FL) introduced on January 26, 2005 the "Biomedical Research Assistance Voluntary Option Act," a bill to amend the Internal Revenue Service Code to allow taxpayers to designate part or all of any income tax refund be paid for use in biomedical research conducted through the NIH. Committees: Energy and Commerce, Subcommittee on Health; Ways and Means.

H.R. 798 - Representative Gordon (D-TN) introduced on February 16, 2005 the "Methamphetamine Remediation Research Act of 2005," a bill to provide for a research program for remediation of closed methamphetamine production laboratories, and for other purposes. Committee: Science, Subcommittee on Environment, Technology, and Standards. Status: passed by the House. Pending in the Senate (Environment and Public Works).

H.R. 812 - Representative Cummings (D-MD) introduced on February 16, 2005 the "Dawson Family Community Protection Act," a bill to amend the Office of National Drug Control Policy Reauthorization Act of 1998 to ensure that adequate funding is provided for certain high intensity drug trafficking areas. Committees: Government Reform; Energy and Commerce. The text of this bill was included in the Office of National Drug Control Policy Reauthorization Act of 2005 (H.R. 2829) which passed the House on March 9).

H.R. 864 - Representative Roybal-Allard (D-CA) introduced on February 16, 2005 a bill to provide for programs and activities with respect to the prevention of underage drinking. Committee: Energy and Commerce, Subcommittee on

Health. Related Bills: See S. 408.

H.R. 1020 - Representative Rogers (R-MI) introduced on March 1, 2005 a bill to declare adequate pain care research, education, and treatment as national public health priorities, and for other purposes. In part the bill would establish within NIH a center to be known as the National Center for Pain and Palliative Care Research. Committees: Energy and Commerce, Subcommittee on Health; Veterans Affairs, Subcommittee on Health; Ways and Means; Armed Services.

H.R. 1054 - Representative Green (R-WI) introduced on March 2, 2005 the "Tools for Community Initiatives Act," which would establish an Office of Faith Based and Community Initiatives in the Executive Office of the President. Committee: Government Reform.

H.R. 1055 - Representative Hooley (D-OR) introduced on March 2, 2005 the "Comprehensive Methamphetamine Response Act," a bill to provide for the designation and funding of high intensity methamphetamine abuse and trafficking areas. Committees: Energy and Commerce, Subcommittee on Health; Judiciary. Related bill: see H.R. 3199 above, under "Passed Bills of Interest."

H.R. 1056 - Representative Hooley (D-OR) introduced on March 2, 2005 the "Methamphetamine Precursor Control Act of 2005," a bill to amend the Controlled Substances Act with respect to the distribution of pseudoephedrine. Section 7 of the bill would authorize funding for NIH to conduct research on medical alternatives to pseudoephedrine. Committees: Energy and Commerce, Subcommittee on Health; Judiciary. Related bill: See H.R. 3199 above, under "Passed Bills of Interest."

H.R. 1106 - Representative Kennedy (D-RI) introduced on March 3, 2005 the "Veterans Medical Research Assistance Voluntary Option Act of 2005," a bill to increase the number of well-trained mental health service professionals (including those based in schools) providing clinical mental health care to children and adolescents, and for other purposes. Committees: Energy and Commerce, Subcommittee on Health; Ways and Means. Related Bills: See S.537.

H.R. 1258 - Representative Ramstad (R-MN) introduced on March 10, 2005 the "Time for Recovery and Equal Access to Treatment in America (TREAT America) Act, a bill to amend the Employee Retirement Income Security Act of 1974, PHSA and the IRS Code of 1986 to provide parity with respect to substance abuse treatment benefits under group health plans and health insurance coverage. Committees: Energy and Commerce, Subcommittee on Health; Education and Workforce, Subcommittee on Employer-Employee Relations; Ways and Means. Related Bills: See S. 803.

H.R. 1290 - Representative Wilson (R-NM) introduced on March 14, 2005 the "Hepatitis C Epidemic Control Prevention Act," to require the Secretary of Health and Human Services to establish, promote, and support a comprehensive prevention, research, and medical management referral program for hepatitis C virus infection. The bill also would require the Director of NIH to establish a Liver Disease Research Advisory Board, which would be charged with developing a Liver Disease Research Plan. Committee: Energy and Commerce, Subcommittee on Health. Related Bills: See S. 521.

H.R. 1350 - Representative Peterson (D-MN) introduced on March 16, 2005 the "Methamphetamine Blister Pack Loophole Elimination Act of 2005," a bill to eliminate the safe-harbor exception for certain packaged pseudoephedrine products used in the manufacture of methamphetamine. Committees: Energy and Commerce, Subcommittee on Health; Judiciary. Related Bills: See H.R. 1446. Related bill: See H.R. 3199 above, under "Passed Bills of Interest."

H.R. 1357 - Representative Weldon (R-FL) introduced on March 17, 2005, the

Human Cloning Prohibition Act of 2005, a bill to prohibit human cloning. Committee: House Judiciary, Subcommittee on Crime, Terrorism, and Homeland Security.

H.R. 1376 - Representative Davis (R-VA) introduced on March 17, 2005 the "Family Smoking Prevention and Tobacco Control Act," a bill to protect the public health by providing the FDA with certain authority to regulate tobacco products. The bill text states that the use of tobacco products by the Nation's children is a pediatric disease of considerable proportions that results in new generations of tobacco-dependent children and adults and that nicotine is an addictive drug. Committee: Energy and Commerce, Subcommittee on Health.

H.R. 1378 - Representative Emerson (R-MO) introduced on March 17, 2005 the "Ephedrine Alkaloids Regulation Act of 2005," a bill to amend the Controlled Substances Act with respect to regulation of ephedrine alkaloids, including ephedrine and pseudoephedrine. The bill states that methamphetamine is a highly addictive drug that can be readily made from products and precursors purchased from retail stores. Committee: Energy and Commerce, Subcommittee on Health. Related bill: See H.R. 3199 above, under "Passed Bills of Interest."

H.R. 1402 - Representative Kennedy (D-RI) introduced on March 17, 2005 the "Paul Wellstone Mental Health Equitable Treatment Act of 2005," a bill to provide for equal coverage of mental health benefits with respect to health insurance coverage unless comparable limitations are imposed on medical and surgical benefits. Committees: Education and the Workforce, Subcommittee on Employer-Employee Relations; Energy and Commerce, Subcommittee on Health.

H.R. 1446 - Representative Souder (R-IN) introduced on March 17, 2005 the "Methamphetamine Abuse Prevention Act of 2005," a bill to eliminate the safe-harbor exception for certain packaged pseudoephedrine products used in the manufacture of methamphetamine, Committees: Energy and Commerce, Subcommittee on Health; Judiciary. Related Bills: See H.R.1350; see H.R. 3199 above, under "Passed Bills of Interest."

H.R. 1528 - Representative James Sensenbrenner (R-WI) introduced on April 6, 2005 the "Defending America's Most Vulnerable: Safe Access to Drug Treatment and Child Protection Act of 2005," which would amend the Controlled Substances Act to protect vulnerable persons from drug trafficking, and for other purposes. Committees: Energy and Commerce, Subcommittee on Health; Judiciary, Subcommittee on Crime, Terrorism and Homeland Security.

H.R. 1639 - Representative DeLauro (D-CT) introduced on April 14, 2005 the "Military Health Services Improvement Act of 2005," which would require pre- and post-deployment mental health screenings for members of the Armed Forces, and for other purposes. Committee: Armed Services.

H.R. 1704 - Representative Portman (R-OH [now resigned from the House]) introduced on April 19, 2005 the "Second Chance Act: Community Safety Through Recidivism Prevention Act of 2005," which would reauthorize the grant program of the Department of Justice for reentry of offenders into the community, to establish a task force on Federal programs and activities relating to the reentry of offenders into the community, and for other purposes. Committees: Judiciary; Education and the Workforce. Related bill: see S. 1934. The most recent hearing on this bill occurred February 8, 2006 (see description, above). The bill is currently undergoing revisions and will be marked up by the Judiciary Committee in the near future.

H.R. 1758 - Representative Andrews (D-NJ) introduced on April 21, 2005 the "Open Air Drug Market Penalty Act of 2005," which would amend the Controlled Substances Act to provide penalties for open air drug markets, and for other

purposes. Committees: Judiciary; Energy and Commerce.

H.R. 1789 - Representative Kennedy (D-RI) introduced on April 21, 2005 the "Health Professionals Substance Abuse Education Act," designed to educate health professionals concerning substance use disorders and addiction. Committee: Energy and Commerce. Related Bill: See S. 538.

H.R. 1862* ** - Representative Stearns (R-FL) introduced on April 26, 2005 the "Drug Free Sports Act," which would direct the Secretary of Commerce to issue regulations requiring testing for steroids and other performance-enhancing substances for certain sports associations engaged in interstate commerce. Committee: Education and Commerce; Education and the Workforce.

H.R. 1946 - Representative Stark (D-CA) introduced on April 27, 2005 the "Medicare Mental Health Modernization Act of 2005," which would amend Title XVIII of the Social Security Act to expand and improve coverage of mental health services under the Medicare program. Committees: Ways and Means; Energy and Commerce. Related Bills: See S. 927.

H.R. 2087 - Representative Frank (D-MA) introduced on May 4, 2005 the "States' Rights to Medical Marijuana Act," which would provide for the medical use of marijuana in accordance with the laws of the various States. Committee: Energy and Commerce.

H.R. 2124 - Representative Weldon (R-FL) introduced on May 5, 2005 the "Clinical Research Act of 2005," which would amend the Public Health Service Act to provide for clinical research support grants, clinical research infrastructure grants, and a demonstration program on partnerships in clinical research, and for other purposes. Committee: Energy and Commerce.

H.R. 2195 - Representative Lynch (D-MA) introduced on May 5, 2005 the "Act to Ban Oxycontin," which would provide for the withdrawal of the drug OxyContin from the commercial market. Committee: Energy and Commerce.

H.R. 2565* ** - Representative Davis (R-VA) on May 24, 2005, introduced the "Office of National Drug Control Policy Reauthorization Act," to reauthorize the Office of National Drug Control Policy Act and to establish minimum drug testing standards for major professional sports leagues. Committees: Government Reform, Energy and Commerce, Education and the Workforce. Related bill: see H.R. 2829 - House leadership chose to move forward with this bill regarding ONDCP reauthorization.

H.R. 3084* ** - On June 28, 2005, Representative Cliff Stearns (R-FL) introduced H.R. 3084, the Drug Free Sports Act of 2005. The bill would direct the Secretary of Commerce to issue regulations requiring testing for steroids and other performance enhancing substances for certain sports associations engaged in interstate commerce. The bill would also require the Secretary of Health and Human Services, in consultation with the NIDA Director, to prescribe the substances for which professional athletes are tested, establish criteria by which professional sports associations may provide substances to athletes prior to or after any drug test, and establish criteria for test administration. The measure also calls for penalties for a positive test, and criteria under which the names of athletes testing positive may be disclosed. Committees: Energy and Commerce, Education and the Workforce. Status: Reported by all committees, awaiting further action.

H.R. 3196 - On June 30, 2005, Representative Henry Waxman (D-CA) introduced H.R. 3196, the Fair Access to Clinical Trials Act (FACT). The measure would require sponsors of privately and publicly funded studies of drugs, biologics, or medical devices to register using a database that builds on the National Library of Medicine's www.clinicaltrials.gov. It would provide public access to basic information on studies before they begin, such as the disease

or condition with which the trial is concerned, the hypothesis being tested, the sponsor and principal investigator, and the sources of funding. Public access to the results of clinical studies, including primary and secondary outcomes and significant adverse events, would also be permitted under the legislation. H.R. 3196 also would authorize the Secretary of HHS to impose penalties for noncompliance, including revoking a sponsor's eligibility for further Federal funding and imposing civil money penalties. Committee: Committee on Energy and Commerce.

H.R. 3739 - On September 13, 2005, Representative John Boozman (R-AR) introduced the "Drug Courts Improvement Act of 2005." This Act would amend existing law by requiring the Attorney General to set uniform standards for mandatory drug testing that drug courts receiving funds from the Department of Justice's (DOJ) Drug Court grant program would be required to follow. In addition, the legislation would require drug courts receiving grant money from this federal program to impose mandatory sanctions whenever a participant fails a drug test. Committee: Judiciary. Text from this bill was included in H.R. 3199 - see above under "Passed bills of Interest."

H.R. 3854 - On September 21, 2005, Representative Christopher Shays (R-CT) introduced H.R. 3854, the Microbicide Development Act, to facilitate the development of microbicides for preventing transmission of HIV and other diseases, and for other purposes. Research provisions would require the Director of the NIH Office of AIDS Research to: 1) expedite implementation of a Federal microbicide research and development strategic plan, 2) expand, intensify and coordinate the relevant activities of appropriate NIH research components, and 3) prepare and submit, within six months of enactment and annually thereafter, a report to Congress on Federal microbicide research implementation strategies. The bill would also require the Director of NIAID to establish a microbicide development unit within its Division of AIDS. The measure also contains provisions for relevant activities at the CDC and the U.S. Agency for International Development. Committees: Energy and Commerce, International Relations. Related bill: see S.550.

H.R. 3889 - On September 22, 2005, Representative Mark Souder introduced H.R. 3889, the "Methamphetamine Epidemic Elimination Act," to further regulate and punish illicit conduct relating to methamphetamine, and for other purposes. Status: passed by the House. Related bill and legislative action: see S. 103, H.R. 314. See above H.R. 3199, under "Passed Bills of Interest."

H.R. 3942 - On September 29, 2005, Representative James Sensenbrenner (R-WI) introduced the Professional Sports Responsibility Act of 2005, to establish a Federal Office of Steroids Testing Enforcement and Prevention to establish and enforce standards for the testing for the illegal use in professional sports of performance enhancing substances and other controlled substances. Committees: Judiciary; Energy and Commerce; Education and the Workforce.

H.R. 3955 - On September 29, 2005, Representative Steve King (R-IA) introduced the "Meth Lab Eradication Act," to amend the Controlled Substances Act to provide for the transfer of ephedrine, pseudoephedrine, and phenylpropanolamine to schedule V of the schedules of controlled substances, and for other purposes. Committees: Energy and Commerce; Judiciary.

H.R. 4212 - On November 2, 2005, Representative Frank Pallone (D-NJ) introduced the Advancing 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, and for other purposes. Committees: Energy and Commerce; Education and the Workforce. Related bill: see S. 1722.

H.R. 4272 - On November 9, 2005, Representative Sam Farr (D-CA) introduced H.R. 4272, the "Steve McWilliams Truth in Trials Act," to amend the

Controlled Substances Act to provide an affirmative defense for the medical use of marijuana in accordance with the laws of the various states, and for other purposes. Committees: Judiciary; Energy and Commerce.

H.R. 4763 - On February 15, 2006 Representative Oberstar (D-MN) introduced the "Methamphetamine Eradication Act," provide a comprehensive Federal response to the problems relating to methamphetamine use and addiction. Committees: Judiciary; Energy and Commerce; Science, Education and the Workforce; Transportation and Infrastructure Committees.

H.R. 4769 - On February 16, 2006, Representative Charles Norwood (R-GA) introduced the "Prescription Drug Abuse Elimination Act of 2006," to amend the Federal Food, Drug, and Cosmetic Act, the Controlled Substances Import and Export Act, and the Public Health Service Act to impose requirements respecting Internet pharmacies, to require manufacturers to implement chain-of-custody procedures, to restrict an exemption respecting the importation of controlled substances for personal use, and for other purposes. Committee: Energy and Commerce.

H.R. 4910 - On March 8, 2006, Represenative Ed Whitfield (R-KY) introduced the "National Drug Testing Integrity Act," to prohibit the manufacture, sale, marketing, or distribution of products or substances designed or intended to defraud a drug test. Committee: Energy and Commerce.

*** - Note: House Leadership and Committee chairs have said in the past that they would resolve the differences in these bills regarding steroids, and intend to have one bill that they will consider moving through the legislative process to focus on steroids issues. Disposition of the issue is unclear at this time.

Director's Report to the National Advisory Council on Drug Abuse - May, 2006

International Activities

NIDA International Forum

International Program Moves to NIDA Director's Office
The NIDA International Program, which had been a component of the Office of Science Policy and Communications, is now part of the Office of the Director. The shift will enhance the International Program's ability to advance NIDA's mission by fostering international cooperation in drug abuse and addiction research, while integrating NIDA's Divisional research priorities and crosscutting research issues within the frameworks of NIDA, NIH, and HHS.

NIDA Launches Latin American Initiative

Acting on its mission to work with neighboring countries in joint efforts to address drug addiction and its consequences, NIDA has launched a Latin American Initiative designed to increase training in areas such as diagnosis, data analysis, and clinical trials; stimulate the creation of regional networks to improve surveillance and research activities; expand NIDA's library of Spanish-language resources; and provide information useful to policymakers. The NIDA International Program will lead efforts to accomplish these goals by partnering with organizations such as the Inter-American Drug Abuse Control Commission (CICAD) at the Organization of American States, the Pan-American Health Organization, and the United Nations Office on Drugs and Crime to support training programs, surveillance activities, and database analyses. The NIDA International Program also will coordinate efforts by other NIDA and NIH components, including DESPR, CTN, and the Fogarty International Center, to promote surveillance activities, clinical trials, and training programs. Initial activities include:

- NIDA supported the participation of Dr. Ivan Montoya, DPMCDA, in the March 2006 organizational meeting of the UNODC Central America Regional Substance Abuse Treatment Network, where representatives from the six participating Central American countries (Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua and Panama) met to identify focus areas in drug abuse research and training and begin developing a clinical research infrastructure.
- The NIDA International Program will partner with DESPR and CICAD to coordinate activities designed to stimulate the organization of an epidemiology network in the Latin American region similar to the NIDA Community Epidemiology Working Group (CEWG). The International Program will support the participation of Latin American scientists and CICAD representatives at the June 2006 CEWG meeting and the organizational LAWEG meeting in October 2006. NIDA will also support the participation of NIDA staff and National Hispanic Science Network (NHSN)

representatives at the LAEWG organizational meeting.

- The NIDA International Forum, which will be held June 16-20, 2006, in conjunction with the College on Problems of Drug Dependence, will include a plenary session to identify relevant activities supported by NIDA and its partner agencies and a Spanish-language workshop to stimulate the creation of regional surveillance and research networks. Representatives from CICAD, PAHO, UNODC, NHSN, and the U.S. Department of State will participate in the NIDA International Forum sessions.

Staff Highlights

Grantee Honors

Research Results

INVEST-Supported Research Identifies Gene Associated with Smoking Initiation and Nicotine Dependence
Research published by 2004-2005 NIDA INVEST Fellow Dr. Lan Zhang, China, and her mentor, Dr. Kenneth Kendler, Virginia Commonwealth University, suggests that the Phosphatase and Tensin Homolog (PTEN) gene may be involved in the etiology of both smoking initiation and nicotine dependence. Their article, published in the American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, Volume 141B, Issue 1, 10 - 14, compares allele and genotype frequencies between smokers and nonsmokers and between low nicotine dependent and high nicotine dependent subjects to identify three SNPs in the PTEN gene that are significantly associated with smoking initiation and a fourth SNP that shows association with nicotine dependence. Haplotype analyses indicate that a major haplotype is associated with smoking initiation and a minor haplotype is observed only in the high nicotine dependence group. Dr. Zhang also presented this research at the International Society of Psychiatric Genetics 2005 Annual Meeting and presented the team's research on the association of the opioid mu receptor gene with smoking initiation and nicotine dependence at the American Society of Human Genetics 2005 Annual Meeting.

DISCA-Supported Research Identifies Culturally Unique Drug Abuse Patterns among U.S. Immigrants from the FSU
2004 NIDA Distinguished International Scientist Dr. Richard E. Isralowitz, Ben Gurion University, Israel, and his DISCA partners, Drs. S. Lala Straussner, New York University, and Andrew Rosenblum, National Development and Research Institutes, New York, have published their joint research in the Journal of Ethnicity in Substance Abuse, Volume 5, Number 1, 91-6. The authors report on their studies of disease risk behaviors and barriers to treatment services among drug-using U.S. immigrants from the Former Soviet Union, concluding that the group's rapid transition to injection drug use and suspicion and avoidance of traditional drug treatment services are unique among U.S. immigrant populations.

Supplement to Drug and Alcohol Dependence Focuses on Links between Drug Abuse and HIV/AIDS
NIDA and the editors of Drug and Alcohol Dependence have published a peer-reviewed journal supplement, Drug Abuse and HIV/AIDS: International Research Lessons and Imperatives, to provide an international perspective on research exploring the intersections between drug abuse and HIV/AIDS. Approximately half of the studies included in the supplement were supported, at least in part, by NIDA research funding, and several of the authors received research training fellowship awards through the NIDA International Program. The 6 full reports and 10 short communications published represent 15 countries and address the following general themes. First, the explosive nature of the spread of the HIV/AIDS epidemic is again evident, particularly in areas where drug abuse is driving HIV transmission rates, like South Central Asia. The second theme emphasizes the interrelationship between HIV prevention and treatment and drug abuse prevention and treatment. The third theme relates to research to understand and overcome barriers to conducting

effective surveillance, prevention, and treatment interventions. Guest Editors for the supplement were Dr. Steven W. Gust, IP Director; Dr. Steffanie A. Strathdee, University of California, San Diego; and Dr. Erin L. Winstanley, Johns Hopkins University. The 16 manuscripts were selected from 34 submissions received in response to a February 2005 open call for papers. The Guest Editors recruited more than 45 referees from 9 countries to conduct an anonymous peer-review. Senior members of the Drug and Alcohol Dependence Editorial Board then reviewed the entire supplement.

NIDA-Sponsored Meetings

NIDA Supports Society on NeuroImmune Pharmacology (SNIP) Meeting
NIDA provided partial support for the Society on NeuroImmune Pharmacology (SNIP) meeting, April 5-9, 2006, in Santa Fe, New Mexico, focusing on the medical consequences of drug abuse-related infections, working with young investigators, and supporting the participation of international researchers at the meeting. Dr. Jag Khalsa, DPMCDA, was a featured speaker at the awards banquet, discussing the medical consequences of drug abuse and NIDA funding opportunities. Dr. Khalsa also reviewed the Institute's international activities. Drs. David Shurtleff and Charles Sharp, DBNBR, served as mentors in a session for young investigators, and Dr. Shurtleff helped conduct a grant writing seminar. NIDA supported the participation of Drs. Claire Gaveriaux-Ruff, France; Christoph Stein, Germany; Prati Pal Singh, India; and Yahuda Shavit, Israel.

Research Training and Exchange Programs

Three Distinguished International Scientist Collaboration Awards (DISCA/USDISCA) Announced
Three researchers have been selected as 2006 NIDA Distinguished International Scientists. The competitive DISCA and USDISCA awards provide support to senior scientists during research exchange visits of 1 to 3 months so that applicants and their partners can cooperate on drug abuse research.

- **Dr. Raka Jain**, All India Institute of Medical Sciences (AIIMS), will work with Dr. Michael H. Baumann, IRP, to evaluate the acute neurochemical effects of modafinil, individually and in combination with cocaine, on extracellular dopamine and serotonin levels in the nucleus accumbens of rats. Modafinil is a potential pharmacotherapy to treat cocaine dependence. Drs. Jain and Baumann began collaborating when she visited the NIDA IRP as part of her 2005 WHO/NIDA/CPDD International Traveling Fellowship. A former NIDA INVEST Fellow, Dr. Jain is an AIIMS professor; directs the pre-clinical behavior laboratory where she conducts research on tolerance, dependence, and abuse liability, and supervises drug testing of patients at the De-Addiction Centre.
- **Dr. Tatiana Tsarouk**, Moscow State Medical Stomatology University, Russia, will work with Dr. Elaine Thompson, University of Washington, on their collaborative efforts to test a drug use and HIV prevention model designed specifically for Russian adolescents. The two began collaborating in 2001, when Dr. Tsarouk spent her NIDA INVEST Fellowship with Dr. Thompson adapting the Reconnecting Youth (RY) and Parents and Youth in Schools (PAYS) interventions to conduct a pilot prevention program in Russian schools. The collaboration continued when NIDA funded an international administrative supplement to expand the PAYS program in Russia. Drs. Tsarouk and Thompson will use the DISCA award to finalize two journal articles and revise an R01 grant application.
- **Dr. Ronald E. See**, Medical University of South Carolina, will work with Dr. Juan J. Canales, Universidad de Valencia, Spain, to assess the underlying neural mechanisms in an animal model of relapse to cocaine-seeking

behavior. By combining Dr. See's studies on the neurobiological substrate of relapse and Dr. Canales's studies of changes in striatal morphology with long term psychostimulant treatments, the investigators will employ an interdisciplinary approach to generate insights on the role of the basal ganglia in addiction. Drs. See and Canales anticipate publishing

Brazilian Named INVEST Fellow
NIDA has selected Dr. Paulo Telles, State University of Rio de Janeiro, Brazil, as an INVEST Drug Abuse Research Fellow. Dr. Telles will work with Dr. Kimberly Page-Shafer, University of California, San Francisco, to analyze hepatitis C (HCV) infection protection or susceptibility among young injection drug users (IDUs). The researchers will use qualitative and quantitative evidence to compare IDUs who are not infected with HCV to IDUs who have recently become infected with HCV in order to identify the prevention interventions and socio-cultural factors that moderate the risk of HCV infection. A psychiatrist, Dr. Telles has conducted research on preventing HIV, HCV, and other sexually transmitted diseases among drug-using populations that was supported by NIDA, the U.S. Centers for Disease Control and Prevention, and the Brazilian government.

NIDA, Department of State Select Humphrey Fellows
NIDA and the U.S. Department of State have selected eight scientists as the 2006-2007 Hubert H. Humphrey Drug Abuse Research Fellows: Mr. Alamgir Golam Mahmood, Bangladesh Ministry of Home Affairs; Kevin Goulbourne, M.D., Western Regional Health Authority, Jamaica; Mehboob Singh, M.D., Patiala Government Medical College, India; Ms. Desiree Molina, Jose Felix Ribas Foundation, Venezuela; Mr. Nassery Ruhullah, Afghan Ministry of Public Health; Peter Ndege, M.D., Kenyatta National Hospital, Kenya; Mr. Duc Nguyen, Vietnam Office on Drugs Control; and Mr. Amani Msami Kisanga, Tanzania Drug Control Commission. The 10-month NIDA Humphrey Drug Abuse Research Fellowships combine academic studies and professional affiliations with NIDA-supported researchers.

NIDA, WHO, CPDD Select International Traveling Fellows
Two scientists have been selected as WHO/NIDA/CPDD International Traveling Fellows: Kostyantyn Dumchev, M.D., Ukraine, and Min Zhao, M.D., Ph.D., China. The Fellowships provide travel support for international researchers to conduct research visits to NIDA grantees and participate in two scientific meetings: the NIDA International Forum and the College on Problems of Drug Dependence (CPDD) Annual Scientific Meeting. Dr. Dumchev will work with Dr. Joseph E. Schumacher, University of Alabama at Birmingham, to analyze data from their pilot study of behavioral treatments for injection drug users (IDUs) in Vinnitsya, Ukraine, and to begin statistical analysis of another study, predictors of HCV/HIV status in Ukrainian IDUs. Dr. Zhao will work with Dr. Walter Ling, UCLA, observing the research and clinical units of the Integrated Substance Abuse Programs, reviewing pharmacological and psychological treatments for drug abuse, and planning their project to develop and validate a Chinese version of the Addiction Severity Index. NIDA, the World Health Organization, and CPDD cosponsor the International Traveling Fellowships.

INVEST Fellows Tour IRP
The 2005-2006 NIDA INVEST Drug Abuse Research Fellows toured the NIDA Intramural Research Program in Baltimore, Maryland, on March 2, 2006. The following IRP staff members met with the Fellows: Kenzie Preston, Ph.D., Chief, Clinical Pharmacology and Therapeutics Research Branch; Marilyn Huestis, Ph.D., Chief, Chemistry and Drug Metabolism Section; Stephen Heishman, Ph.D., Chemistry and Drug Metabolism Section; David A. Gorelick, M.D., Ph.D., Chief, Clinical Pharmacology Section; Eliot Stein, Ph.D., Chief, Neuroimaging Research Branch; Alane Kimes, Ph.D., PET Center; Eric Moolchan, M.D., Chief, Teen Tobacco Addiction Research Center; and David Epstein, Ph.D., Treatment Section.

International Visitors

On January 27, 2006 Mr. Takayuki Harada, Chief Psychologist, Tokyo Detention Center of the Ministry of Justice, Japan visited NIDA. Drs. Beverly Pringle and Bennett Fletcher, DESPR and Ms. Dale Weiss, IP met with Mr. Harada. The discussion centered on drug treatment in correctional institutions both in the United States and Japan.

Mr. Torkild Strandberg, a Member of the Swedish Parliament and Ms. Karin Karlsbro, Head of the Liberal Party's Parliament Office visited NIDA on February 28, 2006. Dr. Liz Ginexi, DESPR and Dr. Steve Gust and Ms. Dale Weiss, IP met with Mr. Strandberg and Ms. Karlsbro. The meeting included a presentation on prevention strategies with a focus on youth and a general overview of NIDA and NIH.

On March 14, 2006 Mr. Yuangao Hou, Vice Director, Research Center for Western Development and Executive Vice-Chair, Liangshan Yi Women and Children's Development Center, China visited NIDA. Mr. Hou met with Dr. Lynda Erinoff, Office of AIDS Research and Dr. Jessica Campbell, DESPR. Mr. Hou discussed his work with the Chinese Yi communities, concentrating on drug and HIV/AIDS issues and the protection of Chinese women and children.

Mr. Manne Jšnsson, Detective Superintendent of the Stockholm County Police, Sweden visited NIDA on April 4, 2006. Meeting with Mr. Jšnsson from NIDA were Dr. Shakeh Kaftarian, DESPR and Ms. Dale Weiss, IP. Mr. Jšnsson explained the drug abuse problems from a police perspective in Stockholm. Dr. Kaftarian provided an overview of prevention strategies aimed at youth.

Dr. Jenishbek Nazaraliev, President of the Medical Centre Nazaraliev in the Kyrgyz Republic visited NIDA on April 5, 2006. Drs. Steve Gust, Erin Winstanley and Ms. Dale Weiss, IP met with Dr. Nazaraliev. Dr. Nazaraliev gave an overview of the treatment program that is available at the Medical Centre Nazaraliev.

Other International Activities

On March 28, 2006, David McCann, Ph.D. presented a summary of recent advances toward understanding the pharmacology of buprenorphine to the WHO Expert Committee on Drug Dependence (ECDD) in Geneva, Switzerland. The presentation emphasized growing evidence that stimulation of nociceptin/orphanin FQ receptors by buprenorphine is critical to the drug's overall activity. Evidence of this non-opiate mechanism of action (expanding our knowledge of dissimilarities between buprenorphine and prototypical opiates such as morphine) contributed to the ECDD's decision that buprenorphine should not be rescheduled internationally for control under the narcotic convention of 1961. Such a rescheduling would have limited - and in some cases precluded - the legitimate medical use of buprenorphine in several countries.

On March 13-18, 2006, Ivan Montoya, M.D. participated in the Third Regional Workshop of the Central American Network of Substance Abuse Treatment Providers, organized by the Regional Office of the United Nations Office of Drug Control and Crime. The workshop took in Panama City, Panama.

Director's Report to the National Advisory Council on Drug Abuse - May, 2006

Meetings/Conferences

The National Advisory Council on Drug Abuse Work Group examining **NIDA's Approach to Grant-Making** held their second meeting on February 7, 2006 to review NIDA's current grant-making practices and to determine if new actions or policies are needed. This meeting was coordinated by Dr. Denise Pintello, OSPC and was chaired by Dr. Constance Weisner, National Advisory Council on Drug Abuse. The Work Group is composed of members of the National Advisory Council on Drug Abuse and other experts in the field of drug abuse research. The Work Group will complete their recommendations and final report by May 2006.

On March 8-9, 2006, NIDA convened the second meeting of the **Basic Science Review Work Group** in Washington, D.C. This meeting was chaired by Dr. Linda Porrino, who is a member of the National Advisory Council on Drug Abuse and was coordinated by Dr. Denise Pintello, OSPC. The purpose for this Work Group is to conduct a comprehensive review of NIDA's basic science research portfolio and to provide recommendations to effectively address the future direction of basic science research at NIDA. The Work Group members will prepare a written report for the National Advisory Council on Drug Abuse in 2006.

NIDA once again participated in **Brain Awareness Week** at the National Museum of Health and Medicine on March 16 and 17, 2006. Sponsored by the Dana Alliance, this event has taken place for several years. This year, NIDA scientists played "Brain Game Challenge" with 6-8th grade students. The students had the opportunity to learn new facts about drug abuse and were given numerous NIDA publications, pencils, erasers, etc.

On April 27, 2006, NIDA participated in the NIH sponsored **Take Your Child to Work Day**. During this event, children of NIH staff circulate to stations set up by the various institutes. NIDA played "Brain Game Challenge," which gave the children the opportunity to learn facts about drug abuse and addiction. The children also received NIDA publications, pencils, erasers, etc.

Wilson M. Compton, M.D., Director, DESPR, Yonette Thomas, Ph.D., Chief, Epidemiology Research Branch, DESPR, and Douglas Richardson, the Executive Director of the Association of American Geographers (AAG), organized a jointly-sponsored **NIDA/AAG Research Symposium on "Geography and Drug Addiction"** on March 8, 2006, in conjunction with the 2006 Annual Meeting of the AAG, held in Chicago, Illinois. The all-day Symposium included plenary, concurrent paper, and poster sessions, as well as a keynote address by Nora Volkow, M.D., NIDA Director.

The Division of Clinical Neuroscience and Behavioral Research (DCNBR) provided conference grant support for a New York Academy of Sciences/Brown Medical School meeting entitled **Resilience in Children**, held February 26-28,

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Staff Highlights

Grantee Honors

2006 in Arlington, VA. NICHD and NIMH also contributed support. The goals of the conference were to examine behavioral-psychosocial and neurobiological aspects of resilience, and to help move the field toward a model that integrates these two perspectives. Dr. Nora Volkow gave a presentation on "Drug Addiction: A Brain Developmental Disorder", and numerous NIDA staff members attended the conference.

Drs. Karen Sirocco and Laurence Stanford, DCNBR, co-organized and co-chaired a trans-NIH workshop entitled **Reward Neurocircuitry in Adolescent Development and Decision Making** on January 20, 2006 in Bethesda, MD.

The 59th meeting of the **Community Epidemiology Work Group (CEWG)**, chaired by Moira O'Brien, DESPR, was held in Phoenix, Arizona, on January 18-20, 2006.

On February 13-14, 2006, NIDA's Special Populations Office sponsored a follow-up **NIDA Special Populations Research Development Seminar Series** meeting in Bethesda, Maryland. Thirteen new minority investigators participated in the two-day workshop, which gave them opportunities to meet with NIDA-funded investigators and senior Institute staff, learn about NIDA's research priorities, and share their own research interests. This was a follow-up meeting for the new investigators, who were required to submit draft research grant applications which were discussed during a scheduled "mock grant review" session.

NIDA cosponsored the annual **Lonnie E. Mitchell HBCU Substance Abuse conference** held April 6-8, 2006 in Washington, DC.

On April 23, 2006 in Atlanta, Georgia, the CTN sponsored an all day pre-conference session entitled, "Treating People with Dignity and Evidenced Based Medicine - Emerging Research Findings on Buprenorphine, Hepatitis C and Prescription Drug Addiction" at the American Association for the Treatment of Opioid Dependence (AATOD) conference. Dr. Betty Tai chaired the session and Dr. Petra Jacobs was the discussant.

The National CTN Steering Committee Meeting was held March 20-23, 2006, in Dallas, Texas. The following meetings/committees convened:

- CIDI Training (Educational) - training sessions for two days
- HIV Special Interest Group
- CTP and PI Caucuses
- Research Development Committee
- Executive Committee
- Node Coordinator Workgroup
- Data and Statistics Center Systems Demonstration - Clinical Research Information System
- The preliminary findings of the following study protocols were presented: CTN 0003 by Dr. Walter Ling; CTN 0004 by Dr. Sam Ball; and CTN 0009 by Dr. Malcolm Reid. Dr. Paul Roman presented preliminary findings of his study on the CTN.
- Twelve-Step Facilitation Protocol Executive Committee
- Research Utilization Committee
- DCRI/EMMES

Dr. Timothy P. Condon, Deputy Director, NIDA, chaired a session entitled "Sharing the Science: Disseminating Evidence Based Treatments" at the International Conference on Treatment of Addiction Behaviors (ICTAB-11) on January 30, 2006 in Santa Fe, New Mexico.

Dr. Timothy P. Condon presented "Methamphetamine: The Science of Addiction" at the National Association of Counties Methamphetamine Action Group on March 3, 2006, in Arlington, Virginia.

Dr. Timothy P. Condon presented "It's a Brain Disease: Beyond a Reasonable Doubt: The Neuroscience of Addiction & Judicial Decision Making" at the Federal Judicial Center's Workshop for U.S. Magistrate Judges on April 6, 2006, in San Francisco, California.

Dr. Timothy P. Condon presented "Blending Research and Practice - An Overview of Where We Are and Where We Are Going: The NIDA/SAMHSA Blending Initiative" at the New Mexico Spring Institute on Addiction Treatment on April 10, 2006, in Albuquerque, New Mexico.

Dr. Cindy Miner, Deputy Director, OSPC served as a consultant at the judging for the 2006 PRISM Awards on February 4, 2006, in Los Angeles, California.

Dr. Cindy Miner, Deputy Director, OSPC presented "NIDA Research: Bringing the Power of Science to Combat Drug Abuse" at the Current Trends In Drug Abuse Research 4th Annual Symposium at Northeastern University on April 12, 2006, in Boston, Massachusetts.

On January 31st and February 7th, 2006, Dr. Ruben Baler, OSPC, made two presentations at the School of Public Health and Health Services, Department of Exercise Science, at George Washington University. The presentations were part of the "Drug Awareness" course offered every semester to incoming freshmen, and included a formal lecture entitled "Addiction is a Brain Disease" that highlighted NIDA's mission, strategies and achievements, as well as a screening, with debate, of the film "Euphoria," produced through a NIDA-funded SBIR grant.

Drs. Lula Beatty, Director, SPO, and Pushpa Thadani, DBNBR, attended a program review meeting of the Neuroscience of Drug Abuse Program at North Carolina Central University established under the HBCU Recruited Scientist Program on March 10, 2006 in Durham. Aims of the program include building a research program in the neuroscience of drug abuse at the Julius L. Chambers Biomedical/Biotechnology Research Institute, NCCU and preparing undergraduate and graduate students in the chemistry, biology and psychology departments for Ph.D. and M.D. training programs.

Dr. Lula Beatty presented a seminar entitled "Why Care About Addiction? Research and Training Opportunities at the National Institute on Drug Abuse," on March 30, 2006 for students and faculty at Livingstone College in North Carolina.

Dr. Lula Beatty participated as a panelist in two sessions at the National African American Drug Policy Coalition summit on April 6 and 7, 2006 in Washington, DC. One talk focused on NIDA's African American Initiative and the other was on Research Mentoring at NIDA.

Dr. Lula Beatty attended the meeting of the Committee on Women in Psychology (CWP) on April 6 and 7, 2006 in Crystal City, VA. CWP is one of the governance committees in the Public Interest Directorate of the American Psychological Association.

Dr. Lula Beatty co-hosted a roundtable and provided finals remarks at NIDA's Research Training Institute on April 18-19, 2006 in Bethesda, Maryland.

Dr. Harold Perl, CCTN, served as chair and discussant for a symposium titled: Implementing evidenced-based treatment methodology: Lessons from Adolescent Portable Therapy (APT), on March 27, 2006 at the 2006 Joint Meeting on Adolescent Treatment Effectiveness, in Baltimore, MD. He also presented a talk titled "Implementation and Adoption of Evidence-Based

Practices: What Do We Know Today and What Will We Need to Do Tomorrow?"

Dr. David Shurtleff, Director, DBNBR, presented a session entitled "Research Funding Opportunities at NIH" at the 12th Annual Meeting of the Society for Neuroimmune Pharmacology in Santa Fe, NM, April 2006.

On April 17, 2006, Dr. David Thomas, DBNBR, chaired a session titled, "Neuronal and Glial Mechanisms of Pain" at the NIH Pain Consortium First Annual Symposium on Advances in Pain Research.

Drs. Cora Lee Wetherington, DBNBR and Vanya V. Quinones, Hunter College, co-organized & co-chaired the symposium, "Progesterone Effects on Reward: Possible Role in Drug Addiction," at the Combined meeting of The Conference on Sex and Gene Expression and The Workshop on Steroid Hormones and Brain Function, March 28 - April 1, 2006, Breckenridge, CO. Other participants included Jill Becker (University of Michigan), Suzette Evans (Columbia University and New York State Psychiatric Institute) and Mehet Sofuoglu (Yale University).

Dr. Minda Lynch, BCSRB/DBNBR, presented in a session entitled "Get Schooled: NIDA Funding for Adolescent Research" at the 11th Biennial Meeting of the Society for Research on Adolescence in San Francisco, CA during March 2006.

Dr. Susan Volman, DBNBR, Dr. Jerry Frankenheim, DBNBR, and Dr. Hal Gordon, DCNBR, co-chaired a workshop entitled "Biological Basis for Co-Occurrence of Substance Abuse and Other Psychiatric Disorders" on April 10-11, 2006 in Bethesda, MD.

On January 25, 2006, Dr. Frankenheim participated in a grantsmanship session with the Travel Fellows at the Winter Conference on Brain Research, Steamboat Springs, CO.

On February 15, 2006, Dr. Frankenheim briefed the Methamphetamine Working Group, Bureau of International Narcotics and Law Enforcement Affairs, US Department of State, regarding methamphetamine pharmacology, toxicology, and NIDA research, at the Department of State headquarters in Washington, DC.

Wilson M. Compton, M.D., Director, DESPR, presented to the steering committee of the SATH-CAP Cooperative Agreement study, Santa Monica, California April 4, 2006.

Wilson M. Compton, M.D. gave a plenary presentation at the Joint Meeting on Adolescent Treatment Effectiveness (JMATE), convened on March 27-29, 2006 in Baltimore, MD.

Wilson M. Compton, M.D. presented to the treatment program interest group of the NIDA Clinical Trials Network, Dallas, Texas March 20, 1006.

Wilson M. Compton, M.D. presented to the Robert Wood Johnson Foundation meeting on models for treating addiction in primary care, Amelia Island, Florida February 16, 2006.

Dr. Elizabeth Robertson, DESPR, is currently serving on the Internal Advisory Work Group, the External Advisory Work Group, and the Evidence-based Work Group for the CSAP Strategic Prevention Framework - State Incentive Grants.

On February 13, 2006, Drs. Cindy Miner, Elizabeth Robertson, Jean Poduska (American Research Institute), and Evelyn Yang (CADCA) presented a workshop for community based organizations on the NIH system, how to apply for grants, developing community researcher partnerships and the view for a community-level organization. The workshop took place at the annual Community Anti-Drug Coalitions of America meeting held at the Washington,

DC Convention Center.

On March 25, 2006, Dr. Elizabeth Robertson, DESPR, participated on a panel titled "NIDA Funding for Adolescent Research at the society for Research on Adolescents in San Francisco.

Dr. Aria Crump, DESPR, presented a DESPR program overview to early career scientists at the NIDA Research Development Seminar Series in Bethesda on February 13-14, 2006.

Dr. Aria Crump, DESPR, participated in a panel entitled "NIH funding for Predocs and Postocs: Allow Us to Encourage You to Submit Grant Applications" at the 11th Biennial meeting of the Society for Research on Adolescence, held March 23-26, 2006.

Dr. Shakeh Kaftarian, DESPR, served on the Planning Committee of the PRIDE 2006 Conference, which was convened on April 6-9, 2006 in Washington, D.C.

Dr. Shakeh Kaftarian, DESPR, organized and chaired two sessions at the 2006 Joint Meeting on Adolescent Treatment Effectiveness (JMATE), convened on March 27-29, 2006 in Baltimore, MD. These sessions were titled "Child Maltreatment and Substance Abuse: Linking Research and Practice" and "Tobacco Cessation: Linking Research and Practice."

Drs. Shakeh Kaftarian and Elizabeth Robertson presented a workshop titled "Preventing HIV Infection: What Youth Should Know" on April 13, 2006 at the annual PRIDE conference in Washington, DC.

Dr. Shakeh Kaftarian, DESPR, convened a meeting of staff from the Agency for Healthcare Research and Quality and NIDA to discuss the relevance of delivery-based networks which AHRQ is presently utilizing to work conducted by NIDA grantees. This meeting took place on Feb 28, 2006 at NIDA.

Dr. Jerry Flanzer, DESPR, co- led a grantmanship workshop focused on obtaining support from NIH, and presented the "Funding Opportunities for Social Workers at NIDA at the Society of Social Worker's 10th Annual Conference, Austin, Texas, January 12, 2006.

Dr. Jerry Flanzer, DESPR, presented an "Update on NIH Support of Social Work Research" at the National Association of Deans and Directors of School of Social Work, Chicago, Illinois, February 16, 2006.

Dr. Jerry Flanzer moderated a panel on Addiction Research and Social Work Practice, at the Annual program meeting of the Council on Social Work Education, Chicago, Illinois, February 18, 2006.

Dr. Jerry Flanzer, DESPR, presented the " Funding Opportunities and Priorities at NIH," at the Annual program meeting of the Council on Social Work Education, Chicago, Illinois, February 20, 2006.

At the recent Society for Research on Adolescence Biennial Meeting in San Francisco, CA, March 23 - 26, 2006, Jessica Campbell, Ph.D., ERB/DESPR, represented NIDA in a poster session and a discussion hour focusing on child and adolescent research support at NIDA.

Kathy Etz, Ph.D., ERB/DESPR, presented on "Funding Opportunities at the NIH and NIDA" in three symposia held at the Society for Research on Adolescence biennial meeting, March 23-26, 2006 San Francisco, CA.

Kathy Etz, Ph.D., ERB/DESPR, and Richard Denisco, M.D., SRB/DESPR, presented on "Current Trends in Drug Abuse Research and Assessment in Primary Care Settings" as part of the George Washington University Internal Medicine seminar series, May 16, 2006, in Washington D.C.

Peter Hartsock, Dr.P.H., ERB/DESPR, described NIDA's AIDS and other infectious diseases modeling program at the "Science and Technology Expert Partnership's Infectious Disease Modeling Conference," McLean, VA, March 2-3, 2006. The conference, supported by the Department of Defense, the White House Office of Science and Technology Policy, the National Intelligence Council, and the Scientific and Technical Intelligence Committee, focuses on developing state-of-the-art mathematical modeling capabilities for predicting and understanding the worldwide spread of infectious diseases of humans, animals, and plants.

Peter Hartsock, Dr. P.H., ERB/DESPR, met with members of the Johns Hopkins Central Asia-Caucasus Institute, Department of Defense, and the Department of State to initiate a Central-Asia wide molecular epidemiologic/remote sensing study of the Silk Road heroin trade and accompanying HIV sub-types. The meeting took place in Washington, D.C. on January 6, 2006.

Peter Hartsock, Dr.P.H., ERB/DESPR, represented NIDA at the Center for Strategic and International Studies' Task Force on HIV/AIDS Conference on HIV/AIDS in Vietnam, March 9, 2006, in Washington, D.C. Dr. Peter Piot, Executive Director of UNAIDS, Tommy Thompson, Former Secretary for DHHS, Senator Richard Lugar, and Senator John Kerry were conference speakers. The conference focused on the rapid growth of the Vietnamese HIV/AIDS epidemic, in which drug abuse plays a major role and the need for more international, especially U.S., involvement providing research and services assistance to Vietnam.

Moira O'Brien, ERB/DESPR, gave a presentation titled, "Methamphetamine Abuse in the U.S.: Patterns and Trends at the National and Local Levels," for the CADCA National Leadership Forum XVI in Washington, D.C., February 15, 2005.

Douglas Rugh, Ph.D., ERB/DESPR, presented results from a study of moderating influences on adolescent alcohol drinking at the January 16, 2006 Society for Social Work Research Meeting in San Antonio, TX.

On February 28, 2006, Frank Vocci, Ph.D., Director, DPMCDA, presented on preclinical and clinical studies involving the development of vaccines for nicotine dependence at the American Society of Preventive Oncology in Bethesda, MD.

On April 22-26, 2006, Jag Khalsa, Ph.D., DPMCDA, presented a symposium on Drug-drug Interactions at the Annual Meeting of the American Association for the Treatment of Opioid Dependence (AATOD), Atlanta. Speakers (Dr. David Greenblatt of Tufts, Dr. Evan Kharasch of the University of Washington, St.Louis, and Dr. Elinore McCance-Katz of VCU) presented the most current research findings on drug-drug interactions between drugs of abuse and antiretroviral medications. A brief summary of the symposium will be placed on NIDA's website.

On May 5, 2006, Jag Khalsa, Ph.D. presented a daylong sympsoium on "Clinical Approaches to HIV and Hepatitis C Infections in Drug Abusers" at the Annual Medical-Scientific Conference of the American Society of Addiction Medicine, San Diego. A number of clinician scientists (immunologists, hepatologists, infectious disease specialists) presented basic as well as clinical research findings on complications and clinical approaches to the management of dual infections in drug abusers. Publication of the proceedings in a professional medical journal is planned.

On February 28 and March 1, 2006, Ivan Montoya, M.D. and Jamie Biswas, Ph.D., DPMCDA, with program officials from NIMH and NIAAA co-organized a two-day workshop on Methodologies for Conducting Pharmacotherapy Trials for Psychiatric Comorbidities. The workshop took place in Bethesda, MD.

On March 27, 2006, Jamie Biswas, Ph.D. gave a presentation and participated as a panel discussant for the Recruitment Issues in Medication Trials for Adolescents With Substance Use Disorders panel at the annual JMATE meeting in Baltimore, Maryland on March 27, 2006.

Dr. Nicolette Borek, DCNBR, chaired a symposium on "Violence and Prenatal Drug Exposure: Impact on Adolescent Behavior" at the 11th Biennial Meeting of the Society for Research on Adolescence, March 23-26, 2006 in San Francisco.

Dr. Borek also presented a talk at SRA on research funding opportunities in DCNBR at the session "Get Schooled: NIDA Funding for Adolescent Research".

Dr. Nicolette Borek, DCNBR, gave two talks on NIDA resources and research funding opportunities to the Behavioral/Community and Therapeutics Leadership Groups at the Network Meeting of the Adolescent Trials Network for HIV/AIDS Interventions in Rockville, MD, March 14-17, 2006. The ATN is a collaborative network cosponsored by NIDA, NICHD, and NIMH.

Dr. Nicolette Borek participated as a scientific collaborator in the Steering Committee meeting of the Maternal Lifestyle Study and co-conducted a site visit at the University of Miami site in Miami, FL, January 17-19, 2006.

Nicolette Borek, Katherine Davenny, Karen Sirocco, and Vince Smeriglio have participated in a numerous activities as scientific collaborators related to the start-up of the Pediatric HIV/AIDS Cohort Study (PHACS). PHACS is a cooperative agreement co-funded by NIDA, NICHD, NIAID, and NIMH to study the growth and development of children exposed to HIV/AIDS and/or antiretrovial therapy (ART) in utero. NIDA staff participated in the PHACS Leadership Group Meetings December 7, 2005 in Bethesda, Maryland and March 20-21, 2006 in Washington, DC, and have participated in ongoing conference calls and meetings to design the study. In addition to providing input to the overall protocol, Drs. Borek and Sirocco serve as NIDA representatives on the Neurodevelopment and Behavior workgroup.

On March 26 - 29, 2006, Dr. Melissa Racioppo, DCNBR, participated in the Joint Meeting on Adolescent Treatment Effectiveness (JMATE) in Baltimore, MD. Multiple symposia and workshops were held at this second annual meeting of clinicians and researchers with an interest in adolescent substance abuse treatment.

In February 2006, Drs. Lisa Onken, DCNBR, and Moira O'Brien, DESPR, gave presentations at CADCA about current research on the epidemiology and treatment of methamphetamine abuse.

In January 2006, Dr. Cecelia Spitznas, DCNBR, participated as a discussant and session chair for a symposium on Mechanism of Action in Behavioral Treatments at the International Conference on Treating Addictive Behaviors in Santa Fe, New Mexico.

A workshop entitled "NeuroAIDS, Drug Abuse, and Inflammation: Building a Collaborative Research Agenda" was held on March 23-24, 2006. The goal of this meeting was to generate discussion to identify and prioritize basic research studies needed to understand the interaction of drug abuse and the processes of HIV-induced neuropathology. This meeting was organized by Diane Lawrence, FNRB, DBNBR and Lynda Erinoff, AIDS Research Program (ARP) and was supported by the ARP.

Dr. Harold Gordon, DCNBR, co-organized (with other members of the Trans-NIH Sleep Research Coordinating Committee) a two-day workshop on Neuroimaging in Sleep Research held on the NIH campus, Bethesda, MD, March 29-30, 2006.

Dr. Harold Gordon represented NIDA at a workshop on Sleep Loss and Obesity

sponsored by International Life Sciences Institute, the National Sleep Foundation, and Atlanta School of Sleep Medicine held in Washington, D.C. March 27-28, 2006.

Dr. Harold Gordon co-organized (with Susan Volman (lead) and Jerry Frankenheim) a two-day workshop on Biological Basis for Co-Occurrence of Substance Abuse and Other Psychiatric Disorders, Bethesda, April 10-11, 2006.

Dr. Steven Grant, DCNBR, represented NIDA at the annual meeting of the Cognitive Neuroscience Society in San Francisco, CA, April 8-12, 2006.

Dr. Steven Grant represented NIDA at a Neuroethics Conference at the University of California, Davis, in Davis, CA, April 7, 2006.

Dr. Steven Grant represented NIDA at the workshop on "NeuroAIDS, Drug Abuse and Inflammation" in Bethesda, MD, March 23-24, 2006.

Dr. Steven Grant represented NIDA at the workshop on "Methodology of Conducting Pharmacologic Clinical Trials in Patients with Alcohol/Drug Dependence and Psychiatric Comorbidity", Bethesda MD, February 28 - 29, 2006.

Dr. Nemeth-Coslett continues to co-chair the Translationally Oriented Approaches, Devices and Strategies (TOADS) work-group. The TOADS workgroup has set aside money to support up to 8 junior researchers to attend the 11th International Conference on Human-Computer Interaction. Researchers who have an interest in using state-of-the-art technologies as an investigative tool in drug abuse research; prevention and treatment were invited, via fliers at Neuroscience and through several ListServes, to submit proposals.

On February 8, 2006, Dr. Yihong Yang, Chief, MRI Physics Unit in the Neuroimaging Research Branch, NIDA, was invited to present the CCTN Classroom Series. He gave a talk entitled "Functional Brain Maps Revealed by Independent Component Analysis." Independent Component Analysis (ICA) is a valuable technique for multivariate data-driven analysis of functional magnetic resonance imaging (fMRI) data sets.

On February 13, 2006, Ahmed Elkashef and Shou-Hua Li spoke on secondary outcomes analysis on a study testing Buproprion--an antidepressant with modest monoamine uptake inhibition, and mild stimulant effects in animals--for the treatment of methamphetamine dependence.

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Media and Education Activities

Press Releases

April 1, 2006 - Combination of Cognitive-Behavioral Therapy and Motivational Incentives Enhance Treatment for Marijuana Addiction. New research supported by NIDA, indicates that people who are trying to end their addiction to marijuana can benefit from a treatment program that combines motivational incentives with cognitive-behavioral therapy. The study was published in the April 2006 issue of the *Journal of Consulting and Clinical Psychology*.

March 9, 2006 - NIDA NewsScan #41

- Bacterial Infections Pose Major Risks for Drug Abusers
- Improving HIV/AIDS Knowledge in Treatment-Seeking Cocaine Abusers
- Mouse Study Reveals Mechanisms By Which Cocaine Strengthens HIV Infection
- Russian Medical System Needs To Adapt to Co-Occurring Drug Abuse, Infectious Diseases

February 1, 2006 - NIDA NewsScan #40

- Epigenetics Offers New Avenues for Addiction Research
- Rat Study Shows Link Between Stress and Relapse to Drug Abuse
- Nicotine, Hypocretin Have Similar Effects on Attention in Rats
- Research in Mice Shows Naloxone Blocks Activity in Brain Pathways Key to Nicotine Addiction
- New Brain Scan Study Suggests Differences in Smokers in Response to Smoking Cues
- Compound Blocks Cocaine-Associated Environmental Cues in Rats
- Scientists Correlate Cocaine Craving, High with Regional Brain Activity
- New Brain Scan Technology Confirms the Effects of Acute Cocaine Abuse in the Human Brain
- Rat Study Suggests Chromatin Remodeling Affects Brain Circuits Involved in Addiction
- Study Identifies Cerebellum's Involvement in Addiction
- Brain Protein May Elicit Neuroprotective Effects on Brain Nerve Cells

May 15, 2006 - Behaviors May Indicate Risk of Adolescent Depression. New findings from a study supported by the National Institute on Drug Abuse, show that girls and boys who exhibit high levels of risky behaviors have similar

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chances of developing symptoms of depression. However, gender differences become apparent with low and moderate levels of risky behaviors with girls being significantly more likely than boys to experience symptoms of depression. The study, which incorporates data from almost 19,000 teens, was published in the May 15, 2006 issue of the *Archives of Women's Mental Health*.

January 20, 2006 - Black, White Teens Show Differences in Nicotine Metabolism.
New research by scientists with NIDA suggests that some of the racial and ethnic differences underlying how adults' bodies metabolize nicotine also are at work during adolescence. The findings have implications for the way teens of different racial and ethnic backgrounds are provided smoking cessation treatments. The study was published in the January 2006 issue of *Ethnicity and Disease*.

January 3, 2006 - Two Research Centers Join the NIDA Clinical Trials Network.
NIDA announced the establishment of two new Clinical Trials Network (CTN) affiliates. This development increases the range of NIDA's research infrastructure to test drug addiction treatments in real-life settings with diverse patient populations.

December 19, 2005 - 2005 Monitoring the Future Survey Shows Continued Decline in Drug Use by Students.
Overall, the 2005 Monitoring the Future (MTF) survey showed good news. While there was no substantive change in any illicit drug use between 2004 and 2005, analysis of the survey revealed an almost 19 percent decline in past month use of any illicit drug by 8th, 10th, and 12th graders between 2001 and 2005. This trend is driven largely by decreasing rates of marijuana use among these students. For example, since 2001, past month use of marijuana has fallen by 28 percent among 8th graders and by 23 percent among 10th graders.

Articles of Interest

April 3, 2006, *Associated Press* - "NIDA Chief Studies the Brain of Addicts" - Interview with Nora D. Volkow M.D.

March 2, 2006, *CNN Headline News* - "The Teenage Brain and Behavior" - Interview with Nora D. Volkow M.D.

March 20, 2006, *NBC Nightline* - "Women Under the Influence" - Interview with Nora D. Volkow M.D.

Winter 2006, *Lens Magazine* - "Two Paths to the Future" - Interview with Nora D. Volkow, M.D.

February 26, 2006, *Washington Post* - "Millions Have Misused ADHD Stimulant Drugs, Study Says" - Interview with Nora D. Volkow M.D.

January 23, 2006, *Washington Post* - "Blacks' Tobacco Risk Revisited" - Interview with Eric T. Moolchan, M.D.

Educational Activities

Mr. Brian Marquis, OSPC, presented a "NIDA Goes Back to School" workshop at the National after School Association Conference in Louisville, KY at the Kentucky International Convention Center on February 24, 2006. Session attendees learned about the campaign and its variety of K-12 science based educational materials about the consequences of drugs abuse on the brain and body.

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In response to continuing trends in inhalant abuse among younger teens as noted in the *2005 Monitoring the Future* study, NIDA continued enhancing public awareness this year through meetings and information dissemination projects nationwide. Most recently, as part of *National Inhalants and Poisons Awareness Week* activities in March 2006, Dr. Nora D.Volkow led the annual kick-off press conference at the National Press Club. Other speakers included ONDCP Deputy Director Mary Ann Solberg; SAMHSA Senior Advisor to the Administrator Beverly Watts Davis; National Inhalants Prevention Coalition Executive Director Harvey Weiss; Jeff Williams, a Cleveland police officer whose son died at age 14 after "huffing" computer keyboard cleaner; and Craig Dant, a 20 year old recovering inhalant user.

Heads Up: Real News about Drugs and Your Body NIDA and SCHOLASTIC INC., continued year 4 of their aggressive outreach to middle school students and teachers in the classroom, with the *Heads Up* science-based article inserts on drug abuse and addiction. *Junior Scholastic, Science World, Up Front, CHOICES, SCOPE,* and *Action* have carried *Heads Up* articles four times a year since 2003. Each issue is distributed to nearly 2 million students and teachers nationwide in classrooms, with an overall reach of nearly 7 million. In April and May, 2006, the SCHOLASTIC magazines carried the article *A Day in the Life of a Teen*, focusing on a teen's decision-making in various daily social settings, with the goal of avoiding drugs.

Conferences/Exhibits

Community Anti-Drug Coalitions of America -- February 14-16, 2006

Lonnie E. Mitchell Historic Black Colleges and Universities Substance Abuse Conference -- April 5-9, 2006

National Science Teachers Association 541th National Convention -- April 6-9, 2006

PRIDE 2006 World Conference -- April 12-15, 2006

American Association for the Treatment of Opioid Dependence Conference -- April 22-25, 2006

American Alliance of Health, Physical Education, Recreation and Dance National Convention and Exposition -- April 25-29, 2006

American Society for Addiction Medicine (ASAM) 37th Annual Medical-Scienfitic Conference -- May 4-7, 2006

American Psychiatric Association (APA) 159th Annual Meeting -- May 20-25, 2006

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Planned Meetings

The National Institute on Drug Abuse (NIDA) is presenting a research track at the **American Psychiatric Association's 159th Annual Meeting**, May 20-25, 2006, in Toronto, Canada. The NIDA program includes sessions on adolescent brain development and its implications for psychiatric treatment; understanding and assessing the complex issue of addiction to prescription medications; the methamphetamine epidemic in the United States; pharmacogenetics and drug abuse research; the neurobiological basis for co-occurring substance abuse and other psychiatric disorders; and nicotine dependence and schizophrenia and the neurobehavioral pathways. This year's program will build on the research tracks NIDA has offered the last several years at the APA meeting to raise awareness of new and emerging issues in addiction and psychiatry and provide important information related to best practices and treatment strategies. A number of NIDA staff, including NIDA's Director, Dr. Nora Volkow, will participate in the 2006 meeting.

NIDA, in collaboration with the Center for Substance Abuse Treatment (CSAT), and the National Association of State Alcohol and Drug Abuse Directors (NASADAD) is planning a meeting **Blending Research and Practice: Enhancing State Capacity to Implement Evidence-Based Practices** on June 4, 2006 at the Albuquerque Marriott Hotel in Albuquerque, New Mexico in conjunction with the 2006 Annual NASADAD/NPN/NTN Conference. This meeting builds on a series of meetings held over the past two years to enhance state-based blending of research, practice, and policy to improve the quality of drug abuse services nationwide.

NIDA is organizing a program of events at this year's **American Psychological Association (APA) Annual Meeting** in New Orleans, August 10-13, 2006. A number of NIDA staff throughout the Institute are involved in organizing and/or presenting on a wide range of session topics such as: environmental influences on brain development; what is the added value of social neuroscience to drug abuse treatment; what we have learned from Katrina and its effects on drug abuse, relapse, risk behaviors, and coping strategies; the epidemiology of HIV/AIDS risks associated with changing patterns and trends in non-injecting drug abuse; the commonality between addiction and obesity; and inhibitory dysregulation and drug abuse. In addition, NIDA Director, Dr. Nora Volkow, will make a presentation in an invited APA Division 28 symposium on the integration of behavioral and brain sciences and research on the nature of addiction. NIDA is also co-sponsoring an Early Career Investigator Poster Session with APA's Divisions 28 and 50 and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as part of the two Divisions' Social Hour.

NIDA will host **Blending Addiction Science & Practice: Bridges to the Future** at the Washington State Convention and Trade Center in Seattle,

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October 16-17, 2006. This 2-day conference will bring together clinicians and researchers, to examine cutting-edge findings about drug use and addiction and their application to clinical practice.

The Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment, the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism, will host the **2006 National Conference on Women, Addiction and Recovery: News You Can Use**, July 12-14, 2006, in Anaheim, CA. This 2 _ -day conference will advance the field of women's substance abuse treatment by presenting the latest research and discussing how it can be applied and implemented to improve clinical practice and service delivery for women with substance use disorders. Over 40 invited speakers will be featured including nationally recognized researchers on women's substance abuse treatment, as well as practitioners testing innovative and promising practices to address a range of problems experienced by women with substance use disorders and their families. NIDA members on the conference planning committee are Drs. Dorynne Czechowicz, Lisa Onken, and Cora Lee Wetherington.

On June 18, 2006, at the College on Problems of Drug Dependence 66th Annual Scientific Meeting, Nathan M. Appel, Ph.D. will co-chair a symposium entitled: Developments in Methamphetamine Abuse Targets and Pharmacotherapies. The symposium will provide an update on several candidate pharmacotherapies that have emerged from different rationales and mechanism-based targets. Dr. Dwoskin will report on lobeline, an alkaloid targeting the vesicular monoamine transporter-2; Dr. Stephen Dewey will report on vigabatrin, an irreversible GABA-transaminase inhibitor; Dr. S. Michael Owens will report on neutralizing monoclonal antibodies directed against methamphetamine; and Dr. Thomas Newton will report on perindopril, an angiotensin converting enzyme inhibitor. Dr. Appel will serve as the discussant.

On June 20, 2006, at the CPDD Annual Scientific Meeting in Scottsdale, Arizona, Nora Chiang, Ph.D. will introduce and chair the NIDA Medications Workshop: New Opportunities for Chemists and Pharmacologists. David McCann, Ph.D. will present "The evolution of NIDA's medications discovery programs," Jane B. Acri, Ph.D. will present "New molecular targets as potential pharmacotherapies for drug addiction," and Ming Shih, Ph.D will present "NIDA resources supporting medications discovery and development." Rik Kline, Ph.D. will serve as the discussant.

Two CTN workshops will be held at the College on Problems of Drug Dependency (CPDD) Annual Meeting June 17-22, 2006, in Scottsdale, AZ. The workshops are entitled: 1) HIV/AIDS Research in the NIDA Clinical Trials Network: Emerging Results and 2) Addressing Health Disparities Research in the CTN.

Two symposia, a workshop, poster and paper will be presented at the 27th Annual Meeting of the Society for Clinical Trials by the CCTN. The meeting will be held May 21-24, 2006 in Orlando, Florida:

- Two symposia: 1) Analytical Issues Unique to Multi-Site Trials: Which Are Resolved and Which Are Still Controversial?; Dr. Paul Wakim, organizer; 2) Group Therapeutic Interventions for Drug Dependence and Mental Health: What questions to ask and how to design trials to answer them?; Dr. Janet Levy, organizer.
- Dr. Mary Ellen Michel, Deputy Director, CCTN, will be an invited speaker at a workshop on Clinical Trials Networks. She will speak on the sponsor's perspective on networks, including advantages and disadvantages, governance, oversight, budgeting, obstacles and opportunities. Nancy Hamilton, Director of Operation PAR in Florida, and Vice-Chair of the CTN Steering Committee, will present the perspective of a participating clinical

center. Michele Straus, Principal Investigator of the Clinical Coordinating Center, EMMES Corporation, will present the role of clinical coordinating centers.

- Carmen Rosa will present a poster titled: "Ensuring Good Clinical Practice: A Multi-Level Approach." The poster will be co-authored by Royce Sampson (Southern Consortium Node) and Aimee Campbell (Long Island Node).
- Dr. Janet Levy will present a paper titled, "Designing Trials to Develop Adaptive Treatment Strategies to Treat Prescription Opioid Dependence." The co-authors are Roger Weiss (Northern New England Node PI) and Carl Pieper (Data and Statistics Center PI).

The next National CTN Steering Committee Meeting is planned for October 16-20, 2006 in Seattle, Washington.

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Publications

NIDA Publications

Epidemiologic Trends in Drug Abuse - Community Epidemiology Work Group - Advance Report - January 2006
NIH Pub. No.: 06-5878
The report provides descriptive information on the most recent significant trends, emerging problems and populations at risk.

Epidemiologic Trends in Drug Abuse - Community Epidemiology Work Group - Executive Summary - January 2006
NIH Pub. No.: 06-5879
This report provides an ongoing assessment of drug abuse in major metropolitan areas of the United States with the purpose of keeping both public and private sector policymakers and researchers informed with current and accurate data.

Epidemiologic Trends in Drug Abuse - Community Epidemiology Work Group - Meeting Proceedings - January 2006
NIH Pub. No.: 06-5880
This report provides an in-depth analysis of the epidemiologic trends and special reports for a limited audience made up primarily of drug abuse researchers who utilize this volume to identify potential areas for further research.

National Survey Results on Drug Use - Overview of Key Findings 2005
NIH Pub. No.: 06-5882
This publication provides a concise review of the findings of the Monitoring the Future Study and comparison of data from previous years.

Problems of Drug Dependence 2005: Proceedings from the 67th Annual Scientific Meeting of the College on Problems of Drug Dependence
NIH Pub. No.: 06-6014
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.

Principles of Drug Abuse Treatment for Criminal Justice Populations: A Research-Based Guide
NIH Pub. No.: 06-5316
Designed as a complement to NIDA's *Principles of Drug Addiction Treatment: A Research-Based Guide*, this booklet provides treatment principles and research findings that are of particular relevance to the criminal justice community and to treatment professionals working with drug abusing offenders.

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Research Report Series: Methamphetamine Abuse and Addiction - Revised
NIH Pub. No.: 06-4210
Includes a description of the potent psychostimulant methamphetamine, details of the drug's effects, and the scope of methamphetamine abuse in the United States. Explains how the drug is used and how it differs from other stimulants. Describes medical complications of methamphetamine abuse and current effective treatments.

Research Report Series: Anabolic Steroids Abuse - Revised
NIH Pub. No.:06-3721
Provides an authoritative, unbiased overview of anabolic steroid use and effects. Brings together the most recent findings from drug research surveys on drug abuse by youth.

Research Report Series: Nicotine Addiction - Revised
NIH Pub. No.: 06-4342
Describes what nicotine is, presents current epidemiological research data regarding its use, and reports on the medical consequences of nicotine use. Emphasizes the effects on the brain as well as current research findings about use during pregnancy. Includes treatment approaches.

NIDA Notes

***NIDA Notes* Volume 20 Issue No. 4**
NIH Pub. No. 06-3478
The lead story discusses research on the factors involved in the rise of prescription drug abuse by college students, looking at characteristics of universities, student populations, and acquisition of prescription medicines. The Director's Column addresses the benefits of human genome mapping to addiction research and the establishment of a NIDA partnership to assist in searching for gene variations that may affect vulnerability to nicotine addiction. Other research findings include the effectiveness of culturally tailored versions of CBT in helping methamphetamine addicts maintain abstinence, reduce risky sexual practices, and minimize depression; the use of nortriptylene therapy and counseling for smoking cessation; and the new "NIDA at Work" feature, which focuses on NIDA's AIDS Research Program.

***NIDA Notes* Volume 20 Issue No. 5**
NIH Pub. No. 06-3478
This is the first issue following a comprehensive redesign of NIDA Notes, now featuring a four-color layout and new features. The lead story discusses research on brain activity patterns in methamphetamine abusers who relapse after treatment. The Director's Perspective looks at the NIDA-funded Criminal Justice-Drug Abuse Treatment Studies (CJ-DATS) project, established in 2002 to look at optimal initiatives and interventions for incarcerated or recently released individuals. Other research reports discuss how methamphetamine abusers benefit from standard community-based drug abuse treatment; the use of Bupropion in treating smokers with schizophrenia; the links between cocaine abuse and HIV infection with coronary calcification; the club drug GHB's action on GABA receptors in the brain; and addiction treatment at pivotal points in prisoners' community reentry. The Tearoff feature discusses data from the 2005 MTF Survey. New features include "Research in Brief," highlights of recently published, NIDA-funded studies; and "What the Numbers Say," a graphic data snapshot of marijuana abuse and perceived risk. Issue 20-5 also features the first of the new "Reference Article" series, a four-page feature on animal models and their translation into human addiction research.

***NIDA International Program* E-News Letter**

The NIDA International Program issues an *E-News Letter* every other month to inform the international drug abuse research community about recent events, funding opportunities, NIDA's the research training and exchange programs for international scientists, and forthcoming meetings.

- February 2006 - This issue reported on the Institute of Medicine review of strategies to prevent and treat HIV in countries where drug use is the primary driver of the HIV/AIDS epidemic; the NIH Pathway to Independence Award Program; and the selection of Dr. Paolo Telles, Brazil, as a NIDA INVEST Fellow.
- April 2006 - This issue reported on the NIDA Latin American Initiative, the NIDA International Program supplement to *Drug and Alcohol Dependence*; NIDA-supported research published by former INVEST Fellow Lan Zhang, China, and former Distinguished International Scientist Richard Isralowitz, Israel; and the selection of the 2006-2007 NIDA Humphrey Drug Abuse Research Fellows and the 2006 WHO/NIDA/CPDD International Traveling Fellows.

CTN-Related Publications

Seven editions of the CTN Bulletin Board were distributed. The Bulletin Board is an electronic report on the progress of the protocols, committees, and node activity in the CTN.

A patient recruitment brochure was translated to Spanish and printed and distributed for Protocol CTN 0014 - Brief Strategic Family Therapy.

A patient recruitment brochure was printed and distributed for Protocol CTN 0029 - Smoking Cessation Study for Smokers with ADHD.

A pamphlet listing General Interviewing Guidelines for CTN clinical staff was approved for distribution throughout the Network.

Other Publications

Two Proceedings volumes have resulted from the NIDA workshop at the American Association of Pharmaceutical Scientists Annual Meeting held in November 2004 in Baltimore, MD. Dr. Rao S. Rapaka served as the Guest Editor for both of these volumes. The two volumes were published as Special Proceedings Volumes by Life Sciences (December 2005 and March 2006).
Natureceuticals (Natural Products), Nutraceuticals, Herbal Botanicals And Psychoactives: Drug-Discovery And Drug-Drug Interactions.
Volume-1: Natureceuticals (Natural Products), Herbal Botanicals, Psychoactive Hallucinogens and Related Products
Volume-2: Nutraceuticals, Herbals And Related Products

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Velez, M.L., Montoya, I.D., Jansson, L.M., Walters, V., Svikis, D., Jones, H.E. et al. Exposure to Violence Among Substance-dependent Pregnant Women and their Children. J. Subst. Abuse Treat, 30, pp. 31-38, 2006.

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Staff Highlights

Staff Changes

The Prevention Research Branch of the Division of Epidemiology, Services, and Prevention Research is pleased to welcome **Dr. Augusto (Augie) Diana** as a Health Scientist Administrator. Prior to joining NIDA, Dr. Diana worked as a Senior Public Health Analyst with the Division of State and Community Assistance at CSAP. Most recently, he was the Alternate Project Officer of CSAP's national cross-site evaluation of the Strategic Prevention Framework State Incentive Grant (SPF SIG) project, and CSAP's major data and technology initiative, the Data Coordination and Consolidation Center (DCCC). Dr. Diana has over 20 years experience conducting social research, most focused on program evaluation of substance abuse prevention programs. Prior to CSAP, Diana held research positions in Boston and Colorado, and taught and trained extensively in research and social service areas, to academic audiences, service providers and the larger community. Dr. Diana's areas of expertise with regard to research, teaching, and training include research methods and statistics, sport and leisure studies, crime and delinquency, substance abuse, and innovative methodological approaches. Dr. Diana received his Ph.D. in sociology from Northeastern University and his undergraduate degree from Fordham University.

Dr. Richard Jenkins recently joined the Prevention Research Branch of the Division of Epidemiology, Services and Prevention Research of NIDA, where he will be serving as a Health Scientist Administrator. Dr. Jenkins comes to NIDA from the Center for Disease Control and Prevention, where he served as a behavioral scientist in the area of HIV prevention. He was previously employed by the Department of Defense Retrovirology Program through the Henry M. Jackson Foundation. He is a clinical psychologist who has served as principal investigator for a variety of studies. His recent research activities have included community-based investigations of factors related to HIV prevalence and risk behavior among men who have sex with men (MSM); factors related to recent HIV seroconversion among MSM; investigations of different methods for collecting sensitive information; design of a community intervention project to reduce HIV risk among MSM; as well as descriptive research regarding the use of substitutes for heroin among injecting drug users.

Marsha Lopez, M.H.S., Ph.D., has joined DESPR's Epidemiology Research Branch. Dr. Lopez comes to NIDA from Walter Reed Army Medical Center where she worked on the Army Medical Surveillance Activity as a Senior Epidemiologist. She completed her Ph.D. in drug and alcohol dependence epidemiology at the Bloomberg School of Public Health, Johns Hopkins University under the guidance of Dr. James Anthony. While at Johns Hopkins, Dr. Lopez was a recipient of the NIDA NRSA award. She has also held a research faculty position at the Center for Substance Abuse Research (CESAR)

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at the University of Maryland, where she conducted analytic studies of data from the CSAT-funded TOPPS program and coordinated methods and results from State drug treatment programs.

Samia Dawud Noursi, Ph.D. has recently joined the Division of Epidemiology, Services, and Prevention Research (DESPR) as a Special Assistant in the Office of the Director. Dr. Noursi holds a Ph.D. in Applied Developmental Psychology from the University of Maryland and was awarded a Post-Doctoral Fellowship at NICHD during which she led a longitudinal study on the effects of domestic violence on children's development. Prior to joining NIDA, Dr. Noursi was a Social Science Analyst in the Division of Services and Intervention Research (DSIR) at NIMH and worked on a variety of projects including efforts to bridge science to services. Dr. Noursi will be responsible for coordinating a number of division-wide initiatives as well as assisting in the management of the division.

Quandra Scudder joined the CCTN January 23, 2006 as a Program Analyst. She has over 10 years of experience in extramural research at the National Institutes of Health (NIH). Previously she was with the National Institute of Neurological Disorders and Stroke (NINDS) for 6 years where she worked with program staff in Neurogenetics on grants, contracts, and other extramural program activities. Before joining NINDS, she was a Program Analyst in the Epidemiology and Biometry Program (EBP), Division of Epidemiology and Clinical Applications (DECA) at the National Heart, Lung, and Blood Institute (NHLBI).

The Epidemiology Research Branch of the Division of Epidemiology, Services, and Prevention Research is pleased to welcome **Dr. Kay Wanke** as a Health Scientist Administrator. Prior to joining NIDA, Dr. Wanke was a postdoctoral fellow in the Genetic Epidemiology Branch at the National Cancer Institute. There she received an NCI Fellows Award for Research Excellence for her investigation of the association of opioid receptor genes with smoking cessation. Before entering the NCI as a Cancer Prevention Fellow in the Tobacco Control Research Branch, she worked as a psychologist at the University of Alabama at Birmingham Sparks Clinics, conducting developmental and cognitive evaluations of infants and children. Dr. Wanke received her Ph.D. in Clinical Psychology from Southern Illinois University at Carbondale and her M.P.H. from the Harvard School of Public Health.

David A. White, Ph.D., joined the Medications Discovery & Toxicology Branch of NIDA's DPMCDA as a Health Scientist Administrator in February 2006. Dr. White received his Ph.D. from West Virginia University in the Department of Pharmacology and Toxicology under the advisement of Dr. Dale L. Birkle, where he assessed the effects of prenatal stress on stress-responsive systems. Before coming to NIDA, Dr. White was a Research Instructor at Emory University in the Department of Pharmacology, working in collaboration with Dr. Stephen G. Holtzman on a number of projects pertaining to opioid dependence. Dr. White also completed a Post-Doctoral Fellowship at Emory under Dr. Holtzman's mentorship.

Dr. James Colliver has rejoined NIDA-DESPR after 18 months at the Office of Applied Studies (OAS) at the Substance Abuse and Mental Health Services Administration. While at OAS, Jim was involved with National Survey on Drug Use and Health (NSDUH) analyzing data and developing reports. He is currently completing a report on NSDUH data on nonmedical use of prescription drugs and was heavily involved with efforts examining epidemiologic data on methamphetamine use from both an epidemiologic and methodological perspective. Now back home in the Epidemiology Research Branch, Jim will be involved with portfolios on drug use.

Tom Kresina, Ph.D. of the Medical Consequences Branch, DPMCDA, who was

responsible for research program on hepatitis C infection, has left the NIH and has been re-assigned to SAMHSA.

Paul Coulis, Ph.D., OEA, has retired after 20 years of government service, of which more than 15 years were served in NIDA. He served as a Program Officer in the Medications Development Division, Clinical Division, the Center on AIDS and Other Medical Consequences of Drug Abuse and, since June 2004, as an SRA in the Office of Extramural Affairs. Prior to joining NIDA in 1991, he held management positions in technology assessment, business development and marketing in the Olympus Corporation and in other corporations in the biotechnology industry. He also served on active duty in the U. S. Navy and was a National Research Council Post-Doctoral Research Associate at the National Naval Medical Center in Bethesda.

After over 35 years of service to the federal government, 33 of which were with NIDA, **Noble Jones** retired March 1, 2006. Mr. Jones was involved with community and bio-ethical issues for DESPR, work which he intends to continue into retirement.

Diana K. Souder, OEA, has retired after 37 years of government service, twenty of which were at NIDA. She started her government career with NLM, moved to NIMH, and then came to NIDA. For most of her career Diana served as a Grants Technical Assistant, including as a Lead GTA, work in which she excelled. She then became Special Assistant to the Director, OEA, NIDA.

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Bryon Adinoff, M.D., CTN Texas Node PI, was recognized with the Kenneth Z. Altshuler Medical Leadership Award at the Vision of Hope luncheon by Turtle Creek Manor on February 3, 2006. Turtle Creek Manor is a Dallas residential treatment program for patients with dual diagnosis.

Dr. Jennifer Beer, Assistant Professor, at the University of California, Davis was appointed as one of 5 Harrington Faculty Fellows for the 2006-2007 academic year at the University of Texas at Austin. The primary purpose of the Harrington Faculty Fellowship is to pursue research, and the Fellows have no teaching obligations. Each Fellow is provided with funding to support a symposium during the period of his or her stay. Dr. Beer plans to organize a symposium on Social Neuroscience in Spring 2007.

Dr. Christopher deCharms' research team won first place for their presentation at the SMRM Workshop on Real Time MRI in Santa Monica, CA in February. The presented work described the rtfMRI pain control experiments: Real Time fMRI: Novel Methods for Controlling Brain Activation Through Training with Application to Pain Control.

Linn Goldberg, M.D., principal investigator of ATLAS, and **Diane Elliot, M.D.**, principal investigator of ATHENA, received the Sports Illustrated Champion award at the National Press Club Washington, D.C. on February 9, 2006. Goldberg and Elliot, professors of medicine (health promotion and sports medicine) in the OHSU School of Medicine, co-developed both programs. ATLAS, initiated in 1993 through a five-year NIDA grant, is the nation's first and only program proven to reduce the desire for and use of anabolic steroids, sports supplements, alcohol and other illicit drugs among male adolescent athletes. ATHENA, initiated in 1999 with another grant from NIDA, is the first and only program proven to reduce disordered eating, body-shaping drug use and other health-harming behaviors among female high school athletes.

Dr. Raul Gonzalez of the University of Illinois, Chicago and Dr. C. Neill Epperson of Yale University received Early Career Travel Awards for attendance at the upcoming American Psychological Association in New Orleans, LA, August 10-12, 2006. Dr. Gonzalez will present a poster at the APA about his research on neurocognitive damage in HIV+ drug abusers. Dr. Epperson will present a poster at the APA about her research on sex, GABA and nicotine.

Howard Kaplan, Ph.D., Texas A& M University, will be presented the Leo G. Reeder award by the Medical Sociology Section of the American Sociology Association in August 2006. The award honors the impact he has made on the field of medical sociology, and recognizes his leadership and effective advocacy for the significance of sociological research in addressing mental health and substance problems.

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Staff Highlights

Grantee Honors

NIDA grantee **Suniya Luthar**, Ph.D., has been selected as one of the eight new members of the Governing Council of the Society for Research in Child Development, and will serve until Spring 2009.

Bill Miller, CTN Southwest Node PI, recently received two honorary awards: the John P. McGovern Award for excellence in substance abuse education and research, from the Association for Medical Education and Research in Substance Abuse (AMERSA), and the Wheelock and Irene Whitney Award from the Johnson Institute, Minneapolis, Minnesota.

Two publications by NIDA-funded researchers were recognized as being in the Top 10 Research Publications in HIV Care in 2005, compiled by the HIV Journal View in January 2006. They are: **A. David Paltiel**, et al., "Expanded screening for HIV in the United States—an analysis of cost-effectiveness." *The New England Journal of Medicine*, February 10, 2005, and Gillian D. Sanders, et al., "Cost-effectiveness of screening for HIV in the era of highly active antiretroviral therapy." *The New England Journal of Medicine*, February 10, 2005.

Dr. Stephen J. Wilson, University of Pittsburgh (Julie Fiez, Mentor), **Dr. Raul Gonzalez**, University of Chicago, (Eileen Martin, Mentor), **Mikisha Doop**, B.A., Vanderbilt University, (Sohee Park, Mentor), and **Francesca Filbey**, PhD., University of Colorado (Kent Huchinson, Mentor) were selected to attend the NIDA Trainee Conference in Bethesda, MD, April 17-18, 2006.