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

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

Research Findings - Basic Neuroscience Research

NIDA Funded Researchers Identify Gene Variant Linking Nicotine Addiction and Lung Cancer

Scientists have identified a genetic variant that not only makes smokers more susceptible to nicotine addiction but also increases their risk of developing two smoking-related diseases, lung cancer and peripheral arterial disease. The variant is closely linked to two of the known subunits of nicotine receptors (alpha3 and alpha5), the sites on the surface of many cells in the brain, lungs, and body that can be bound by nicotine. When nicotine attaches to these receptors in the brain, there are changes in cell activity that result in its addictive effects. Activation of nicotinic receptors in the lung may cause cell proliferation. The study, published in the April 3, 2008 issue of the journal Nature1, highlights the advances that are being made in genetics research using the method of genome wide association, which can now identify many gene variants that increase the risk of complex bio-behavioral disorders. Carriers of this genetic variant are more likely than non-carriers to be heavy smokers, dependent on nicotine, and less likely to quit smoking. While the variant does not increase the likelihood that a person will start smoking, it increases the likelihood of addiction for those who do smoke. The study funded by NIDA and the European Union was carried out by deCODE Genetics, a biopharmaceutical company based in Reykjavik, Iceland. The same variant was identified as one that increased risk for lung cancer in two articles appearing in the April 3rd, 2008, issues of Nature2 and Nature Genetics3, and partially funded by two other NIH institutes - the National Cancer Institute and the National Human Genome Research Institute. Previous work by scientists at the Washington University and Perlegen Biosciences led by Dr. Laura Bierut4,5, the University of Pennsylvania led by Dr. Wade Berrettini6, University of Colorado, Boulder by Dr. Isabel Schlaepfer7 all funded by NIDA also have shown independently that the alpha-5/alpha-3 nicotinic receptor subunit alleles increase the risk for heavy smoking. Future research will determine whether the association of the alpha3/alpha5 gene variant with lung cancer is due entirely to its effect on the increased quantity of cigarettes smoked or is a direct effect of nicotine on lung tissue to promote tumor growth in the lungs. 1. Thorgeirsson, T.E., Geller, F., Sulem, P., Rafnar, T., Wiste, A., et al. Variant Associated with Nicotine Dependence, Lung Cancer and Peripheral Arterial Disease. Nature, 452(7187), pp. 638-642, 2008. 2. Amos, C.I., Wu, X., Broderick, P., et al. Genome-Wide Association Scan of Tag SNPs Identifies a Susceptibility Locus for Lung Cancer at 15q25.1. Nature Genetics, Apr 2, 2008 , epub ahead of print. 3. Hung, R.J., McKay, J.D., Gaborieau, V., Boffetta, P., Hashibe, M., Zaridze, D., et al.. A Susceptibility Locus for Lung Cancer Maps to Nicotinic Acetylcholine Receptor Subunit Genes on 15q25. Nature, 452(7187), pp. 633-637, 2008. 4. Bierut, L.J., Madden, P.A.F., Breslau, N., Johnson, E.O., Hatsukami, D., Pomerleau, O.F., Swan, G.E., Rutter, J., Bertelsen, S., Fox, L.,

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Fugman, D., Goate, A.M., Hinrichs, A.L., Konvicka, K., Martin, N.G., Montgomery, G.W., Saccone, N.L., Saccone, S.F., Wang, J.C., Chase, G.A., Rice, J.P. and Ballinger, D. Novel Genes Identified in a High-Density Genome Wide Association Study for Nicotine Dependence. Human Molecular Genetics, 16(1), pp. 24-35, 2007. 5. Saccone, S.F., Hinrichs, A.L., Saccone, N.L., Chase, G.A., Konvicka, K., Madden, P.A.F., Breslau, N., Johnson, E.O., Hatsukami, D., Pomerleau, O., Swan, G.E., et. al. Cholinergic Nicotinic Receptor Genes Implicated in a Nicotine Dependence Association Study Targeting 348 Candidate Genes with 3713 SNPs. Human Molecular Genetics, 16(1), pp. 36-49, 2007. 6. Berrettini, W., Yuan, X., Tozzi, F., Song, K., Francks, C., Chilcoat, H., Waterworth, D., Muglia, P. and Mooser, V. _-5/_-3 Nicotinic Receptor Subunit Alleles Increase Risk for Heavy Smoking. Molecular Psychiatry, 13, pp. 368-373, 2008. 7. Schlaepfer, I.R., Hoft, N.R., Collins, A.C., Corley, R.P., Hewitt, J.K., Hopfer, C.J., Lessem, J.M., McQueen, M.B., Rhee, S.H. and Ehringer, M.A. The CHRNA5/A3/B4 Gene Cluster Variability as an Important Determinant of Early Alcohol and Tobacco Initiation in Young Adults. Biological Psychiatry, epub ahead of print.

DRD1 Associated with Nicotine Dependence

Genes in the dopaminergic system mediate the reinforcing and dependence producing properties of nicotine. In this study, Dr. Huang and his colleagues from the Li laboratory examined single-nucleotide polymorphisms (SNPs) within or near the dopamine D1 receptor gene (DRD1) for their association with nicotine dependence (ND), which was assessed by smoking quantity (SQ), the Heaviness of Smoking Index (HSI), and the Fagerstroem Test for ND (FTND). The samples were obtained from 2,037 participants representing 200 European American (EA) and 402 African American (AA) families. They found significant associations with rs686 in the AA sample and of rs686 and rs4532 in the pooled sample after correcting for multiple testing. Haplotype-based association analysis revealed that haplotype C-T-A, formed by rs265973, rs265975, and rs686, was significantly associated with all three ND measures in both the AA and the pooled sample. The haplotype T-A-T, formed by rs265975, rs686, and rs4532, showed a significant association with FTND in the pooled sample. Using a luciferase reporter assay, rs686, located in the 3 untranslated region, caused differential luciferase activities, indicating that rs686 is a functional polymorphism affecting expression of DRD1. Huang, W., Ma, J.Z., Payne, T.J., Beuten, J., Dupont, R.T., Li, M.D. Significant Association of DRD1 with Nicotine Dependence. Human Genetics, 123, pp. 133-140, 2008.

Salvinorin A derivatives

Salvinorin A is a diterpene acetate ester, first isolated from the leaves of a Mexican sage in the 1980s. It has generated scientific interest for its hallucinogenic drug abuse properties, and because of its particular binding selectivity as an agonist at the kappa opioid receptor (KOR), without measurably affecting other receptors, including the mu, delta, and serotonin receptors. Its precise positioning and orientation within the transmembrane helices of the kappa receptor are still under study, and may involve induced conformational change in one of the helices upon binding, which does not take place in the mu or delta receptors, even though the three opioid receptors have a fairly conserved set of amino acid residues in the cavity where ligands bind. Interest in kappa agonists as potential analgesic therapeutics has acknowledged the existence of certain side effects, including depressive-like effects and diuresis. In the case of salvinorin A, analgesic testing results in rodents suggest a short time period (ten-fifteen minutes) to reach optimal effect, and subsiding in twenty-thirty minutes, perhaps due to enzymatic hydrolysis to the more stable Salvinorin B alcohol at the two position in the molecule. Salvinorin B has not yet been positively identified in primates as an in-vivo metabolite of Salvinorin A, but is a reasonable possibility. In order to

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test the idea that alcohol or ether modifications at position two in Salvinorin A may produce more stable species, and possibly partial kappa agonists, or even antagonists, a number of such derivatives have been examined by several research groups. In a collaboration between Dr. David Lee and Dr. Lee-Yuan Liu Chen, the properties of 2-methoxymethyl Salvinorin B (2-MOM Salv B) have recently been reported The binding of this compound to CHO cell membranes containing tagged KOR was three-fold greater than that of Salvinorin A, and it produced full agonism in the GTPgamma S functional assay. By measuring the loss of cell surface fluorescence, 2-MOM Salv. B was seventy-fold more effective than Salv. A in promoting internalization of the KOR. It also induced down regulation of the KOR more efficiently than did Salvinorin A, after four hours of exposure, as measured by loss of the Western immunoblot band representing the fully glycosylated tagged KOR. In terms of its in-vivo effects, 2-MOM Salv B produced persistent antinociception (ninety to one hundred twenty minutes) in rats (hot plate testing) at 2.5 and 5 mg/kg ip injection doses, and hypothermia at a dose of 1 mg/kg thirty-sixty minutes after ip injection, while Salvinorin A did not show antinociception or hypothermia at 10 mg/kg. In mice, 2-MOM Salv. B caused immobility at .05-1 mg/kg persisting three hours, a more pronounced effect than seen in rats at higher doses. The antagonist nor-BNI was able to block the antinociceptive, hypothermic, and motor effects of 2-MOM Salv. B. The synthetic modification of Salvinorin A at the two position by introduction of short chain ether substituents has been shown to regulate the properties of the KOR in both in-vitro and in-vivo animal test systems. Wang, Y., Chen, Y., Xu, W., Lee, D.Y.W., Ma, Z., Rawls, S.M., Cowan, A., and Liu-Chen, L.-Y. 2-Methoxymethyl-Salvinorin B Is a Potent _ Opioid Receptor Agonist with Longer Lasting Action in Vivo Than Salvinorin A. The Journal of Pharmacology and Experimental Therapeutics, 324(3), pp. 1073-1083, 2008.

A Comprehensive Profile of Brain Enzymes that Hydrolyze the Endocannabinoid 2-Arachidonoylglycerol: Endogenous Ligands for Cannabinoid Receptors ("Endocannabinoids") Include the Lipid Transmitters Anandamide and 2-Arachidonoylglycerol (2-AG)

Endocannabinoids modulate a diverse set of physiological processes and are tightly regulated by enzymatic biosynthesis and degradation. Termination of anandamide signaling by fatty acid amide hydrolase (FAAH) is well characterized, but less is known about the inactivation of 2-AG, which can be hydrolyzed by multiple enzymes in vitro, including FAAH and monoacylglycerol lipase (MAGL). Dr. Cravatt and colleagues have taken a functional proteomic approach to comprehensively map 2-AG hydrolases in the mouse brain. Their data reveal that approximately 85% of brain 2-AG hydrolase activity can be ascribed to MAGL, and that the remaining 15% is mostly catalyzed by two uncharacterized enzymes, ABHD6 and ABHD12. Interestingly, MAGL, ABHD6, and ABHD12 display distinct subcellular distributions, suggesting that they may control different pools of 2-AG in the nervous system. Blankman, J.l., Simon, G.M. and Cravatt, B.F. A Comprehensive Profile of Brain Enzymes that Hydrolyze the Endocannabinoid 2-Arachidonoylglycerol. Chemistry & Biology, 14(12), pp. 1347-1356, 2007.

A Practical Synthesis of the Kappa Opioid Receptor Selective Agonist (+)-5R,7S,8S-N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxospiro[4,5]dec-8-yl] benzeneacetamide (U69,593)

Morphine has been the treatment of choice for relief of severe pain for decades, but its side-effect profile, including respiratory depression and addiction, prompted researchers to seek alternative remedies. One of the approaches was to develop receptor subtype selective analgesics, reasoning that eliminating the

action at multiple receptors might also eliminate unwanted side-effects. Szmuszkovicz (1999) reported the synthesis of arylacetamides such as U50, 488, spiradoline, and U69, 593 as a class of opioid agonists selective for the kappa opioid receptor. In animal studies, these compounds showed potent analgesic effects. However they exhibited unacceptable side effect profiles such as hallucinations and psychotomimesis. While these compounds were not a suitable replacement for morphine, they provided valuable research tools to identify the role of kappa opioid receptors in both normal and disease states. In this paper, the authors have reported a novel approach to the synthesis of the kappa-opioid receptor agonist, U69, 593 to produce higher yields than reported previously. This approach improved upon current methods by substituting stable and isolable cyclic sulfates for the unstable epoxides. It also provided access to gram quantities of the target compound and displayed excellent control of the relative stereochemistry. The absolute stereochemistry as well as biological activity of the U69, 593 was verified using X-ray crystal structure analysis and binding assays for the kappa opioid receptor. McElroy, T., Thomas, J.B., Brine, G.A., Navarro, H.A., Deschamps, J. and Carroll, F.I. A Practical Synthesis of the Kappa Opioid Receptor Selective Agonist (+)-5R, 7S, 8S-N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxospiro[4,5]dec-8-yl]-benzeneacetamide (U69,593). Synthesis, 6, pp. 943-947, 2008.

Spinal _-Opioid Receptor-Bearing Neurons are Essential for Morphine-Induced Analgesia

The role of spinal cord _-opioid receptor (MOR)-expressing dorsal horn neurons in pain and morphine analgesia is not completely understood. NIDA-grantee Dr. Ronald Wiley (Vanderbilt University) and colleagues used intrathecal dermorphin-saporin (Derm-sap) to selectively destroy MOR-expressing dorsal horn neurons in rats. Derm-sap treatment attenuated the analgesic action of both intrathecal and systemic morphine in several pain models, while having no effect on baseline responses to painful stimuli. Thus, MOR-expressing dorsal horn neurons are essential for the actions of morphine on pain, but not critical for the response to pain in the absence of analgesics. This finding suggests that the analgesic actions of opioids may be modified by altering the activity of MOR-expressing dorsal horn neurons. Kline IV, R.H. and Wiley, R.G. Spinal _-Opioid Receptor-Expressing Dorsal Horn Neurons: Role in Nociception and Morphine Antinociception. Journal of Neuroscience, 28(4), pp. 904-913, 2008.

Secondary Cells in the Rostral Ventromedial Medulla Contribute to Opioid-Induced Analgesia via a Novel Pain Suppression Pathway

In the rostral ventromedial medulla (RVM), _-opioid agonists are believed to inhibit "secondary cells," which disinhibit descending neurons that inhibit pain transmission. These secondary cells are generally presumed to be inhibitory interneurons that serve only to regulate the activity of these output neurons. Dr. Mary Heinricher and colleagues have been studying the relationship of these secondary cells to output cells involved in producing analgesia. They found that opioid administration in rats caused these secondary cells to cease firing before the output neurons begin to fire. This suggests that the secondary cells do not directly modulate descending pain pathways, but rather modulate pain via a mechanism that is independent of their direct action on primary descending output neurons in the RVM. Cleary, D.R., Neurbert, M.J. and Heinricher, M.M. Are Opioid-Sensitive Neurons in the Rostral Ventromedial Medulla Inhibitory Interneurons? Neuroscience, 151(2), pp. 564-571, 2008.

Cannabinoid Agonists Produce Analgesia via a Direct Action on TRP Channels

The cannabinoid agonists WIN 55,212-2 and AM1241 produce analgesia in

inflammatory pain models. However, the mechanisms responsible for cannabinoid-induced analgesia in sensory neurons are far from understood. Dr. Kenneth Hargreaves and colleagues have been studying potential cannabinoid actions at TRPV1 and TRPA1 channels in sensory neurons that are involved in producing analgesia, since these channels are importantly involved in pain transmission. The applications of WIN 55,212-2 and AM1241 inhibited the responses of sensory neurons to chemical pain-inducing irritants, capsaicin and mustard oil. Using TRPA1-specific small interfering RNA or TRPA1-deficient mice, it was shown that the TRPA1 channel is a sole target through which WIN 55,212-2 and mustard oil activate sensory neurons. In contrast, the AM1241 effect was mediated by an unknown channel. The knockdown of TRPA1 activity abolished the desensitizing effects of WIN 55,212-2 and AM1241 on capsaicin-activated currents. Furthermore, the WIN 55,212-2 or AM1241-induced analgesia of capsaicin-evoked pain was not present in TRPA1 knockout mice. Together, these findings demonstrate that cannabinoids exert at least some of their peripheral analgesic actions via TRPA1 channels located on sensory neurons. Akopian, A.N., Ruparel, N.B., Patwardhan, A., and Hargreaves, K.M. Cannabinoids Desensitize Capsaicin and Mustard Oil Responses in Sensory Neurons via TRPA1 Activation. Journal of Neuroscience, 28(5), pp. 1064-1075, 2008.

Live MR Imaging of Neuronal Transport of Mn2+ in the Hippocampal-Septal Circuit

Dr. Russell Jacobs and his colleagues have continued their studies on functional neuronal tract tracing in live mice by the use of manganese (Mn2+)-enhanced three-dimensional magnetic resonance imaging (MRI). Mn2+, a calcium analogue that enters neurons and other cells through divalent ion channels and is transported along neuronal pathways and across synapses, was injected into the right hippocampus of normal mice and in animals with a trisomic model of Down's syndrome (DS) and imaged with 11.7T high-resolution MRI at 0.5, 6, and 24 hours afterwards to examine signal intensity changes over time in the hippocampal-septal pathway. This pathway was chosen for study since it has been implicated both in normal memory functioning and as well in the cognitive impairment of Down's syndrome and thus allowed potential functional differences to be observed. The investigators describe a pattern of Mn2+-enhanced signal in vivo that correlated with the histological pattern in brains fixed with a classic neuronal tracer. They showed dynamic tract patterns of Mn2+ transport from the hippocampus to the septum over the 24 hours following injection. Co-registration of images from a cohort of animals allowed the investigators to apply statistical analysis that, somewhat unexpectedly, showed more robust transport in the DS model mice and indicated the complexity of neuronal transport. This powerful new technology, which was originally developed under the NIDA CEBRA program, shows great promise to provide new insights into normal neuronal functioning and in diseases with known or suspected transport defects. Bearer, E., Zhang, X. and Jacobs, R. Live Imaging of Neuronal Connections by Magnetic Resonance: Robust Transport in the Hippocampal-Septal Memory Circuit in a Mouse Model of Down Syndrome. NeuroImage 37, pp. 230-242, 2007.

Morphine Induces Defects in Early Response of Alveolar Macrophages to Streptococcus Pneumoniae by Modulating TLR9-NF-{kappa}B Signaling

Drug abuse is a significant risk factor for the development of community-acquired pneumonia where Streptococcus pneumoniae is one of the most common diagnoses among opiate abusers. This organism is responsible for more than 25% of all cases of pneumonia and is associated with an overall mortality rate of 23% among hospitalized patients. Researchers have used a mouse model of chronic morphine administration followed by intranasal

inoculation with S. pneumoniae to understand the underlying mechanisms by which chronic morphine use impairs host innate immune response and increases susceptibility to S. pneumoniae. In this model, chronic morphine treatment delayed neutrophil recruitment, increased lung bacterial burden, and increased mortality in S. pneumoniae-infected mice. In addition, morphine inhibited transcription factor NF-kappaB activation and decreased the production of inflammatory cytokines (TNF- , IL-1, and IL-6) and chemokines (MIP-2 and KC) in both bronchoalveolar lavage fluid and lung tissue of infected mice. Additional studies in the mouse model showed that increased mortality and bacterial outgrowth observed in morphine-treated infected mice were further exaggerated following depletion of alveolar macrophages, suggesting that the effect of morphine is, at least in part, mediated via alveolar macrophages. To further understand the underlying molecular mechanisms whereby morphine impairs the activity of alveolar macrophages, researchers used an in vitro alveolar macrophages and lung epithelial cells infection model. In this model, exposure of cells to pneumococci resulted in significant release of MIP-2 from alveolar macrophages, but not from lung epithelial cells. Morphine treatment reduced MIP-2 release from pneumococci-stimulated alveolar macrophages. Furthermore, morphine treatment inhibited S. pneumoniae-induced NF-kappaB-dependent gene transcription in alveolar macrophages following 2 h of in vitro infection. S. pneumoniae infection resulted in a significant induction of NF-kappaB activity in TLR9 stably transfected HEK 293 cells (but not in TLR2 and TLR4 transfected HEK 293 cells), which was inhibited by morphine. Moreover, morphine treatment also decreased bacterial uptake and killing by alveolar macrophages. Taken together, these results suggest that morphine treatment impairs TLR9-NF-kappaB signaling in alveolar macrophages and subsequently diminishes bacterial clearance during the early stages of infection, leading to a compromised innate immune response. Wang, J., Barke, R.A., Charboneau, R., Schwendener, R. and Roy, S. Morphine Induces Defects in Early Response of Alveolar Macrophages to Streptococcus pneumoniae by Modulating TLR9-NF-_B Signaling. Journal of Immunology, 180(5), pp. 3594-3600, 2008.

Action Potential-Independent and Nicotinic Receptor-Mediated Transmission via Miniature Postsynaptic Currents Occurs at Hippocampal CA3-Mossy Fiber Synapses

Transmitter release across synapses is largely evoked by incoming trains of presynaptic action potentials. Although action potential-independent, spontaneous transmitter release can also be measured (termed miniature excitatory or inhibitory postsynaptic currents), the randomness and small quantal amounts of transmitter released through this mechanism have resulted in the assumption that these miniature events may not be functionally significant. This paper now shows that in hippocampal mossy fiber boutons, activation of 7-subtype nicotinic acetylcholine receptors (7-nAChR) results in a large increase in the amplitude of spontaneous release, indicating an increased concerted release of multiple quanta from the fibers. The effects of 7-nAChR activation are mediated by biologically-relevant doses of nicotine. Increased spontaneous release results from 7-nAChR-promoted increase in internal calcium levels and activation of presynaptic calcium/calmodulin-dependent protein kinase II (CaMKII). These results demonstrate a novel form of synaptic plasticity mediated by presynaptic 7-nAChR that may play a role in inducing an alternate homeostatic state in the brain that potentially contributes to nicotine addiction. Sharma, G., Grybko, M. and Vijayaraghavan, S. The Journal of Neuroscience, 28(10), pp. 2563-2575, 2008.

Dopamine and Corticotropin-Releasing Factor Synergistically Alter Basolateral Amygdala-to-Medial Prefrontal Cortex Synaptic Transmission: Functional Switch after Chronic Cocaine Administration

Basolateral amygdala (BLA) neurons provide a major excitatory input to medial prefrontal cortex (mPFC)-layer V pyramidal neurons. As the amygdala encodes the emotional intensity of environmental stimuli and outcome-action associations, altered BLA-to-mPFC synaptic transmission could lead to defective emotional information processing and decision making within the mPFC that may result in misguided and inappropriate behaviors. Recent research by Gallagher and colleagues determined the effect of chronic cocaine on excitatory transmission within the BLA-mPFC pathway regulated by dopamine and corticotropin-releasing factor (CRF). In naive animals, activation of D(1/5) receptors depressed BLA-mPFC glutamatergic transmission (EPSCs), whereas CRF1 receptor activation alone had no effect. However, if activation of D(1/5) and CRF1 receptors occurred together, there was an enhanced, synergistic depression of glutamatergic transmission to levels greater than through D(1/5) receptor activation alone. After chronic cocaine administration, the function of DA(1/5) and CRF receptors switched from inhibitory to excitatory. In cocaine-treated animals, BLA-mPFC EPSCs were reduced compared to untreated animals. But now, activation of either D(1/5) or CRF2 receptors increased the cocaine-induced, depressed EPSCs. Additionally, simultaneous activation of presynaptic D(1/5) and CRF2 receptors led to further enhancement of cocaine-suppressed excitatory transmission. These data indicate that CRF acting synergistically with DA normally potentiates D(1/5)-induced synaptic depression. However, after chronic cocaine, the combined synergistic actions of DA and CRF switch polarity to enhance facilitation of BLA-mPFC glutamatergic transmission. These functional changes may underlie the altered, possibly aberrant, decision-making process induced by chronic cocaine. Orozco-Cabal, L., Liu, J., Pollandt, S., Schmidt, K. Shinnick-Gallagher, P. and Gallagher, J.P. Dopamine and Corticotropin-Releasing Factor Synergistically Alter Basolateral Amygdala-to-Medial Prefrontal Cortex Synaptic Transmission: Functional Switch after Chronic Cocaine Administration. The Journal of Neuroscience, 28(2), pp. 529-542, 2008.

Cannabinoids Restore Activity-Driven Synapse Loss Between Hippocampal Neurons

Dendritic pruning and loss of synaptic contacts are early events in many neurodegenerative diseases. These effects are dynamic and appear to differ mechanistically from the cell death process. Cannabinoids modulate synaptic activity and afford protection in some neurotoxicity models. Recent research by Kim et al. examined the effects of cannabinoids on activity-induced changes in the number of synapses between rat hippocampal neurons in culture. Morphology and synapses were visualized by confocal imaging of neurons expressing DsRed2 and postsynaptic density protein 95 fused to enhanced green fluorescent protein (PSD95-GFP). Reducing the extracellular Mg2+ concentration to 0.1 mM for 4 hr. induced intense synaptic activity that decreased the number of PSD95-GFP puncta by 45 +/- 13 %. Synapse loss was an early event, required activation of NMDA receptors and was mediated by the ubiquitin-proteasome pathway. Full and partial cannabinoid receptor agonists inhibited PSD loss in a manner reversed by the CB1 receptor antagonist rimonabant. The protection was mimicked by inhibition of presynaptic Ca2+ channels, and the full agonist WIN55,212-2 did not prevent PSD loss elicited by direct application of glutamate, suggesting a presynaptic mechanism. Prolonged exposure to WIN55,212-2, but not the partial agonist THC, desensitized the protective effect. Treating cells that had undergone PSD loss with WIN55,212-2 reversed the loss and enabled recovery of a full complement of synapses. The modulation of synaptic number by acute and prolonged exposure to cannabinoids may account for some of the effects of these drugs on the plasticity, survival and function of neural networks. Kim, H.J., Waataja, J.J. and Thayer, S. Cannabinoids Inhibit Network-Driven Synapse Loss Between Hippocampal Neurons in Culture. Journal of

Pharmacology and Experimental Therapeutics, epub ahead of print.

Opioid Receptor Subtype Expression Patterns Differ in HIV tat-exposed Glial Cell Populations: Implications for HIV- and Opioid-Induced Neuropathogenesis

Recent research suggests that substance abuse, including opiate use, may increase the risk or severity of HIV-1-associated neurological impairment, whereas glial cells and infiltrating macrophages are the predominant targets of HIV infection in the brain. Opioid analgesia is also thought to involve glial signaling, and there is a question as to whether pain management in HIV patients would exacerbate disease. To explore the role of opioids and glial signaling in HIV-induced neuronal dysfunction, and to complement their findings in animal models, a team of NIDA-supported investigators characterized expression of mu, delta and kappa opioid receptors on cultured microglia and astrocytes in the absence or presence of low doses of morphine and/or HIV Tat. Morphine treatment caused significantly decreased cell surface expression of opioid receptors in microglia but not in astrocytes. However, morphine treatment in the presence of Tat significantly increased intracellular expression of opioid receptors and prevented morphine-induced cell surface opioid receptor down-regulation in microglia. These findings show that cell surface opioid receptor expression is regulated by morphine differently in microglia and astrocytes, and that HIV-Tat could increase opioid receptor signaling in microglia by increasing receptor expression and/or altering ligand-induced trafficking of opioid receptors. The significance of these findings is that opiate exposure could either predispose HIV-infected individuals to CNS infection by suppressing microglial immune responses, or precipitate neurological abnormalities by increasing viral burden in the CNS. Turchan-Cholewo, J., Dimayuga, F.O., Ding, Q., Keller, J.N., Hauser, K.F., Knapp, P.E. and Bruce-Keller, A.J. Cell-Specific Actions of HIV-Tat and Morphine on Opioid Receptor Expression in Glia. Journal of Neuroscience Research, epub ahead of print.

Methamphetamine Inhibits Innate Immunity Against HCV Infection

There is little known about the interactions between hepatitis C virus (HCV) and methamphetamine, which is a highly abused psychostimulant and a known risk factor for human immunodeficiency virus (HIV)/HCV coinfection. A recent study by NIDA-supported investigators examined whether methamphetamine has the ability to inhibit innate immunity in the host cells, facilitating HCV replication in human hepatocytes. Methamphetamine inhibited intracellular interferon alpha expression in human hepatocytes, which was associated with the increase in HCV replication. In addition, methamphetamine also compromised the anti-HCV effect of recombinant interferon alpha. Methamphetamine also inhibited the expression of the signal transducer and activator of transcription 1, a key modulator in interferon-mediated immune and biological responses, and down-regulated the expression of interferon regulatory factor-5, a crucial transcriptional factor that activates the interferon pathway. These in vitro findings that methamphetamine compromises interferon alpha-mediated innate immunity against HCV infection indicates that methamphetamine exposure may be a cofactor in the immunopathogenesis of HCV disease. Ye, L., Peng, J.S., Wang, X., Wang, Y.J., Luo, G.X. and Ho, W.Z. Methamphetamine Enhances Hepatitis C Virus Replication in Human Hepatocytes. Journal of Viral Hepatitis, 15, pp. 261-270, 2008.

SynCAMs Organize Synapses Through Heterophilic Adhesion

Synapses are asymmetric cell junctions with precisely juxtaposed presynaptic

and postsynaptic sides. Trans-synaptic adhesion complexes are thought to organize developing synapses. The molecular composition of these complexes, however, remains incompletely understood, precluding us from understanding how adhesion across the synaptic cleft guides synapse development. Dr. Thomas Biederer and colleagues define two immunoglobulin super-family members, SynCAM 1 and 2, that are expressed in neurons in the developing brain and localize to excitatory and inhibitory synapses. They function as cell adhesion molecules and assemble with each other across the synaptic cleft into a specific, transsynaptic SynCAM 1/2 complex. Additionally, SynCAM 1 and 2 promote functional synapses as they increase the number of active presynaptic terminals and enhance excitatory neurotransmission. The interaction of SynCAM 1 and 2 is affected by glycosylation, indicating regulation of this adhesion complex by posttranslational modification. The SynCAM 1/2 complex is representative of the highly defined adhesive patterns of this protein family, the four members of which are expressed in neurons in divergent expression profiles. SynCAMs 1, 2, and 3 each can bind themselves, yet preferentially assemble into specific, heterophilic complexes as shown for the synaptic SynCAM 1/2 interaction and a second complex comprising SynCAM 3 and 4. Their results define SynCAM proteins as components of novel heterophilic transsynaptic adhesion complexes that set up asymmetric interactions, with SynCAM proteins contributing to synapse organization and function. Fogel, A.I., Akins, M.R., Krupp, A.J., Stagi, M., Stein, V. and Biederer, T. SynCAMs Organize Synapses through Heterophilic Adhesion. Journal of Neuroscience, 27(46), pp. 12516-12530, 2008.

Methamphetamine Facilitates Vesicular Accumulation of Glutamate in Corticostriatal Glutamatergic Terminals

Dr. Bryan Yamamoto's group was first to show that excess glutamate (GLU) released in the striatum plays a critical role in methamphetamine (METH) neurotoxicity to dopaminergic neuron terminals, probably via glutamatergic excitotoxicity. Their recent studies provide evidence of how striatal glutamatergic transmission is increased by METH. The uptake and storage of GLU in synaptic vesicles is a primary step in glutamatergic neurotransmission. The proteins responsible for GLU uptake by vesicles in corticostriatal glutamatergic neurons are the vesicular GLU transporter-1 (VGLUT1) and the vesicle-associated glyceraldehyde-3-phosphate dehydrogenase (GAPDH)/3-phosphoglycerate kinase complex that generates the ATP (which translates into energy) required for uptake by VGLUT1. However, there was no information linking VGLUT1 with METH. The Yamamoto group now reports that METH increases cortical VGLUT1 mRNA, striatal VGLUT1 protein in sub-cellular fractions, and the Vmax (maximal rate of GLU uptake) of striatal vesicular GLU uptake. METH also increases GAPDH protein in the crude vesicle fraction. METH-induced increases in cortical VGLUT1 mRNA, as well as striatal VGLUT1 and GAPDH, are GABA(A) receptor-dependent because they are blocked by GABA(A) receptor antagonism in the substantia nigra. These results show that VGLUT1 can be dynamically regulated via a polysynaptic pathway to facilitate vesicular accumulation of GLU for subsequent release after METH. Specifically, based on earlier work of the Yamamoto group, it is evident that METH-induced increases in striatonigral GABA release act via nigral GABA(A) receptors that in turn decrease GABAergic nigrothalamic activity, disinhibit thalamocortical activity, and increase corticostriatal GLU release. The time course of enhanced VGLUT1 function parallels the protracted increases in extracellular GLU within the striatum. The underlying transcriptional events mediating the VGLUT1 and GAPDH sensitivities to METH have yet to be determined. Mark, K.A., Quinton, M.S., Russek, S.J., Yamamoto, B.K. Dynamic Changes in Vesicular Glutamate Transporter 1 Function and Expression Related to Methamphetamine-Induced Glutamate Release. Journal of Neuroscience, 27(25), pp. 6823-6831, 2007.

Nicotine, Immunity and Disease

Nicotine acts through two cholinergic receptors: nicotinic and muscarinic. A recent finding points to the involvement of both muscarinic receptors (mAChRs) and nicotinic receptors (nAChRs) on lymphocytes. Therefore, it is likely that these cholinergic receptors play a role in regulating immune responses. Indeed, activation of nAChRs inhibits adaptive and innate immune responses. However, very little is known about the role of mAChRs in the regulation of immune and inflammatory responses. Chronic nicotine administration has been demonstrated to increase the lung burden of influenza virus and Cryptococcus neoformans; two very prominent diseases associated with AIDS. As acetylcholine can react with both nicotinic and muscarinic receptors, it is difficult to ascertain whether the muscarinic (mAChR) and/or nicotinic (nAChR) receptors are driving different actions. In a recent study using selective muscarinic agonists/antagonists, Dr. Sopori's group showed that while mAChR agonists (oxotremorine) stimulate, mAChR antagonists (atropine) inhibit immune and inflammatory responses. Thus, activation of nicotinic and muscarinic receptors has opposite effects on the immune/inflammatory responses. Razani-Boroujerdi, S., Behl, M., Hahn, F.F, Pena-Philippides, J.C., Hutt, J. and Sopori, M.L. Role of Muscarinic Receptors in the Regulation of Immune and Inflammatory Responses. Journal of Neuroimmunology, 194, pp. 83-88, 2008.

Persistent Alterations in Mesolimbic Gene Expression with Abstinence from Cocaine Self-Administration

Addiction is a chronic relapsing disorder characterized by compulsive drug seeking behavior in the face of adverse consequences. This raises the question of what factors mediate persistent changes in the brain following abstinence that increase the probability of relapse. NIDA funded investigators at Pennsylvania State University now show persistent changes in mesolimbic gene expression that lasts longer than 100 days following 10 days of chronic cocaine administration in rats. At 100 days the expression of fos, arc, egr1, and Nr4a1 in the nucleus accumbens and prefrontal cortex were all significantly reduced when compared to controls. Future research will determine whether these decreases in gene expression are causally related to relapse and whether changes in chromatin remodeling affect these changes. Chromatin remodeling refers to enzymatic modification of histone proteins that surround DNA on a chromosome. Enzymatic modifications of histones are thought to determine which genes are expressed or repressed. Also, it will be of interest to determine whether persistent changes of gene expression seen in the periphery can predict relapse. Freeman, W.M., Patel, K.M., Brucklacher, R.M., Lull, M.E., Erwin, M., Morgan, D., Roberts, D.C.S. and Vrana, K.E. Persistent Alterations in Mesolimbic Gene Expression with Abstinence from Cocaine Self-Administration. Neuropsychopharmacology, 2007, epub ahead of print.

Homer Proteins: An Unanticipated Role in the Immune System

Homer proteins are cytoplasmic scaffolds with important functions at the excitatory synapses of some neurons. Dr. Worley and colleagues have previously shown that mouse mutants in Homer2 have increased behavioral sensitivity to cocaine. Although the neuronal functions of Homer proteins are becoming better understood, Homers have a wide tissue distribution including expression in the immune system. In order to study the neuronal functions of Homer proteins in living animals, Dr. Worley generated mice with deletions in each of the Homer subtypes. Interestingly mice with a Homer3 deletion had abnormal lymph nodes suggesting a potential defect in immune function. To further investigate this, Dr. Worley grew T cells (from the immune system) that lacked the Homer2 and Homer3 subtypes. Dr. Worley and co-workers found that Homer2 and 3 negatively regulate T cell activation. A variety of experimental strategies was then used to elucidate the molecular basis of this

negative regulation. It was found that Homer2 and 3 could directly bind to specific NFAT transcription factor subtypes that regulate Interleukin-2 expression in T cells. Normally calcineurin, a calcium-stimulated protein phosphatase, binds the NFAT transcription factor in an identical location leading to NFAT activation. However Homer binding can compete with calcineurin binding, reducing NFAT function. Interestingly Homer3 binds NFAT through a special EVH1 protein domain and Dr. Worley found that this domain can be phosphorylated by the AKT1 protein kinase, which reduces Homer binding to NFAT. Thus Homer proteins can serve as structural as well as molecular scaffolds that are capable of integrating some of the multiple signaling pathways that regulate Interleukin-2 expression and T cell function. The serendipitous observation of an immune cell phenotype in the Homer mutant mice allowed Dr. Worley and colleagues to characterize the Homer/NFAT/calcineurin/AKT1 signaling pathways in great detail in immune cells. For the future, researchers will likely turn their attention back to the nervous system to see if these Homer regulated pathways function similarly in neurons. Huang, G.N., Huso, D.L., Bouyain, S., Tu, J., McCorkell, K.A., May, M.J., Zhu, Y., Lutz, M., Collins, S., Dehoff, M., Kang, S., Whartenby, K., Powell, J., Leahy, D. and Worley, P.F. NFAT Binding and Regulation of T Cell Activation by the Cytoplasmic Scaffolding Homer Proteins. Science, 319 (5862), pp. 476-481, 2008.

BDNF/Trk Activity Is Essential for Cocaine Responses in Adult and Increased Neuroplasticity in Postweanling Mice

It has been reported that drug-induced conditioned place preference increases with age. The molecular mechanisms underlying the increased psychostimulant effect with increased age are not fully understood. A group of NIDA researchers at Temple University, led by Dr. Ellen Unterwald, decided to look into the changing cell and molecular activities of the learning and memory circuitries by comparing the postweanling, periadolescent, and adult male CD-1 mice exposed to cocaine (20 mg/kg). The rewarding effects of cocaine were assessed, as were the response to a Trk antagonist and the regulation of dopamine and cAMP-regulated phosphoprotein, 32 kDa (DARPP-32). DARPP-32 protein has been previously found to be specifically required for drug-induced place preference. The team observed that cocaine was rewarding in both periadolescent and adult mice using a conditioned place preference procedure. In contrast, postweanling mice failed to demonstrate significant cocaine-induced place preference. Because neurotrophins, including brain-derived neurotrophic factor (BDNF) and TrkB are developmentally regulated, their role in the age specific effects of cocaine was determined using the Trk receptor antagonist K252a. Their results suggest that in postweanling mice activation of Trk receptors, likely by endogenous BDNF, reduced the rewarding effects of cocaine, because the pretreatment of mice with Trk receptor antagonist K252a enhanced the development of cocaine place preference. Furthermore, repeated cocaine was associated with increased DARPP-32 protein in postweanlings and DARPP-32 induction was prevented with K252a. These results indicate an association between BDNF, cocaine reward, and DARPP-32 in postweanling mice. Meanwhile, Dr. Unterwald points out that although inhibition of Trk clearly enhanced the acquisition of cocaine place preference and diminished the upregulation of DARPP-32, these data do not prove a direct cause and effect relationship between DARPP-32 levels and the absence or presence of a rewarding effect of cocaine. The team plans to study further whether postweanling mice are more or less sensitive to the rewarding properties of cocaine. Niculescu, M., Perrine, S.A., Miller, J.S., Ehrlich, M.E., Ellen, M. and Unterwald E.M. Trk: A Neuromodulator of Age-Specific Behavioral and Neurochemical Responses to Cocaine in Mice. Journal of Neuroscience, 28, pp. 1198-1207, 2008.

Regulation of CB1 Cannabinoid Receptor Trafficking by the

Adaptor Protein AP-3

G-Protein coupled receptors (GPCRs) are generally thought of as cell surface receptors, although they are not always cell surface receptors;GPR30 as an example. But for GPCRs that function at the cell surface, it is generally thought that they need to be at the cell surface to be functional. The cannabinoid receptor 1 (CB1) is a GPCR found both at the cell surface and in intracellular vesicles. Dr. Devi recently reported that the majority of the endogenous CB1 receptors do not reach the cell surface. How and why these receptors traffic to the vesicles has been unknown and was the focus of the present study. Rozenfeld and Devi found that intracellular endogenous CB1 receptors do not have an endocytic origin. Their data suggest that CB1 receptors traffic directly to lysosomes rather than trafficking first to the cell surface and then trafficking to the lysosomes by endocytosis. They found that these receptors associate with the adaptor protein AP-3 and follow an AP-3-dependent trafficking from the biosynthetic compartment to the lysosomal compartment. If they reduced the expression of AP-3 by knocking down the delta subunit (AP-3) they observed enhanced cell surface localization of CB1 receptors. Finally, they showed that CB1 receptors in the late endosomal/lysosomal compartment are associated with heterotrimeric G proteins and appear to mediate signal transduction. These results suggest that intracellular CB1 receptors may be functional and that their spatial segregation may significantly affect receptor function. Rozenfeld, R. and Devi, L.A. Regulation of CB1 Cannabinoid Receptor Trafficking by the Adaptor Protein AP-3. The FASEB Journal, epub ahead of print March 7, 2008.

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

Research Findings - Basic Behavioral Research

Sex Differences and Hormonal Factors in the Acquisition and Maintenance of Cocaine Self-administration in Adolescent Rat

Previous research has reported that females more rapidly acquire self-administration than males, that a greater percentage of females acquire self-administration, and that females exhibit greater motivation for cocaine as assessed via a progressive ratio (PR) schedule. Additionally, cocaine self-administration in females is modulated by estrogen, whereas testosterone has not been found to play a role in cocaine self-administration in males. Dr. Wendy Lynch compared these behavioral outcomes in male and female rats during adolescence. Replicating prior findings with adult rats, female adolescents acquired cocaine self-administration more rapidly than males, a greater percentage of females than males acquired self-administration, and females received more infusions than males under the PR schedule. In females, serum estradiol concentration, but not progesterone concentration, was positively correlated with number of infusions obtained under the PR schedule, and for four of the five rats it accounted for 50% of the variance in number of infusions. Additionally, number of infusions varied with the estrus cycle. In males however, serum testosterone was unrelated to the number of infusions. In a parallel control study, Dr. Lynch compared acquisition of lever-pressing for sucrose reinforcement and subsequent behavior under a PR schedule in adolescent males versus females, in order to assess potential sex differences in general learning and motivation. She found that males and females did not differ in the rate of acquisition, nor did they differ in the number of pellets received under the PR schedule. This research suggests that the observed sex differences in cocaine self-administration in adults, as well as the modulation by estrogen and the estrus cycle, are reflective of sex differences and underlying mechanisms that are present in adolescents. The contribution of the organization and activational effects of gonadal hormones in these sex differences remains to be understood. Lynch, W.J. Acquisition and Maintenance of Cocaine Self-Administration in Adolescent Rats: Effects of Sex and Gonadal Hormones. Psychopharmacology, 197, pp. 237-246, 2008.

Cued Reinstatement of MDMA (Ecstasy)-Seeking is Predicted by Magnitude of Prior Self-administration in Rats

MDMA produces subjective effects that resemble those characteristic of both hallucinogenic drugs and the psychostimulants. Animal studies using progressive ratio schedules of i.v. self-administration, to examine relative reinforcement, have demonstrated that MDMA is a weak reinforcer compared to stimulants (dopamine releasers) such as cocaine and methamphetamine. While there have been reports that some MDMA users meet diagnostic criteria for dependence, there is still controversy over the addictive properties of this drug,

given the typical pattern of human abuse. That is, while most individuals abuse ecstasy on an intermittent basis, there are data to suggest that some develop a problematic pattern of abuse that is characteristic of addiction. One important feature of addiction is the relapse to drug taking behavior seen after a period of abstinence. The reinstatement model mimics features of human relapse in that animals develop self-administration, drug taking is extinguished, and then a return to drug seeking can be prompted by re-exposure to the drug, re-introduction of drug-associated cues, or stress. A recent study published by Dr. George Rebec and colleagues examined individual differences in i.v. self-administration of MDMA and assessed whether or not contingent drug cues, that readily reinstate psychostimulant seeking behavior, can also prompt a return to drug seeking for MDMA. In this study, seven animals acquired self-administration on a FR5 operant schedule, with a mean dose of 0.30 mg/kg/infusion. As has previously been reported for this drug, there were widespread differences in the magnitude of self injection, ranging from 4 to 135 responses/session. After 14 daily 2-hour sessions all animals underwent extinction, during which time saline was substituted for drug infusions. As expected, all rats extinguished lever press behavior (mean presses/session = 1.29). Reinstatement testing followed with drug-associated cue presentations delivered contingently upon responses made on the lever previously associated with MDMA infusions; however, saline was delivered through the i.v. catheters during this testing. Responses increased to an average of 33.57, but again with great variability across animals (SEM+15.33). The interesting finding from this study was that a strong positive correlation was found between individual mean response rates during the last five self-administration sessions and the rate of responding during cue presentation during reinstatement ($r=0.97$, $p<0.001$). Additional tests to examine drug-induced reinstatement were conducted with 5.0 mg/kg MDMA, (a dose known to elicit behavioral activation), and the researchers found no evidence for drug primed reinstatement (contrary to what is observed for cocaine or amphetamine). While preliminary, these findings are important not only because they demonstrate great individual variability in MDMA self-administration that parallels observations of human abuse patterns with this drug, but because they suggest that these different phenotypes may be predictive of the chronic relapsing condition of drug addiction with ecstasy. Animals that have higher rates of cocaine intake also are more vulnerable to reinstate drug-seeking behavior. However, unlike cocaine and amphetamine, MDMA relapse does not appear to be triggered by drug priming. These differences may reflect the drug's different patterns of neurotransmitter activation, as MDMA increases synaptic levels of both serotonin and dopamine. Ball, K.T., Walsh, K.M. and Rebec, G.V. Reinstatement of MDMA (Ecstasy) Seeking by Exposure to Discrete Drug-Conditioned Cues. Pharmacology, Biochemistry and Behavior, 87, pp. 420-425, 2007.

Reducing Dopamine Transmission Increases Demand for Cigarettes and Reduces Attentional Bias

NIDA K08 awardee, Brian Hitsman, investigated the effect of depleting the amino acid tyrosine/phenylalanine, which results in reduced dopamine transmission, on attentional bias to smoking related cues, the relative value of cigarettes, craving, and mood. To do this, smokers were restricted to a low protein diet for 24 hours, and fasted overnight, prior to a test session. Using a within-subject, double-blind methodology, each participant was given a tyrosine/phenylanine-free beverage (depleted session), or a beverage with balanced amino acids (non-depleted session). Reaction times during a modified Stroop task containing smoking-related words and neutral words were used to assess attentional bias. Relative value of cigarettes versus money was assessed using a cigarette purchase task (CPT). The brief questionnaire of smoking urges (QSU-brief) was used to assess craving and mood, and the Hamilton depression rating scale (HDRS) was used to assess depressive symptoms. There were no differences between the depleted and non-depleted

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sessions in the QSU-brief or the HDRS. The "depleted session" was associated with a significant increase in intensity of demand for cigarettes relative to money. There was also a trend towards a more persistent willingness to purchase cigarettes during the "depleted session." There was a decreased attentional bias to smoking-related cues during the "depleted session;" however this was only present when it was preceded by the "non-depleted session." The finding that tyrosine/phenylanine depletion caused an increased demand for cigarettes is consistent with the literature. However the lack of an effect on craving was surprising. It is suggested that this discrepancy may be due to different mechanisms of reducing dopamine transmission (e.g., dopamine antagonist administration versus dopamine depletion). Acute tyrosine/phenylanaline depletion may influence smoking behavior. However additional studies (perhaps with alternative measures of craving and attention) are needed. Hitsman, B., MacKillop, J., Lingford-Hughes, A., Williams, T.M., Ahmad, F., Adams, S., Nutt, D.J. and Munafo, M.R. Effects of Acute Tyrosine/Phenylalanine Depletion on the Selective Processing of Smoking-Related Cues and the Relative Value of Cigarettes in Smokers. Psychopharmacology, 196, pp. 611-621, 2008.

CRF Receptors Mediate Nicotine-Seeking Behavior in an Animal Model of Relapse

Smokers trying to quit often relapse when under stress. NIDA grantee Dr. Bruijnzeel and colleagues have modeled human relapse with an animal model called "response reinstatement". In this model, rats previously allowed to self-administer nicotine by pressing a lever are put through a period of extinction, when no nicotine is available. Over time, the nicotine seeking behavior (e.g., leverpress behavior) stops, or extinguishes. Once the behavior has been extinguished, a mild footshock reinstates the nicotine-seeking behavior and the animal once again engages in lever pressing behavior in an attempt to obtain nicotine (nicotine seeking behavior). Since both norepinephrine and corticotropin-releasing factor (CRF; a hormone involved in biological responses to stress) have been implicated as modifiers of stress-induced relapse, the effects of pretreatment with clonidine (an _2 adrenergic agonist) and the CRF antagonist D-Phe CRF(21-41) were evaluated. Blockade of CRF receptors significantly attenuated footshock-induced reinstatement of leverpress behavior (e.g., nicotine-seeking), as did clonidine treatment. Blockade of CRF receptors appeared to be selective for nicotine-seeking, as control rats that lever-pressed for food returned to their lever-pressing behavior. Thus, pretreatment with D-Phe CRF(21-41) attenuated footshock-induced reinstatement of nicotine-seeking, but not food-seeking. This was not the case with clonidine because it significantly reduced both nicotine- and food-seeking. These results suggest that CRF receptors may be a potential target for pharmacotherapies aimed at reducing stress-induced relapse to smoking. Zislis, G., Desai, T.V., Prado, M., Shah, H.P. and Bruijneel, A.W. Effects of the CRF Antagonist D-Phe CRF(21-41) and the _2-adrenergic Receptor Agonist Clonidine on Stress-Induced Reinstatement of Nicotine-Seeking Behavior in Rats. Neuropharm., 53, pp. 958-966, 2007.

Cocaine's Behavioral Differences in Adolescence Suggests a Developmental Dissociation Between Locomotor and Reward Effects

Adolescence is a period of development associated with the highest incidence of drug use initiation. Early use is predictive of later problem abuse behaviors, dependence and addiction. Therefore recent research efforts using animal models have examined age-related differences in the sensitivity to drugs of abuse, and the vulnerability to initiate drug taking behavior. These studies report that periadolescent rats (post-natal days 21-37) are less responsive to psychomotor stimulant effects, show a similar or lower degree of

psychostimulant-induced sensitization, lower neuroendocrine effects from cocaine, and less taste aversion with amphetamine. However, there are conflicting reports that indicate no age-related difference in operant responding or conditioned place preference for cocaine. Thus, Dr. Loren Parsons and his colleagues undertook an investigation to examine both locomotor and reinforcing effects of cocaine in periadolescent (PA) versus adult (A) rats, and also assessed basal extracellular levels of dopamine (DA) in the nucleus accumbens after i.v. or i.p. drug administration. To test for differences in cocaine induced motor activity, testing was begun on PND 37-39 (periadolescent) or 73-75 (adult) and animals were injected with 10 or 20mg/kg i.p. cocaine versus vehicle on days 1, 5, 10 and 15 of the study. Separate groups of animals were implanted with i.v. catheters on PND 29-31 (PA) or 67-69 (A) and tested for spontaneous acquisition of cocaine self-administration (0.25mg/infusion) 7-9 days later. Other groups received either i.v. or i.p. cocaine on PND 30-33 or 70-74 to conduct dialysis studies. Cocaine was administered i.v. in three successive doses from 0.37 to 2.92 mg/kg following by dialysate collection to quantify dopamine levels and cocaine concentrations in the nucleus accumbens. In the i.p. injection group, animals received 20 mg/kg prior to dialysate collection. On the measure of locomotor behavior, PA and A groups were no different in their response to acute cocaine. With repeated administration of 10 mg/kg, both age groups showed evidence of psychostimulant sensitization, but under different conditions (i.e., dose and day). Rate of acquisition and amount of drug self-administered was no different between the two age groups. Also, both basal DA and DA in vivo recovery revealed no difference between groups. However, i.v. cocaine produced higher brain cocaine concentrations in the A group after mid- and high-dose injections; (no difference was noted following the i.p. injection). The results suggest PA hyposensitivity to i.p. cocaine's effects on motor activity, even though levels of extracellular DA were no different. Thus, age differences were seen on drug-induced locomotor activation but not on measures of drug reward, which suggest a developmental dissociation between the locomotor activating versus reinforcing effects of cocaine. Collectively, this and other studies that attempt to probe mechanisms for developmental differences in drug response suggest that the differences are complex, may depend on the psychostimulants used, the behaviors that are measured, and the developmental period. Frantz, K.J., O'Dell, L.E. and Parsons, L.H. Behavioral and Neurochemical Responses to Cocaine in Periadolescent and Adult Rats. Neuropsychopharmacology, 32, pp. 625-637, 2007.

Noradrenergic Transport Inhibitors Reinstate Cocaine-Seeking Behavior

The present study examined the ability of selective NE transport inhibitors to mimic or modulate the relapse-inducing effects of cocaine in the reinstatement model in squirrel monkeys. Twelve animals acquired i.v. cocaine self administration and maintained stable responding for 6-8 months. After responding was extinguished, tests for cocaine-primed (plus cue presentation) reinstatement were conducted and cycles of cocaine self-administration followed by repeated extinction were imposed between drug tests. The following tests for reinstatement were conducted: priming with cocaine (0.1 to 1.0 mg/kg), the selective dopamine transport inhibitor GBR 12909 (GBR), and selective NE transport inhibitors (nisoxetine and talsupram). Antagonism experiments were conducted to evaluate the degree to which DA and/or NE receptor mechanisms contribute to the cocaine-like priming effects of GBR and nisoxetine. Priming with GBR dose-dependently reinstated cocaine seeking. Both NE transport inhibitors also reinstated cocaine seeking but only to 36-55% of the maximal rates engendered by cocaine or GBR. All three drugs also enhanced the ability of cocaine to prime reinstatement; however the NE transport inhibitors were without effect on the ability of GBR to induce reinstatement. Antagonist tests with the DA receptor antagonist flupenthixol

(flu), an alpha1 NE antagonist, or the alpha2 NE agonist clonidine, before priming doses of GBR or nisoxetine produced the following results: flu reducing priming effects of GBR only, while the alpha1 antagonist, the alpha2 agonist, and a beta NE antagonist all blocked nisoxetine priming only. Priming effects of cocaine were reduced by flu and clonidine only. The finding that NE transport inhibitors can reinstate cocaine seeking, (albeit only one half as effectively as the DA transport blocker), contrasts with observations for a relatively minor role of NE transmitter systems in rodent relapse models. The results suggest that NE receptors systems involving both alpha and beta NE receptor subtypes may be involved in relapse to cocaine seeking, possibly via DA modulation by NE in the frontal cortex. Alternatively, these receptor systems may be involved as a function of their role in endogenous stress mechanisms. Platt, D.M., Rowlett, J.K. and Spealman, R.D. Noradrenergic Mechanisms in Cocaine-Induced Reinstatement of Drug Seeking in Squirrel Monkeys. Journal of Pharmacology and Experimental Therapeutics, 322, pp. 894-902, 2007.

Methamphetamine Self-Administration and Voluntary Exercise Have Opposite Effects on Neuroplasticity

George Koob and his colleagues tested the effects of methamphetamine self-administration and running wheel activity on cell proliferation, survival and death in the medial prefrontal cortex (mPFC) of the rat. Different group of rats had either intermittent 1 hr access to methamphetamine (I-ShA), or daily 1hr (ShA) or 6 hr (LgA) access to methamphetamine self-administration. Separate groups of rats had either access to running wheels in the home cage (voluntary exercise) or no access (exercise controls). Results showed that self-administration of methamphetamine was at a stable and low level for Group I-ShA. Groups ShA and LgA both showed escalation of methamphetamine self-administration over sessions with LgA showing the largest increase in self-administration. Therefore, the self-administration data from the I-ShA, ShA, and LgA groups provide evidence for distinct patterns of methamphetamine intake that may be related to human patterns of use: recreational, chronic abuse, and dependence. Histological results indicated that Group I-ShA showed an increase in cell proliferation and survival, but that ShA and LgA showed decreases in proliferation and survival. All groups showed increased cell death. Voluntary exercise enhanced proliferation and survival but, in contrast to methamphetamine exposure, did not alter cell death or mature cell phenotypes. Furthermore, enhanced cell survival by I-ShA and voluntary exercise had profound effects on gliogenesis with differential regulation of oligodendrocytes versus astrocytes. In addition, new cells in the adult mPFC were detected, although enhanced cell survival by I-ShA and voluntary exercise did not result in increased neurogenesis. These findings demonstrate that mPFC gliogenesis is vulnerable to psychostimulant abuse and physical activity with distinct underlying mechanisms. The susceptibility of mPFC gliogenesis to even modest doses of methamphetamine could account for the pronounced pathology linked to psychostimulant abuse. Mandyam, C.D., Wee, S., Eisch, A.J. Eisch, Richardson, H.N., and Koob, G.F. Methamphetamine Self-Administration and Voluntary Exercise Have Opposing Effects on Medial Prefrontal Cortex Gliogenesis. Journal of Neuroscience, 27, pp. 11442-11450, 2007.

Personality and Gender Moderate Amphetamine's Effects on Risk Taking

Dr. Harriet de Wit and her colleagues examined how gender and personality (temperament) moderate the effects of d-amphetamine on risk taking, measured by performance on the BART (Balloon Analogue Risk Task). Previous research indicates that stimulant drugs can either increase or decrease impulsive behavior, depending upon a number of factors including gender and variation in personality traits related to reward and punishment sensitivity. The

present study assessed personality using the Multidimensional Personality Questionnaire Brief Form, because this questionnaire is an empirically derived measurement instrument that assesses three orthogonal factors related to reward sensitivity, behavioral impulsivity, and negative affect. These include the personality dimensions of Agentic Positive Emotionality (AgPEM), which is thought to reflect individual differences in the function of ascending VTA dopamine projections that modulate behavioral approach and incentive motivation; Constraint (CON), which measures impulsive spontaneity and approach-versus-avoidance of physical harm, which could be relevant to drug-induced changes in the relative frequency of impulsive choices versus successful impulse control; and Negative Emotionality (NEM), which measures anxiety proneness, interpersonal alienation and aggression, which could be relevant to drug-induced changes in aggressive impulsive behavior. Forty healthy men and women, aged 18 to 35, completed the BART after ingesting placebo or d-amphetamine (10, 20 mg). There were three main findings. First, for male participants, there were strong, positive correlations between the personality trait of AgPEM and amphetamine-induced increases in risk taking on the BART risk task. Second, there was evidence of discriminant validity, as correlations between AgPEM and drug-induced risk behavior were significantly greater than correlations with trait CON and trait NEM in the same participants. Third, 20 mg d-amphetamine significantly decreased risk behavior in men with scores in the lower half of the distribution for AgPEM, and significantly increased risk behavior in men with scores in the upper half of the distribution on AgPEM. The drug did not affect risk taking in women. Overall, the current findings suggest that the personality trait of AgPEM could constitute a preexisting risk factor (neural, metabolic, or behavioral characteristics) for amphetamine-induced changes in risk-taking in healthy young adult males, and could affect behavioral responses to stimulant drugs when used recreationally or therapeutically. White, T.L., Lejuez, C.W., and de Wit, H. Personality and Gender Differences in Effects of d-Amphetamine on Risk Taking. Experimental and Clinical Psychopharmacology, 15, pp. 599-609, 2007.

Emotional Environments Can Retune the Valence of Appetitive Versus Fearful Motivations Mediated by Nucleus Accumbens

In drug abuse research, the nucleus accumbens (NAc) is commonly thought of as part of "reward" circuitry, but in fact, it is well known that NAc mediates both appetitive motivation for rewards and fearful, defensive motivation towards threats. Appetitive and defensive motivations are generated in a graded manner along the rostral to caudal axis of the NAc shell, as shown by studies in Kent Berridge's and Anne Kelley's laboratories. Microinjections of the AMPA glutamate receptor inhibitor DNQX near the rostral pole of NAc elicit intense feeding and other appetitive behaviors and conditioned place preference; whereas such injections near the caudal pole evoke fearful behaviors such as distress vocalizations, defensive burying, and conditioned avoidance. Injections in more central areas produce a mixture of appetitive and fearful behaviors corresponding to their relative rostral-caudal position. In the current study, Reynolds and Berridge tested whether or not the valence of the behaviors generated at locations along the gradient could be retuned, or shifted, by the emotional valence of the external environment. They tested three different environments in a three chambered apparatus. One was a home-like environment (dark and quiet), the second was a conventional laboratory environment, and the third was stressful and over-stimulating (bright light and unpredictable presentations of loud punk-rock music). First they confirmed the rats' preference for the home environment and avoidance of the stressful one in an experiment where rats could self-administer selected pairs of environments (home vs. standard and standard vs. stressful). Rats could turn on the light and sound components of a specified environment by entering one end compartment, and then turn these off and another environment on by going to the opposite end. As expected, the animals

preferred to turn on the dark, quiet home condition over the standard condition, and they preferred the standard over the stressful environment. Next, they microinjected DNQX at various locations along the rostro-caudal axis of NAc, while rats were confined in one of the three environments, and observed the amounts of appetitive (eating) vs. fearful (defensive burying) behaviors. They found that environmental exposure shifted the gradient along the rostro-caudal axis of NAc shell. In the home environment, sites that elicited appetitive behaviors extended much more caudally than in the standard environment, and the 'fearful zone' shrank to about one-third of its original size. The opposite was true for exposure to the stressful environment, which extended sites that elicited fearful behaviors much more rostrally, confining sites that evoked purely appetitive behaviors to the rostral pole. Thus, at many intermediate sites, remapping by environmental ambience completely switched the appetitive vs. fearful valence of DNQX-motivated behaviors. These data suggest that corticolimbic circuits that involve NAc can flexibly retune affective-generating functions from moment to moment as the external environment changes. This remapping has implications for understanding how these circuits tune adaptive motivations and how these can be altered in disorders of pathological motivation such as addiction. Reynolds, S.M. and Berridge, K.M. Emotional Environments Retune the Valence of Appetitive Versus Fearful Functions in Nucleus Accumbens. Nature Neuroscience, 11(4), pp. 423-425, 2008.

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Research Findings - Behavioral and Brain Development Research

Prenatal Cocaine Exposure, Gender, and Preadolescent Substance Use and Other Health Risk Behaviors

Dr. Michael Lewis and his colleagues examined prenatal cocaine exposure, gender, and environmental risk as predictors of self-reported substance use, aggression, and a disregard for safety precautions on the Youth Risk Behavior Survey in a sample of 10.5 year olds (n = 154, including 60 who were prenatally exposed to cocaine). Gender tended to moderate the effects of prenatal cocaine exposure because exposure effects were found for boys but not girls. Boys who were prenatally exposed to cocaine reported engaging in more high-risk behavior. In examining individual outcomes, cocaine exposed boys had the highest scores for aggression, substance use, and a disregard for safety precautions, although these differences were significant only for the composite health risk behavior measure. The findings extend earlier work showing that prenatal cocaine exposure places boys at risk for problems of inhibitory control, emotional regulation, and antisocial behavior. Research is needed to examine whether the effects of prenatal cocaine on health risk behaviors persist into adolescence, when such behaviors tend to increase. Bennett, D., Bendersky, M., and Lewis, M. Preadolescent Health Risk Behavior as a Function of Prenatal Cocaine Exposure and Gender. Journal of Behavioral Pediatrics, 28(6), pp. 467- 472, 2007.

Longitudinal Analysis of the Effects of Prenatal Cocaine Exposure on Growth

Dr. Gale Richardson and her colleagues at the University of Pittsburgh investigated the effects of prenatal cocaine exposure on offspring growth from 1 through 10 years of age using a repeated-measures growth-curve model. Cross-sectional analyses showed that children exposed to cocaine during the first trimester (n = 99) were smaller on all growth parameters at 7 and 10 years, but not at 1 or 3 years, than the children who were not exposed to cocaine during the first trimester (n = 125). The longitudinal analyses indicated that the growth curves for the 2 groups diverged over time: children who were prenatally exposed to cocaine grew at a slower rate than children who were not exposed. These analyses controlled for other factors associated with child growth. This is the first study of the long-term effects of prenatal cocaine exposure to conduct longitudinal growth-curve analyses using four time points in childhood. Children who were exposed to cocaine during the first trimester grew at a slower rate than those who were not exposed. These findings indicate that prenatal cocaine exposure has a lasting effect on child development. Richardson, G.A., Goldschmidt, L., and Larkby, C. Effects of Prenatal Cocaine Exposure on Growth: A Longitudinal Analysis. Pediatrics,

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120(4), pp. e1017-1027, 2007.

fMRI and Working Memory in Adolescents with Prenatal Cocaine Exposure

This fMRI study examined prefrontal cortex activation during task performance on an n-back task with 34 adolescents, 17 who were exposed to cocaine and 17 who were not exposed. Five functionally derived regions of interest (ROI) were defined; in addition, 2 a priori anatomical ROIs were generated for Brodmann regions 10 and 46. Groups had similar performance on the n-back task (P >/= .4), with both showing a fewer number of correct responses on the 2-back than the 1-back (P < .001), indicating increased demands on working memory with greater task difficulty. In functionally derived ROIs, imaging results showed increased activation for both groups in the 2-back versus the 1-back condition. In anatomical ROIs, both groups showed greater activation in the 2-back versus the 1-back condition, with activation in the non-exposed group proportionally greater for the left prefrontal region (P = .05). In this sample of adolescents, participants who were exposed to cocaine and participants who were not exposed were similar in performance on an executive function task and in fMRI activation patterns during task performance. Hurt, H., Giannetta, J.M., Korczykowski, M., Hoang, A., Tang, K.Z., Betancourt, L., Brodsky, N.L., Shera, D.M., Farah, M.J., and Detre, J.A. Functional Magnetic Resonance Imaging and Working Memory in Adolescents with Gestational Cocaine Exposure. Journal of Pediatrics, 152(3), pp. 371-377, 2008.

Smoking During Teenage Pregnancies and Offspring Behavioral Problems

Dr. Nancy Day and her colleagues at the University of Pittsburgh prospectively examined the relationship between prenatal tobacco exposure (PTE) and child behavior in a birth cohort of 357 offspring of teenage mothers. PTE was defined as any exposure across pregnancy and, in separate analyses, exposure within each trimester. Outcomes included measures of behavior problems, activity, and attention. On average, the children were 6.4 years of age, 48% were females, and 69% were Black. Data on maternal tobacco and other substance use were collected prenatally and postnatally: 46% of the mothers smoked in the first trimester and 58% smoked 6 years later. Child urinary cotinine measured exposure to environmental tobacco smoke (ETS). PTE predicted significantly increased offspring activity; impulsivity; and aggression, externalizing, and total behavior problems in step 1. PTE remained a significant predictor of increased activity when maternal psychological characteristics, home environment, and ETS were added. The results were similar when PTE was examined by trimesters, although later pregnancy tobacco exposure predicted the most behavioral outcomes. In the final model, PTE (all three trimesters) and PTE (second trimester) were significant predictors of increased activity and attention problems, respectively. Other predictors of child behavior included maternal anxiety, depression, hostility, and home environment. ETS was not a significant predictor of child behavior when PTE was considered. Smoking during pregnancy among adolescents is a significant predictor of increased activity and attention problems in their offspring after controlling for covariates in the prenatal and current environments. Smoking cessation interventions are recommended for this population to avoid the effects of PTE on the offspring of pregnant adolescents. This is particularly important because these mothers will likely become pregnant again and many will increase their level of tobacco use as they mature. Cornelius, M.D., Goldschmidt, L., DeGenna, N., and Day, N.L. Smoking During Teenage Pregnancies: Effects on Behavioral Problems in Offspring. Nicotine and Tobacco Research, 9(7), pp. 739-750, 2007.

Planned Meetings

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Volumetric MRI Study of Brain in Children with Intrauterine Exposure to Cocaine, Alcohol, Tobacco, and Marijuana

This study used volumetric MRI to study brain volumes of thirty-five 10- to 14-year-old children with (n=14) and without (n=21) intrauterine exposure to cocaine, alcohol, cigarettes, or marijuana. Volumetric MRI was performed to determine the effect of prenatal drug exposure on volumes of cortical gray matter; white matter; subcortical gray matter; cerebrospinal fluid; and total parenchymal volume. Head circumference was also obtained. Analyses of each individual substance were adjusted for demographic characteristics and the remaining 3 prenatal substance exposures. Regression analyses adjusted for demographic characteristics showed that children with intrauterine exposure to cocaine had lower mean cortical gray matter and total parenchymal volumes and smaller mean head circumference than comparison children. After adjustment for other prenatal exposures, these volumes remained smaller but lost statistical significance. Similar analyses conducted for prenatal ethanol exposure adjusted for demographics showed significant reduction in mean cortical gray matter; total parenchymal volumes; and head circumference, which remained smaller but lost statistical significance after adjustment for the remaining 3 exposures. Notably, prenatal cigarette exposure was associated with significant reductions in cortical gray matter and total parenchymal volumes and head circumference after adjustment for demographics that retained marginal significance after adjustment for the other 3 exposures. Finally, as the number of exposures to prenatal substances grew, cortical gray matter and total parenchymal volumes and head circumference declined significantly with smallest measures found among children exposed to all 4. These data suggest that intrauterine exposures to cocaine, alcohol, and cigarettes are individually related to reduced head circumference; cortical gray matter; and total parenchymal volumes as measured by MRI at school age. Adjustment for other substance exposures precludes determination of statistically significant individual substance effect on brain volume in this small sample; however these substances may act cumulatively during gestation to exert lasting effects on brain size and volume. Rivkin, M.J., Davis, P.E., Lemaster, J.L., Cabral, H.J., Warfield, S.K., Mulkern, R.V., Robson, C.D., Rose-Jacobs, R., and Frank, D.A. Volumetric MRI Study of Brain in Children with Intrauterine Exposure to Cocaine, Alcohol, Tobacco, and Marijuana. Pediatrics, 121(4), pp. 741-750, 2008.

Methadone Maintenance and Breastfeeding in the Neonatal Period

In a sample of methadone-maintained breastfeeding women and a matched group of formula-feeding women, this study evaluated concentrations of methadone in breast milk among breastfeeding women and concentrations of methadone in maternal and infant plasma in both groups. Eight methadone-maintained (dose: 50-105 mg/day), lactating women provided blood and breast milk specimens on days 1, 2, 3, 4, 14, and 30 after delivery, at the times of trough and peak maternal methadone levels. Eight matched formula-feeding subjects provided blood samples on the same days. Infant blood samples for both groups were obtained on day 14. Urine toxicological screening between 36 weeks of gestation and 30 days after the birth confirmed that subjects were not using illicit substances in the perinatal period. Concentrations of methadone in breast milk were low (range: 21.0-462.0 ng/mL) and not related to maternal dose. There was a significant increase in methadone concentrations in breast milk over time for all 4 sampling times. Concentrations of methadone in maternal plasma were not different between groups and were unrelated to maternal dose. Concentrations of methadone in infant plasma were low (range: 2.2-8.1 ng/mL) in all samples. Infants in both groups underwent neurobehavioral assessments on days 3, 14, and 30; there were no significant effects of breastfeeding on neurobehavioral outcomes. Fewer infants in the breastfed group required pharmacotherapy for neonatal abstinence

syndrome, but this was not a statistically significant finding. Results contribute to the recommendation of breastfeeding for methadone-maintained women. Jansson, L.M., Choo, R., Velez, M.L., Harrow, C., Schroeder, J.R., Skakleya, D.M., and Huestis, M.A., Methadone Maintenance and Breastfeeding in the Neonatal Period. Pediatrics, 121(1), pp. 106-114, 2008.

Impact of Prenatal Cocaine Exposure on Attention and Response Inhibition as Assessed by Continuous Performance Tests

This longitudinal study examined the influence of prenatal cocaine exposure on attention and response inhibition measured by continuous performance tests (CPTs) at ages 5 and 7 years. The sample included 415 children from the Miami Prenatal Cocaine Study (219 cocaine-exposed, 196 non-cocaine-exposed as determined by maternal self-report and infant bioassays). Children were enrolled prospectively at birth and assessed comprehensively through age 7 years. Deficits in attention and response inhibition were estimated in relation to prenatal cocaine exposure using generalized estimating equations within the general linear model. Results indicate cocaine-associated increases in omission errors at ages 5 and 7 as well as increases in response times for target tasks (i.e., slower reaction times) and decreased consistency in performance at age 7. There were no demonstrable cocaine-associated deficits in commission errors. Estimates did not change markedly with statistical adjustment for selected prenatal and postnatal covariates. Evidence supports cocaine-associated deficits in attention processing through age 7 years. Accornero, V.H., Amado, A.J., Morrow, C.E., Xue, L., Anthony, J.C., and Bandstra, E.S. Impact of Prenatal Cocaine Exposure on Attention and Response Inhibition as Assessed by Continuous Performance Tests. Journal of Developmental Behavioral Pediatrics, 28(3), pp. 195-205, 2007.

Sensation Seeking and Risk-Taking Propensity as Mediators in the Relationship Between Childhood Abuse and HIV-related Risk Behavior

Although a wealth of literature suggests that childhood physical, emotional, and sexual abuse are related to later-life HIV-related risk behaviors, few studies have explored disinhibition (e.g., impulsivity, risk-taking propensity, and sensation-seeking) as a risk factor in this relationship. In this cross-sectional study Dr. Carl Lejuez and his colleagues at the University of Maryland examined impulsivity, risk-taking propensity, and sensation seeking as mediators in the relationship between abuse history and engagement in HIV-related risk behaviors among a sample of 96 inner-city African American adolescents. Findings indicated that abuse history was positively related to self-reported engagement in HIV-related risk behaviors, as well as risk-taking propensity and sensation seeking. Abuse history was not related to impulsivity. Further, while sensation-seeking and risk-taking propensity (to a lesser extent) mediated this relationship, impulsivity did not. These findings provide an initial step in the examination of the mechanisms underlying the relationship between childhood abuse and engagement in HIV-related risk behaviors. Bornovalova, M.A., Gwadz, M.A., Kahler, C., Aklin, W.M., and Lejuez, C.W. Sensation Seeking and Risk-Taking Propensity as Mediators in the Relationship between Childhood Abuse and HIV-Related Risk Behavior. Child Abuse and Neglect, 32(1), pp. 99-109, 2008.

P3 Components of the Event-Related Potential and Marijuana Dependence in Southwest California Indians

Marijuana use and abuse is very high in Native Americans; however, little is known about neurobiological measures that are associated with marijuana addiction in this population. This study utilized event-related potentials to

examine the responses to a facial recognition task in an adult sample of 317 Southwest California (SWC) Indians with (1) no drug dependence diagnosis; (2) marijuana use, but not other drug dependence diagnosis; and (3) marijuana dependence, as well as other drug dependence diagnosis. After taking age, gender, and the presence of a lifetime diagnosis of alcohol dependence into consideration; an increased latency in the P350 and P450 component peaks was found in those individuals with a diagnosis of marijuana dependence and also marijuana dependence co-morbid with other drug dependence. The amplitudes of these late component peaks were not associated with a diagnosis of marijuana dependence. Women appeared to be more impacted by a marijuana dependence diagnosis in that the P450 latencies were longer in females than in males which may be indicative of greater toxicity. The findings suggest that marijuana dependence may be associated with delays in the evaluation and identification of emotional stimuli in SWC Indians. Further longitudinal studies will be necessary to determine whether pre-disposing or co-morbid factors are a possible cause of the P300 latency effects in this high risk and understudied ethnic group. Ehlers, C., Gilder, D., and Phillips, E. P3 Components of the Event-Related Potential and Marijuana Dependence in Southwest California Indians. Addiction Biology, 13(11), pp. 130-142, 2008.

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

Research Findings - Clinical Neuroscience Research

"What Might Have Been" Does Not Influence Smoker's Decision, Despite Normative Brain Activation

Read Montague and colleagues at the Baylor College of Medicine hypothesized that anomalies in how the brain responds to "fictive errors" -i.e. notification that better outcomes could have resulted (from choice(s) the subject did not make) contribute to the diminished influence of potential consequences of choices that are made. Using a simple investment game and functional magnetic resonance imaging in chronic cigarette smokers, they measured neural and behavioral responses to error signals derived from actual experience and from fictive outcomes. In nonsmokers, both fictive and experiential error signals predicted subjects' choices and possessed distinct neural correlates. In chronic smokers, choices were not guided by error signals derived from what might have happened, despite ongoing and robust neural correlates of these fictive errors. These data provide human neuroimaging support for computational models of addiction and suggest the addition of fictive learning signals to reinforcement learning accounts of drug dependence. Chiu, P.H., Lohrenz, T.M., and Montague, P.R. Smokers' Brains Compute, But Ignore, A Fictive Error Signal In A Sequential Investment Task. Nature Neurosci., 11(4), pp. 514-520, 2008.

Placebo and Nocebo Effects are Defined by Opposite Opioid and Dopaminergic Responses

Zubieta and colleagues administered a saline solution (placebo) to healthy subjects undergoing a pain challenge and analyzed brain responses (dopamine and opioid receptors) as measured with PET. Most subjects reported a reduction in pain, though some reported an increase. Those that reported analgesic effects showed increases in neurotransmission of the DA D2/D3 receptor system in the ventral basal ganglia and of the endogenous opioid/mu-opioid receptor system in the rostral and subgenual anterior cingulate, orbitofrontal cortex, anterior and posterior insulae, medial thalamus, nucleus accumbens, amygdala and the periaqueductal gray. Those that reported an increase in pain had decreases in these same areas. The circuits involved in these responses are part of reward and motivated behavior which suggests that activation depends, in part, on subject expectations. Scott, D.J., Stohler, C.S., Egnatuk, C.M., Wang, H., Koeppe, R.A., and Zubieta, J. K. Placebo and Nocebo Effects are Defined by Opposite Opioid and Dopaminergic Responses. Archives of General Psychiatry, 65(2), pp. 220-231, 2008.

Significant Association of D1 Dopamine Receptors with Nicotine Dependence

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M.D. Li and colleagues studied SNPs within or near the D1 receptor gene (DRD1) for family-based association analyses using smoking phenotypes as assessed by scores on three smoking indices. There were more than 2000 participants from more than 200 families of European and 400 from African ancestry. Significant associations with one SNP (rs686) and one haplotype (which included rs686) were found in the AA sample and the pooled sample. Furthermore, luciferase activity demonstrated that the rs686/A allele had a higher expression level for DRD1 than does the rs686/G allele. These findings demonstrate that the DRD1 is significantly associated with nicotine dependences from both single SNP- and haplotype-based analyses and that the polymorphisms seem to affect the expression level. Huang, W., Ma, J.Z., Payne, T.J., Beuten, J., Dupont, R.T., and Li, M.D. Significant Association of DRD1 with Nicotine Dependence. Human Genetics, 123, pp. 133-140, 2008.

Impaired "Remembering to Remember" in HIV+ Individuals Increases Risk of Social Support in Everyday Functioning and may Jeopardize Adherence to Medication

Igor Grant and colleagues at University of California, San Diego investigated whether HIV infection is associated with impaired ability to carry out an intention in the future, such as remembering to take a medication at a specific time - an aspect of episodic memory referred to as prospective memory. Prospective memory is believed to be a cognitive process that is needed for successful management of the instrumental activities of daily living. In a cohort of 66 HIV-infected individuals, prospective memory accounted for a significant proportion of variance in self-reported dependence on others for carrying out instrumental activities of daily living, over and above that which was explained by retrospective memory and by current affective distress. Analysis of component cognitive processes revealed that the relationship between HIV-associated deficits in prospective memory and dependence in instrumental activities of daily living was driven by impaired cue detection and by deficits in self-initiated intention retrieval. Results were not better explained by demographic factors, HIV disease severity, psychiatric comorbidity, or substance use. Collectively, these data support the potential incremental ecological validity of prospective memory as a predictor of whether an HIV+ individual will become dependent on others for carrying out daily living. Woods, S.P., Iudicello, J.E., Moran, L.M., Carey, C.L., Dawson, M.S., Grant, I., HIV Neurobehavioral Research Center Group. HIV-associated Prospective Memory Impairment Increases Risk of Dependence in Everyday Functioning. Neuropsychology, 22(1), pp. 110-117, 2008.

Individual Differences in Expectation of Pain Relief Associated with Opioid and Dopaminergic Responses

Dr. Zubieta and colleagues at University of Michigan used PET neuroreceptor imaging to investigate individual differences in healthy volunteers' alterations in self-reported physical pain after administration of inert substances and endogenous opioid and dopamine release. In 75% of the subjects, pain (placebo effect) reduction was associated with activation of opioid neurotransmission in the anterior cingulate, orbitofrontal and insular cortices, nucleus accumbens, amygdala, and periaqueductal gray matter (PAG), and dopaminergic (DA) activation in the ventral basal ganglia, including the nucleus accumbens. Regional magnitudes of brain DA and opioid activation correlated with the subjects' perceived efficacy of the inert substances, changes in expectations as a consequence of cognitive-emotional self-assessments of the efficacy, and positive affective state. In addition, greater DA and opioid activity in the nucleus accumbens predicted higher pain relief, and vice versa. It was estimated that nucleus accumbens DA responses accounted for 25% of the variance in inert substances-induced analgesic effects. In contrast, in the

remaining 25% of the sample there was enhanced perception of pain after inert substances administration (nocebo response), and these subjects exhibited a corresponding reduction in regional DA and endogenous opioid activity. These studies demonstrate psychophysical responses to the expected therapeutic effect of inert substances administration elicits analgesia or hyperanalgesia, corresponding to dynamic, opposite responses of DA and _-opioid neurotransmission in a distributed yet fully overlapped network of brain regions typically implicated in reward responses and motivated behavior. Scott, D.J., Stohler, C.S., Egnatuk, C.M., Wang, H., Koeppe, R.A., and Zubieta, J.K. Individual Differences in Reward Responding Explain Inert Substances-induced Expectations and Effects. Neuron, 55(2), pp. 325-336, 2007.

Tetrahydrocannabinol Administration Blunts Amygdala Responses to Threatening Stimuli

K. Phan and colleagues at University of Chicago used fMRI to determine the effects of tetrahydrocannabinol (THC) on amygdala responses to social threat signals in healthy, recreational cannabis users. They used a well-validated task to activate the amygdala and a double-blind crossover design for administration of tetrahydrocannabinol (THC) or placebo. They found that THC significantly reduced amygdala reactivity to social signals of threat but did not affect activity in primary visual and motor cortex. These findings fit well with the notion that THC and other cannabinoids may have an anxiolytic role in central mechanisms of fear behaviors and provide a rationale for exploring novel therapeutic strategies that target the cannabinoid system for disorders of anxiety and social fear. Phan, K.L., Angstadt, M., Golden, J., Onyewuenyi, I., Popovska, A., and de Wit, H. Cannabinoid Modulation of Amygdala Reactivity to Social Signals of Threat in Humans. Journal of Neuroscience, 28(10), pp. 2313-2319, 2008.

Alpha Synuclein Protein Levels are Elevated in Recently Abstinent Cocaine Abusers

D. C. Mash and associates analyzed serum levels of alpha synuclein in recently abstinent cocaine abusers and healthy controls. There was an average 8-fold increase (though a wide variation) that was correlated in the abstinent abusers with both intensity of "desire to use" and days of use (in the prior month). The gene for alpha synuclein maps to chromosome 4q21.3-22 which has been associated with drug abuse. While it is not clear how alpha synuclein measured peripherally relates to the levels in the brain, Mash has shown that cocaine abuse leads to state-dependent increases in the post-mortem brain. Because alpha synuclein is involved in the modulation of dopaminergic activity, these preliminary results support a role for alpha gene expression in the intensity of craving for drugs. Mash, D.C., Adi, N., Duque, L., Pablo, J., Kumar, M., and Ervin, F.R. Alpha Synuclein Protein Levels are Increased in Serum from Recently Abstinent Cocaine Abusers. Drug and Alcohol Dependence, 94(1-3), pp. 246-50, 2008.

Efficacy of Bupropion for Smoking Cessation is Influenced by D2 Dopamine Receptors Taq1A Polymorphism

Sean David and colleagues analyzed two comparable randomized placebo-controlled clinical trials of bupropion pharmacotherapy which included 722 smokers and assessed smoking cessation at 10 weeks as well as follow-up after 12 months. Smokers with the A2/A2 genotype of the DRD2 receptor gene were three times as likely (relative to placebo) to be abstinent both at the end of treatment (35% vs. 15%) and at 6-month follow-up (27% vs. 12%) though by 12 months much of the advantage had disappeared (16% vs. 11%). That bupropion therapy may be most beneficial for individuals with a specific

genotype provides a strong rationale for examining the characteristics of the gene variant or genes linked with it to determine the cause of this observation. David, S.P., Strong, D.R., Munafo, M.R., Brown, R.A., Lloyd-Richardson, E.E., Wileyto, P.E., Evins, E.A., Shields, P.G., Lerman, C., and Niaura, R. Bupropion Efficacy for Smoking Cessation is Influenced by the DRD2 Taq1A Polymorphism: Analysis of Pooled Data from Two Clinical Trials. Nicotine & Tobacco Research, 9(12), pp. 1251-1257, 2007.

"Suggestive" and "Significant" Susceptibility Genetic Loci for Nicotine Dependence

M. Li at the University of Virginia has provided a comprehensive update of which gene variants are likely candidates lending susceptibility for nicotine dependence. Thirteen regions on 11 chromosomes have been found to be suggestive or significant in at least two independent samples. The strongest support (most replications) is for regions on chromosomes 9, 10, 11, and 17. Others are 3-7, 20, and 22; there were two regions, each, on chromosomes 5 and 9. On chromosome 9 there are three gene variants in one region that have been associated with nicotine dependence: GABA-B receptor unit 2, neurotrophic tyrosine kinase receptor 2 (NTRK2), and Src homology 2 domain-containing transforming protein C3 (SHC3). The region on chromosome 11 contains beta-arrestin 1 which is an important regulator of signal transduction. On chromosome 17, GABA-A receptor-associated protein (GABARAP), Discs, large homolog 4 or post-phosphatase regulatory subunit B1 (PP1R1B) or dopamine- and cAMP-reguated phosphoprotein, 32-KD; DARPP32, and beta-arrestin 2 are associated with nicotine dependence. Finally, within the linkage region on chromosome 12 are ionotropic N-methyl-D-aspartate glutamate receptor 9NMDA) subunit 2B, and neurotrophin 3, GABA-A receptor-associated protein-like protein 1; and on chromosome 22 is beta-adrenergic receptor kinase 2. These findings across studies provide a focus for future work to determine the mechanisms underlying nicotine dependence as well as the individual differences associated with different genotypes. Li, M.D., Identifying Susceptibility Loci for Nicotine Dependence: 2008 Update Based on Recent Genome-wide Linkage Analyses. Human Genetics, 123, pp. 119-131, 2008.

Performance on Stroop Task Predicts Treatment Compliance in Cocaine-Dependence

Chris Streeter and colleagues at the Harvard Medical School used logistic regression analysis to predict therapy completion from psychometric and laboratory cognitive measures. Models using the Stroop task performance as a predictor variable performed better than a model featuring depression scores alone. These findings suggest that the Stroop task can be used to identify cocaine-dependent subjects at risk for treatment dropout. The Stroop task is a widely available, reliable, and valid instrument that can be easily employed to identify and tailor interventions for at-risk individuals with the aim of improving treatment compliance. Streeter, C.C., Terhune, D.B., Whitfield, T.H., Gruber, S., Sarid-Segal, O., Silveri, M.M., et al. Performance on the Stroop Predicts Treatment Compliance in Cocaine-Dependent Individuals. Neuropsychopharmacology, 33(4), pp. 827-836, 2007.

Dopamine Increases in Striatum Elicit Craving in Cocaine Abusers Only When Coupled with Cocaine Cues

Gene-Jack Wang and colleagues at Brookhaven National Laboratory evaluated the extent to which dopamine increases by themselves can induce craving in cocaine abusers. Using PET and [11C]raclopride, they showed that, in cocaine abusers, oral methylphenidate significantly increased dopamine in striatum but did not induce craving unless subjects were concomitantly exposed to video

scenes of subjects self-administering cocaine. This suggests that dopamine increases associated with conditioned cues are not primary responses but reflect downstream stimulation of dopamine cells. The fact that methylphenidate induced craving only when given with the cocaine cues highlights the context dependency of methylphenidate's effects and suggests that its use for the treatment of ADHD subjects with comorbid drug abuse should not increase craving. Volkow, N.D., Wang, G., Telang, F., Fowler, J.S., Logan, J., Childress, A., et al. Dopamine Increases In Striatum Do Not Elicit Craving in Cocaine Abusers Unless They are Coupled with Cocaine Cues. NeuroImage, 39(3), pp. 1266-1273, 2008.

Joint Diffusion Tensor Imaging/Volumetric MRI Study Indicates that Structural Brain Abnormalities in Cocaine-Dependent Adults Scale with Duration of Use

Kelvin Lim and colleagues at the University of Minnesota investigated the macrostructural and microstructural correlates of cocaine abuse using structural MRI and diffusion tensor imaging (DTI). Their DTI data revealed that cocaine users had less structured white matter orientation (lower fractional anisotropy; FA) than controls in inferior frontal white matter. FA differences were not seen in other areas. Significant volumetric differences were not seen, but both gray and white matter inferior frontal volumes trended toward smaller in the cocaine group. The data suggested that duration of use was associated with decreased gray and white matter volumes. FA and gray matter volume were correlated in cocaine users suggesting that length of cocaine use was associated with severity of the brain abnormalities. Lim, K.O., Wozniak, J.R., Mueller, B.A., Franc, D.T., Specker, S.M., Rodriguez, C.P., Silverman, A.B., and Rotrosen, J.P. Brain Macrostructural and Microstructural Abnormalities In Cocaine Dependence. Drug and Alcohol Dependence, 92(1-3), pp. 164-172, 2008.

Providing a Cue that Signals Upcoming Cognitive Conflict Enhances Anterior Cingulate Activation and Go/Nogo Task Performance of Methamphetamine Abusers

Martin Paulus and colleagues at the University of California- San Diego used functional MRI to measure anterior cingulate cortex (ACC) activation during performance of a go/nogo response inhibition task in which certain go stimuli (cues) were much more likely than others (noncues) to be followed by nogo trials. Methamphetamine abusers and controls had statistically comparable performance, but only methamphetamine abusers showed an ACC response and lower false alarm rates in trials with warning cues as compared with noncues. Cue-related ACC activity in methamphetamine abusers was positively correlated with this cue-related improvement in inhibitory performance. The ACC, an area associated with error detection and response conflict, may predict the degree to which advanced warning may attenuate MD individuals' difficulty with response inhibition. Leland, D.S., Arce, E., Miller, D.A., and Paulus, M.P. Anterior Cingulate Cortex and Benefit of Predictive Cueing on Response Inhibition in Stimulant Dependent Individuals. Biological Psychiatry, 63(2), pp. 184-190, 2008.

Does Early Onset of Non-Medical Use of Prescription Drugs Predict Subsequent Prescription Drug Abuse and Dependence? Results from a National Study

This study, conducted as part of a training grant (Dr. Margaret Gnegy, PI) by Dr. McCabe and colleagues at the University of Michigan, examined the associations between early onset of non-medical use of prescription drugs (NMUPD; i.e. sedatives, tranquilizers, opioids, stimulants) and the development

of prescription drug abuse and dependence in the United States. Data were collected from structured diagnostic interviews. A nationally representative cross-sectional sample of civilian non-institutionalized adults aged 18 years or older in the United States was studied. A higher percentage of individuals who began using prescription drugs non-medically at or before 13 years of age were found to have developed prescription drug abuse and dependence versus those individuals who began using at or after 21 years of age. These odds were reduced by approximately 5% with each year non-medical use was delayed, and were reduced by about 2% with each year onset was delayed when controlling for relevant covariates. The results of this study indicate that early onset of NMUPD was a significant predictor of prescription drug abuse and dependence. These findings reinforce the importance of developing prevention efforts to reduce NMUPD and diversion of prescription drugs among children and adolescents. McCabe, S.E., West, B.T., Morales, M., Cranford, J.A., and Boyd, C.J. Does Early Onset of Non-Medical Use of Prescription Drugs Predict Subsequent Prescription Drug Abuse and Dependence? Results From a National Study. Addiction, 102(12), pp. 1920-1930, 2007.

The Delta-Opioid Receptor Agonist SNC80 [(+)-4-[alpha(R)-alpha-[(2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl]-(3-methoxybenzyl)-N,N-diethylbenzamide] Synergistically Enhances the Locomotor-Activating Effects of Some Psychomotor Stimulants, but not Direct Dopamine Agonists, in Rats

The nonpeptidic delta-opioid agonist SNC80 produces many stimulant-like behavioral effects in rodents and monkeys. This study, conducted as part of a training grant project (Dr. Margaret Gnegy, PI) by Dr. Jutkiewicz and colleagues at the University of Michigan, evaluated acute cross-tolerance between delta-opioid agonists and other locomotor-stimulating drugs. Locomotor activity was measured in male Sprague-Dawley rats implanted with radiotransmitters, and activity levels were recorded in the home cage environment. Three-hour SNC80 pretreatment produced tolerance to further delta-opioid receptor stimulation but also augmented greatly amphetamine-stimulated locomotor activity in a dose-dependent manner. Pretreatments with other delta-opioid agonists and oxymorphindole also modified amphetamine-induced activity levels. SNC80 pretreatment enhanced the stimulatory effects of the dopamine/norepinephrine transporter ligands cocaine and nomifensine, but not the direct dopamine receptor agonists SKF81297 and quinpirole. In conclusion, SNC80 enhanced the locomotor-stimulating effects of monoamine transporter ligands suggesting that delta-opioid receptor activation might alter the functional activity of monoamine transporters or presynaptic monoamine terminals. Jutkiewicz, E.M., Baladi, M.G., Folk, J.E., Rice, K.C., and Woods, J.H. The Delta-Opioid Receptor Agonist SNC80 [(+)-4-[alpha(R)-alpha-[(2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl]-(3-methoxybenzyl)-N,N-diethylbenzamide] Synergistically Enhances the Locomotor-Activating Effects of Some Psychomotor Stimulants, but not Direct Dopamine Agonists, in Rats. Journal of Pharmacology and Experimental Therapeutics, 324(2), pp. 714-724, 2008.

A Coalescent Simulation of Marker Selection Strategy for Candidate Gene Association Studies

Recent efforts have focused on the challenges of finding alleles that contribute to health-related phenotypes in genome-wide association studies. However, in candidate gene studies, where the genomic region of interest is small and recombination is limited, factors that affect the ability to detect disease-susceptibility alleles remain poorly understood. In particular, it is unclear how varying the number of markers on a haplotype, the type of marker (e.g., single

nucleotide polymorphism (SNP), short tandem repeat (STR)), including the causative site (cs) as a genetic marker, or population demographics influences the power to detect a candidate gene. As part of a training grant project (Dr. Margaret Gnegy, PI) at the University of Michigan, Dr. Cole and her colleagues evaluated the power of association tests using coalescent-modeled computer simulations. Results show that the effective number of markers on a haplotype is dependent on whether the cs is included as a marker. When the analyses include the cs, highest power is achieved with a single-marker association test. However, when the cs is excluded from analyses, the addition of more nonfunctional SNPs on the haplotype increases power to a certain point under most scenarios. Typically, it is found that a rapidly expanding population always has lower power compared to a population of constant size; although utilizing markers with a frequency of at least 5% improves the chance of detecting an association. Comparing the mutational properties of a nonfunctional SNP versus an STR, multi-allelic STRs provide more or comparable power than a bi-allelic SNP unless SNP frequencies are constrained to 10% or more. Similarly, including an STR with SNPs on a haplotype improves power unless SNP frequencies are 5% or more. Cole, S.M. and Long, J.C. A Coalescent Simulation Of Marker Selection Strategy For Candidate Gene Association Studies. American Journal Of Medical Genetics. Part B, Neuropsychiatric Genetics, 147(1), pp. 86-93, 2008.

Acute Effect of Methadone Maintenance Dose on Brain fMRI Response to Heroin-Related Cues

Environmental drug-related cues have been implicated as a cause of illicit heroin use during methadone maintenance treatment of heroin dependence. Dr. Daniel Langleben and colleagues from the University of Pennsylvania sought to identify the functional neuroanatomy of the brain response to visual heroin-related stimuli in methadone maintenance patients. Event-related functional magnetic resonance imaging was used to compare brain responses to heroin-related stimuli and matched neutral stimuli in 25 patients in methadone maintenance treatment. Patients were studied before and after administration of their regular daily methadone dose. The heightened responses to heroin-related stimuli in the insula, amygdala, and hippocampal complex, but not the orbitofrontal and ventral anterior cingulate cortices, were acutely reduced after administration of the daily methadone dose. The medial prefrontal cortex and the extended limbic system in methadone maintenance patients with a history of heroin dependence remains responsive to salient drug cues, which suggests a continued vulnerability to relapse. Vulnerability may be highest at the end of the 24-hour interdose interval. Langleben, D.D., Ruparel, K., Elman, I., Busch-Winokur, S., Pratiwadi, R., Loughead, J., O'Brien, C.P., and Childress, A.R. Acute Effect of Methadone Maintenance Dose on Brain fMRI Response to Heroin-Related Cues. American Journal of Psychiatry, 165(3), pp. 390-394, 2008.

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

Bipolar and substance use disorders frequently co-occur, and both are associated with impulsivity, impaired judgment, and risk-taking. In this study, Dr. Meade and colleagues at Harvard Medical School and McLean Hospital, aimed to: (1) describe the rates of HIV sexual and drug risk behaviors among patients with co-occurring bipolar and substance use disorders, (2) test whether acute mania, psychiatric severity, and drug severity independently predict HIV risk, and (3) examine the relationship between specific substance dependencies and sexual risk behaviors. Participants (N=101) were assessed for psychiatric diagnoses, substance abuse, and HIV risk behavior using structured clinical interviews and self-report questionnaires. The majority

(75%) were sexually active in the past 6 months and reported high rates of sexual risk behaviors, including unprotected intercourse (69%), multiple partners (39%), sex with prostitutes (24%, men only), and sex trading (10%). In a multivariate linear regression model, recent manic episode, lower psychiatric severity, and greater drug severity were independent predictors of total HIV risk. Cocaine dependence was associated with increased risk of sex trading. Results underscore the importance of HIV prevention for this population. Meade, C.S., Graff, F.S., Griffin, M.L., and Weiss, R.D. HIV Risk Behavior Among Patients with Co-occurring Bipolar and Substance Use Disorders: Associations with Mania and Drug Abuse. Drug and Alcohol Dependence, 92(1-3), pp. 296-300, 2008.

Mesofrontal and Striatal Activation Related to Envisioning of Distal and Proximal Emotional Events

Antoine Bechara and colleagues at University of Southern California used fMRI to investigate whether activation of incentive neurocircuitry is modulated by temporal distance of a variety of envisioned emotional events. Healthy volunteers imagined positive and negative events pertaining to the near future or far future while their brain activity was measured with fMRI. They showed that the anterior part of the ventromedial prefrontal cortex (vmPFC) was more active in envisioning emotional events in the far future than in the near future, whereas the caudate nucleus was engaged in envisioning emotional (especially positive) situations in the near future. This suggests that the anterior part of the vmPFC might assign emotional values to mental representations of future events that pertain to long-term goals, while the caudate might support more concrete simulations of rewarding situations in the near future. Being able to envision emotional events that might happen in the future could be critical in decisions about whether to abstain or relapse to use of an abused drug. D'Argembeau, A., Xue, G., Lu, Z., Van der Linden, M., and Bechara, A. Neural Correlates of Envisioning Emotional Events In The Near and Far Future. NeuroImage, 40(1), pp. 398-407, 2008.

Presence of a Social Stressor Inhibits the Ability to Learn from Bad Choices in a Gambling Task in Men More than in Women

Antoine Bechara and colleagues at University of Southern California used neuropsychological testing to investigate whether decision making during a task is disrupted by an emotional stressor unrelated to the task. Drug-dependent individuals typically encounter a variety of social stressors, some of which are self-initiated. Two groups of healthy volunteers played the Iowa Gambling Task, with one group anticipating having to give a public speech. Those who anticipated having to give a speech took longer to learn to make advantageous choices. In addition, a gender interaction was present later in the game. Stressed female participants exhibited more explicit knowledge and more advantageous performance than stressed males. These results indicate that effects of anticipatory stress on decision making are complex and depend on both the nature of the task and the individual. Preston, S.D., Buchanan, T.W., Stansfield, R.B., and Bechara, A. Effects Of Anticipatory Stress On Decision Making In A Gambling Task. Behavioral Neuroscience, 121(2), pp. 257-263, 2007.

Photic Stimuli of Specific Wavelengths May Provide a Novel Probe of Dopaminergic Tone in Human Subjects

Perry Renshaw and colleagues at McLean Hospital used the functional magnetic resonance imaging (fMRI) BOLD method to measure visual cortical activation in human subjects (N = 6) in response to 8 Hz flashing red and blue light stimuli during placebo conditions and during the oral administration of d-

amphetamine. While, there was no effect of D-amphetamine administration on the percent BOLD signal change to red or blue light, there was a specific augmentation of the spatial extent of activation (as measured by the number of activated pixels; p = 0.018) to blue, but not red light following D-amphetamine administration. Thus, blue light function may have utility as an assay of CNS DA tone. Cowan, R.L., Wood, J., Dietrich, M.S., Frederick, B.D., Lukas, S.E., and Renshaw, P.F. Differential Effects of D-Amphetamine on Red and Blue Light-Induced Photic Activation: A Novel Bold fMRI Assay of Human Dopamine Function. Synapse, 62(4), pp. 268-272, 2008.

Right-Left Asymmetry of D2 Receptor Availability in Striatum is Reflective of Individual Differences in Psychometric Scores of Incentive Motivation

Gene-Jack Wang and colleagues at Brookhaven National Laboratory examined the relationship between self-reported degree of incentive motivation and asymmetry of D2 receptor availability in healthy volunteers. Nineteen healthy participants were studied with positron emission tomography (PET) and [11C]raclopride to assess the availability of dopamine D2 receptors in left and right striatum. Incentive motivation was assessed by the Achievement scale of the Multidimensional Personality Questionnaire. The Achievement score was negatively correlated with the Asymmetry Index ([R - L]/[R + L]) of D2 receptor availability (r = -.721, p = .001), suggesting that greater positive incentive motivation is associated with higher receptor availability in the left relative to the right hemisphere. Tomer, R., Goldstein, R.Z., Wang, G., Wong, C., and Volkow, N.D. Incentive Motivation is Associated with Striatal Dopamine Asymmetry. Biological Psychology, 77(1), pp. 98-101, 2008.

Emotional Stimuli and Context Moderate Effects of Nicotine on Specific but Not Global Affects

David Gilbert and colleagues at the University of Southern Illinois investigated how nicotine interacts with the emotional and cognitive modulation of attention. The study involved the presence or absence of emotionally positive and negative stimuli and attentional choice to avoid attending to emotionally negative stimuli. Two groups of habitual smokers (32 per group) performed attentional tasks in which they either had the freedom to look back and forth at 2 simultaneously presented pictures or viewed single pictures without attentional choice. Blocks of pictures contained one of 4 combinations of picture types: a) emotionally negative + neutral, b) negative + positive, c) positive + neutral, or d) neutral + neutral. Participants wore a nicotine patch on one day and a placebo patch on a second day. Nicotine reduced anxiety most when negative pictures were presented in combination with neutral pictures, but it had no effect on anxiety when negative pictures were presented in combination with positive pictures and when negative pictures were not presented. In contrast, nicotine only reduced depressive affect when the participant had attentional choice between positive and negative pictures. Nicotine also enhanced positive affect and reduced negative affect as measured by the Positive and Negative Affect Schedule, but these effects were not moderated by task manipulations. Nicotine tended to enhance eye-gaze orientation to emotional pictures versus neutral pictures in women, but it had no significant effect on eye-gaze in men. Overall, the findings support the view that nicotine's ability to reduce specifically negative affect is moderated by overall emotional context and attentional freedom. Gilbert, D.G., Riise, H., Dillon, A., Huber, J., Rabaanovich, N.E., and Sugai, C. Exp. Clin. Psychopharmacol., 16(1), pp. 33-42, 2008.

Interactions Between Genotype and Retrospective ADHD Symptoms Predict Lifetime Smoking Risk in a Sample of Young

Adults

Joseph McClernon and colleagues at Duke University investigated whether ADHD symptoms interact with candidate gene variation to predict smoking risk. Attention-deficit/hyperactivity disorder (ADHD) symptoms are associated with an increased risk of smoking, and genetic studies have identified similar candidate genes associated with both ADHD and smoking phenotypes. Participants were a subsample of individuals from the National Longitudinal Study of Adolescent Health (Add Health), a nationally representative sample of adolescents followed from 1995 to 2002. The sample analyzed included a subset from Add Health of 1,900 unrelated individuals with genotype data. Multiple logistic regression was used to examine relationships between self-reported ADHD symptoms, genotype, and lifetime history of regular smoking. Polymorphisms in the Dopamine D2 receptor gene and, the MAO-A gene (females only) interacted with retrospective reports of ADHD symptoms in contributing to risk for smoking. Trends were observed for interactions between the Dopamine D4 receptor gene and the MAO-A gene (males only) and ADHD symptoms to predict smoking risk. No main effect for any of these polymorphisms was observed. No main effects or interactions with CYP2A6, DAT, and SLC6A4 genes were found. These findings suggest that genotypes associated with catecholamine neurotransmission interact with ADHD symptoms to predict lifetime smoking risk in a sample of young adults. McClernon, F.J., Fuemmeler, B.F., Kollins, S.H., Kail, M.E., and Ashley-Koch, A.E. Nicotine Tob. Res., 10(1), pp. 117-127, 2008.

Persistent Cognitive and Dopamine Transporter Deficits in Abstinent Methamphetamine Users

Una McCann and colleagues at Johns Hopkins School of Medicine investigated potential persistent psychomotor deficits secondary to METH abuse and their relationship to brain dopamine transporter (DAT) availability, as measured using quantitative PET methods with [(11)C]WIN 35428 in abstinent methamphetamine (METH) users. The study sought to determine whether cognitive deficits and brain DAT reductions fully reverse with sustained abstinence, or whether behavioral deficits in METH users are related to dopamine (DA) deficits. Twenty-two abstinent METH users and 17 healthy non-METH using controls underwent psychometric testing to test the hypothesis that METH users would demonstrate selective deficits in neuropsychiatric domains known to involve DA neurons (e.g., working memory, executive function, motor function). A subset of subjects also underwent PET scanning with [(11)C]WIN 35428 to assess DAT availability. METH users were found to have modest deficits in short-term memory, executive function, and manual dexterity. Exploratory correlational analyses revealed that deficits in memory, but not executive or motor function deficits, were associated with decreases in striatal DAT binding potential. These results suggest a possible relationship between DAT binding potential and memory deficits in abstinent METH users. One interpretation of these results is that METH produces lasting effects on central DA neurons in humans, but further study is needed to address the potential role of changes in brain serotonin in cognitive deficits in abstinent METH users. McCann, U.D., Kuwabara, H., Kumar, A., Palermo, M., Abbey, R., Brasic, J., Ye W, Alexander, M., Dannals, R.F., Wong, D.F., and Ricaurte, G.A. Synapse, 62(2), pp. 91-100, 2008.

Increased Activation in the Brain's Visuospatial and Reward Circuitry May Underlie Abstinence-Induced Cravings to Smoke

Ze Wang and colleagues at the University of Pennsylvania used arterial spin labeled (ASL) perfusion magnetic resonance imaging to characterize the neural substrates of abstinence-induced cravings to smoke. Chronic smokers were

scanned during a resting state on two separate occasions: (1) smoking satiety and (2) abstinence (after [>=]12 h of smoking deprivation), in counterbalanced order. Smoking abstinence (vs satiety) was associated with increased cerebral blood flow (CBF) in anterior cingulate cortex (ACC)/medial orbitofrontal cortex (OFC) and left OFC. Abstinence-induced cravings to smoke were predicted by CBF increases (abstinence minus satiety) in the right OFC, right dorsolateral prefrontal cortex, occipital cortex, ACC, ventral striatum/nucleus accumbens, thalamus, amygdala, bilateral hippocampus, left caudate, and right insula. These data suggest that increased activation in the brain's visuospatial and reward circuitry underlies abstinence-induced cravings to smoke, and thereby, may be important in relapse. Wang, Z., Faith, M., et al. Neural Substrates of Abstinence-Induced Cigarette Cravings in Chronic Smokers. Journal of Neuroscience, 27(51), pp. 14035-14040, 2007.

Unexpected Versus Expected Cocaine Delivery Elicit Different Patterns of Human Orbitofrontal Cortex Recruitment

Shi-Jiang Li and colleagues at the Medical College of Wisconsin investigated how cocaine expectation modulates human brain responses to acute cocaine administration in non-treatment-seeking cocaine abusers. Distinct regional characteristics in BOLD responses to expected and unexpected cocaine infusions were observed in the medial orbitofrontal gyrus, frontal pole, and anterior cingulate gyrus regions. They reported active engagement in the amygdala and the lateral orbitofrontal cortex by unexpected (but not expected) cocaine infusion. Cocaine expectation did not change BOLD responses to acute cocaine administration in a set of subcortical substrates, however, including the nucleus accumbens, ventral putamen, ventral tegmental area, and thalamus. These results suggest that cocaine expectation modulates the neural-sensitivity adaptation between the expected events and the actual outcomes, but did not modulate the pharmacological characteristics of cocaine. Kufahl, P., Li, Z., Risinger, R., Rainey, C., Piacentine, L., Wu, G., Bloom, A., Yang, Z, and Li S-J. Expectation Modulates Human Brain Responses To Acute Cocaine: A Functional Magnetic Resonance Imaging Study. Biological Psychiatry, 63(2), pp. 222-230, 2008.

Individual Differences in Working Memory Capacity Reflect Dopamine Synthesis Capacity in the Striatum

Mark D'Esposito and colleagues at the University of California at Berkeley demonstrated that working memory capacity as measured by listening span predicts dopamine synthesis capacity in the striatum. They showed that subjects with low working memory capacity have low DA synthesis capacity in the striatum, whereas subjects with high working memory capacity have high DA synthesis capacity in the striatum. Cools, R., Gibbs, S.E., Miyakawa, A., Jagust, W., and D'Esposito, M. Working Memory Capacity Predicts Dopamine Synthesis Capacity in the Human Striatum. Journal of Neuroscience, 28(5), pp. 1208-1212, 2008.

Taq1A DRD2 Genotype Governs Brain Activation Affects of Cabergoline, A D2 Receptor Agonist, During a Reversal Learning Task

NIDA NRSA trainee Michael X. Cohen and colleagues at the University of Bonn used functional MRI and a learning task to show that cabergoline increased neural reward responses in the medial orbitofrontal cortex, cingulate cortex and striatum for Taq1A A1+ subjects but decreased reward responses in these regions for A1- subjects. In contrast, cabergoline decreased task performance and frontostriatal connectivity in A1+ subjects but had the opposite effect in A1- subjects. Further, the drug effect on functional connectivity predicted the

drug effect on feedback-guided learning. Thus, individual variability in how dopaminergic drugs affect the brain reflects genetic disposition. These findings may help to explain the link between genetic disposition and risk for addictive disorders. Cohen, M.X., Krohn-Grimberghe, A., Elger, C.E., and Weber, B. Dopamine Gene Predicts the Brain's Response to Dopaminergic Drug. European Journal of Neuroscience, 26(12), pp. 3652-3660, 2007.

Brain Regions Governing "Regret" Identified with fMRI

Greg Berns and colleagues at Emory University used fMRI to investigate the neural correlates of regret and rejoice. They found that activation of medial orbitofrontal cortex, left superior frontal cortex, right angular gyrus, and left thalamus, correlated with the degree of regret. A different network, including the rostral anterior cingulate, left hippocampus, left ventral striatum, and brain stem/midbrain correlated with rejoice. The right inferior orbitofrontal cortex, pre-supplementary motor area, anterior cingulate, and posterior cingulate showed similar patterns of activation with both regret and rejoice, suggesting that these regions may be associated with surprise from the realization of relatively unlikely events. These results suggest that distinct, but overlapping networks are involved in the experiences of regret and rejoice. Chandrasekhar, P.V.S., Capra, C.M., Moore, S., Noussair, C., and Berns, G.S. Neurobiological Regret and Rejoice Functions for Aversive Outcomes. NeuroImage, 39(3), pp. 1472-1484, 2008.

Propranolol Enhances Problem-Solving Skills in the Individuals Who Need the Most Help

David Beversdorf and colleagues at The Ohio State University compared various doses of beta-adrenergic antagonists for their effect on cognitive flexibility in problem solving, and how task difficulty interacts with propranolol benefits. Overall, more anagram problems were solved while on propranolol 40 mg than on placebo. Subjects least able to solve the problems benefited significantly from 40 mg of propranolol. Also, for all subjects the most difficult problems were solved more quickly with propranolol 40 mg than placebo. Benefits were also seen for word fluency and backward digit span. Therefore, noradrenergic modulation of cognitive flexibility is affected by how much difficulty the subject is encountering when searching for the solution, a pattern consistent with what might be expected in an effect on the search of the semantic and associative network. These data may represent a promising avenue for enhancement of decision-making capacity away from relapse. Campbell, H.L., Tivarus, M.E., Hillier, A., and Beversdorf, D.Q. Increased Task Difficulty Results in Greater Impact of Noradrenergic Modulation of Cognitive Flexibility. Pharmacology Biochemistry and Behavior, 88(3), pp. 222-229, 2007.

Ability to Wait for a Larger, Delayed Reward Relates to Both BOLD Signal in the Lateral Orbitofrontal Cortex and COMT Genotype

Mark D'Esposito and colleagues at the University of California at Berkeley used a combination of brain imaging and a candidate genetic analysis to investigate how the brain activations related to reward delay related to polymorphisms in the catechol-O-methyltransferase (COMT) gene. Bias for immediate rewards in healthy volunteers during decision making was found to scale with fMRI BOLD signal magnitude in the posterior parietal cortex (PPC), dorsal prefrontal cortex (dPFC), and rostral parahippocampal gyrus regions. Conversely, the tendency of an individual to wait for a larger, delayed reward was positively correlated with BOLD signal in the lateral orbitofrontal cortex. The Val158Met COMT genotype predicted both impulsive choice behavior and activity levels in the dPFC and PPC during decision making. These genotype effects remained

significant after controlling for alcohol abuse history. The results provide evidence that polymorphisms in the COMT gene influences brain activity related to impulsivity and therefore may influence risk or relapse for substance abuse.
Boettiger, C.A., Mitchell, J.M., Tavares, V.C., Robertson, M., Joslyn, G., D'Esposito, M., et al. Immediate Reward Bias in Humans: Fronto-Parietal Networks and a Role for the Catechol-O-Methyltransferase 158(Val/Val) Genotype. Journal of Neuroscience 27(52), pp. 14383-14391, 2007.

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

Research Findings - Epidemiology and Etiology Research

Specificity of Genetic Factors for Dependence on Licit and Illicit Drugs

Although genetic risk factors have been found to contribute to dependence on both licit and illicit psychoactive substances, we know little of how these risk factors interrelate. This study sought to clarify the structure of genetic and environmental risk factors for symptoms of dependence on cannabis, cocaine, alcohol, caffeine, and nicotine in males and females. Four thousand eight hundred sixty-five adult members of male-male and female-female pairs from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders were assessed for lifetime symptoms of abuse of and dependence on cannabis, cocaine, alcohol, caffeine, and nicotine by structured interview. Controlling for greater symptom prevalence in males, genetic and environmental parameters could be equated across sexes. Two models explained the data well. The best-fit exploratory model contained 2 genetic factors and 1 individual environmental factor contributing to all substances. The first genetic factor loaded strongly on cocaine and cannabis dependence; the second, on alcohol and nicotine dependence. Nicotine and caffeine had high substance-specific genetic effects. A confirmatory model, which also fit well, contained 1 illicit drug genetic factor--loading only on cannabis and cocaine--and 1 licit drug genetic factor loading on alcohol, caffeine, and nicotine. However, these factors were highly intercorrelated (r = + 0.82). Large substance-specific genetic effects remained for nicotine and caffeine. The authors conclude that the pattern of genetic and environmental risk factors for psychoactive substance dependence was similar in males and females, and that genetic risk factors for dependence on common psychoactive substances cannot be explained by a single factor. Rather, two genetic factors-one predisposing largely to illicit drug dependence, the other primarily to licit drug dependence-are needed. Furthermore, a large proportion of the genetic influences on nicotine and particularly caffeine dependence appear to be specific to those substances. Kendler, K., Myers, J., and Prescott, C. Specificity of Genetic and Environmental Risk Factors for Symptoms of Cannabis, Cocaine, Alcohol, Caffeine, and Nicotine Dependence. Arch. Gen. Psychiatry, 64(11), pp. 1313-1320, 2007.

Assessment of Cocaine and Other Drug Dependence in the General Population

There is a need for large-scale epidemiological surveys to be faithful to diagnostic specifications and to limit time- and participant-burden associated with each section of potentially lengthy interviews. This study examined whether one "gating" approach devised for recent large-scale international psychiatric surveys results in a reduced number of identified cases of drug

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dependence and/or biases in the estimated associations with background characteristics. Data were analyzed from a recently released cross-sectional, nationally representative household survey, the United States National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Participants included 43,093 English speaking adults aged 18 years and over. The primary outcome measures included dependence upon cocaine and other illegal drug dependence, defined in two ways: "ungated" and "gated". "Ungated" dependence included all persons meeting criteria for DSM-IV dependence, without regard for DSM-IV drug abuse clinical features. "Gated" dependence required at least one feature of DSM-IV drug abuse. There was no statistically robust decrement in the estimated prevalence of cocaine or other drug dependence using a "gated" assessment. Patterns of association of cocaine dependence with background characteristics were not appreciably different when the gated and ungated approaches were applied. In panoramic mental health surveys, the inefficiency of an ungated approach must be balanced against the anticipated number of cases of dependence without associated social role impairments or harm. In this study, the reduction in the number of identified cocaine dependence cases appeared to be so small that even in a sample of over 40,000 participants, attenuation in population prevalence would prove difficult to detect. Degenhardt, L., Bohnert, K., and Anthony, J. Assessment of Cocaine and Other Drug Dependence in the General Population: Drug Alcohol Depend., 93(3), pp. 227-232, 2008.

Neighborhood Income and Income Distribution and the Use of Cigarettes, Alcohol, and Marijuana

Evidence about the relationship between contextual variables and substance use is conflicting. Relationships between neighborhood income and income distribution and the prevalence and frequency of substance use in 59 New York City (NYC) neighborhoods were assessed while accounting for individual income and other socio-demographic variables. Measures of current substance use (in the 30 days prior to the survey) were obtained from a random-digit-dial phone survey of adult residents of NYC and data from the 2000 U.S. Census to calculate median neighborhood income and income distribution (assessed using the Gini coefficient). Among 1355 respondents analyzed (female=56.2%, mean age=40.4), 23.9% reported cigarette, 40.0% alcohol, and 5.4% marijuana use in the previous 30 days. In ecologic assessment, neighborhoods with both the highest income and the highest income maldistribution had the highest prevalence of drinking alcohol (69.0%) and of smoking marijuana (10.5%) but not of cigarette use; there was no clear ecologic association between neighborhood income, income distribution, and cigarette use. In multilevel multivariable models adjusting for individual income, age, race, sex, and education, high neighborhood median income and maldistributed neighborhood income were both significantly associated with a greater likelihood of alcohol and marijuana use but not of cigarette use. Both high neighborhood income and maldistributed income also were associated with greater frequency of alcohol use among current alcohol drinkers. These observations suggest that neighborhood income and income distribution may play more important roles in determining population use of alcohol and marijuana than individual income, and that determinants of substance use may vary by potential for drug dependence. Further research should investigate specific pathways that may explain the relationship between neighborhood characteristics and use of different substances. Galea, S., Ahern, J., Tracy, M., and Vlahov, D. Neighborhood Income and Income Distribution and the Use of Cigarettes, Alcohol, and Marijuana. Am. J. Prev. Med., 32 (6 Suppl), pp. S195-S202, 2007.

Incidence of Drug Problems in Young Adults Exposed to Trauma and Posttraumatic Stress Disorder

Most estimated associations of posttraumatic stress disorder (PTSD) with DSM-

IV drug dependence and abuse are from cross-sectional studies or from prospective studies of adults that generally do not take into account suspected causal determinants measured in early childhood. This study examined risk for incident drug disorders associated with prior DSM-IV PTSD. A multiwave longitudinal study was conducted among a sample of young adults first assessed at entry to first grade of primary school in the fall semesters of 1985 and 1986, with 2 young adult follow-up assessments. Participants were young adults (n = 988; aged 19-24 years) free of clinical features of DSM-IV drug use disorders at the first young adult assessment and therefore at risk for newly incident drug use disorders during the 1-year follow-up period. During the 12-month interval between the 2 young adult follow-up assessments, several outcomes were assessed, including: newly incident (1) DSM-IV drug abuse or dependence; (2) DSM-IV drug abuse; (3) DSM-IV drug dependence; and (4) emerging dependence problems (1 or 2 newly incident clinical features of DSM-IV drug dependence), among subjects with no prior clinical features of drug use disorders. Prior PTSD (but not trauma only) was associated with increased risk for drug abuse or dependence (adjusted relative risk, 4.9; 95% confidence interval, 1.6-15.2) and emerging dependence problems (adjusted relative risk, 4.9; 95% confidence interval, 1.2-20.1) compared with the no-trauma group controlling for childhood factors. Subjects with PTSD also had a greater adjusted relative risk for drug abuse or dependence compared with subjects exposed to trauma only (adjusted relative risk, 2.0; 95% confidence interval, 1.1-3.8) controlling for childhood factors. Association of PTSD with subsequent incident drug use disorders remained substantial after statistical adjustment for early life experiences and predispositions reported in previous studies as carrying elevated risk for both disorders. Posttraumatic stress disorder might be a causal determinant of drug use disorders, possibly representing complications such as attempts to self-medicate troubling trauma-associated memories, nightmares, or painful hyperarousal symptoms. Reed, P., Anthony, J., and Breslau, N. Incidence of Drug Problems in Young Adults Exposed to Trauma and Posttraumatic Stress Disorder: Do Early Life Experiences and Predispositions Matter? Arch. Gen. Psychiatry, 64(12), pp. 1435-1442, 2007.

Study Describes Current Patterns of Extra-Medical Drug Use

In 1994, epidemiological patterns of extra-medical drug use in the United States were estimated from the National Comorbidity Survey. This paper describes such patterns based upon more recent data from the National Comorbidity Survey Replication (NCS-R). The NCS-R was a nationally representative face-to-face household survey of 9282 English-speaking respondents, aging 18 years and older, conducted in 2001-2003 using a fully structured diagnostic interview, the WHO Composite International Diagnostic Interview (CIDI) Version 3.0. The estimated cumulative incidence of alcohol use in the NCS-R was 92%; tobacco, 74%; extra-medical use of other psychoactive drugs, 45%; cannabis, 43% and cocaine, 16%. Statistically robust associations existed between all types of drug use and age, sex, income, employment, education, marital status, geography, religious affiliation and religiosity. Very robust birth cohort differences were observed for cocaine, cannabis, and other extra-medical drug use, but not for alcohol or tobacco. Trends in the estimated cumulative incidence of drug use among young people across time suggested clear periods of fluctuating risk. These epidemiological patterns of alcohol, tobacco, and other extra-medical drug use in the United States in the early 21st century provide an update of NCS estimates from roughly 10 years ago, and are consistent with contemporaneous epidemiological studies. New findings on religion and religiosity, and exploratory data on time trends, represent progress in both concepts and methodology for such research. These estimates lead to no firm causal inferences, but contribute to a descriptive epidemiological foundation for future research on drug use and dependence across recent decades, birth cohorts, and population subgroups. Degenhardt, L., Chiu, W., Sampson, N., Kessler, R.,

and Anthony, J. Epidemiological Patterns of Extra-Medical Drug Use in the United States: Evidence from the National Comorbidity Survey Replication, 2001-2003. Drug Alcohol Depend., 90 (2-3), pp. 210-223, 2007.

Lifetime Prevalence and Age-of-Onset Distributions of Mental Disorders in the World Health Organization's World Mental Health Survey Initiative

Data are presented on the lifetime prevalence, projected lifetime risk, and age-of-onset distributions of mental disorders in the World Health Organization (WHO)'s World Mental Health (WMH) Surveys. Face-to-face community surveys were conducted in 17 countries in Africa, Asia, the Americas, Europe, and the Middle East. The combined numbers of respondents were 85,052. Lifetime prevalence, projected lifetime risk, and age of onset of DSM-IV disorders were assessed with the WHO Composite International Diagnostic Interview (CIDI), a fully-structured lay administered diagnostic interview. Survival analysis was used to estimate lifetime risk. Median and inter-quartile range (IQR) of age of onset is very early for some anxiety disorders (7-14, IQR: 8-11) and impulse control disorders (7-15, IQR: 11-12). The age-of-onset distribution is later for mood disorders (29-43, IQR: 35-40), other anxiety disorders (24-50, IQR: 31-41), and substance use disorders (18-29, IQR: 21-26). Median and IQR lifetime prevalence estimates are: anxiety disorders 4.8-31.0% (IQR: 9.9-16.7%), mood disorders 3.3-21.4% (IQR: 9.8-15.8%), impulse control disorders 0.3-25.0% (IQR: 3.1-5.7%), substance use disorders 1.3-15.0% (IQR: 4.8-9.6%), and any disorder 12.0-47.4% (IQR: 18.1-36.1%). Projected lifetime risk is proportionally between 17% and 69% higher than estimated lifetime prevalence (IQR: 28-44%), with the highest ratios in countries exposed to sectarian violence (Israel, Nigeria, and South Africa), and a general tendency for projected risk to be highest in recent cohorts in all countries. These results document clearly that mental disorders are commonly occurring. As many mental disorders begin in childhood or adolescence, interventions aimed at early detection and treatment might help reduce the persistence or severity of primary disorders and prevent the subsequent onset of secondary disorders. Kessler, R., Angermeyer, M., Anthony, J., DE Graaf, R., Demyttenaere, K., Gasquet, I., DE Girolamo, G., Gluzman, S., Gureje, O., Haro, J., Kawakami, N., Karam, A., Levinson, D., Medina Mora, M., Oakley Browne, M., Posada-Villa, J., Stein, D., Adley Tsang, C., Aguilar-Gaxiola, S., Alonso, J., Lee, S., Heeringa, S., Pennell, B., Berglund, P., Gruber, M., Petukhova, M., Chatterji, S., and Ustuen, T. Lifetime Prevalence and Age-of-Onset Distributions of Mental Disorders in the World Health Organization's World Mental Health Survey Initiative. World Psychiatry, 6(3), pp. 168-176, 2007.

Screening for Drug Abuse Among Medical and Nonmedical Users of Prescription Drugs in a Probability Sample of College Students

This study examined the prevalence of medical and nonmedical use of 4 classes of prescription drugs (opioid, stimulant, sleeping, and sedative or anxiety) and assessed probable drug abuse among 4 mutually exclusive groups of medical and nonmedical use of prescription drugs. Data were obtained from a 2005 self-administered Web-based survey of college students from a large, Midwestern 4-year university. The survey used a probability sample design, yielded a 68% response rate and a final sample of 3639 college students. The sample had a mean age of 19.9 years, and respondents were 53.6% female, 67.4% white, 12.1% Asian, 6.0% African American, 4.2% Hispanic, and 10.2% other racial categories. Medical and nonmedical use of prescription drugs was measured. Probable drug abuse was assessed using a modified version of the Drug Abuse Screening Test, Short Form. A total of 40.1% of respondents reported no lifetime use of at least 1 of 4 classes of prescription drugs, 39.7% reported medical use only, 15.8% reported both medical and nonmedical use, and 4.4% reported nonmedical use only. The odds of a positive screening

result for drug abuse were greater among medical and nonmedical users (adjusted odds ratio, 5.5; 95% confidence interval, 3.4-7.3) and nonmedical users only (adjusted odds ratio, 6.5; 95% confidence interval, 4.0-10.6) compared with nonusers. The odds of a positive screening result for drug abuse did not differ between medical users only and nonusers. These findings suggest that nonmedical users of prescription drugs are at heightened risk for drug abuse, whereas medical users without a history of nonmedical use are generally not at increased risk. The authors conclude that drug abuse screening should be routine for college students, especially among individuals with any history of nonmedical use of prescription drugs. McCabe, S. Screening for Drug Abuse Among Medical and Nonmedical Users of Prescription Drugs in a Probability Sample of College Students. Arch. Pediatr. Adolesc. Med., 162(3), pp. 225-231, 2008.

Misperceptions of Non-medical Prescription Drug Use Among College Students

This study compared undergraduate students' perceived versus actual prevalence rates of non-medical use of marijuana, prescription opioids and prescription stimulants. In 2005, a randomly selected sample of 3639 college students self-administered a Web survey regarding their substance use behaviors and attitudes (68% response rate). Analysis showed that the majority of undergraduate students overestimated the prevalence of non-medical use of prescription stimulants (70.2%) and prescription opioids (69.9%) and marijuana use (50.5%) among peers on their campus. The mean difference between perceived versus actual past-year use was considerably greater for non-medical use of prescription stimulants (mean difference=12.2, 95% CI=11.7-12.7) and prescription opioids (mean difference=8.8, 95% CI=8.3-9.2) than marijuana (mean difference=2.9, 95% CI=2.2-3.6). Multivariate regression analysis revealed overestimation of non-medical use of prescription drugs was significantly associated with gender and medical use of prescription drugs. The authors conclude that the study results provide strong evidence of misperception of non-medical prescription drug use among college students and suggest that future research and prevention efforts should assess the impact of correcting misperceived norms on reducing non-medical prescription drug use. McCabe, S. E. Misperceptions of Non-medical Prescription Drug Use: A Web Survey of College Students. Addict. Behav., 33, pp. 713-724, 2008.

Association Between Early Onset of Non-medical Use of Prescription Drugs and Subsequent Prescription Drug Use and Dependence

This study examined the associations between early onset of non-medical use of prescription drugs (NMUPD) (i.e. sedatives, tranquilizers, opioids, stimulants) and the development of prescription drug abuse and dependence in the United States. Data were collected from structured diagnostic interviews using the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Alcohol Use Disorder and Associated Disabilities Interview Schedule: Diagnostic and Statistical Manual version IV (DSM-IV). National prevalence estimates were derived from the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC, n = 43,093). NESARC included a nationally representative cross-sectional sample of civilian non-institutionalized adults aged 18 years or older in the United States, of whom 52% were women, 71% white, 12% Hispanic, 11% African American, 4% Asian and 2% Native American or of other racial background. Analyses revealed that a higher percentage of individuals who began using prescription drugs non-medically at or before 13 years of age were found to have developed prescription drug abuse and dependence as compared with those individuals who began using at or after 21 years of age. Multivariate logistic regression analyses indicated that

the odds of developing any life-time prescription drug abuse among non-medical users was reduced by approximately 5% with each year non-medical use was delayed [adjusted odds ratio (AOR) = 0.95, 95% CI = 0.94, 0.97], and that the odds of developing any lifetime prescription drug dependence were reduced by about 2% with each year onset was delayed (AOR = 0.98, 95% CI = 0.96, 1.00) when controlling for relevant covariates. The authors conclude that early onset of NMUPD was a significant predictor of prescription drug abuse and dependence. These findings reinforce the importance of developing prevention efforts to reduce NMUPD and diversion of prescription drugs among children and adolescents. McCabe, S., West, B., Morales, M., Cranford, J., and Boyd, C. Does Early Onset of Non-medical Use of Prescription Drugs Predict Subsequent Prescription Drug Abuse and Dependence? Results from a National Study. Addiction, 102(12), pp. 1920-1930, 2007.

Nonmedical Use of Prescription Stimulants Among College Students: Associations with Attention-Deficit-Hyperactivity Disorder and Polydrug Use

This study examined nonmedical use of prescription stimulants (NPS), in a cohort of first year college students at a large public university and assessed whether NPS and overuse of a medically prescribed stimulant for ADHD were independently associated with an increased risk of other illicit drug use and dependence on alcohol and marijuana. A cohort of 1253 first-year college students aged 17-20 years completed a 2-hour personal interview to ascertain medical use and overuse of prescription stimulants, NPS, nonmedical use of other prescription drugs and illicit drug use, and dependence on alcohol and marijuana. Comparisons were made among nonusers, nonmedical users, and medical users of prescription stimulants for ADHD (ADHD+), some of whom overused their drug. Of 1208 students who were not using prescription stimulants medically for ADHD (ADHD-), 218 (18.0%) engaged in NPS. Of 45 ADHD+ students, 12 (26.7%) overused their ADHD drug at least once in their lifetime, and seven (15.6%) nonmedically used someone else 's prescription stimulants at least once in their lifetime. Among 225 nonmedical users, NPS was infrequent and mainly associated with studying, although 35 (15.6%) used prescription stimulants to party or to get high. Lifetime NPS was associated with past-year other drug use. Both NPS and overuse of prescribed stimulants for ADHD were independently associated with past-year use of five drugs, controlling for sociodemographic characteristics; NPS was also associated with alcohol and marijuana dependence. These findings suggest that physicians should be vigilant for possible overuse and/or diversion of prescription stimulants for ADHD among college students who are medical users of these drugs, as well as the occurrence of illicit drug use with NPS. The authors recommend that comprehensive drug prevention activities that involve parents as well as college personnel should be encouraged to raise awareness of NPS and its association with illicit drug use. Arria, A., Caldeira, K., O'Grady, K., Vincent, K., Johnson, E., and Wish, E. Nonmedical Use of Prescription Stimulants among College Students: Associations with Attention-Deficit-Hyperactivity Disorder and Polydrug Use. Pharmacotherapy, 28(2), pp. 156-169, 2008.

Non-prescribed Use of Pain Relievers Among Adolescents in the United States

This study examined gender-specific prevalences, patterns, and correlates of non-prescribed use of pain relievers (mainly opioids) in a representative sample of American adolescents (N=18,678). Data were drawn from the public use data file of the 2005 U.S. National Survey on Drug Use and Health, a survey of non-institutionalized American household residents. Patterns of non-prescribed use of prescription pain relievers were examined, and logistic regression procedures were conducted to identify correlates of non-prescribed

use. Analysis showed that approximately one in 10 adolescents aged 12-17 years reported non-prescribed use of pain relievers in their lifetime (9.3% in males and 10.3% in females). The mean age of first non-prescribed use was 13.3 years, which was similar to the mean age of first use of alcohol and marijuana but older than the age of first inhalant use. Among all non-prescribed users, 52% reported having used hydrocodone products (Vicodin, Lortab, Lorcet, and Lorcet Plus, and hydrocodone), 50% had used propoxyphene (Darvocet or Darvon) or codeine (Tylenol with codeine), and 24% had used oxycodone products (OxyContin, Percocet, Percodan, and Tylox). Approximately one quarter (26%) of all non-prescribed users had never used other non-prescribed or illicit drugs. There were gender variations in correlates of non-prescribed use. These findings indicate that use of non-prescribed pain relievers occurs early in adolescence. The authors suggest that research is needed to understand whether early use of non-prescribed pain relievers is related to later drug use. Wu, L., Pilowsky, D., and Patkar, A. Non-Prescribed Use of Pain Relievers among Adolescents in the United States. Drug Alcohol Depend., 94(1-3), pp. 1-11, 2008.

Specificity of Psychosocial Risk Factors for Child Psychiatric Disorders

Most psychosocial risk factors appear to have general rather than specific patterns of association with common childhood and adolescence disorders. However, previous research has typically failed to 1) control for comorbidity among disorders, 2) include a wide range of risk factors, and 3) examine sex by developmental stage effects on risk factor-disorder associations. This study tests the specificity of putative psychosocial risk factors while addressing these criticisms. Eight waves of data from the Great Smoky Mountains Study (N = 1,420) were used, covering children in the community age 9-16 years old. Youth and one parent were interviewed up to seven times using the Child and Adolescent Psychiatric Assessment, providing a total of 6,674 pairs of interviews. A wide range of putative neighborhood, school, peer, family, and child risk factors, and common and comorbid youth disorders were assessed. The authors found that a majority of putative risk factors were specific to one disorder or one disorder domain. A unique or ''signature set '' of putative risk factors was identified for each disorder. Several putative risk factors were associated with a disorder in preadolescent males, preadolescent females, adolescent males, or adolescent females only. They conclude that there is a need to define risk factors and disorders narrowly, to control comorbidity and other risk factors, and to consider developmental patterns of specificity by sex. This may augment efforts in the prevention arena. Shanahan, L., Copeland, W., Costello, E., and Angold, A. Specificity of Putative Psychosocial Risk Factors for Psychiatric Disorders in Children and Adolescents. J. Child. Psychol. Psychiatry, 49(1), pp. 34-42, 2008.

Family Risk for ADHD and SUD

This study sought to examine the bidirectional comorbidity between attention deficit hyperactivity disorder (ADHD) and psychoactive substance use disorder (alcohol or drug abuse or dependence). First-degree relatives from a large group of pediatrically and psychiatrically referred boys with (112 probands, 385 relatives) and without (105 probands, 358 relatives) ADHD were comprehensively assessed by blind raters with structured diagnostic interviews. Familial risk analysis examined the risks in first-degree relatives for ADHD, psychoactive substance use disorder, alcohol dependence, and drug dependence after stratifying probands by the presence and absence of these disorders. The authors found that ADHD in the proband was consistently associated with a significant risk for ADHD in relatives. Drug dependence in probands increased the risk for drug dependence in relatives irrespective of ADHD status, whereas alcohol dependence in relatives was predicted only by

ADHD probands with comorbid alcohol dependence. In addition, ADHD in the proband predicted drug dependence in relatives, and drug dependence in comparison probands increased the risk for ADHD in relatives. Both alcohol dependence and drug dependence bred true in families without evidence for a common risk between these disorders. The authors conclude that these patterns of familial risk suggest that the association between ADHD and drug dependence is most consistent with the hypothesis of variable expressivity of a common risk between these disorders, whereas the association between ADHD and alcohol dependence is most consistent with the hypothesis of independent transmission of these disorders. Findings also suggest specificity for the transmission of alcohol and drug dependence. These conclusions are consistent with recently published findings from genetic epidemiologic studies. Biederman, J., Petty, C., Wilens, T., Fraire, M., Purcell, C., Mick, E., Monuteaux, M., and Faraone, S. Familial Risk Analyses of Attention Deficit Hyperactivity Disorder and Substance Use Disorders. Am. J. Psychiatry, 165(1), pp. 107-115, 2008.

Trajectories of Cigarette Smoking among African Americans and Puerto Ricans from Adolescence to Young Adulthood: Associations with Dependence on Alcohol and Illegal Drugs

This study predicts that heterogeneous smoking trajectories covering four time points pose differential risks for dependence on alcohol and illegal drugs in young adulthood in an African American and Puerto Rican community sample (N = 475). The trajectory analysis yielded four smoking groups: nonsmokers, maturing out smokers, late-starting smokers, and early-starting continuous smokers. The early starting continuous group was more likely to become both alcohol- and drug-dependent in young adulthood than the other groups. Late-starting smokers were at higher risk than nonsmokers for drug dependence. Interventions are necessary from preadolescence through late adolescence to reduce the numbers of early and late smokers and their specific risks for substance dependence. Brook, J., Balka, E., Ning, Y., and Brook, D. Trajectories of Cigarette Smoking Among African Americans and Puerto Ricans from Adolescence to Young Adulthood: Associations with Dependence on Alcohol and Illegal Drugs. Am. J. Addict., 16(3), pp. 195-201, 2007.

The Formation of a Socioeconomic Disparity: A Case Study of Cocaine and Marijuana Use in the 1990s'

Around 1990, the reputation of cocaine use changed from glamorous to undesirable, and at the same time, a socioeconomic disparity in cocaine use emerged. This study examined (1) whether the socioeconomic disparity was created by differential incidence, differential cessation, or both, (2) whether a socioeconomic disparity also developed in marijuana use, and (3) whether disparities formed across race, Hispanic ethnicity, and/or gender. The analyses center on 6544 respondents aged 14-21 in 1979 in the National Longitudinal Survey of 1979 that provided information on past-year use of powder cocaine and marijuana use before and after 1990--specifically, in 1984, 1988, 1992, 1994, and 1998. Both differential incidence and differential cessation across education contributed to the formation of the socioeconomic disparity in cocaine use, although differential cessation played a more influential role in this cohort. A socioeconomic disparity in marijuana use also came about around the same time. No emerging disparities by race, Hispanic ethnicity, or gender were observed. This case study suggests that the redefinition of a health behavior as unhealthy will result in a socioeconomic disparity in the behavior across socioeconomic strata as a result of both differential incidence and cessation, but disparities will not necessarily form by race, ethnicity, or gender. Miech, R., and Chilcoat, H. The Formation of A Socioeconomic Disparity: A Case Study of Cocaine and Marijuana Use in the 1990s. Am. J. Prev. Med., 32 (6 Suppl), pp. S171-s176, 2007.

Personality, Adrenal Steroid Hormones, and Resilience in Maltreated Children

In this investigation, resilience in adaptive functioning among maltreated and nonmaltreated low-income children (N = 677) was examined in relation to the regulation of two stress-responsive adrenal steroid hormones, cortisol and dehydroepiandrosterone (DHEA), as well as the personality constructs of ego resiliency and ego control. Maltreatment status was not related to differences in average levels of morning or afternoon cortisol or DHEA. However, lower morning cortisol was related to higher resilient functioning, but only in nonmaltreated children. In contrast, among physically abused children, high morning cortisol was related to higher resilient functioning. Morning and afternoon DHEA was negatively related to resilient functioning. Although diurnal change in cortisol was not related to resilience, for DHEA, maltreated children with high resilience showed an atypical rise in DHEA from morning to afternoon. Morning and afternoon cortisol/DHEA ratios were positively related to resilient functioning, but did not interact with maltreatment status. Ego resiliency and ego control strongly differentiated maltreated and nonmaltreated children, and the personality variables were substantially predictive of resilience. When considered together, demonstrated effects of personality, cortisol, and DHEA maintained independent contributions in predicting resilience among high-risk youth. Cicchetti, D., and Rogosch, F. Personality, Adrenal Steroid Hormones, and Resilience in Maltreated Children: A Multilevel Perspective. Dev. Psychopathol., 19(3), pp. 787-809, 2007.

Tripling of Methamphetamine/Amphetamine Use among Homeless and Marginally Housed Persons, 1996-2003

Methamphetamine/amphetamine (MA)-related morbidity and mortality have been increasing in the United States. MA use is associated with high-risk sexual behavior and syringe-sharing practices. Homeless and marginalized housed persons (H/M) have high rates of substance use and mental health disorders, but little is known about trends of MA use among the H/M. The objective of this study was to quantify increases in MA use among H/M in San Francisco and to determine which demographic and behavioral subgroups have experienced the greatest increases in MA use. Researchers conducted serial cross-sectional population-based studies in three waves: 1996-1997, 1999-2000, and 2003 and studied 2,348 H/M recruited at shelters and lunch lines. The main outcome was self-reported current (30-day) MA use. There was a tripling of current MA use among H/M persons from 1996 to 2003, with a 7-fold increase in smoked MA use. MA use doubled or tripled in most demographic and behavioral subgroups, whereas it quadrupled in those under age 35. There was a 5-fold increase among HIV-infected persons. The increase in MA use among H/M places a vulnerable population at additional increased risk for HIV infection and MA-use related morbidity and mortality. In particular, among HIV-infected H/M, the increase in MA use has important public health implications for the development and secondary transmission of drug-resistant HIV related to a synergism of neurocognitive decline, poor adherence to HIV medications, and increased sexual risk behavior. These findings are important for clinicians caring for H/M persons, to inquire about MA use, refer interested MA users to MA dependence treatment programs, and provide targeted HIV sexual risk reduction counseling. HIV-infected H/M MA users should be closely monitored for adherence to HIV or other chronic medications, to avoid unnecessary morbidity and mortality. The results also point to the need for research to elucidate the most effective prevention and treatment for MA use and dependence among the H/M. Das-Douglas, M., Colfax, G., Moss, A., Bangsberg, D., and Hahn, J. Tripling of Methamphetamine/Amphetamine Use among Homeless and Marginally Housed Persons, 1996-2003. J. Urban Health, 85(2), pp. 239-249, 2008.

Alcohol-use Disorders and Nonmedical Use of Prescription Drugs Among U.S. College Students

This study examined: 1) the association between DSM-IV, alcohol-use disorders (AUDs) and nonmedical use of prescription drugs (NMPD) among U.S. college students, and 2) individual-level and college-level characteristics associated with the co-occurrence of AUDs and NMPD. Data were collected from self-administered mail surveys, sent to a random sample of approximately 14,000 college students from a nationally representative sample of 119 U.S. colleges and universities. Analyses revealed that the prevalence of past-year NMPD was highest among those with AUDs: multivariate logistic regression analyses indicated that college students with past-year DSM-IV alcohol abuse only (adjusted odds ratio [AOR]=4.46, 95% confidence interval [CI]=3.59-5.55) and students with past-year DSM-IV alcohol dependence (AOR=9.17, 95% CI=7.05-11.93) had significantly increased odds of NMPD in the past year compared with students without AUDs. The co-occurrence of AUDs and NMPD was more likely among college students who were male, white, earned lower grade point averages, and attended co-ed colleges and institutions located in Southern or Northeastern U.S. regions. These findings provide evidence that NMPD is more prevalent among those college students with AUDs, especially individuals with past-year DSM-IV alcohol dependence. The authors conclude that the assessment and treatment of AUDs among college students should take into account other forms of drug use such as NMPD. McCabe, S., West, B., and Wechsler, H. Alcohol-use Disorders and Nonmedical Use of Prescription Drugs among U.S. College Students. J. Stud. Alcohol Drugs, 68(4), pp. 543-547, 2007.

The Occurrence of Cannabis Use Disorders and Other Cannabis-related Problems Among First-year College Students

This study reports the prevalence of cannabis use disorders (CUD) and other cannabis-related problems in a large cohort (n=1253) of first-year college students, 17 to 20 years old, at one large public university in the mid-Atlantic region of the U.S. Interviewers assessed past-year cannabis use, other drug use, and cannabis-related problems (including DSM-IV criteria for CUD). The prevalence of CUD was 9.4%(wt) among all first-year students and 24.6% among past-year cannabis users (n=739). Among 474 cannabis users who reported cannabis use >/=5 times in the past year, concentration problems (40.1%), driving while high (18.6%) and missing class (13.9%) were among the most prevalent cannabis-related problems, even among those who endorsed no CUD criteria. Placing oneself at risk for physical injury was also commonly reported (24.3%). The study results show that a significant proportion of cannabis-using college students met diagnostic criteria for disorder. Even in the absence of disorder, users appear to be at risk for potentially serious cannabis-related problems. The authors conclude that these findings highlight the need for improved screening and early intervention for drug-related problems among first-year college students. Caldeira, K., Arria, A., O 'Grady, K., Vincent, K., and Wish, E. The Occurrence of Cannabis Use Disorders and Other Cannabis-related Problems among First-year College Students. Addict. Behav., 33(3), pp. 397-411, 2008.

Rapid Increase in the Diagnosis of Youth Bipolar Disorder

Although bipolar disorder may have its onset during childhood, little is known about national trends in the diagnosis and management of bipolar disorder in young people. The purpose of this study was to present national trends in outpatient visits with a diagnosis of bipolar disorder and to compare the treatment provided to youth and adults during those visits. Investigators compared rates of growth between 1994-1995 and 2002-2003 in visits with a

bipolar disorder diagnosis by individuals aged 0 to 19 years vs those aged 20 years or older. For the period of 1999 to 2003, we also compare demographic, clinical, and treatment characteristics of youth and adult bipolar disorder visits. Patient visits from the National Ambulatory Medical Care Survey (1999-2003) with a bipolar disorder diagnosis (n = 962) were assessed drawn from outpatient visits to physicians in office-based practice. Visits with a diagnosis of bipolar disorder by youth (aged 0-19 years) and by adults (aged > or = 20 years) were assessed. The study indicated the estimated annual number of youth office-based visits with a diagnosis of bipolar disorder increased from 25 (1994-1995) to 1003 (2002-2003) visits per 100,000 population, and adult visits with a diagnosis of bipolar disorder increased from 905 to 1679 visits per 100,000 population during this period. In 1999 to 2003, most youth bipolar disorder visits were by males (66.5%), whereas most adult bipolar disorder visits were by females (67.6%); youth were more likely than adults to receive a comorbid diagnosis of attention-deficit/hyperactivity disorder (32.2% vs 3.0%, respectively; P < .001); and most youth (90.6%) and adults (86.4%) received a psychotropic medication during bipolar disorder visits, with comparable rates of mood stabilizers, antipsychotics, and antidepressants prescribed for both age groups. There has been a recent rapid increase in the diagnosis of youth bipolar disorder in office-based medical settings. This increase highlights a need for clinical epidemiological reliability studies to determine the accuracy of clinical diagnoses of child and adolescent bipolar disorder in community practice. Moreno, C., Laje, G., Blanco, C., Jiang, H., Schmidt, A., and Olfson, M. National Trends in the Outpatient Diagnosis and Treatment of Bipolar Disorder in Youth. Arch. Gen. Psychiatry, 64(9), pp. 1032-1039, 2007.

The Impact of Sociodemographic Factors and Psychiatric Disorders on Maternal Smoking During Pregnancy

Maternal smoking during pregnancy increases birth complication risk and has long-term developmental consequences for child development. This study investigated the relative importance of sociodemographic factors and psychiatric disorders for smoking among 453 pregnant women in the National Epidemiological Survey on Alcohol and Related Conditions. Women with less than a high school education and those with current-year nicotine dependence had the highest risk of smoking (90.5%), compared with women with a college degree and without nicotine dependence (3.9%). More effective and accessible interventions for nicotine dependence among pregnant smokers are needed. Gilman, S., Breslau, J., Subramanian, S., Hitsman, B., and Koenen, K. Social Factors, Psychopathology, and Maternal Smoking During Pregnancy. Am. J. Public Health, 98(3), pp. 448-453, 2008.

Exposure to Smoking Depictions in Movies: Its Association with Established Adolescent Smoking

This longitudinal study of a representative US adolescent sample was designed to assess the association between exposure to movie smoking and established adolescent smoking. Adolescents were surveyed by telephone in their homes. Participants included sixty-five hundred twenty-two US adolescents aged 10 to 14 years at baseline, who were resurveyed at 8 months (8M) (n = 5503), 16 months (16M) (n = 5019), and 24 months (24M) (n = 4575). The main Exposure measured was exposure to smoking in 532 box-office hits released in the 5 years prior to the baseline survey. The outcome measure was established smoking (having smoked more than 100 cigarettes during lifetime). Of 108 incident established smokers with data at the 24M survey, 85% were current (30-day smokers) and 83% endorsed at least 1 addiction symptom. Established smoking incidence was 7.4, 15.8, and 19.7 per 1000 person-years of observation for the baseline-to-8M, 8M-to-16M, and 16M-to-24M observation periods, respectively. In a multivariate survival model, risk of established

smoking was predicted by baseline exposure to smoking in movies with an adjusted overall hazard ratio of 2.04 (95% confidence interval, 1.01-4.12) for teens in the 95th percentile of movie-smoking exposure compared with the 5th percentile. This effect was independent of age; parent, sibling, or friend smoking; and sensation seeking. Teens low on sensation seeking were more responsive to the movie-smoking effect (hazard ratio, 12.7; 95% confidence interval, 2.0-80.6) compared with teens who were high on sensation seeking (hazard ratio, 1.01; 95% confidence interval, 0.4-2.6). In this national US adolescent sample, exposure to smoking in movies predicted risk of becoming an established smoker, an outcome linked with adult dependent smoking and its associated morbidity and mortality. Sargent, J., Stoolmiller, M., Worth, K., Dal Cin, S., Wills, T., Gibbons, F., Gerrard, M., and Tanski, S. Exposure to Smoking Depictions in Movies: Its' Association with Established Adolescent Smoking. Arch. Pediatr. Adolesc. Med., 161(9), pp. 849-856, 2007.

Getting Into Ecstasy: Comparing Moderate and Heavy Young Adult Users

In this article, the authors examine factors associated with initial and present Ecstasy use among young adults. Face-to-face structured interviews were conducted in Atlanta, Georgia among 261 active Ecstasy users. The median age at which respondents first heard of Ecstasy was 16 years, whereas the median age of first Ecstasy use was 18 years. Initial Ecstasy use frequently involved polydrug use, including alcohol (50.4%). In terms of their current use, 47.5% of respondents were considered heavy Ecstasy users (using on 10 or more separate occasions in the last 90 days). White respondents, those who used more than one pill during their initial use, and those who used again within one month after their initial use were more likely to be current heavy Ecstasy users. Women, those who waited a longer time between initial and subsequent Ecstasy use, and those who considered themselves in the upper SES bracket were less likely to be current heavy Ecstasy users. A better understanding of initial and current Ecstasy use patterns, including polydrug use, is essential for effective prevention and intervention efforts. Sterk, C., Theall, K., and Elifson, K. Getting Into Ecstasy: Comparing Moderate and Heavy Young Adult Users. J. Psychoactive Drugs, 39(2), pp. 103-113, 2007.

Social Anxiety and Risk for Alcohol and Cannabis Dependence

Social anxiety disorder (SAD) is highly comorbid with alcohol use disorders (AUDs) and cannabis dependence. However, the temporal sequencing of these disorders has not been extensively studied to determine whether SAD serves as a specific risk factor for problematic substance use. The present study examined these relationships after controlling for theoretically-relevant variables (e.g., gender, other Axis I pathology) in a longitudinal cohort over approximately 14 years. The sample was drawn from participants in the Oregon Adolescent Depression Project., who were originally recruited as adolescents from high schools in 1987-89, at a mean age of 16.6 years. The sample, half female, was followed at ages 24 and 30; the final data point was collected from 816 participants, 59% women, 59% Caucasian. After excluding those with substance use disorders at baseline, SAD at study entry was associated with 6.5 greater odds of cannabis dependence (but not abuse) and 4.5 greater odds of alcohol dependence (but not abuse) at follow-up after controlling for relevant variables (e.g., gender, depression, conduct disorder). The relationship between SAD and alcohol and cannabis dependence remained even after controlling for other anxiety disorders. Other anxiety disorders and mood disorders were not associated with subsequent cannabis or alcohol use disorder after controlling for relevant variables. Among the internalizing disorders, SAD appears to serve as a unique risk factor for the subsequent onset of cannabis and alcohol dependence. Buckner, J., Schmidt, N., Lang, A., Small, J., Schlauch, R., and Lewinsohn, P. Specificity of Social Anxiety Disorder

as a Risk Factor for Alcohol and Cannabis Dependence. J. Psychiatr. Res., 42(3), pp. 230-239, 2008.

Correlates of Cannabis Initiation in Young Women

As rates of cannabis use have increased in young women over the last decade, the authors sought to characterize the potential correlates of onset of cannabis use during emerging adulthood. Using data from 1065 females (collected 1994-2005) who participated in both the baseline (ages 16-23) and follow-up wave (ages 20-29) of interviews of the Missouri Adolescent Female Twin Study, they examined the associations between correlates from the peer, parental and individual domains and new onsets of cannabis use, using logistic regression. Univariate models revealed that initiation of cannabis use was associated with alcohol and cigarette use at baseline, peer attitude towards alcohol/cigarette/ cannabis use, peer substance use and other aspects of impulse-disinhibited behavior. However, multivariate stepwise modeling retained only the significant influences of alcohol use at baseline and peer attitudes towards cannabis as correlates of cannabis initiation. The authors concluded that having peers with favorable attitudes towards alcohol, cigarette and cannabis use is an important correlate of initiation of cannabis use in women, and that prevention and intervention efforts need to take this into account when developing drug resistance training programs for adolescents. Agrawal, A., Lynskey, M., Bucholz, K., Madden, P., and Heath, A. Correlates of cannabis initiation In a Longitudinal Sample of Young Women: The Importance of Peer Influences. Prev. Med., 45(1), pp. 31-34, 2007.

Misuse and Diversion of Stimulants Prescribed for ADHD

This paper provides a systematic review of the literature to evaluate the extent and characteristics of stimulant misuse and diversion in attention-deficit/hyperactivity disorder (ADHD) and non-ADHD individuals. The review covered available studies looking at misuse and diversion of prescription ADHD medications using misuse, diversion, stimulants, illicit use, and ADHD medications as key words for the search. It identified 21 studies representing 113,104 subjects. The studies reported rates of past year nonprescribed stimulant use to range from 5% to 9% in grade school- and high school-age children and 5% to 35% in college-age individuals. Lifetime rates of diversion ranged from 16% to 29% of students with stimulant prescriptions asked to give, sell, or trade their medications. Recent work suggests that whites, members of fraternities and sororities, individuals with lower grade point averages, use of immediate-release compared to extended-release preparations, and individuals who report ADHD symptoms are at highest risk for misusing and diverting stimulants. Reported reasons for use, misuse, and diversion of stimulants include to concentrate, improve alertness, "get high," or to experiment. The authors conclude that individuals both with and without ADHD misuse stimulant medications. The literature highlights the need to carefully monitor high-risk individuals for the use of nonprescribed stimulants and educate individuals with ADHD as to the pitfalls of the misuse and diversion of the stimulants. Wilens, T., Adler, L., Adams, J., Sgambati, S., Rotrosen, J., Sawtelle, R., Utzinger, L., and Fusillo, S. Misuse and Diversion of Stimulants Prescribed for ADHD: A Systematic Review of the Literature. J. Am. Acad. Child Adolesc. Psychiatry, 47(1), pp. 21-31, 2008.

Race/Ethnicity and Gender Differences in Drug Use and Abuse Among College Students

This study examined race/ethnicity and gender differences in drug use and abuse for substances other than alcohol among undergraduate college students. A probability-based sample of 4,580 undergraduate students at a

Midwestern university completed a cross-sectional Web-based questionnaire that included demographic information and several substance use measures. Male students were more likely to report drug use and abuse than female students. Hispanic and White students were more likely to report drug use and abuse than Asian and African American students prior to coming to college and during college. Results of multiple logistic regression analysis for past 12-month illicit use of prescription drugs or illicit drugs revealed that after controlling for race, there was no statistically significant effect of gender. With respect to race, results using African Americans as the reference group showed that, controlling for gender, the odds of past 12-month drug use were statistically significantly higher among Whites (OR=1.86) and Hispanics (OR=2.14). The authors conclude that the findings of the present study reveal several important racial/ethnic differences in drug use and abuse that need to be considered when developing collegiate drug prevention and intervention efforts. McCabe, S., Morales, M., Cranford, J., Delva, J., McPherson, M., and Boyd, C. Race/Ethnicity and Gender Differences in Drug Use and Abuse Among College Students. J. Ethn. Subst. Abuse, 6(2), pp. 75-95, 2007.

Racial and Ethnic Changes in Heroin Injection in the United States: Implications for the HIV/AIDS Epidemic

Racial/ethnic differences in drug injection prevalence contribute to disparities in HIV infection rates in the US between Whites, Blacks and Hispanics. This study examined trends in the demographic characteristics of heroin injection drug users (IDUs) that may impact future HIV rates. Descriptive analyses were conducted of (1) the national Treatment Episode Data Set for 1992-2004 and of the 2002-2004 baseline data from (2) CIDUS-III, a 5-city study that recruited 3285 young IDUs, and (3) NIHU-HIT, a Chicago study of 647 young noninjecting heroin users. Between 1992 and 2004, heroin was the injected drug most often reported at admission to drug treatment. During this period, the proportion of admissions reporting injection declined 44% among Blacks but only 14% for Whites. The peak age for heroin IDUs in treatment increased 10 years for Blacks while declining over 10 years for Whites. CIDUS-III enrolled about 8 times more White (64%) than Black (8%) young IDUs despite recruiting two-thirds of the sample in cities where Blacks constituted 27-64% of the population. Blacks comprised 53% of noninjecting heroin users in the Chicago NIHU-HIT, but only 2% of Chicago's CIDUS-III sample of heroin IDUs. Among current noninjecting heroin users, Whites were more likely than Blacks to have ever injected ($X(d.f.=1)(2)=17.1$, $p<0.001$). Qualitative data supported greater resistance to injection among young Blacks than Whites. These findings suggest that, among heroin users, young Blacks are resisting injection while young Whites exhibit the opposite tendency. New research should investigate reasons for this trend and its impact on the HIV epidemic and future service needs. Broz, D., and Ouellet, L. Racial and Ethnic Changes in Heroin Injection in the United States: Implications for the HIV/AIDS Epidemic. Drug Alcohol Depend., 94(1-3), pp. 221-233, 2008.

Intimate Partner Violence Perpetration against Main Female Partners among HIV-Positive Male Injection Drug Users

Intimate partner violence (IPV) against women is a serious public health and social problem and is associated with a host of adverse health outcomes and behaviors, including HIV risk behaviors, among women who are victimized. Historically, research has focused on correlates of IPV victimization among women; thus, there is less information on the role of men in perpetrating IPV, particularly among men at risk for transmitting HIV to their female partners. The authors assessed the self-reported prevalence and correlates of perpetration and threat of perpetration of physical and/or sexual IPV against a main female partner among 317 HIV-positive men who were current injection drug users (IDUs). More than 40% of men reported perpetrating physical

(39%) and/or sexual (4%) violence against their main female partners in the past year. Multivariate analyses revealed that low education, homelessness, psychologic distress, and unprotected sex with main and nonmain HIV-negative female partners were positively associated with IPV perpetration against main female partners. These findings reveal that IPV perpetration is prevalent among HIV-positive male IDUs and associated with sexual HIV transmission risk behaviors. IPV assessment and treatment among HIV-positive men in HIV care is recommended as a way to prevent IPV perpetration and victimization and to reduce potential HIV transmission. Frye, V., Latka, M., Wu, Y., Valverde, E., Knowlton, A., Knight, K., Arnsten, J., and O 'Leary, A. Intimate Partner Violence Perpetration against Main Female Partners among HIV-Positive Male Injection Drug Users. J. Acquir. Immune Defic. Syndr., 46 Suppl 2, pp. S101-S109, 2007.

Blood Contamination in Children's Saliva: Prevalence, Stability, and Impact on the Measurement of Salivary Cortisol, Testosterone, and Dehydroepiandrosterone

The prevalence, stability, and impact of blood contamination in children's saliva on the measurement of three of the most commonly assayed hormones were examined. Participants were 363 children (47% boys; ages 6-13 years) from economically disadvantaged families who donated saliva samples on 2 days in the morning, midday, and late afternoon. Samples (n=2178) were later assayed for cortisol (C), testosterone (T), and dehydroepiandrosterone (DHEA). To index the presence of blood (and its components) in saliva, samples were assayed for transferrin. Transferrin levels averaged 0.37 mg/dl (SD=0.46, range 0.0-5.5, Mode=0), and were: (1) highly associated within individuals across hours and days, (2) positively correlated with age, (3) higher for boys than girls, (4) higher in PM than AM samples, and (5) the highest (>1.0 mg/dl) levels were rarely observed in samples donated from the same individuals. Transferrin levels were associated with salivary DHEA and C, but less so for T. As expected, the relationships were positive, and explained only a small portion of the variance. Less than 1% of the statistical outliers (+2.5 SDs) in salivary hormone distributions had correspondingly high transferrin levels. The researchers conclude that blood contamination in children's saliva samples is rare, and its effects on the measurement of salivary hormones is small. Guidelines and recommendations are provided to steer investigators clear of this potential problem in special circumstances and populations. Granger, D., Cicchetti, D., Rogosch, F., Hibel, L., Teisl, M., and Flores, E. Blood Contamination in Children's Saliva: Prevalence, Stability, and Impact on the Measurement of Salivary Cortisol, Testosterone, and Dehydroepiandrosterone. Psychoneuroendocrinology, 32(6), pp. 724-733, 2007.

Puberty is Associated with Changes in the Form and Frequency of Self-Harm

A cross-sectional survey of 12- to 15-year-olds in 300 secondary schools in the U.S. state of Washington in February-April 2002 and the Australian state of Victoria was conducted to ascertain the association between pubertal stage and deliberate self-harm. A total of 3,332 students in grades 7 and 9 provided complete data on episodes of deliberate self-harm in the previous 12 months and pubertal stage. Pubertal stage was assessed with the Pubertal Development Scale, The prevalence of deliberate self-harm was 3.7% with a more than twofold higher rate in females. Late puberty was associated with a more than fourfold higher rate of self-harm (odds ratio 4.6, 95% confidence interval 1.5-14) after adjustment for age and school grade level. In contrast age had a protective association (odds ratio 0.7, confidence interval 0.4-1.0). The sharpest rises in prevalence across puberty were for self-laceration and self-poisoning in females. Higher rates of depressive symptoms, frequent alcohol use, and initiation of sexual activity largely accounted for the

association between self-harm and pubertal stage in multivariate models. Puberty is associated with changes in the form and frequency of self-harm. For adolescents with a gap between puberty and brain development, risk factors such as early sexual activity and substance abuse may be particularly potent. Patton, G., Hemphill, S., Beyers, J., Bond, L., Toumbourou, J., McMorris, B., and Catalano, R. Pubertal Stage and Deliberate Self-harm in Adolescents. J. Am. Acad. Child Adolesc. Psychiatry, 46(4), pp. 508-514, 2007.

Sexual Abstinence in Adolescence Predicts Adult Mental Health Differentially for Males and Females

Investigators examined whether adolescent sexual abstinence predicts better adult mental health. 1,917 adolescents, recruited from middle schools at age 13, were surveyed at ages 13, 18, 23, and 29. In bivariate analyses, adolescent sexual abstinence was associated with better mental health at age 29 for females, but not males; three adolescent factors, educational prospects, family bonding, and unconventionality were investigated as explanatory variables of this relationship. The abstinence-mental health relationship was nonsignificant when educational prospects was included in multivariate models, and marginally significant when family bonding and unconventionality were included; all three explanatory factors accounted for significant proportions of the variance in adult mental health. Girls' who are uninvolved in school, have weak family backgrounds, and exhibit unconventionality may have poor adult mental health, whether or not they abstain from sex in adolescence. Interventions that strengthen adolescents' connections to families and schools may reduce risk for long-term mental health problems. Bogart, L., Collins, R., Ellickson, P., and Klein, D. Association of Sexual Abstinence in Adolescence with Mental Health in Adulthood. J. Sex Res., 44(3), pp. 290-298, 2007.

Adolescent Work Related to Slight Decreases in Problem Behavior

Researchers have found mixed support for documenting whether work is protective or harmful during adolescence. This study of 592 African American youth (53% female; M = 14.8 years, SD = .60) examined the association between work and problem behaviors. Youth were followed from mid-adolescence to young adulthood over eight Waves (90% response rate over the first four Waves and a 68% response rate across all eight Waves). Investigators explored three competing operationalizations of work: work history (never worked, worked), work intensity (no work, 20 h or less, and 21 h or over), and work trajectories (never worked, episodic work, stopped working, late starter, and consistent worker). Non-working youth reported higher marijuana use during young adulthood than their working counterparts. Nonworkers reported lower self-acceptance during young adulthood than those working greater number of hours per week. Differences in work trajectories for cigarette use, depression, and anxiety during adolescence imply that when and for how long youth work are also important factors to explore. The findings lend tentative support to the work benefits perspective and suggest that the association between work and problem behaviors may depend in part on how work is measured. Bauermeister, J. A., Zimmerman, M. A., Barnett, T. E., and Caldwell, C. H. Working in High School and Adaptation in the Transition to Young Adulthood among African American Youth. J. Youth Adolescence, 36 pp. 877-890, 2007.

Individual Action and Community Context: the Health Intervention Project

HIV risk-reduction efforts have traditionally focused on the individual. The need for including the role of the social context and community is being recognized. Social capital provides social relationships and potential resources that may

hinder or trigger risk or protective health behaviors, especially for individuals with limited economic means. Sixty-five adult inner-city female drug users, who were included in a woman-focused HIV risk-reduction intervention trial, participated in in-depth interviews in Atlanta, Georgia, between 2002 and 2004. The interviews focused on the women's individual behavioral changes during the 6 months since completion of the intervention as well as on the impact of community conditions. Topics discussed were sexual and drug use behaviors, social relationships, social capital, and community physical and social infrastructure. The data were analyzed using the constant comparison methods. The respondents indicated that poor physical and social infrastructure led to alienation and negatively affected their behavioral change efforts. Social capital and social support mediated these negative influences. Drug-related violence was especially debilitating in their efforts to reduce HIV risk associated with crack cocaine or injection drug use and associated sexual behavior. Environmental conditions and opportunity structures played salient roles in the women's success. Individual actions and community context must be considered simultaneously when facilitating and assessing behavioral interventions. Sterk, C., Elifson, K., and Theall, K. Individual Action and Community Context: the Health Intervention Project. Am. J. Prev. Med., 32(6 Suppl), pp. S177-S181, 2007.

Identifying Injection Drug Users at Risk of Nonfatal Overdose

Drug overdose is the second leading cause of accidental deaths among U.S. adults aged 15-64 years. Emergency physicians have a unique opportunity to provide overdose prevention interventions, because habitual drug users are in frequent need of medical care. The authors evaluated associations between individual-level risk factors and experiencing an overdose in the past six months to determine which characteristics and behaviors may be most predictive of overdose. They used data from a sample of street-recruited habitual drug users who participated in face-to-face interviews about overdose from November 2001 to February 2004. This analysis was restricted to 772 respondents who had been injecting for at least one year and who had injected heroin within the past two months. A total of 16.6% of participants had overdosed in the past six months. Characteristics and behaviors that were independently associated with an increased risk of a recent overdose were having had a prior overdose (odds ratio [OR], 28.58; 95% confidence interval [CI] = 14.10 to 57.96), using cocaine/crack in the past six months (OR, 2.07; 95% CI = 1.25 to 3.45), using alcohol in the past six months (OR, 1.90; 95% CI = 1.01 to 3.57), experiencing serious withdrawal symptoms in the past two months (OR, 2.70; 95% CI = 1.58 to 4.61), and younger age. Drug users who have previously experienced a nonfatal overdose are at very high risk of experiencing future overdoses. Further longitudinal studies are needed to identify robust predictors of overdose risk over time in habitual drug users, but these data suggest that drug users who have overdosed warrant aggressive prevention efforts such as agonist maintenance treatment or provision of take-home naloxone. Coffin, P., Tracy, M., Bucciarelli, A., Ompad, D., Vlahov, D., and Galea, S. Identifying Injection Drug Users at Risk of Nonfatal Overdose. Acad. Emerg. Med., 14(7), pp. 616-623, 2007.

Large Percentage of Daily Smokers Remain Non-Nicotine Dependent

Current theoretical models of nicotine dependence assume a close relationship between use and dependence; however, previous data suggest that many daily smokers fail to develop nicotine dependence as currently defined. To determine what percentage of daily smokers fail to meet DSM-IV criteria for nicotine dependence within their lifetime, how non-dependence relates to duration and quantity of cigarette use, and whether other tobacco use and/or specific dependence criteria differentiate never-dependent and dependent smokers a

cross-sectional study was conducted. Data were collected via personal interview from a nationally representative sample of 8213 past year daily smokers were analyzed. Results indicated that approximately 39.4% of daily smokers never reached nicotine dependence. While the probability of remaining non-dependent decreased with smoking quantity and duration since the onset of daily smoking, a substantial portion of individuals (37.7%) who reported smoking >or=10 cigarettes per day and began smoking daily >or=10 years prior, remained never nicotine dependent. The absence of nicotine dependence in heavy daily smokers may result from limitations in the measurement of dependence and/or nicotine exposure. Alternatively, some individuals may be relatively resistant to becoming nicotine dependent despite extensive use. The latter explanation would have important implications for understanding the nature of nicotine dependence. Donny, E., and Dierker, L. The Absence of DSM-IV Nicotine Dependence in Moderate-to-Heavy Daily Smokers. Drug Alcohol Depend., 89(1), pp. 93-106, 2007.

Cigarette Smoking Rates in an Adolescent Treatment Sample at Eight-Year Follow Up

This study examined the relationship between cigarette smoking and alcohol use outcomes over an 8-year period following treatment for adolescent alcohol and other drug (AOD) use disorders. A sample of 166 adolescents were recruited during inpatient AOD abuse treatment. Included were 123 (74% of the full sample) participants, of whom 41% were female, 81% identified themselves as White and who averaged 15.9 years of age (SD = 1.3) when entering treatment. Using interviews conducted at the time of treatment and 2-, 4-, 6- and 8-years post-treatment, the investigators found that 26% of participants had quit smoking for > 1 year at the 8-year assessment, while 44% reported persistent smoking over time. Overall smoking rates decreased significantly over time. Those with the highest alcohol involvement trajectory reported significantly greater likelihood of persistent smoking as well as higher current smoking and cigarette consumption across time points. The investigators reported that the significant declines observed in smoking from adolescence into young adulthood were contrary to expectations, indicating that this behavior may be less stable than previously thought among adolescent AOD abusers. Smoking involvement over time was greater within the highest alcohol use trajectory, consistent with previous evidence for a positive relationship between these behaviors'. However, when compared with the general population smoking rates remained very high regardless of alcohol involvement. Thus, individuals treated for AOD abuse as adolescents remained at elevated risk for tobacco related disease regardless of post-treatment AOD use outcomes. Myers, M., Doran, N., and Brown, S. Is Cigarette Smoking Related to Alcohol Use During the 8 Years Following Treatment for Adolescent Alcohol and Other Drug Abuse? Alcohol Alcohol, 42(3), pp. 226-233, 2007.

Adult Smokers in Colombia: Who Isn't Giving It Up?

Without ongoing surveillance systems to assess tobacco product demand and exposure levels, many low and middle income countries monitor smoking via periodic cross-sectional surveys. In this article, the authors provide updated estimates for the prevalence of adult smoking in Colombia and contribute additional information useful for tobacco control initiatives. Data are from the 2003 Colombian National Study of Mental Health (NSMH). A national probability sample of 4426 adults (age 18-65) was assessed via a computer-assisted interview. An estimated 49% of the adult population had smoked at least once in their lifetimes; one in three adults (31%) had smoked regularly. Nearly half of regular smokers had been able to quit (44%; 95% CI=40-48). Several personal and smoking-related characteristics were associated with failing to quit: being a younger age, employed as compared to being a homemaker, and a history of daily use. Quitters and non-quitters were equivalent with respect to

sex, educational status, and age of smoking onset. These findings may help guide tobacco control activities in Colombia and other low and middle income countries. Storr, C., Cheng, H., Posada-Villa, J., Aguilar-Gaxiola, S., and Anthony, J. Adult Smokers in Colombia: Who Isn't Giving It Up? Addict Behav., 33(3), pp. 412-421, 2008.

Health Status of Illicit Stimulant Drug Users in Rural Ohio

The SF-8 health survey was used to assess the physical and mental health status of a community sample of not-in-treatment, illicit stimulant drug-using adults (n = 249) living in rural Ohio. Physical health status scores indicative of poor health were present in 30.5% of the sample. Poor physical health was associated with older age (OR = 1.06; 95% C.I. = 1.02-1.11), chronic disease (OR = 2.24, 95% C.I. = 1.14-4.40), and frequent opioid use (OR = 3.14, 95% C.I. = 1.16-8.50). Poor mental health status scores were present in 63.9% of the sample. Men were less likely (OR = 0.25, 95% C.I. = 0.11-0.53), and Whites more likely (OR = 3.97, 95% C.I. = 1.56-10.13), to have poor mental health scores. Frequency and type of drug use had no measurable effect on mental health status. These findings suggest that physical and mental health problems are likely to be pervasive among nonmedical drug users in rural areas. Falck, R., Wang, J., and Carlson, R. Health Status of Illicit Stimulant Drug Users in Rural Ohio. J. Psychoactive Drugs, Suppl 4, pp. 401-405, 2007.

Depressive Symptomatology in Young Adults with a History of MDMA Use: A Longitudinal Analysis

Research suggests that methylenedioxymethamphetamine (MDMA)/ ecstasy can cause serotonin depletion as well as serotonergic neurodegradation that may result in depression. This longitudinal study used the Beck Depression Inventory (BDI-II) to assess depressive symptomatology every six months over a two-year period among a community sample of young adult MDMA/ecstasy users (n = 402). Multilevel growth modeling was used to analyze changes in BDI scores. Between baseline and 24 months, the mean BDI score declined from 9.8 to 7.7. Scores varied significantly across individuals at baseline and declined at a rate of 0.36 points every six months. Persons with higher baseline scores were more likely to have their scores decrease over time. Several factors were significantly associated with score levels, independent of time: gender - men's scores were lower than women's; ethnicity - whites' scores were lower than those of non-whites; education - persons with at least some university education had scores that were lower than those without any college experience; benzodiazepines - current users' scores were higher than non-users; opioids - current users' scores were higher than non-users; and cumulative ecstasy use - people who had used MDMA more than 50 times had scores that were higher than persons who had used the drug less often. The results reported here show low levels of depressive symptoms among a sample that, after 24 months, consisted of both current and former MDMA users. The low and declining mean scores suggest that for most people MDMA/ecstasy use does not result in long-term depressive symptomatology. Falck, R., Jichuan Wang, and Carlson, R. Depressive Symptomatology in Young Adults with a History of MDMA Use: A Longitudinal Analysis. J. Psychopharmacol., 22(1), pp. 47-54, 2008.

Associations among Correlates of Schedule Adherence to Antiretroviral Therapy (ART): A Path Analysis of a Sample of Crack Cocaine Using Sexually Active African-Americans with HIV Infection

Adherence to HIV medication regimens is a function of multiple dimensions including psychological functioning, social support, adherence self-efficacy and

optimism regarding treatment. Active substance use can also negatively affect adherence. An understanding of the nature of the associations among the correlates of adherence can better inform the design of interventions to improve adherence. This study developed an exploratory path model of schedule adherence using data from a sample of 130 African-American HIV-positive crack cocaine users on highly active antiretroviral therapy (ART). The model was based on the Transactional Model of Stress and Coping developed by Lazarus and Folkman. Following the theory, the effects of psychological distress on schedule adherence were found to be mediated by patients' relationship with their doctor and optimism towards antiretroviral treatment. Adherence was also associated with patients' self-efficacy regarding their medical regimen which, in turn, was associated with their social support. Atkinson, J., Schoennesson, L., Williams, M., and Timpson, S. Associations among Correlates of Schedule Adherence to Antiretroviral Therapy (ART): A Path Analysis of a Sample of Crack Cocaine Using Sexually Active African-Americans with HIV Infection. AIDS Care, 20(2), pp. 260-269, 2008.

An Investigation of a Personal Norm of Condom-Use Responsibility among African American Crack Cocaine Smokers

The purpose of this study was to investigate the unique contribution of a personal norm of condom-use responsibility to the formation of intentions to reduce risks for HIV by using male condoms during vaginal sex. Data were collected from 402 male and 157 female heterosexual African American crack cocaine smokers in Houston, Texas, US. Two structural equation models of the intention to use a condom with the last sex partner were estimated. One model included measures of condom-use attitudes, subjective norms and condom-use self-efficacy. A second model included these three measures and a fourth measure of a personal norm of condom-use responsibility. Separate models were estimated for men and women. The addition of a personal norm of condom-use responsibility provided a significantly better fit to the data than did models including only outcome expectations, subjective norms and self-efficacy. Results also showed distinctly different underlying cognitive structures of condom-use intention for men and women. A personal norm of condom-use responsibility had a strong direct effect on men's intentions to use condoms with the last sex partner. Other variables appeared to have no direct effect on men's intentions. Women's intentions were strongly influenced by a personal norm and social subjective norms. Situational self-efficacy and outcome expectations had weaker, yet significant, effects on women's intentions. These findings suggest promising directions for the development of sexual risk reduction interventions that emphasize the effect of condom-use responsibility on men's intentions to use condoms. Williams, M., Bowen, A., Ross, M., Timpson, S., Pallonen, U., and Amos, C. An Investigation of a Personal Norm of Condom-Use Responsibility Among African American Crack Cocaine Smokers. AIDS Care, 20(2), pp. 225-234, 2008.

Personal and Partner Measures in Stages of Consistent Condom Use among African-American Heterosexual Crack Cocaine Smokers

Measures of personal condom use and use by last sex partner were examined in five stages of change for consistent condom use among 449 urban sexually active, heterosexual, African-American crack smokers. The measures included participants'' personal and last sex partner's perceived responsibility, personal and perceived negative attitudes, and participants' self-efficacy to use condoms. The relationships between measures and stages were examined using analyses of variance and multivariate logistic regression. Over 90% of participants did not use condoms consistently. Two-thirds of the inconsistent users were in the precontemplation stage. The rest were equally divided between contemplation and preparation stages. Personal responsibility

outperformed other measures in initial intention to become a regular condom user; partner's perceived responsibility dominated continued intention and actual consistent condom use. Negative attitudes and self-efficacies had strong relationships to the stages of consistent condom use in univariate analyses but these relationships became substantially weaker when the responsibility, attitude, and self-efficacy concepts were entered simultaneously into multivariate analyses. Pallonen, U., Williams, M., Timpson, S., Bowen, A., and Ross, M. Personal and Partner Measures in Stages of Consistent Condom Use among African-American Heterosexual Crack Cocaine Smokers. AIDS Care, 20(2), pp. 212-220, 2008.

An Examination of Perceived Norms and Exchanging Sex for Money or Drugs among Women Injectors in Baltimore, MD

Injection drug users who exchange sex for money or drugs may serve as a bridge group for transmitting HIV between injectors and non-injectors. While many individual characteristics have been linked to exchanging sex, little attention has been given to the influence of social network members. The present study assessed the relationship between exchanging sex and perceptions of peers' sex exchange behaviour and attitude toward sex exchange. The sample was composed of 267 women heroin and cocaine injectors in Baltimore, MD, USA. The results indicate that women who believed that their friends exchanged sex were more than twice as likely to exchange sex in the past 90 days (95% CI: 1.49-2.70). Participants who thought their peers disapproved of sex exchange were 20% less likely to exchange sex (95% CI: 0.67-0.95). These findings suggest the need for peer education interventions that promote norms about safer behaviours. Davey-Rothwell, M., and Latkin, C. An Examination of Perceived Norms and Exchanging Sex for Money or Drugs among Women Injectors in Baltimore, MD. Int. J. STD AIDS, 19(1), pp. 47-50, 2008.

Income Generating Activities of People who Inject Drugs

Injection drug users (IDU) commonly generate income through prohibited activities, such as drug dealing and sex trade work, which carry significant risk. However, little is known about the IDUs who engage in such activities and the role of active drug use in perpetuating this behavior. Researchers evaluated factors associated with prohibited income generation among participants enrolled in the Vancouver Injection Drug Users Study (VIDUS) using logistic and linear regression. They examined which sources of income respondents would eliminate if they did not require money to pay for drugs. Among 275 IDUs, 145 (53%) reported engaging in prohibited income generating activities in the past 30 days. Sex work and drug dealing accounted for the greatest amount of income generated. Non-aboriginal females were the group most likely to report prohibited income generation. Other variables independently associated with prohibited income generation include daily heroin injection (AOR=2.3) and daily use of crack cocaine (AOR=3.5). Among these individuals, 68 (47%) indicated they would forgo these earnings if they did not require money for illegal drugs, with those engaged in sex trade work (62%) being most willing to give up their illegal source of income. These findings suggest that the costs associated with illicit drugs are compelling IDUs, particularly those possessing markers of higher intensity addiction, to engage in prohibited income generating activities. These findings also point to an opportunity to explore interventions that relieve the financial pressure of purchasing illegal drugs and reduce engagement in such activities, such as low threshold employment and expansion of prescription and substitution therapies. Debeck, K., Shannon, K., Wood, E., Li, K., Montaner, J., and Kerr, T. Income Generating Activities of People who Inject Drugs. Drug Alcohol Depend., 91(1), pp. 50-56, 2007.

Cocaine- and Opiate-Related Fatal Overdose in New York City, 1990-2000

In New York City (NYC), the annual mortality rate is higher for accidental drug overdoses than for homicides; cocaine and opiates are the drugs most frequently associated with drug overdose deaths. This study assessed trends and correlates of cocaine- and opiate-related overdose deaths in NYC during 1990-2000. Data were collected from the NYC Office of the Chief Medical Examiner (OCME) on all fatal drug overdoses involving cocaine and/or opiates that occurred between 1990-2000 (n = 8,774) and classified into three mutually exclusive groups (cocaine only; opiates-only; cocaine and opiates). Risk factors for accidental overdose were examined in the three groups and compared using multinomial logistic regression. Overall, among decedents ages 15-64, 2,392 (27.3%) were attributed to cocaine only and 2,825 (32.2%) were attributed to opiates-only. During the interval studied, the percentage of drug overdose deaths attributed to cocaine only fell from 29.2% to 23.6% while the percentage of overdose deaths attributed to opiates-only rose from 30.6% to 40.1%. Compared to New Yorkers who fatally overdosed from opiates-only, fatal overdose attributed to cocaine-only was associated with being male (OR = 0.71, 95% CI 0.62-0.82), Black (OR = 4.73, 95% CI 4.08-5.49) or Hispanic (OR = 1.51, 95% CI 1.29-1.76), an overdose outside of a residence or building (OR = 1.34, 95% CI 1.06-1.68), having alcohol detected at autopsy (OR = 0.50, 95% CI 0.44-0.56) and older age (55-64) (OR = 2.53 95% CI 1.70-3.75)). As interventions to prevent fatal overdose become more targeted and drug specific, understanding the different populations at risk for different drug-related overdoses will become more critical. Bernstein, K., Bucciarelli, A., Piper, T., Gross, C., Tardiff, K., and Galea, S. Cocaine- and Opiate-Related Fatal Overdose in New York City, 1990-2000. BMC Public Health, 7(147), pp. 31-42, 2007.

The Sociology of Ecstasy Drug Markets

The study conducted 120 in-depth interviews with men and women in the San Francisco Bay area that sold five or more doses of Ecstasy five or more times in the six months prior to the interview. The research focused on the circumstances and motivations surrounding initiation of sales, sales settings, seller and buyer characteristics and their relationships and social identities. The social class of Ecstasy drug sellers, mostly White, male, middle class, educated, in school, or employed and housed, protected them from having to take the risks of public sales, or selling to unknown persons and therefore from exposure to the criminal justice system and community social stigma. Ecstasy dealers in this study did not have sophisticated, planned sales practices because they sold primarily to their friends, and Ecstasy use was sporadic rather than daily. Business transactions were sporadic and informal. If a dealer's customers were friends and family, the perception of risk would remain low; the sales practices would remain relaxed and informal. This paper suggests that drug seller social characteristics and the availability of sale setting types are critical to developing a sociological understanding of drug markets. Sales, P., and Murphy, S. San Francisco's Freelancing Ecstasy Dealers: Towards a Sociological Understanding of Drug Markets. Journal of Drug Issues, 37(4), pp. 919-950, 2007.

Sampling and Recruitment in Multilevel Studies among Marginalized Urban Populations: The IMPACT Studies

Illicit drug use in urban settings is a major public health problem. A range of individual level factors are known to influence drug use and its consequences, and a number of recent studies have suggested that the neighborhood in which an individual lives may also play a role. However, studies seeking to identify

neighborhood-level determinants of drug use, particularly among marginalized urban populations, need to overcome significant challenges, particularly in the area of sampling and recruitment. One key issue is defining functional neighborhoods that are relevant to local residents. Another arises from the need to sample a representative or even a diverse population when studying marginalized groups such as illicit drug users. These are common problems that raise particular challenges when both need to be addressed in the same study. For example, many sampling approaches for neighborhood-level studies have included some form of random sample of households, but this may systematically overlook marginalized populations. On the other hand, the sampling approaches commonly used in studies of hidden populations such as chain referral, snow ball, and more recently, respondent-driven sampling, typically expand beyond a geographic "neighborhood." In this paper, researchers describe the organization and rationale for the IMPACT Studies [the Inner-City Mental Health Study predicting HIV/AIDS, Club, and Other Drug Transitions studies are aimed at determining the association between neighborhood-level characteristics and substance abuse, HIV and other pathogens, and PTSD]. Ompad, D., Galea, S., Marshall, G., Fuller, C., Weiss, L., Beard, J., Chan, C., Edwards, V., and Vlahov, D. Sampling and Recruitment in Multilevel Studies among Marginalized Urban Populations: The IMPACT Studies. J. Urban Health, 85(2), pp. 268-280, 2008.

Gender Differences in Drug Use and Sexual Risk Behaviors among Non-Injecting Heroin Users in Puerto Rico

During the 1990s non-injected heroin use (NIHU) increased notably in several countries. However, few studies have actually examined the drug-using practices and other problem behaviors of NIHUs. In this study, researchers compared male and female NIHUs from Puerto Rico across a number of domains. Recruitment proceeded through visits to drug-copping areas and the local hangouts in their vicinity. Subjects were eligible if they were 18 to 25 years old, had never injected any drugs, and had recently used heroin or cocaine. Study participants were administered a computer-assisted personal interview. Of the 412 NIHUs recruited at the time of this study, 74 (18.0%) were females. Female NIHUs were more likely to report sexual assaults and more likely to manifest severe symptomatology of PTSD than male NIHUs (35.1% vs. 3.6%, $p<.01$, and 40.5% vs. 25.7%, $p=.01$, respectively). Females were less likely to report a source of emotional support than males (86.5% vs. 95.3%, $p<.01$). Close to one in four of the females (23.0%) reported a history of sexually transmitted infections, compared to three percent of the males ($p<.01$). HIV seroprevalence among females was 4.3% compared to 0.6% among males ($p=.01$). These findings suggest that female heroin users have a host of different needs compared to male heroin users. Given the scarcity of existing programs for female drug users in Puerto Rico, designing supportive systems that effectively address the specific needs of drug-using women should become a high-priority public health issue. Sosa-Zapata, I., Colon, H., Robles, R., and Cabassa, M. Gender Differences in Drug Use and Sexual Risk Behaviors among Non-Injecting Heroin Users in Puerto Rico., P. R. Health Sci. J., 26(3), pp. 205-211, 2007.

Potential Risk Factors for Injecting among Mexican American Non-Injecting Heroin Users

Researchers examined potential risk factors for initiating, resuming, and transitioning to injecting in a prospective cohort study of 300 Mexican American non-injecting heroin users (NIUs) with distinct injecting histories (i.e., never vs. former injectors). Participants were recruited using multiple sampling approaches, including respondent driven sampling and outreach. The majority of participants were male (77%) and the average age was 22 years (females were significantly older, at 23 years, compared to males, at 21 years,

p<.001). NIUs with an injecting history were more likely to use heroin with an IDU, and women were significantly more likely than men to have an IDU sex partner. The young age of the study sample and length of use of non-injecting heroin (for many, more than 4 years of use) suggest the NIU population is at high risk for transitioning to injection drug use. The study also found the cultural characteristic of "fatalism" -- a belief that one's fate is determined by destiny and is inevitable -- among study participants. Former injectors reported that they expected one day to acquire or transmit an infectious disease, including HIV, HBV, or HCV. Attitudes about injecting, perceived vulnerability for infections, fatalism, and length of time using non-injection heroin were found to be important factors for predicting resumption of injecting among former IDUs. These findings bring to light culturally unique risk factors for injecting that may be incorporated into interventions appropriate to the cultural and social context of the Mexican American community. Valdez, A., Neaigus, A., and Cepeda, A. Potential Risk Factors for Injecting among Mexican American Non-Injecting Heroin Users. J. Ethn. Subst. Abuse, 6(2), pp. 49-73, 2007.

The Impact of Education and Race/Ethnicity Differences on Alcohol Dependence

This study attempts to clarify social inequalities in alcohol dependence by investigating SES and race-ethnicity effects on the development of alcohol dependence following first alcohol use. The literature has shown that while lower socioeconomic status (SES) is related to higher risk for alcohol dependence, minority race-ethnicity is often associated with lower risk. Cross-sectional data from the National Epidemiologic Survey on Alcohol and Related Conditions (n = 43,093). Survival analysis was used to model alcohol dependence onset according to education, race-ethnicity and their interaction. Compared with non-Hispanic whites, age-adjusted and sex-adjusted risks of alcohol dependence were lower among Blacks and Hispanics and higher among American Indians. Individuals without a college degree had higher risks of alcohol dependence than individuals with a college degree or more; however, the magnitude of risk varied significantly by race-ethnicity; odds ratios for less than a college degree were 1.12, 1.46, 2.24, 2.35 and 10.99 among Hispanics, whites, Blacks, Asians, and American Indians, respectively. There was no association between education and alcohol dependence among Hispanics. Race-ethnicity differences in the magnitude of the association between education and alcohol dependence suggest that aspects of racial-ethnic group membership mitigate or exacerbate the effects of social adversity. Gilman, S., Breslau, J., Conron, K., Koenen, K., Subramanian, S., and Zaslavsky, A. Education and Race-Ethnicity Differences in the Lifetime Risk of Alcohol Dependence. J. Epidemiol. Community Health, 62(3), pp. 224-230, 2008.

Family and School Associations of Emotional Distress for Asian-American Sexual Minority Youth

This study examined family and school correlates of emotional distress among Asian-American sexual minority youth in the Midwestern United States. Responses from 91 predominantly Asian-American youth who participated in a state-wide, school-based census survey, the 2001 Minnesota Student Survey (MSS), and reported recent same-gender sexual activity were analyzed. The students ranged in age from 13-19 years and 37% of respondents were female. Results showed that sexual minority youth who perceived lower levels of family caring and those with negative perceptions of school climate reported lower self-esteem, which was associated with greater emotional distress. These results highlight the importance of safe and caring environments, and culturally sensitive support for Asian-American sexual minority adolescents., Homma, Y., and Saewyc, E. The Emotional Well-Being of Asian-American Sexual Minority Youth in School. J. LGBT Health Res., 3(1), pp. 67-78, 2007.

The Health and Health Behaviors of Young Men Who Have Sex with Men

This study examined the range of health and mental health problems for which young men who have sex with men (YMSM) may be at risk. An audio-computer-assisted survey was administered to a large, ethnically diverse sample of 526 YMSM (aged 18-24 years) recruited from bars, clubs, and other social venues using a venue-based probability sampling method. Subjects reported a range of health and mental health problems, and involvement in health-compromising behaviors, such as overweight/obesity, depression, and suicidal thoughts/attempts, and many were found to have high rates of sexually transmitted infections. Moreover, many reported not having insurance coverage and/or limited access to care. Many of the health concerns and risks reported by these young men are preventable and can be addressed by any number of sectors, including health care and social service providers, religious organizations, schools, and employers. Kipke, M., Kubicek, K., Weiss, G., Wong, C., Lopez, D., Iverson, E., and Ford, W. The Health and Health Behaviors of Young Men Who Have Sex with Men. J. Adolesc. Health, 40(4), pp. 342-350, 2007.

Challenges to HIV Prevention among Men Who Have Sex with Transgender Women

Although transgender women are acknowledged as a priority population for HIV prevention, there is little knowledge regarding men who have sex with transgender women (MSTGWs). MSTGWs challenge conventional sexual orientation categories in public health and HIV prevention research, and warrant increased attention from the public health community. This study utilized qualitative techniques to assess how MSTGWs describe their sexual orientation identities, and to explore the correspondence between men's identities and sexual behaviors with transgender women. The investigators conducted in-depth semi-structured individual interviews with 46 MSTGWs in San Francisco. They observed a diversity in the ways participants identified and explained their sexual orientation, and found no consistent patterns between how men described their sexual orientation identity versus their sexual behavior and attraction to transgender women. Findings from this qualitative study question the utility of category-based approaches to HIV prevention with MSTGWs and offer insights into developing HIV interventions for these men. Operario, D., Burton, J., Underhill, K., and Sevelius, J. Men Who Have Sex with Transgender Women: Challenges to Category-Based HIV Prevention. AIDS Behav., 12(1), pp. 18-26, 2008.

Alcohol Intoxication Related to Divorce

This study tested the relationships between various forms of substance use during marriage and subsequent divorce among US young adults. Three waves of survey data collected at approximately ages 18, 23 and 29 years were used. Using multivariate logistic regression and controlling for factors present at the two early waves, investigators tested for prospective relationships between substance use at the second assessment and divorce by the third. Study participants were drawn from a longitudinal panel following adolescents on the west coast of the United States into young adulthood. The analytic subsample consisted of the 454 individuals currently married at the age 23 survey. Predictors were past-year frequency of alcohol intoxication, marijuana use and cigarette use, as well as any hard drug use in the past year. Covariates included substance use prior to marriage, demographic and socio-economic factors, marital discord and religiosity. Controlling for other factors, more frequent alcohol intoxication during marriage was an independent predictor of

later divorce. Frequency of marijuana use had a significant bivariate relationship with divorce that was not significant in the multivariate model. These data are consistent with the notion that alcohol intoxication is related causally to divorce among young adults. Collins, R., Ellickson, P., and Klein, D. The Role of Substance Use in Young Adult Divorce. Addiction, 102(5), pp. 786-794, 2007.

A Folk Model of Treatment Readiness among Drug Users in Ohio

Despite the benefits of substance abuse treatment, only a small proportion of drug users actually enter treatment. Understanding "readiness" is critical for engaging drug users in treatment and for involving them in the recovery process. This paper reports findings from ethnographic interviews with 35 active drug users as they were entering treatment services, including descriptions of how they perceive readiness for treatment. Drug users expressed readiness for treatment in terms that reflect twelve step programs -- a folk model of treatment. A better understanding of drug users' perceptions about drug treatment can help to inform interventions designed to improve readiness for treatment. Redko, C., Carlson, R., and Rapp, R. A Folk Model of Treatment Readiness among Drug Users in Ohio. J. Ethn. Subst. Abuse, 6(2), pp. 15-40, 2007.

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Research Findings - Prevention Research

The Negative Impacts of Starting Middle School in Sixth Grade

This study examined administrative data on public school students in North Carolina. The sample included data from 99 public school districts, 243 schools with 44,709 sixth graders. Just 11 percent of the students in the sample were in elementary schools. Analyses revealed that sixth grade students attending middle schools were much more likely to be cited for discipline problems than those attending elementary school. That difference remained after adjusting for the socioeconomic and demographic characteristics of the students and their schools. Furthermore, the higher infraction rates recorded by sixth graders who were placed in middle school persisted at least through ninth grade. An analysis of end-of-grade test scores provides complementary findings. A plausible explanation is that sixth graders are at an especially impressionable age; in middle school, the exposure to older peers and the relative freedom from supervision have deleterious consequences. These findings are relevant to the current debate over the best school configuration for incorporating the middle grades. Based on their results, the authors suggest that there is a strong argument for separating sixth graders from older adolescents. Cook, P.J., MacCoun, R., Muschkin, C., and Vigdor, J. The Negative Impacts of Starting Middle School in Sixth Grade. Journal of Policy Analysis and Management, 27(1), pp. 104-121, 2008.

Fast Track Randomized Controlled Trial to Prevent Externalizing Psychiatric Disorders: Findings From Grades 3 to 9

This study tests the efficacy of the Fast Track Program in preventing antisocial behavior and psychiatric disorders among groups varying in initial risk. Schools within four sites (Durham, NC; Nashville, TN; Seattle, WA; and rural central Pennsylvania) were selected as high-risk institutions based on neighborhood crime and poverty levels. After screening 9,594 kindergarteners in these schools, 891 highest risk and moderate-risk children (69% male and 51% African American) were randomly assigned by matched sets of schools to intervention or control conditions. The 10-year intervention (begun in 1991 with three yearly cohorts) included parent behavior-management training, child social-cognitive skills training, reading tutoring, home visiting, mentoring, and a universal classroom curriculum. Outcomes included criterion counts and psychiatric diagnoses after grades 3, 6, and 9 for conduct disorder, oppositional defiant disorder, attention-deficit/hyperactivity disorder, any externalizing disorder, and self-reported antisocial behavior. Grade 9 outcomes were assessed between 2000 and 2003, depending upon cohort. Significant interaction effects between intervention and initial risk level were found at each age but most strongly after grade 9. Assignment to intervention had a significant positive effect in lowering criterion count scores and diagnoses for

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conduct disorder, attention-deficit/hyperactivity disorder, and any externalizing disorder, and lowering antisocial behavior scores, but only among those at highest risk initially. Prevention of serious antisocial behavior can be efficacious across sex, ethnicity, and urban/rural residence, but screening is essential. Bierman, K.L., Coie, J.D., Dodge, K.A., Foster, E.M., Greenberg, M.T., Lochman, J.E., McMahon, R.J., and Pinderhughes, E.E. Fast Track Randomized Controlled Trial to Prevent Externalizing Psychiatric Disorders: Findings from Grades 3 to 9. J. Am. Acad. Child Adolesc. Psychiatry, 46(10), pp. 1250-1262, 2007.

Overcoming Adolescents' Resistance to Anti-Inhalant Appeals

This research was concerned with factors that affect adolescents' evaluations of persuasive anti-inhalant messages and the association of these evaluations with usage intentions. Sixth and 7th graders (N=894) received anti-inhalant messages that varied as a result of the factorial combination of message source (doctor or peer), suggested harm (social or physical), and target (message was addressed directly or indirectly to receivers). Manipulated variables were crossed with inhalant-user status (resolute nonuser, vulnerable nonuser, and user). Significant target and status effects on message evaluation were found. Significant interactions of status with each of the manipulated variables also emerged. Results indicated that indirectly targeted messages were significantly more effective than targeted ones. However, this result was evident only among users and vulnerable nonusers. These groups, which would be expected to be the most resistant to anti-inhalant appeals, were significantly more influenced by indirect messaging than when messages were addressed directly to them. This result suggests that indirectly targeted messages have a greater chance of success when the messages' audiences are resistant to the topic under consideration. The simple effects analyses showed that resolute nonusers almost invariably responded more favorably to the messages than either users or vulnerable nonusers. Their lack of discrimination in response to the experimental condition indicates their willingness to accept anti-inhalant messages delivered directly or indirectly, by peer or adult, threatening social or physical harms. The ad appeals were not counter-attitudinal for this group, but rather reinforcing, and possibly helped bolster a pre-established position. Implications for the application of these findings are clear. In health communication appeals, it is imperative to identify the audience we wish to influence. The consistent interaction of user status with every manipulated variable indicates that a one-size-fits-all approach will not succeed. This study provides guidance on the particular form of appeal most likely to succeed and points to topics that might improve future prevention efforts. Crano, W., Siegel, J., Alvaro, E., and Patel, N. Overcoming Adolescents' Resistance to Anti-Inhalant Appeals. Psychol. Addict. Behav., 21(4), pp. 516-524, 2007.

School Readiness Intervention for Foster Children Increases Social Competence and Self-Regulation

Foster children are at great risk for poor school outcomes. Given that school readiness is a powerful predictor of later school success, the promotion of school readiness skills in foster children is an opportunity for preventive intervention. Results are presented from a preliminary evaluation of a program designed to improve school readiness in foster children. Twenty-four foster children were randomly assigned to the intervention group (IG; n = 11) or the foster care services as usual comparison group (CG; n = 13). There were 6 intervention group males and 5 control group males. The mean age was 6.49 years (SD = 0.86) for IG children and 6.61 years (SD = 1.16) for CG children. The intervention consisted of therapeutic playgroups (twice weekly for 7 weeks during the summer) focusing on social competence and self-regulation skills. Attendance rates for the playgroups are reported. In addition, group

differences on data collected before and after the intervention are reported. Intervention group children exhibited increased social competence and self-regulation. Comparison group children exhibited poorer performance in these domains over time. Results are discussed in terms of how the study has informed a current randomized efficacy trial of a school-readiness intervention. Pears, K.C., Fisher, P.A., and Bronz, K.D. An Intervention to Promote Social Emotional School Readiness in Foster Children: Preliminary Outcomes From a Pilot Study. School Psychology Review, 36(4), pp. 665-673, 2007.

Family-based Therapeutic Intervention May Reverse Disruptions in HPA Axis Functioning

Atypical diurnal patterns of hypothalamic-pituitary-adrenal (HPA) axis activity have been observed in samples of individuals following early life adversity. A characteristic pattern arising from disrupted care giving is a low early-morning cortisol level that changes little from morning to evening. Less well understood is the plasticity of the HPA axis in response to subsequent supportive care giving environments. Monthly early-morning and evening cortisol levels were assessed over 12 months in a sample of 3-6-year-old foster children enrolled in a randomized trial of a family-based therapeutic intervention (N=117; intervention condition, n=57; regular foster care condition, n=60), and a community comparison group of same-aged, non-maltreated children from low-income families (n=60). Latent growth analyses revealed stable and typical diurnal (morning-to-evening) cortisol activity among non-maltreated children. Foster children in the intervention condition exhibited cortisol activity that became comparable to the non-maltreated children over the course of the study. In contrast, children in regular foster care condition exhibited increasingly flattened morning-to-evening cortisol activity over the course of the study. In sum, improvements in care giving following early adversity appear to have the potential to reverse or prevent disruptions in HPA axis functioning. Fisher, P., Stoolmiller, M., Gunnar, M., and Burraston, B. Effects of a Therapeutic Intervention for Foster Preschoolers on Diurnal Cortisol Activity. Psychoneuroendocrinology, 32(8-10), pp. 892-905, 2007.

Cueing Prenatal Providers to Counsel Pregnant Women with Behavioral Health Risks

This study examined the impact of the Health in Pregnancy (HIP) computer program on prenatal providers' counseling about behavioral risks with patients, in particular risk for intimate partner violence (IPV) during pregnancy. English-speaking women 18 years or older, less than 26-weeks pregnant, and receiving prenatal care at one of five participating clinics in the San Francisco area, were randomized in parallel groups in a controlled trial. Participants reporting one or more risks were randomized to intervention or control in stratified blocks. Providers received summary "cueing sheets" alerting them to their patient's risk(s) and suggesting counseling statements. Thirteen percent (37/286) of the sample reported current IPV. Provider cueing resulted in 85% of the IPV-intervention group reporting discussions with their provider, compared to 23.5% of the control group ($p<0.001$). Thus IPV discussions were influenced strongly by cueing providers. Provider cueing may be an effective and appropriate adjunct to routine risk counseling in prenatal care. Calderon, S., Gilbert, P., Jackson, R., Kohn, M., and Gerbert, B. Cueing Prenatal Providers Effects on Discussions of Intimate Partner Violence. Am. J. Prev. Med., 34(2), pp. 134-137, 2008.

Efficacy of a Culturally Adapted Intervention for Youth Living with HIV in Uganda

This study examined whether a culturally adapted version of a previously

evaluated efficacious HIV prevention program reduced sexual risk behaviors of youth living with HIV (YLH) in Uganda. YLH, 14 to 21 years, were randomized to intervention (N=50) or control (N=50) conditions. Significantly more YLH in the intervention used condoms consistently and decreased their number of sexual partners in comparison to the control condition. Western interventions can be culturally adapted to retain efficacy in reducing the sexual risk behavior of YLH. Lightfoot, M. A., Kasirye, R., Comulada, W.S., and Rotheram-Borus, M.J. Efficacy of a Culturally Adapted Intervention for Youth Living with HIV in Uganda. Prev. Sci., 8(4), pp. 271-273, 2007.

Reducing HIV Infection Among New Injecting Drug Users in the China-Vietnam Cross Border Project

The objective of this study was to assess an HIV prevention program for injecting drug users (IDU) in the cross border area between China and Vietnam. Serial cross-sectional surveys (0, 6, 12, 18, 24 and 36 months) of community-recruited current IDUs. The project included peer educator outreach and the large-scale distribution of sterile injection equipment. Serial cross-sectional surveys with HIV testing of community recruited IDUs were conducted at baseline (before implementation) and 6, 12, 18, 24 and 36 months post-baseline. HIV prevalence and estimated HIV incidence among new injectors (individuals injecting drugs for < 3 years) in each survey wave were the primary outcome measures. Results showed that the percentages of new injectors among all subjects declined across each survey wave in both Ning Ming and Lang Son. HIV prevalence and estimated incidence fell by approximately half at the 24-month survey and by approximately three quarters at the 36-month survey in both areas (all $p<0.01$). It was concluded that the implementation of large-scale outreach and syringe access programmes was followed by substantial reductions in HIV infection among new injectors, with no evidence of any increase in individuals beginning to inject drugs. This project may serve as a model for large-scale HIV prevention programming for IDUs in China, Vietnam, and other developing/transitional countries. Des Jarlais, D., Kling, R., Hammett, T., Ngu, D., Liu, W., Chen, Y., Binh, K., and Friedmann, P. Reducing HIV Infection among New Injecting Drug Users in the China-Vietnam Cross Border Project. AIDS, 21 Suppl 8, pp. S109-S114, 2007.

Brief Interventions for College Students Can Influence Multiple Health Behaviors

This study examined the effects of brief image-based interventions, including a multiple behavior health contract, a one-on-one tailored consultation, and a combined consultation plus contract intervention, for impacting multiple health behaviors of students in a university health clinic. A total of 155 college students attending a major southern university were recruited to participate in a study evaluating a health promotion program titled Project Fitness during the fall 2005 and spring 2006. The majority of the participating students were female (66%), with a mean age of 19 years. The sample was diverse, with a slight majority being Caucasian (52%), followed by Hispanic (14%), African American (11%), and Asian youth (7%). Participants were randomly assigned to one of three treatments as they presented at the clinic: 1) a multiple behavior health contract, 2) a one-on-one tailored consultation, or 3) a combined consultation plus contract intervention. Baseline and 1-month post-intervention data were collected using computer-assisted questionnaires in a quiet office within the student health clinic. Omnibus repeated-measures analyses of variance were significant for drinking driving behaviors, $F(2,136) = 4.43$, $p = .01$, exercise behaviors, $F(5,140) = 6.12$, $p = .00$, nutrition habits, $F(3,143) = 5.37$, $p = .00$, sleep habits, $F(2,144) = 5.03$, $p = .01$, and health quality of life, $F(5,140) = 3.09$, $p = .01$, with improvements on each behavior across time. Analysis of group-by-time interaction effects showed an increase

in the use of techniques to manage stress, F (2,144) = 5.48, p = .01, and the number of health behavior goals set in the last 30 days, F (2,143) = 5.35, p = .01, but only among adolescents receiving the consultation, or consultation plus contract. Effect sizes were consistently larger across health behaviors, and medium in size, when both consult and contract were used together. Brief interventions using a positive goal image of fitness, and addressing a number of health habits using a contract and consultation strategy alone, or in combination, have the potential to influence positive changes in multiple health behaviors of college students attending a university primary health care clinic. Werch, C., Bian, H., Moore, M., Ames, S., DiClemente, C., and Weiler, R. Brief Multiple Behavior Interventions in a College Student Health Care Clinic. J. Adolesc. Health, 41(6), pp. 577-585, 2007.

Stability of Psychopathic Characteristics in Childhood: The Influence of Social Relationships

The current study is a preliminary longitudinal investigation of the stability of psychopathic characteristics, including social relationships as a moderator, within a group of aggressive children (N = 80). Data were collected from the children, their parents, teachers, and peers. Results indicated that the psychopathic characteristics (callous-unemotional traits, impulsive conduct problems, and narcissism) were relatively stable across three time points. Social relationship variables (child self-report of social competence, teacher-rated social competence, and peer-rated social preference) were generally correlated with psychopathic characteristics. Self-report of social competence moderated change from Time 1 to Time 2 narcissism based on parent report. Both peer-rated social preference and teacher-rated social competence moderated change from Time 1 to Time 3 impulsive conduct problems. These results provide preliminary support that psychopathic characteristics are generally stable in aggressive children and that social relationships are a potentially valuable point of intervention when children present with these characteristics. Barry, T.D., Barry, C.T., Deming, A.M., and Lochman, J.E. Stability of Psychopathic Characteristics in Childhood: The Influence of Social Relationships. Criminal Justice and Behavior, 35(2), pp. 244-262, 2008.

Diet Initiation Predicts Smoking Initiation Among Adolescent Females

This study was aimed at examining the relation between dieting and smoking initiation among adolescents. Prospective data from a nationally representative study were used. Specifically, the study used two waves (1994 to 1996) of the National Longitudinal Study of Adolescent Health. The sample included 7795 non-Latino Caucasian and non-Latino African-American adolescents. Dieting status was the independent variable and trying smoking and initiation of regular smoking were the dependent variables. Covariates included age, ethnicity, overweight status, false self-perception about being overweight, and availability of cigarettes at home. Logistic regression and latent transition analyses were used. Females had a higher prevalence of dieting (55%) when compared with males (25%). Dieting initiation was a significant predictor for initiation of regular smoking among females (OR = 1.94, p = .010), but not among males. Inactive dieting was a significant predictor among males (OR = 1.74, p = .031), but not among females. Compared to nondieters, initiating and consistent female dieters reported a higher probability of transitioning to having tried regular smoking, although results from logistic regression suggested that the association between consistent dieting and initiation of regular smoking was not significant. This analysis suggests that there is a positive relation between initiating dieting and initiating regular smoking among females, but among males it is the inactive dieters who show a positive relationship. Results illustrate the importance of examining the association between dieting and the initiation of regular smoking. Maldonado-Molina, M.,

Komro, K., and Prado, G. Prospective Association Between Dieting and Smoking Initiation among Adolescents. Am. J. Health Promot., 22(1), pp. 25-32, 2007.

Effects of a Foster Parent Training Intervention on Placement Changes of Children in Foster Care

Placement disruptions undermine efforts of child welfare agencies to promote safety, permanency, and child well-being. Child behavior problems significantly contribute to placement changes. The aims of this investigation were to examine the impact of a foster parent training and support intervention (KEEP) on placement changes and to determine whether the intervention mitigates placement disruption risks associated with children's placement histories. The sample included 700 families with children between ages 5 and 12 years, from a variety of ethnic backgrounds. Families were randomly assigned to the intervention or control condition. The number of prior placements was predictive of negative exits from current foster placements. The intervention increased chances of a positive exit (e.g., parent/child reunification) and mitigated the risk-enhancing effect of a history of multiple placements. Incorporating intervention approaches based on a parent management training model into child welfare services may improve placement outcomes for children in foster care. Price, J., Chamberlain, P., Landsverk, J., Reid, J., Leve, L., and Laurent, H. Effects of a Foster Parent Training Intervention on Placement Changes of Children in Foster Care. Child Maltreat., 13(1), pp. 64-75, 2008.

Adapting Evidence-Based Curricula to Unique Adolescent Cultures

It is recommended that community settings adapt curricula to meet their youths' unique needs to be effective, particularly with diverse cultures. The cultural adaptation process employed for the keepin' it REAL program is offered as an example. The original keepin' it REAL curriculum targeted middle-school youth. This project utilized youth as experts in the process of adapting the keepin' it REAL curriculum's student workbook and videos, extending the age target to 14- to 19-year olds in high-risk, unique community settings: alternative schools, public high schools, a homeless shelter, a juvenile justice day program, a YMCA-run program for youth at low-income housing centers, a drop-in center for GLBTQ youth, and a youth advocacy group on the US-Mexico border in Texas. In Phase I the researchers engaged adolescents in the adaptation of the curriculum to make it culturally appropriate for their own setting. In Phase II the team evaluated the effectiveness of the adapted curriculum in comparison with the original curriculum. The goal was to assess whether adaptations improved the curriculum as well as providing opportunities for adolescents to take an active role in making prevention curricula relevant. Overall, preliminary data suggest that participating in adaptation processes may genuinely change attitudes about drug use, suggesting that more research needs to be done on consideration of the adaptation process as an intervention in and of itself. Steiker, L. Making Drug and Alcohol Prevention Relevant: Adapting Evidence-Based Curricula to Unique Adolescent Cultures. Fam. Community Health, 31 Suppl 1 pp. S52-S60, 2008.

Increasing Adoption of Evidence-Based Practices Through Community Coalition Networks

This study examined the effect of community coalition network structure on the effectiveness of an intervention designed to accelerate the adoption of evidence-based substance abuse prevention programs. At baseline, 24 cities were matched and randomly assigned to 3 conditions (control, satellite TV training, and training plus technical assistance). The intervention programs consisted of 6 interactive televised training segments on evidence-based

prevention programs administered approximately every 6 months; 3 of these training segments occurred during the period of this study. Television broadcasts were complemented with planning meetings, where skills learned in training were shared with other members who did not participate in the live broadcast training. Training moved from large introductory sessions to smaller audience sessions that targeted those who would actively implement prevention programs; 343 leaders participated in the first session, 196 participated in the second session and 130 participated in the third session. The topics of the first 3 sessions were (1) identifying risk factors and protective factors of drug abuse, (2) organizing the community, and (3) understanding how to interact with local media using established community approaches for communicating public health issues and information. The study surveyed 415 community leaders at baseline and 406 at 18-month follow-up about their attitudes and practices toward substance abuse prevention programs. Network structure was measured by asking leaders whom in their coalition they turned to for advice about prevention programs. The outcome was a scale with 4 subscales: coalition function, planning, achievement of benchmarks, and progress in prevention activities. Multiple linear regression and path analysis were used to test the hypotheses. The intervention had a significant effect on decreasing the density of coalition networks. The change in density subsequently increased adoption of evidence-based practices. Optimal community network structures for the adoption of public health programs are unknown, but it should not be assumed that increasing network density or centralization are appropriate goals. Lower-density networks may be more efficient for organizing evidence-based prevention programs in communities. Valente, T.W., Chou, C.P., and Pentz, M. Community Coalitions as a System: Effects of Network Change on Adoption of Evidence-Based Substance Abuse Prevention. Am. J. Public Health, 97(5), pp. 880-886, 2007.

Systemic Factors that Influence Screening for Prenatal Behavioral Risks

This study examined how systemic factors might facilitate or impede providers' ability to screen for and intervene on prenatal behavioral risks. Eight focus groups of 60 prenatal care providers were convened to explore methods for assessing and counseling pregnant women about tobacco, alcohol, and illicit drug use. Because practice setting was often mentioned as either an inducement or barrier to risk prevention, a re-analysis of focus group transcripts to examine systemic factors was conducted. Results indicated that practice setting strongly influenced providers' behavior, and settings differed by continuity of care, availability of resources, and organized support for risk prevention. The most striking contrasts were found between private practice and a large HMO. Thus, each setting had features that facilitated prevention counseling. Understanding such systemic factors could lead to improved risk prevention practices during pregnancy across all health care settings. Gilbert, P., Herzig, K., Thakar, D., Viloria, J., Bogetz, A., Danley, D., Jackson, R., and Gerbert, B. How Health Care Setting Affects Prenatal Providers' Risk Reduction Practices: A Qualitative Comparison of Settings. Women Health, 45(2), pp. 41-57, 2007.

Effects of Communities that Care on Community Level Prevention Services Outcomes

The Community Youth Development Study (CYDS) is a community-randomized trial of the Communities That Care (CTC) prevention system. Using data from 2001 and 2004 administrations of the Community Key Informant Survey, this study reports changes in three community-level outcomes 1.5 years after implementing CTC in 12 communities. Respondents consisted of 534 community leaders in 24 communities representing multiple sectors within each community. Results of multilevel analyses controlling for respondent and

community characteristics indicated that (a) CTC and control communities had comparable baseline levels of adopting a science-based approach to prevention, collaboration across community sectors, and collaboration regarding specific prevention activities; and (b) CTC communities exhibited significantly greater increases in these outcomes between 2001 and 2004 relative to control communities. These results suggest that CTC was successful in changing proximal system outcomes theorized to lead to more effective prevention services and, ultimately, reduced risk, enhanced protection, and improved adolescent health and behavior outcomes. Brown, E., Hawkins, J., Arthur, M., Briney, J., and Abbott, R. Effects of Communities That Care on Prevention Services Systems: Findings from The Community Youth Development Study At 1.5 Years. Prev. Sci., 8(3), pp. 180-191, 2007.

Community Coalitions to Prevent Drug Abuse: Influence of Community and Team Member Factors on Team Functioning

This research examines the early development of community teams participating in a university-community partnership project called PROSPER. PROSPER supports local community teams in rural areas and small towns to implement evidence-based programs intended to support positive youth development and reduce early substance use. The study evaluated 14 community teams and included longitudinal data from 108 team members, examining how community demographics and team member characteristics, perceptions, and attitudes at initial team formation were related to local team functioning 6 months later, when teams were planning for prevention program implementation. Community demographics (poverty), perceived community readiness, characteristics of local team members (previous collaborative experience) and attitudes toward prevention played a substantial role in predicting the quality of community team functioning 6 months later. Greenberg, M., Feinberg, M., Meyer-Chilenski, S., Spoth, R., and Redmond, C. Community and Team Member Factors that Influence the Early Phase Functioning of Community Prevention Teams: The PROSPER Project. J. Prim. Prev., 28(6), pp. 485-504, 2007.

Measuring Community-Wide Prevention Collaboration

This study assesses a measure of community-wide collaboration on prevention-specific activities (i.e., prevention collaboration) in context of the theory of community change used in the Communities That Care prevention system. Using data from a sample of 599 community leaders across 41 communities, the measure was examined with regard to its factor structure, associations with other concurrent community-level measures, and prediction by individual- and community-level characteristics. Results of multilevel confirmatory factor analysis provide evidence for the construct validity of the measure and indicate significant ($p < .05$) associations with concurrent validity criteria. Female community leaders reported significantly higher levels of prevention collaboration and community leaders sampled from religious organizations reported lower levels of prevention collaboration than did their respective counterparts. Although no community-level characteristics were associated significantly with prevention collaboration, community clustering accounted for 20-28% of the total variation in the measure. Findings support the use of this measure in assessing the importance of collaboration in community-based prevention initiatives. Brown, E., Hawkins, J., Arthur, M., Abbott, R., and Van Horn, M. Multilevel Analysis of a Measure of Community Prevention Collaboration. Am. J. Community Psychol., 41(1-2), pp. 115-126, 2008.

Racial/Ethnic Differences in the Protective Effects of Self-Management Skills on Adolescent Substance Use

This study examined whether cognitive and behavioral self-management skills measured in the 7th grade served a protective function in 9th grade substance use across ethnically diverse samples of adolescents. Structural equation modeling indicated that a second order Self-Management Skills latent factor consisting of first order latent factors of Decision-Making, Self-Regulation, and Self-Reinforcement skills was protective for adolescent substance use across racial/ethnic subgroups. Self-Management Skills were more strongly protective for suburban White youth and less protective for urban minority youth. These findings are consistent with previous research showing that predictive power of risk and protective factors derived from psychosocial theories varies across racial/ethnic subgroups of youth and is weaker among racial/ethnic minority youth compared to White youth. Griffin, K., Botvin, G., and Scheier, L. Racial/Ethnic Differences in the Protective Effects of Self-Management Skills on Adolescent Substance Use. Subst. Abuse, 27(1-2), pp. 47-52, 2006.

Antisocial Psychopathy and HIV Risk Among Alcohol and Other Drug (AOD) Abusing Adolescent Offenders

While the consensus is that HIV prevalence has remained low among adolescent offenders, the prevalence of STDs and HIV transmission risk behaviors is alarming, particularly for those abusing alcohol and other drugs and those displaying antisocial or conduct disorder characteristics. In the current study, 269 male and 110 female inner city, culturally diverse alcohol and other drug (AOD) abusing adolescent offenders completed measures of (a) psychopathy, using the Millon Adolescent Clinical Inventory (MACI) (b) HIV transmission risk behavior, (c) prevention skills and attitudes and (d) social desirability. Results showed that those with high levels of psychopathy reported more AOD use, overall unprotected sex and more sexual activity when influenced by alcohol and/or marijuana. High psychopathy adolescent offenders also reported lower self-efficacy and sexual response-efficacy, less favorable safer sex and condom attitudes and less favorable intentions to engage in safer sex behaviors, when controlling for social desirability. Data suggest that adolescent offenders, who are either in court-ordered treatment or detention, should be assessed for psychopathy and provided with tailored risk reduction interventions, geared toward attitudinal and behavioral change. A discussion of integrating neurobiological measures to improve the next generation of tailored interventions for this risk group is offered in conclusion. Malow, R.M., Devieux, J., Rosenberg, R., Nair, M., McMahon, R., Brown, E.J., and Kalichman, S.C. Antisocial Psychopathy and HIV Risk Among Alcohol and Other Drug (AOD) Abusing Adolescent Offenders. American Journal of Infectious Diseases, 3(4), pp. 230-239, 2007.

Drinking By High School Seniors: Implications for Prevention

The transition from high school to college provides a potentially critical window to intervene and reduce risky behavior among adolescents. This study examined high school seniors' motivations (e.g., social, coping, enhancement) for alcohol use and patterns of use. Latent class analysis was used to examine the relationship between different patterns of drinking motivations and behaviors in a sample of 12th graders (N = 1,877) from the 2004 Monitoring the Future survey. A person-centered approach was used to identify types of motivations that cluster together within individuals and relates membership in these profiles to drinking behaviors. Results suggest four profiles of drinking motivations for both boys and girls, including Experimenters, Thrill-seekers, Multi-reasoners, and Relaxers. Early initiation of alcohol use, past year drunkenness, and drinking before 4 P.M. were associated with greater odds of membership in the Multi-reasoners class as compared to the Experimenters class. Although the strength of these relationships varied for boys and girls, findings were similar across gender suggesting that the riskiest drinking behavior was related to membership in the Multi-reasoners class. These

findings can be used to inform prevention programming. Specifically, targeted interventions that tailor program content to the distinct drinking motivation profiles described above may prove to be effective in reducing risky drinking behavior among high school seniors. Coffman, D., Patrick, M., Palen, L., Rhoades, B., and Ventura, A. Why Do High School Seniors Drink? Implications for a Targeted Approach to Intervention. Prev. Sci., 8(4), pp. 241-248, 2007.

Sexual Behavior During Emerging Adulthood

Emerging adults (M = 18.99 years, SD = .50) completed cross-sectional questionnaires (N = 943) and targeted follow-up telephone surveys (N = 202) across the transition to college. Gender, personal goals (dating, friendship, academic), and past sexual behavior were examined as predictors of reasons to have and not to have sex. Men rated Self-focused reasons to have sex as more important; women rated Partner-focused reasons to have sex and Ethical reasons not to have sex as more important. Importance of Pregnancy/ STD reasons not to have sex did not differ by gender. Before college entrance, sexual history and personal goals predicted endorsement of reasons for/against sex. Personal goals predicted first intercourse during freshman year. Limitations of the study include the single university sample and use of closed-ended self-report measures. Personal goals and reasons for/against sex are associated with sexual behavior and should be addressed in programs designed to promote sexual health among emerging adult college students. Patrick, M., Maggs, J., and Abar, C. Reasons to Have Sex, Personal Goals, and Sexual Behavior During the Transition to College. J. Sex Res., 44(3), pp. 240-249, 2007.

Relation of Executive Function to Risk Behaviors in Female College Students

Relations among executive function, behavioral approach sensitivity, emotional decision making, and risk behaviors (alcohol use, drug use, and delinquent behavior) were examined in single female college students (N = 72). Hierarchical multiple regressions indicated a significant Approach Sensitivity x Working Memory interaction in which higher levels of alcohol use were associated with the combination of greater approach tendency and better working memory. This Approach Sensitivity x Working Memory interaction was also marginally significant for drug use and delinquency. Poor emotional decision making, as measured by a gambling task, was also associated with higher levels of alcohol use, but only for individuals low in inhibitory control. Findings point to the complexity of relations among aspects of self-regulation and personality and provide much needed data on neuropsychological correlates of risk behaviors in a nonclinical population. Patrick, M.E., Blair, C., and Maggs, J.L. Executive Function, Approach Sensitivity, and Emotional Decision Making as Influences on Risk Behaviors in Young Adults. J. Clin. Exp. Neuropsychol., 30(4), pp. 449-462, 2008.

Four Developmental Trajectories of Adolescent Physical Aggression

Latent growth mixture modeling was used to identify discrete patterns of physical aggression from Grades 7 to 11 among a sample of 1,877 youth (952 boys and 925 girls). These middle school students were participating in a field trial designed to test the effects of a drug prevention program. This study included only those students who were randomly assigned to the control condition schools. Students completed annual paper-and-pencil surveys in school at Grades 7 through 11. Four trajectory classes adequately explained the development of physical aggression in both boys and girls: Low/No Aggression; Persistent High Aggression; Desisting Aggression, characterized by

decreasing risk throughout adolescence; and Adolescent Aggression, characterized by low early risk that increases until Grade 9, levels out, and then declines in late adolescence. Girls were less likely than boys were to be in any trajectory besides the Low/No Aggression trajectory. Parental supervision, deviant peer association, academic orientation, impulsivity, and emotional distress at Grade 7 were all strongly associated with trajectory class membership. These associations did not differ by gender. These findings strongly suggest that the processes involved in the development of physical aggression in adolescence operate similarly in boys and girls. Martino, S., Ellickson, P., Klein, D., McCaffrey, D., and Edelen, M. Multiple Trajectories of Physical Aggression among Adolescent Boys and Girls. Aggress. Behav., 34(1), pp. 61-75, 2008.

Psychosocial Factors That Moderate or Directly Affect Substance Use Among Inner-City Adolescents

The purpose of this longitudinal study was to predict main effects and interactions of psychosocial risk and protective factors on poly-drug use intensity and future smoking among inner-city adolescents. A panel sample of baseline, 1-year and 2-year follow-ups (N=1459) from the control group of a longitudinal smoking prevention trial participated. The analysis of the poly-drug use outcome indicated that refusal assertiveness undermined perceived friends' drug use and siblings' smoking, and that low risk-taking undermined perceived friends' drug use. There was a main effect for low psychological wellness. The significant interactions between perceived friends' drug use with refusal assertiveness and decision-making skills were observed for future smoking. Moreover, perceived peer smoking norms, siblings' smoking, and high risk-taking also showed significant main effects for increasing future smoking. Epstein, J., Bang, H., and Botvin, G. Which Psychosocial Factors Moderate or Directly Affect Substance Use among Inner-City Adolescents? Addict. Behav., 32(4), pp. 700-713, 2007.

Considering Best Strategies for Recruiting Schools into Prevention Trials

Recruiting schools into a matched-pair randomized control trial (MP-RCT) to evaluate the efficacy of a school-level prevention program presents challenges for researchers. This study examined the effectiveness of 2 procedures for recruiting schools into a prevention study and assigning them to conditions. In 1 procedure (recruit and match/randomize), schools were recruited and matched prior to randomization, and in the other (match/randomize and recruitment), schools were matched and randomized prior to recruitment. The impact of each procedure on the randomization process was considered, as was the ability to recruit schools into the study. After implementing the selected procedure, the equivalence of both treatment and control group schools and the participating and nonparticipating schools on school demographic variables was evaluated. The recruit and match/randomize procedure was chosen because it would provide the opportunity to build rapport with the schools and prepare them for the randomization process, thereby increasing the likelihood that they would accept their randomly assigned conditions. Neither the treatment and control group schools nor the participating and nonparticipating schools exhibited statistically significant differences from each other on any of the school demographic variables. Recruitment of schools prior to matching and randomization in an MP-RCT may facilitate the recruitment of schools and thus enhance both the statistical power and the representativeness of study findings. Future research would benefit from the consideration of a broader range of variables (e.g., readiness to implement a comprehensive prevention program) both in matching schools and in evaluating their representativeness to nonparticipating schools. Ji, P., Dubois, D., Flay, B., and Brechling, V. "Congratulations, You Have Been Randomized Into the Control Group!(?)":

Issues to Consider When Recruiting Schools for Matched-Pair Randomized Control Trials of Prevention Programs. J. Sch. Health, 78(3), pp. 131-139, 2008.

Methods for Interval Estimation

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

Indirect Measures of Alcohol-related Cognitions Predict Use

Recently there has been increased interest in the role of implicit cognitive processes in the development of addictive behaviors. In this study, the authors compared 3 indirect measures of alcohol-related cognitions in the prospective prediction of alcohol use in at-risk adolescents. Implicit alcohol-related cognitions were assessed in 88 Dutch at-risk adolescents ranging in age from 14 to 20 years (51 males, 37 females) by means of varieties of word association tasks, Implicit Association Tests, and Extrinsic Affective Simon Tasks adapted for alcohol use. Alcohol use and alcohol-related problems were measured with self-report questionnaires at baseline and after 1 month. Results showed that the indirect measures predicted unique variance in prospective alcohol use after controlling for the direct measure of alcohol-related cognitions and background variables. The results indicate that the word association tasks were the best indirect measure of alcohol-related cognitions. These indirect measures appear to assess cognitive motivational processes that affect behavior in ways not reflected by direct measures of alcohol-related cognitions. Thush, C., Wiers, R., Ames, S., Grenard, J., Sussman, S., and Stacy, A. Apples and Oranges? Comparing Indirect Measures of Alcohol-Related Cognition Predicting Alcohol Use in At-Risk Adolescents. Psychol. Addict. Behav., 21(4), pp. 587-591, 2007.

Response Inconsistencies for Sex and Drug Use Behaviors Among South African High School Students

This study aims to describe patterns of inconsistent reports of sexual intercourse among a sample of South African adolescents. Consistency of reported lifetime sexual intercourse was assessed using five semiannual waves of data. Odds ratios related inconsistent reporting to demographic variables and potential indicators of general and risk-behavior-specific reliability problems. Participants were high school students from Mitchell's Plain, a low-income township near Cape Town, South Africa. Students (N = 2,414) were participating in a research trial of a classroom-based leisure, life skill, and sexuality education program. The sample for the present study was restricted to participants who reported lifetime sexual intercourse in at least one of the first four survey assessments (n = 713). This subsample was mostly male (69%) and "colored" (mix of African, Asian, and European ancestry) and had a mean age at baseline of 14 years. Of the sexually active participants in the

sample, nearly 40% reported being virgins after sexual activity had been reported at an earlier assessment. Inconsistent reporting could not be predicted by gender or race or by general indicators of poor reliability (inconsistent reporting of gender and birth year). However individuals with inconsistent reports of sexual intercourse were more likely to be inconsistent reporters of substance use. These results suggest that researchers need to undertake efforts to deal specifically with inconsistent risk behavior data. These may include modification of data collection procedures and use of statistical methodologies that can account for response inconsistencies. Palen, L., Smith, E., Caldwell, L., Flisher, A., Wegner, L., and Vergnani, T. Inconsistent Reports of Sexual Intercourse among South African High School Students. J. Adolesc. Health, 42(3), pp. 221-227, 2008.

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

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

Coping Skills Training and Contingency Management Treatments for Marijuana Dependence: Exploring Mechanisms of Action

Dr. Kadden and colleagues at the University of Connecticut conducted this study to explore the mechanisms of behavior change from a marijuana treatment trial in which behavioral treatments for marijuana dependence were evaluated. Participants were 240 adult marijuana smokers from an out-patient treatment research facility located in the university medical center. The participants were assigned to one of four 9-week treatment conditions: 1) case management control condition; 2) Motivational Enhancement/Cognitive Behavioral Therapy; 3) Contingency Management; or 4) a combination of Motivational Enhancement/Cognitive Behavioral Therapy and Contingency Management. Results indicated that regardless of treatment condition, abstinence in near-term follow-ups was predicted most clearly by abstinence during treatment, but long-term abstinence was predicted by use of coping skills and especially by post-treatment self-efficacy for abstinence. It was concluded that the most efficacious treatments for marijuana dependence are likely to be those that increase self-efficacy. Litt, M.D., Kadden, R.M., Kabela, E.C., and Petry, N.M. Coping Skills Training and Contingency Management Treatments for Marijuana Dependence: Exploring Mechanisms of Behavior Change. Addiction, 103(4), pp. 638-648, 2008.

Treating Tobacco Dependence in Clinically Depressed Smokers: Effect of Smoking Cessation on Mental Health Functioning

Dr. Prochska and colleagues at the University of California, San Francisco, conducted this study to examine the effect of smoking cessation on mental health functioning among depressed smokers. Participants were 322 actively depressed smokers recruited from outpatient mental health clinics. All participants completed a computer-delivered expert system program that provided feedback matched to their stage of change for quitting. Participants interested in quitting smoking could receive 6 sessions of individual cognitive-behavioral counseling combined with a nicotine patch. The control group received brief cessation advice. Ten indicators of mental health functioning were obtained at baseline and at 4 follow-up assessment periods. Of 40 comparisons, only one was significant: successful quitters were less likely to report alcohol use at 6-months compared with smokers. There were no group differences for depressive symptoms, which declined significantly over time for participants who stopped smoking as well as for those who continued to smoke. No indication of worse outcomes were found among successful quitters. The authors conclude that individuals who have clinical depression can be helped to stop smoking without adversely affecting their mental health

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recovery and should be offered concurrent tobacco dependence and depression treatment rather than delaying smoking cessation until the depression resolves. Prochaska, J.J., Hall, S.M., Tsoh, J.Y., Eisendrath, S., Rossi, J.S., Redding, C.A., Rosen, A.B., Meisner, M., Humfleet, G.L. and Gorecki, J.A. Treating Tobacco Dependence in Clinically Depressed Smokers: Effect of Smoking Cessation on Mental Health Functioning. American Journal of Public Health, 98, pp. 446-448, 2008.

Tobacco Use among Individuals with Schizophrenia: What Role has the Tobacco Industry Played?

This study examined the role the tobacco industry has played in promoting and maintaining cigarette use among individuals diagnosed with schizophrenia. Previously secret tobacco industry documents were analyzed and it was determined that the tobacco industry monitored or directly funded research supporting the idea that individuals with schizophrenia were less susceptible to the harms of tobacco and that they needed tobacco as self-medication. The tobacco industry promoted smoking in psychiatric settings by providing cigarettes and supporting efforts to block hospital smoking bans. Findings from the documents indicate that the tobacco industry engaged in a variety of direct and indirect efforts that likely contributed to the slowed decline in smoking prevalence in schizophrenia via slowing nicotine dependence treatment development for this population and slowing the rate of policy implementation on psychiatric units. The authors conclude that an awareness of the tobacco industry's efforts to preserve smoking among individuals with schizophrenia is needed to better inform treatment and policy strategies. Prochaska, J.J., Hall, S.M. and Bero, L.A. Tobacco Use among Individuals with Schizophrenia: What Role has the Tobacco Industry Played? Schizophrenia Bulletin, Feb. pp. 1-13, 2008.

Craving, Withdrawal, and Smoking Urges on Days Immediately Prior to Smoking Relapse

Dr. Allen and colleagues at the University of Minnesota conducted this study to identify temporal patterns of standardized symptom scores (for craving, withdrawal, and smoking urges) that would either refute or support the assumption that these factors are key contributors to relapse in smokers. Data were analyzed from 137 female smokers, aged 18-40 years, who completed 30 days of a protocol for a longitudinal smoking cessation trial. All subjects were followed post quit date, regardless of their subsequent smoking status. Measures of craving, withdrawal and smoking urges were completed at baseline and daily for 30 days, beginning on their quit date. A total of 26 women quit smoking and 11 relapsed. A consistent symptom severity pattern was observed, in which craving, withdrawal, and smoking urges increased leading up to the day of relapse and then subsided quickly. These findings suggest an association between patterns of symptom intensity and relapse. The authors conclude that frequent symptom monitoring might be clinically important for relapse prevention. Allen, S.S., Bade, T., Hatsukami, D., and Center, B. Craving, Withdrawal, and Smoking Urges on Days Immediately Prior to Smoking Relapse. Nicotine & Tobacco Research, 10(1), pp. 35-45, 2008.

Motivational Enhancement Therapy for High-Risk Adolescent Smokers

Dr. Helstrom and colleagues conducted this study to test the effectiveness of Motivational Enhancement Therapy (MET) in a sample of delinquent adolescent smokers and to examine how comorbid problems (alcohol use) and intrapersonal factors (impulsivity) moderated treatment outcome. Eighty-one adjudicated adolescent smokers were randomly assigned to receive either one

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session of MET or tobacco education control. Assessment was conducted at baseline and at one and six months post treatment. Results suggest that although between-group differences on outcome measures were not significant at follow-up, smoking behavior decreased in both groups with approximately 10% achieving 1-month smoking abstinence at 6-month follow-up. The brief MET was better than standard educational material with respect to decreasing smoking behavior for a subset of adolescents. Adolescents who consumed less alcohol and were less impulsive responded relatively well to MET in terms of self-reported decreases in smoking rates. However, for adolescents who endorsed higher rates of alcohol, or who were higher in impulsivity, MET generally performed worse than the control treatment. In fact, this subset of adolescents responded better to the control condition. The authors conclude that MET may be an effective intervention for some adolescent smokers but may be contraindicated for adolescents who have concomitant problems with alcohol use or impulsivity. Helstrom, A., Hutchison, K., and Bryan, A. Motivational Enhancement Therapy for High-Risk Adolescent Smokers. Addictive Behaviors, 32(10), pp. 2404-2410, 2007.

Cigarette Smoking in Opioid-Using Patients Presenting for Hospital-Based Medical Services

The authors examined cigarette smoking practices in 126 out-of-treatment opioid users presenting at a hospital for non-psychiatric medical services. In general, the study found the prevalence of smoking (92%) to be comparable to that reported in methadone treatment samples. Nineteen percent preferred unfiltered cigarettes. Women were more likely to smoke menthol cigarettes; men were more likely to smoke unfiltered cigarettes. Caucasians tended to smoke more than other ethnicities and exhibited greater dependence. The authors conclude that opioid users are a particularly high-risk group for continued smoking and they highlight the need for treatment programs to include smoking cessation interventions. Haas, A.L., Sorensen, J.L., Hall, S.M., Lin, C., Delucchi, D., Sporer, K., and Chen, T. Cigarette Smoking in Opioid-Using Patients Presenting for Hospital-Based Medical Services. The American Journal on Addictions, 17, pp. 65-69, 2008.

Combining Cognitive Behavioral Therapy with Contingency Management for Smoking Cessation in Adolescent Smokers

Investigators at Yale University conducted this study to evaluate the optimal format of cognitive behavioral therapy (CBT) to combine with contingency management (CM) in a four-week, high school-based smoking cessation program. In this pilot study, two different formats of CBT were compared. Thirty-four adolescent smokers were randomly assigned to receive either a standard weekly version of longer duration CBT or a more frequent brief behavioral intervention. Results indicated a trend toward a higher seven-day point prevalence end-of-treatment abstinence rate and percent days abstinent during treatment in the CBT condition. In addition, significantly more participants in the CBT group completed treatment. These preliminary results suggest that when combined with CM, the standard weekly format of CBT is more acceptable to adolescents. Cavallo, D.A., Cooney, J.L., Duhig, A.M., Smith, A.E., Liss, T.B., Fetridge A.K., Babuscio, T., Nich, C., Carroll, K.M., Rounsaville, B.J., and Krishnan-Sarin, S. Combining Cognitive Behavioral Therapy with Contingency Management for Smoking Cessation in Adolescent Smokers: A Preliminary Comparison of Two Different CBT Formats. The American Journal on Addictions, 16, pp. 468-474, 2007.

A Test of Motivational Plus Nicotine Replacement Interventions for HIV Positive Smokers

The authors conducted this study to test the acceptability, feasibility and preliminary effectiveness of two delivery formats of a combination of interventions that included motivational and pharmacological components for smoking cessation among HIV positive smokers. Forty adult daily smokers receiving HIV care were randomly assigned to one of two treatment conditions: 1) a single session of motivational interviewing plus nicotine patch, or 2) self-guided reading plus nicotine patch. The motivational interviewing included personalized feedback, consequences of smoking, and readiness to change components. The self-guided reading contained self-assessment of smoking habits, recommendations about setting a quit date, seeking help, substituting habits, self-monitoring and other tips. Participants in both groups set a quit date and were given a 1-month supply of nicotine patches. Both interventions led to significant reductions in cigarettes smoked per day and CO expiration at the 3-month follow-up, with no differences between groups. Compliance with the nicotine patch was poor and declined over time. The authors conclude that smoking cessation interventions for people with HIV can be helpful and should include components that encourage some smoke-free days, increase self-efficacy, and attend to adherence to nicotine replacement treatment. Ingersoll, K.S., Cropsey, K.L., and Heckman, C.J. A Test of Motivational Plus Nicotine Replacement Interventions for HIV Positive Smokers. AIDS Behavior, December 8, 2007 (Epub ahead of print).

The Impact of an Integrated Treatment on HIV Risk Behavior among Homeless Youth: A Randomized Controlled Trial

Drs. Slesnick and Kang conducted this study to examine an integrated individual intervention that included cognitive-behavioral treatment and HIV prevention as compared to treatment as usual on self-reported HIV risk behaviors among homeless youth. The integrated intervention focused on skills building and education. The treatment as usual condition included a place to rest during the day, food, showers, clothing, and case management that linked youth with community resources at the youth's request. Participants were 180 adolescents who were recruited from a drop-in center and were assessed at entry into the program and at 3 and 6 month follow-ups. Findings showed an interaction between treatment condition, age and time. In the interaction, youth assigned to the integrated treatment reported greater condom use than youth assigned to treatment as usual, with younger youth assigned to treatment as usual showing no change in condom use. The number of sexual partners reported by youth in both treatment conditions was also reduced over time. However, youth in both conditions continued to engage in other high-risk behaviors. The integrated treatment findings are promising and suggest that interventions which target both HIV risk behavior in addition to other life areas (substance use, mental health, and housing) among homeless youth may be necessary in order to significantly impact high-risk behaviors among this unique group. Slesnick, N. and Kang, M.J. The Impact of an Integrated Treatment on HIV Risk Behavior among Homeless Youth: A Randomized Controlled Trial. Journal of Behavioral Medicine, October 2007 (Epub ahead of print).

Older Versus Younger Treatment-Seeking Smokers

The purpose of this study was to describe treatment seeking smokers aged 50 years or older and compare them with younger smokers (aged<50) presenting to the same smoking treatment facility during the same time period. The subjects (n=810) were participating in one of two studies: one was limited to smokers aged 50 years or older; the other was open to smokers aged 18 years or older. As predicted, smokers aged 50+ were more tobacco dependent, had better psychological functioning, and had poorer physical functioning than those aged <50. Contrary to predictions, no differences were found in motivation to quit cigarette smoking or in alcohol use. Women aged 50+ were

less likely to report marijuana use than women aged <50, and less likely than men to receive a positive diagnosis for alcohol abuse. Despite higher scores on measures of tobacco dependence, older smokers were less likely to be diagnosed as tobacco dependent or as having tobacco withdrawal using DSM-IV criteria. Rates of alcohol abuse and dependence were high in both age groups, but were higher for smokers aged <50. Hall, S.M., Humflet, G.L., Gorecki, J.A., Munoz, R.F., Reus, V.I., and Prochaska, J.J. Older Versus Younger Treatment-Seeking Smokers: Differences in Smoking Behavior, Drug and Alcohol Use, and Psychosocial and Physical Functioning. Nicotine & Tobacco Research, 10(3), pp. 463-470, 2008.

Nicotine Interventions with Comorbid Populations

Dr. Sharon Hall wrote this article to selectively review research on smoking treatment for individuals with comorbid psychiatric or non-nicotine substance abuse disorders. With the exception of research on those with a history of major depressive disorder, research on smoking cessation in these populations is sparse. However, the prevalence of smoking is very high in these populations and individuals express an interest in quitting. Multiple barriers to implementation of interventions exist. Research findings to date indicate that provision of cigarette smoking interventions in substance abuse treatment patients is efficacious and does not appear to interfere with abstinence from alcohol or illicit drugs. The data available on smoking cessation in populations with psychiatric disorders suggest at least moderate efficacy and little evidence of exacerbation of these disorders. Integration of interventions into existing treatment clinics appears desirable. Further research is recommended in both the treatment and prevention of cigarette smoking in individuals with psychiatric and substance abuse disorders. It is reasonable to offer existing treatments to these subgroups of smokers, since there is some evidence of efficacy and little evidence of harm. Hall, S.M. Nicotine Interventions with Comorbid Populations. American Journal of Preventive Medicine, 33(6S), pp. S406-S412, 2007.

Posttraumatic Stress Disorder and Smoking Relapse

This paper addresses the gap in the literature regarding factors potentially influencing smoking relapse among individuals with Posttraumatic Stress Disorder (PTSD). PTSD is associated with high prevalence of cigarette smoking, heavy cigarette consumption, and low cessation rates. To date little is known about mechanisms impeding smoking cessation among this recalcitrant group of smokers. The assessment of mechanisms related to relapse would be an important first step in improving smoking cessation treatment efficacy. Such knowledge would aid in the development of tailored relapse prevention strategies for this population. Mechanisms reviewed that may be particularly relevant to smoking relapse among PTSD smokers include negative affect, positive affect, attention, anxiety sensitivity, distress tolerance, and self-efficacy. Cook, J.W., McFall, M.M. Calhoun, P.S. and Beckham, J.C. Posttraumatic Stress Disorder and Smoking Relapse. Journal of Traumatic Stress, 20(6), pp. 989-998, 2007.

Message Framing for Smoking Cessation

Research on message framing tests whether or not gain-framed messages (i.e., emphasizing the benefits of quitting smoking) are more persuasive in promoting cessation than loss-framed messages (i.e., emphasizing the costs of continuing to smoke). The authors conducted this study to examine how gender differences in perceptions of risk of quitting smoking influence the effects of framed interventions. Participants were 249 adult smokers (129 females, 120 males) in a clinical trial of message framing for smoking cessation

with bupropion. The results showed that women reported a higher perceived risk of cessation than men. Participants who anticipated high risks associated with quitting smoking reported fewer days to relapse. Further, females in the gain-framed condition who reported low perceived risks of cessation had a greater number of days to relapse, as opposed to females in the loss-framed condition. These findings suggest that message framing interventions for smoking cessation should consider the influence of gender and risk perceptions associated with quitting on the effectiveness of framed interventions. Toll, B.A., O'Malley, S.S., Mazure, C.M., Latimer, A., McKee, S.A. Message Framing for Smoking Cessation: The Interaction of Risk Perceptions and Gender. Nicotine & Tobacco Research, 10(1), pp. 195-200, 2008.

Dimensions of Depressive Symptoms and Smoking Cessation

Dr. Leventhal and colleagues conducted this study to evaluate whether certain dimensions of depressive symptoms have a greater influence on smoking cessation than others. Certain psychopathologic components of depressive symptoms [negative affect (NA), somatic features (SF), low positive affect/anhedonia (PA), and interpersonal disturbance (IP)] were examined in a sample of 157 non-clinically depressed social drinkers enrolled in a clinical trial for smoking cessation. The subscales of the Center for Epidemiologic Studies Depression Scale (CESD) were used to predict (a) baseline tobacco dependence severity and motives for smoking, (b) abstinence-provoked nicotine withdrawal, and (c) smoking abstinence over the follow-up period. From a clinical standpoint, the findings suggest that interventions targeting anhedonia and low positive affect may be useful for smokers trying to quit. Leventhal, A.M., Ramsey, S.E., Brown, R.A., LaChance, H.R., and Kahler, C.W. Dimensions of Depressive Symptoms and Smoking Cessation. Nicotine & Tobacco Research, 10(3), pp. 507-517, 2008.

Promising Results from Behavioral and HIV Risk Reduction with Buprenorphine

Dr. Schottenfeld and colleagues conducted this study to see if behavioral drug and HIV risk reduction counseling (BRDC) and abstinent contingent buprenorphine reduced HIV risk and drug abuse in opioid dependent patients in Malaysia. Following a two-week induction onto buprenorphine, twenty-four participants were randomized in this pilot trial to either standard treatment (physician managed buprenorphine administered non-contingently) or enhanced treatment. The enhanced treatment included behavioral drug and HIV risk reduction counseling and abstinent contingent buprenorphine. Buprenorphine ingestion was observed by staff and only administered following submission of a drug negative urine specimen. Both groups decreased use of opioids significantly over time. However, participants assigned to the enhanced treatment had longer consecutive periods of abstinence and a higher proportion of drug negative urines during treatment. Both groups reduced HIV risk behaviors from baseline. Although preliminary, these findings are significant because this short term community friendly intervention can be delivered by nurses in regular medical settings. Therefore, it is likely to be useful in many developing countries that are setting up an infrastructure to treat opioid abuse but which lack counselors or therapists with advanced training. Chawarski, M.C., Mazlan, M., Schottenfeld, R.S. Behavioral Drug and HIV Risk Reduction Counseling (BDRC) with Abstinence-Contingent Take-Home Buprenorphine: A Pilot Randomized Clinical Trial. Drug and Alcohol Dependence, 94(1-3), pp. 281-284, 2008.

Buprenorphine and Brief Medical Management In Primary Care Reduces HIV Risk

Dr. Sullivan and colleagues examined HIV risk behavior participants (N=166) enrolled in a 24-week clinical trial who were receiving either standard or intensive medical management and either once weekly or thrice weekly medication management (buprenorphine) administered in primary care. Medical management was conducted by nurses and lasted 20 minutes for the standard and 45 minutes for the intensive conditions. None of the study conditions specifically targeted HIV sexual risk behavior. HIV risk was assessed at baseline, 12 and 24 weeks. None of the conditions showed any difference in abstinence (results reported elsewhere) although all participants reduced opioid use. Results showed a significant decrease in injection drug use from baseline across conditions. Additionally, the percentage of people endorsing "having sex with a steady partner while 'high'" decreased as well. Infrequent condom use did not change significantly. These results are important because they show that buprenorphine plus brief medical management approaches delivered in a primary care setting can reduce HIV risk. Additionally, they suggest the effect of these interventions are primarily through reducing drug use as well as certain risky behavior while under the influence of opioids. However, the results also indicate changes to the intervention are needed to directly address infrequent condom use which continues to put patients and their partners at risk. Sullivan L.E., Moore, B.A., Chawarski, M.C., Pantalon, M.V., Barry, D., O'Connor, P.G., and Schottenfeld, R.S., Fiellin, D.A. Buprenorphine/Naloxone Treatment in Primary Care is Associated with Decreased Human Immunodeficiency Virus Risk Behaviors. Journal of Substance Abuse Treatment, 2007. (Epub ahead of print).

Live Teleconferencing Improves Therapist Motivational Interviewing Skills

Dr. Nunes and colleagues conducted this study to determine whether live teleconferencing could be used to help therapists learn motivational interviewing (MI) skills following a workshop training session. Currently, workshop training is the dominant method of training therapists in MI. However, studies show most therapists do not become proficient in MI skills following a single workshop. During Teleconferencing Supervision (TCS) the trainer watches a live video of the student conducting therapy and listens to the session over the telephone. Supervisors then provide immediate feedback over the phone via a microphone in the student therapist's ear. In this study, thirteen clinicians from community substance abuse treatment programs were recruited and trained in a workshop by an expert MI trainer. Twelve of thirteen participants completed all of the training which included the workshop and 5 teleconference supervision sessions and separate in depth supervision sessions in between sessions with patients. Initial trainee skillfulness was examined through a role play MI session following the workshop rated by expert MI coders using a standardized rating instrument. These were then compared to tapes of actual sessions with substance using clients at 8 and 20 weeks to examine the impact of the telesupervision. Initial skill levels were low. At the study end points motivational interviewing skills including open ended questions had improved to expert level. However, most advanced skills typically did not improve beyond beginner proficiency. These findings are important because they demonstrate the feasibility of a novel approach to provide community therapists with access to expert training in research based behavioral treatment. Additionally they suggest that long-term sustained monitoring and feedback (supervision) is likely to be necessary for community treatment providers to adeptly administer the treatments NIDA seeks to disseminate. Smith, J.L, Amrhein, P.C., Brooks, A.C., Carpenter, K.M., Levin, D., Schreiber, E.A., Travaglini, L.A., and Nunes, E.V. Providing Live Supervision via Teleconferencing Improves Acquisition of Motivational Interviewing Skills after Workshop Attendance. Am. J. Drug Alcohol Abuse, 33(1), pp. 163-168, 2007.

Longest Abstinence Length Predicts Incentive Treatment Outcome for Cocaine

Dr. Petry and colleagues conducted this study to determine whether there was a difference in outcome between standard contingency management "incentive" treatment that reinforces abstinence with escalating voucher values for drug negative urines and a novel prize based approach where participants submitting drug negative urines draw for prizes. In the prize condition prizes ranged from verbal reinforcement (slips of paper that say good "job" to small prizes worth about $1 up to jumbo prizes worth $100. Under this prize system the probability of winning a prize is inversely proportional to the size of that prize and the number of chances to draw increase with each consecutive drug negative urine sample a participant provides. Across 12 weeks of treatment and the number of chances the maximal expected earnings for a participant in this trial was $300. Seventy-six drug users were assigned at random to either standard drug treatment or standard drug treatment plus voucher contingencies (V) or standard drug treatment plus prizes (P). The median number of weeks of consecutive abstinence was 0 in the standard treatment and 6 in both contingent conditions. At 6 and 12 weeks post-treatment no difference existed between the groups. However, regardless of group assignment, the longest duration of abstinence predicted long term abstinence. Overall, the total earnings of both contingency groups did not differ significantly. Results are significant because community treatment providers wishing to use this alternate method can be assured it is as effective as the standard method. Additionally, findings indicate that many methods which enable a drug user to achieve a long period of abstinence may be effective for establishing a trajectory of abstinence. Petry, N.M., Alessi, S.M., Hanson, T., and Sierra S. Randomized Trial of Contingent Prizes versus Vouchers in Cocaine-Using Methadone Patients. Journal of Consulting and Clinical Psychology, 75(6), pp. 983-991, 2007.

Dually Diagnosed Veterans in Vocational Rehabilitation Benefit from Incentives

Dr. Rounsaville and colleagues examined whether adding incentives exchangeable for goods and services contingent on submitting a drug free urine would improve abstinence and vocational rehabilitation in veterans with a substance use and mental health disorder. One hundred participants were randomly assigned to standard vocational rehabilitation (VR) or vocational rehabilitation plus the opportunity to earn up to $1170 in incentives for completing tasks related to abstinence, job searches and employment maintenance (VR+). Relative to VR, Veterans in VR+ transitioned more quickly to competitive employment and at higher rates and had more abstinence during the first 16 weeks of the program. These results are significant because obtaining employment may be difficult for dually diagnosed veterans, but it is crucial for successful rehabilitation. Additionally, these findings suggest that restructuring traditional work for pay contingencies to include direct financial reimbursement for clinical goal achievement may increase abstinence in this difficult to treat population. Drebing, C.E., Van Ormer, E.A., Mueller, L., Hebert, M., Penk, W.E., Petry, N.M., Rosenheck, R., and Rounsaville, B. Adding Contingency Management Intervention to Vocational Rehabilitation: Outcomes for Dually Diagnosed Veterans. Journal of Rehabilitation Research Development, 44(6), pp. 851-866, 2007.

Dose Response for Cash Incentives but not Goods-Based Incentives

Dr. Stitzer and colleagues examined whether providing goods in exchange for abstinence or money in exchange for abstinence resulted in either better

abstinence outcomes or more cocaine use in methadone-maintained cocaine-dependent people attempting to abstain from cocaine. In a 16-week study with 12 participants, incentives (both goods based and checks) worth $0.00, $25, $50 and $100 were compared in a case-controlled randomized design with a nine day washout period between each incentive condition. Checks worth $50 and $100 produced greater abstinence rates than control checks ($0). However, this effect was not observed for goods-based incentives. Additionally, the cash conditions did not produce more cocaine use. These results are important for two reasons. First, most incentive programs give goods rather than cash because of the perception that goods are safer for patients. However, this study suggests that providing money directly may be more effective. Additionally, the reason why most incentive programs use prize or voucher programs that require a great deal of staff effort to shop for and monitor prizes is out of concern that providing money in exchange for abstinence might trigger relapse. These preliminary results suggest that in the face of ongoing money incentives to become abstinent, drug users are actually unlikely to relapse and costly extra voucher and prize components may not be essential. Vandrey, R., Bigelow, G.E., and Stitzer, M.L. Contingency Management in Cocaine Abusers: A Dose-Effect Comparison of Goods-Based versus Cash-Based Incentives. Experimental Clinical Psychopharmacology, 15(4), pp. 338-343, 2007.

Drop-In Centers Help Homeless Youth Substance Users but do not Affect Education or Permanent Housing

Dr. Slesnick and colleagues conducted this study to examine the impact of drop-in centers where homeless youth in an urban community could receive case management, substance abuse treatment and access to essential basic survival services such as meals, clothing and daytime shelter. Youth were assessed at baseline, 6 months, and 12 months via semi-structured interviews and questionnaires conducted over 3 years. Significant improvements were found in mental health, substance abuse and days housed up to 12 months after baseline. Additionally, decreased substance use was associated with improvements in housing status. However, most youth did not acquire permanent housing even if substance use decreased. Additionally, education, employment and medical service utilization remained low and did not improve over time. These findings are significant because they suggest that while drop-in centers can impact high risk behaviors, reducing substance use does not translate into ending homelessness for youth. To rehabilitate homeless youth, additional measures are needed. Many youth avoid shelters and foster care due to fear of exploitation by adults. Additionally, local laws that forbid minors from leasing apartments appear to be a barrier to stability that make education and employment possible. Adult homeless treatment programs have shown housing to be essential for effective care. This study corroborates findings from other researchers that suggest the homeless adolescent care system would likely benefit from independent living programs that integrate housing, substance abuse and mental health services similar to those afforded to adults. Slesnick, N., Kang, M.J., Bonomi, A.E., and Prestopnik, J.L. Six- and Twelve-Month Outcomes among Homeless Youth Accessing Therapy and Case Management Services Through an Urban Drop-In Center. Health Services Research, 43(1), pp. 211-229, 2007.

Behavioral Treatment for Drug Abuse Comparable in Efficacy to Other Interventions in Psychiatry

Dr. Otto and colleagues conducted a meta-analysis of psychosocial treatments for substance use disorders examining thirty-four well controlled treatments. Contingency management (CM), relapse prevention, cognitive behavioral therapy (CBT) and combinations of CM and CBT were included. Overall results of the meta-analysis showed these interventions had a moderate effect size,

comparable to that yielded by other psychiatric interventions. They showed the most efficacy for marijuana users and the least for polysubstance users. Drop out was significantly greater in control group participants than in the experimental conditions. CM, particularly when combined with CBT, produced the largest effect sizes. Results are significant because they suggest the average participant in these psychosocial interventions achieves better outcomes than 67% of control group participants. Finally, additional work is need related to improving treatment efficacy for polysubstance uses. Dutra, L., Stathopoulou, G., Basden, S.L., Leyro, T.M., Powers, M.B., and Otto, M.W. A Meta-Analytic Review of Psychosocial Interventions for Substance Use Disorders. Am J Psychiatry, 165(2), pp. 179-87, 2008. (Epub ahead of print).

Motivational Enhancement Therapy Reduces Viral Load in HIV+ Youth

Dr. Naar King and colleagues adapted a motivational enhancement therapy for use with youth and conducted a pilot test to determine whether it would reduce HIV risk behaviors and viral load in HIV+ youth and maintain those improvements over time. Thirty-two HIV+ participants between ages 16-25 were assigned either to treatment as usual or to the four session experimental motivational enhancement treatment (MET) adapted from a similar intervention geared at addressing substance use and HIV medication in adults called Healthy Choices. Youth assigned to MET received individual counseling sessions where information was feedback from their assessment and they could chose to work on 2 of 3 problem behaviors including sexual risk, health behavior including HIV medication taking, and substance use behaviors. The goals for the first two sessions (weeks 1 & 2) were to motivate and help establish a self-directed change plan. In follow-up sessions weeks 6 and 10, counselors reviewed progress, problem solved barriers, and helped youth think of strategies to prevent relapse. The treatment group showed greater reductions in viral load and alcohol use compared with the control group at 6-month follow-up but none in marijuana use or unprotected sex. Reductions for the treatment group in marijuana use, alcohol use and viral load were maintained at 9 months. This is significant because MET treatments have not previously been shown to have an impact on this population. It is especially noteworthy that four sessions of therapy could effect reductions in viral load. More research is needed on how this treatment impacts viral load as well as how it can be improved to affect more risk behaviors. Naar-King, S., Lam, P., Wang, B., Wright, K., Parsons, J.T., and Frey, M.A. Brief Report: Maintenance of Effects of Motivational Enhancement Therapy to Improve Risk Behaviors and HIV-Related Health in a Randomized Controlled Trial of Youth Living with HIV. J. Pediatr. Psychology, 33(4), pp. 441-445, 2008.

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

Research Findings - Research on Pharmacotherapies for Drug Abuse

Cocaine Withdrawal Symptoms Identify "Type B" Cocaine-dependent Patients

Recent studies of substance dependence typologies briefly show that multivariate systems originally developed for identifying subtypes of alcoholics, such as Babor's Type A and B system may also be valid in abusers of other substances, such as cocaine. Type B patients are characterized by an earlier onset of addiction and more severe symptoms of their addiction, psychopathology, and impulsivity. The Type B classification has also been associated with deficits in serotonergic function. The investigators have found that patients who exhibit more severe cocaine withdrawal symptoms, as measured by scores on the Cocaine Selective Severity Assessment (CSSA), have poor treatment outcome and share many characteristics with "Type B" patients. In this paper, the investigators review baseline characteristics of cocaine-dependent patients from several recently completed outpatient cocaine dependence treatment trials to assess the association of cocaine withdrawal symptom severity and the Type B profile. Identifying subtypes of cocaine-dependent patients may improve our ability to treat cocaine dependence by targeting treatments for specific subtypes of patients. The investigators examined the ability of the CSSA scores to capture Type B characteristics in cocaine dependence by analyzing a series of cocaine medication trials that included 255 cocaine-dependent subjects. High CSSA scores at baseline were associated with a history of violent behavior, a family history of substance abuse, antisocial personality disorder, higher addiction severity, and co-morbid psychiatric diseases. Patients with high CSSA scores are also more likely to meet criteria for Type B (Type II) cocaine dependence. Identifying Type B cocaine-dependent patients may help to develop targeted psychosocial or pharmacological treatments for these difficult-to-treat patients. Ahmadi, J., Kampman, K., Dackis, C., Sparkman, T., and Pettinati, H. Cocaine Withdrawal Symptoms Identify "Type B" Cocaine-dependent Patients. Am. J. Addict., 17, pp. 60-64, 2008.

Effects of Co-morbid Major Depressive Disorder (MDD) or Attention-Deficit/Hyperactivity Disorder (ADHD) on the Outcome of Pharmacological Treatment for Cocaine Dependence

Cocaine-dependent patients with MDD (n=66), ADHD (n=53), or those subjects without co-morbid disorders (cocaine-dependent alone, n=48) were treated for 12-weeks with venlafaxine, methylphenidate, or gabapentin, respectively, in concurrent single-blind, placebo-controlled clinical trials. Using logistic-regression modeling techniques, it was found that patients with either MDD or ADHD exhibited an improved outcome over time compared with patients with

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CD alone - if abstinence was achieved at baseline. However, if subjects remained cocaine-dependent at baseline, patients with either MDD or ADHD were associated with poorer outcome as compared with patients with CD alone. These findings suggest that the diagnosis and treatment of co-occurring disorders such as depression or ADHD may be important aspects of treatment planning for cocaine-dependence and indicate that the baseline level of cocaine use should be included as a covariate in the clinical evaluation of such treatment. Levin, F.R., Bisaga, A., Raby, W., Aharonovich, E., Rubin, E., Mariani, J., Brooks, D.J., Garawi, F., and Nunes, E.V. Effects of Major Depressive Disorder and Attention-Deficit/Hyperactivity Disorder on the Outcome of Treatment for Cocaine Dependence. J. Subst. Abuse Treat. 34(1), pp. 80-89, 2008.

Cocaine Users Differ from Normals on Cognitive Tasks which Show Poorer Performance During Drug Abstinence

In this publication, seventeen non-treatment seeking cocaine-dependent individuals participated in three-week longitudinal inpatient studies of cognitive changes during drug use and abstinence. Protocols included three days drug-free baseline, three days cocaine self-administration, and two weeks complete abstinence. A repeatable cognitive battery showed attention and delayed verbal recognition memory but not working memory to be impaired in cocaine users compared to age- and sex-matched normative values. Attention was significantly poorer during the first and second week of abstinence compared to days on which cocaine was used, suggesting that certain cocaine-induced impairments may be acutely normalized by cocaine use, but may resurface during abstinence. Pace-Schott E.F., Morgan P.T., Malison R.T., Hart C.L., Edgar C., Walker M., and Strickgold R. Cocaine Users Differ from Normals on Cognitive Tasks which Show Poorer Performance During Drug Abstinence. Am. J. of Drug and Alcohol Abuse, 34(1), pp. 109-121, 2008.

A Randomized, Double-Blind, Placebo-Controlled Trial of Long-Acting Risperidone in Cocaine-Dependent Men

There is no approved pharmacotherapy for cocaine dependence. Risperidone is an atypical antipsychotic drug with combined dopamine-2/serotonin-2 (D(2)/5-HT(2)) antagonist activity that has been effective in reducing cocaine use in some animal studies. The investigators tested the efficacy of a long-acting, injectable preparation of risperidone on cocaine use in active cocaine users. Thirty-one cocaine-dependent men who met DSM-IV diagnostic criteria for current cocaine dependence entered a 12-week, randomized, double-blind, placebo-controlled trial of intramuscular risperidone, 25 mg every other week. The primary outcome measure was cocaine use as measured by urinary concentration of cocaine metabolites. Secondary outcomes were self-report of cocaine use and craving, depressive symptoms as measured by the Hamilton Rating Scale for Depression (HAM-D), and adverse events. Participants were recruited during a 12-month period from October 2005 to September 2006. Both groups reduced their cocaine use during the study. There were no between-group differences in the primary measure of cocaine use (urinary metabolites [F = 0.7, p = .41]) or on craving measures. Those assigned to risperidone reported significantly worsened depressive symptoms (mean +/- SD HAM-D change scores: +7.4 +/- 8.8 vs. -2.3 +/- 5.8, respectively, F = 7.5, p = .018) and gained significantly more weight (mean weight change: +6.3 +/- 9.4 lb vs. -4.0 +/- 8.9 lb, respectively, F = 4.65, p = .044) than those assigned to placebo. Treatment with long-acting injectable risperidone in active cocaine users was not associated with reduction in cocaine use or craving and was associated with worsening of depressive symptoms and weight gain. Loebl, T., Angarita, G. A., Pachas, G. N., Huang, K. L., Lee, S. H., Nino, J. et al. A Randomized, Double-Blind, Placebo-Controlled Trial of Long-Acting Risperidone in Cocaine-Dependent Men. J. Clin. Psychiatry, pp. e1-e7, 2008.

Levodopa Pharmacotherapy for Cocaine Dependence: Choosing the Optimal Behavioral Therapy Platform

The dopamine precursor levodopa has shown some, albeit relatively weak, promise in treating cocaine dependence. This study sought to identify the most appropriate behavioral therapy platform for levodopa pharmacotherapy by evaluating its effect when administered in combination with behavioral platforms of varying intensities. A total of 161 treatment-seeking cocaine dependent subjects received sustained release levodopa/carbidopa (400/100mg bid, Sinemet) or placebo delivered in combination with Clinical Management (ClinMan); ClinMan+cognitive behavioral therapy (CBT); or ClinMan+CBT+voucher-based reinforcement therapy (VBRT) in a 12-week randomized, placebo-controlled, double-blind (for medication condition) trial. Medication compliance was monitored with riboflavin (100mg/capsule) and the Medication Event Monitoring System. Protocol compliance was addressed in weekly, 10-min nurse-delivered ClinMan sessions. Weekly, 1-h CBT sessions focused on coping skills training. VBRT (with escalating reinforcer value) provided cash-valued vouchers contingent on cocaine-negative urine toxicology results. Urine benzoylecgonine assays collected thrice-weekly were analyzed by intention-to-treat criteria using generalized linear mixed models. Levodopa main effects were found on all outcome measures of cocaine use. Contrasts testing the levodopa-placebo difference within each behavioral platform found reliable effects, favoring levodopa, only in the VBRT platform. Levodopa treatment with vouchers produced higher proportions of cocaine-negative urines and longer periods of consecutive abstinence compared to other treatment combinations. This is the first study to find a significant treatment effect for levodopa and, in doing so, to demonstrate that the magnitude of this effect is dependent upon conditions of the behavioral therapy platform. The data support use of levodopa with abstinence-based reinforcement therapy as one efficacious combination in cocaine dependence disorder treatment. Schmitz, J.M., Mooney, M.E., Moeller, F.G., Stotts, A.L., Green, C., and Grabowski, J. Levodopa Pharmacotherapy for Cocaine Dependence: Choosing the Optimal Behavioral Therapy Platform. Drug Alcohol Depend., 94, pp. 142-150, 2008.

A Double Blind, Placebo-Controlled Trial that Combines Disulfiram and Naltrexone for Treating Co-occurring Cocaine and Alcohol Dependence

This is a double blind, placebo-controlled trial that evaluated the efficacy of disulfiram, naltrexone and their combination in patients with co-occurring cocaine and alcohol dependence. Two-hundred eight patients were randomized to disulfiram (250 mg/day), naltrexone (100 mg/day), the combination, or placebo for 11 weeks. Outcomes were in-trial abstinence from cocaine and/or alcohol. Few safety concerns were reported, although medication adherence was low in a number of patients for both medications, alone or in combination. In the primary analyses (GEE modeling), abstinence from cocaine as measured by cocaine-negative urines and days of self-reported abstinence from cocaine or alcohol did not differ between placebo and any of the medication groups. However, patients taking disulfiram (alone or in combination) were most likely to achieve combined abstinence from cocaine and alcohol. Secondary analyses revealed that patients taking the disulfiram-naltrexone combination were most likely to achieve 3 consecutive weeks of abstinence from cocaine and alcohol. There was an association between disulfiram treatment and abstinence from cocaine and alcohol. More patients taking the disulfiram-naltrexone combination achieved 3 consecutive weeks of abstinence in treatment than placebo-treated patients. Pettinati, H.M., Kampman, K.M., Lynch, K.G., Xie, H., Dackis, C., Rabinowitz, A.R. et al. A Double Blind, Placebo-Controlled Trial that Combines Disulfiram and Naltrexone for Treating Co-occurring Cocaine and

Alcohol Dependence. Addict. Behav., 33, pp. 651-667, 2008.

Treatment of Opioid-Dependent Pregnant Women: Clinical and Research Issues

This article addresses common questions that clinicians face when treating pregnant women with opioid dependence. Guidance, based on both research evidence and the collective clinical experience of the authors, which include investigators in the Maternal Opioid Treatment: Human Experimental Research (MOTHER) project, is provided to aid clinical decision making. The MOTHER project is a double-blind, double-dummy, flexible-dosing, parallel-group clinical trial examining the comparative safety and efficacy of methadone and buprenorphine for the treatment of opioid dependence in pregnant women and their neonates. The article begins with a discussion of appropriate assessment during pregnancy and then addresses clinical management stages including maintenance medication selection, induction, and stabilization; opioid agonist medication management before, during, and after delivery; pain management; breast-feeding; and transfer to aftercare. Lastly, other important clinical issues including managing co-occurring psychiatric disorders and medication interactions are discussed. Treatment of Opioid-Dependent Pregnant Women: Clinical and Research Issues. Jones, H.E., Martin, P.R., Heil, S.H., Kaltenbach., Selby, P., Coyle, M.G., Stine, S.M., O'Grady, K.E., Arria, A.M., and Fischer, G. J. Substance Abuse Treat., Jan 11, 2008.

Opioid Use Disorder in the United States: Insurance Status and Treatment Access

In the United States, insurance status and rates of treatment for individuals with opioid use disorder are unknown. This study employed a cross-sectional survey: 2002-2004 National Survey on Drug Use and Health (NSDUH). Bivariate and multivariate associations between demographics, treatment and insurance status and presence or absence of opioid use disorder were investigated. On unadjusted analysis, young respondents, respondents of Hispanic ethnicity (OR 1.5; 95% CI 1.1-2.2), unemployed respondents (OR 2.6; 95% CI 1.8-3.8) and respondents with Medicaid (OR 4.5; 95% CI 2.5-8.3) or lack of insurance (OR 3.2; 95% CI 1.8-5.9) were more likely to have opioid use disorder. On unadjusted analysis among those with any substance use disorder, 12-16 year olds were more likely to have opioid use disorder (OR 3.4; 95% CI 2.0-5.8) than a non-opioid substance use disorder, as were women (OR for men 0.6; 95% CI 0.5-0.7) and unemployed respondents (OR 1.5; 95% CI 1.02-2.1). Only 15.2% of those with past-year opioid use disorder received treatment in the past year. Respondents treated for opioid use had higher rates of Medicaid ($p<0.01$), Medicare ($p<0.01$) and other public assistance ($p=0.01$) compared with those treated for other substances. Treatments for opioid use were more likely to be hospital ($p=0.04$) and inpatient rehabilitation ($p=0.02$) settings compared to treatment for other substance use. Among those with opioid use disorder, not being employed was independently associated with receiving treatment (AOR 3.5; 95% CI 1.4-8.5). The authors conclude that in the U.S., high rates of unemployment, Medicaid and uninsurance among those with opioid use disorder and low rates of treatment suggest that efforts to expand treatment must include policy strategies to help reach a population with significant barriers to treatment access. Becker, W.C., Fiellin, D.A., Merrill, J.O., Schulman, B., Finkelstein, R., Olsen, Y. et al. Opioid Use Disorder in the United States: Insurance Status and Treatment Access. Drug Alcohol Depend., 94, pp. 207-213, 2008.

Office-based Maintenance Treatment of Opioid Dependence: How Does It Compare with Traditional Approaches?

The increasing global public health burden of heroin dependence and prescription opioid dependence warrants further expansion of treatment models. The most effective intervention for opioid dependence remains maintenance with methadone, a full mu-opioid receptor agonist, or buprenorphine, a partial mu-opioid receptor agonist.A growing body of evidence supports the use of opioid receptor agonist maintenance in office-based settings. Office-based opioid treatment (OBOT) can expand treatment access in a less stigmatized environment, which enables integrated care of co-morbid conditions. The current review primarily examines OBOT in the US, although a comparison with the British and French models is provided, given that the public health impact and implementation of OBOT will likely vary between countries because of policy and logistical differences. The comparative effectiveness of maintenance treatment in office-based and traditional programme-based models of care requires further study. Clinical and practical considerations when providing treatment for opioid dependence in traditional versus office-based settings include patient selection and monitoring, health economics, management of co-morbid conditions, and access to ancillary psychosocial treatment. OBOT is not a replacement for more structured, traditional models of care, but provides an additional opportunity to help address the tremendous public health impact of opioid dependence. Gunderson, E.W. and Fiellin, D.A. Office-based Maintenance Treatment of Opioid Dependence: How Does it Compare with Traditional Approaches? CNS Drugs, 22, pp. 99-111, 2008.

Cannabis Reinforcement and Dependence: Role of the Cannabinoid CB1 Receptor

Awareness of cannabis dependence as a clinically relevant issue has grown in recent years. Clinical and laboratory studies demonstrate that chronic marijuana smokers can experience withdrawal symptoms upon cessation of marijuana smoking and have difficulty abstaining from marijuana use. This paper will review data implicating the cannabinoid CB1 receptor in regulating the behavioral effects of Delta(9)-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis, across a range of species. The behavioral effects that will be discussed include those that directly contribute to the maintenance of chronic marijuana smoking, such as reward, subjective effects, and the positive and negative reinforcing effects of marijuana, THC and synthetic cannabinoids. The role of the CB1 receptor in the development of marijuana dependence and expression of withdrawal will also be discussed. Lastly, treatment options that may alleviate withdrawal symptoms and promote marijuana abstinence will be considered. Cooper, Z.D. and Haney, M. Cannabis Reinforcement and Dependence: Role of the Cannabinoid CB1 Receptor. Addict. Biol. Epub ahead of print, 2008.

Cannabis Withdrawal is Common Among Treatment-Seeking Adolescents with Cannabis Dependence and Major Depression, and is Associated with Rapid Relapse to Dependence

Recently, reports have suggested that cannabis withdrawal occurs commonly in adults with cannabis dependence, though it is unclear whether this extends to those with comorbid depression or to comorbid adolescents. The investigators hypothesized that cannabis withdrawal would be common among our sample of comorbid adolescents and young adults, and that the presence of cannabis withdrawal symptoms would be associated with a self-reported past history of rapid reinstatement of cannabis dependence symptoms (rapid relapse). The participants in this study included 170 adolescents and young adults, including 104 with cannabis dependence, 32 with cannabis abuse, and 34 with cannabis use without dependence or abuse. All of these subjects demonstrated current depressive symptoms and cannabis use, and most demonstrated current DSM-IV major depressive disorder and current comorbid cannabis dependence.

These subjects had presented for treatment for either of two double-blind, placebo-controlled trials involving fluoxetine. Cannabis withdrawal was the most commonly reported cannabis dependence criterion among the 104 subjects in our sample with cannabis dependence, being noted in 92% of subjects, using a two-symptom cutoff for determination of cannabis withdrawal. The most common withdrawal symptoms among those with cannabis dependence were craving (82%), irritability (76%), restlessness (58%), anxiety (55%), and depression (52%). Cannabis withdrawal symptoms (in the N=170 sample) were reported to have been associated with rapid reinstatement of cannabis dependence symptoms (rapid relapse). These findings suggest that cannabis withdrawal should be included as a diagnosis in the upcoming DSM-V, and should be listed in the upcoming criteria list for the DSM-V diagnostic category of cannabis dependence. Cornelius, J.R., Chung, T., Martin, C., Wood, D.S., and Clark, D.B. Cannabis Withdrawal is Common Among Treatment-seeking Adolescents with Cannabis Dependence and Major Depression, and is Associated with Rapid Relapse to Dependence. Addict. Behav., Epub ahead of print, 2008.

Effects of THC and Lofexidine in a Human Laboratory Model of Marijuana Withdrawal and Relapse

Individuals seeking treatment for their marijuana use rarely achieve sustained abstinence. The objectives of the study are to determine if THC, a cannabinoid agonist, and lofexidine, an alpha(2)-adrenergic receptor agonist, given alone and in combination, decreased symptoms of marijuana withdrawal and relapse, defined as a return to marijuana use after a period of abstinence. Nontreatment-seeking, male volunteers (n = 8), averaging 12 marijuana cigarettes/day, were maintained on each of four medication conditions for 7 days: placebo, tetrahydrocannabinol (THC) (60 mg/day), lofexidine (2.4 mg/day), and THC (60 mg/day) combined with lofexidine (2.4 mg/day); each inpatient phase was separated by an outpatient washout phase. During the first three inpatient days, placebo marijuana was available for self-administration (withdrawal). For the next 4 days, active marijuana was available for self-administration (relapse). Participants paid for self-administered marijuana using study earnings. Self-administration, mood, task performance, food intake, and sleep were measured. THC reversed the anorexia and weight loss associated with marijuana withdrawal, and decreased a subset of withdrawal symptoms, but increased sleep onset latency, and did not decrease marijuana relapse. Lofexidine was sedating, worsened abstinence-related anorexia, and did not robustly attenuate withdrawal, but improved sleep and decreased marijuana relapse. The combination of lofexidine and THC produced the most robust improvements in sleep and decreased marijuana withdrawal, craving, and relapse in daily marijuana smokers relative to either medication alone. These data suggest the combination of lofexidine and THC warrant further testing as a potential treatment for marijuana dependence. Haney, M., Hart, C.L., Vosburg, S.K., Comer, S.D., Reed, S.C., and Foltin, R.W. Effects of THC and Lofexidine in a Human Laboratory Model of Marijuana Withdrawal and Relapse. Psychopharmacology (Berl), 197, pp. 157-168, 2008.

The Acetylcholinesterase Inhibitor Rivastigmine Does Not Alter Total Choices for Methamphetamine, but May Reduce Positive Subjective Effects, in a Laboratory Model of Intravenous Self-administration in Human Volunteers

A human laboratory model of intravenous methamphetamine self-administration may facilitate study of putative treatments for methamphetamine addiction. The investigators conducted a double-blind, placebo-controlled, between groups investigation of the acetylcholinesterase (AChE) inhibitor rivastigmine in non-treatment-seeking volunteers who met

criteria for methamphetamine abuse or dependence. Safety and subjective effects data derived from days 1-10 of this protocol are described in a separate publication. In this report, the investigators describe self-administration outcomes in participants randomized to treatment with rivastigmine (0 mg, N=7; 1.5 mg, N=6; 3 mg, N=9); data that were collected on days 11-15 of the inpatient protocol. On day 11, participants sampled two infusions of methamphetamine (0 and 30 mg, IV). On days 12-15, participants made ten choices each day to receive an infusion of either methamphetamine (3 mg, IV) or saline or a monetary alternative ($0.05-$16). The study design allowed for evaluation of differences in behavior on days in which infusions were performed by the physician (experimenter-administered) versus by the participant using a PCA pump (self-administered), and when monetary alternatives were presented in either ascending or descending sequence. The data show that rivastigmine (1.5 and 3 mg), as compared to placebo, did not significantly alter total choices for methamphetamine ($p=0.150$). Importantly, the number of infusion choices was greater when methamphetamine was available then when saline was available ($p<0.0001$), and the number of money choices was greater when saline was available then when methamphetamine was available ($p<0.0001$). The total number of choices for methamphetamine was not altered as a function of a participant's preferred route of methamphetamine use ($p=0.57$), and did not differ significantly whether they were experimenter-administered or self-administered ($p=0.30$). In addition, total choices for methamphetamine were similar when money was available in an ascending versus descending sequence ($p=0.49$). The participants' years of methamphetamine use, recent use of methamphetamine (in the past 30 days), or baseline craving (indexed here as "Desire") on the day of the self-administration task were not predictive of number of choices for methamphetamine. In a subset of participants (N=8) for which data was available, individual dose of methamphetamine (3x3 mg, IV) produced significant increases in positive subjective effects, and a preliminary analysis revealed that 3 mg rivastigmine was associated with reductions in these responses, as compared to placebo. In summary, the current report indicates that there were no effects of rivastigmine on total choices for methamphetamine, that there were low levels of methamphetamine self-administration but these were 8 times greater than saline, and that choice behavior was insensitive to alternative reinforcers. In addition, the investigators showed that rivastigmine may reduce the positive subjective effects produced by methamphetamine during self-administration. De La, G.R., Mahoney, J.J., III, Culbertson, C., Shoptaw, S., and Newton, T.F. The Acetylcholinesterase Inhibitor Rivastigmine Does Not Alter Total Choices for Methamphetamine, but May Reduce Positive Subjective Effects, in a Laboratory Model of Intravenous Self-administration in Human volunteers. Pharmacol. Biochem. Behav., 89, pp. 200-208, 2008.

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

Acetylcholine (ACh) has been implicated in the reinforcing and locomotor-activating effects produced by methamphetamine (Meth). Of interest, recent data suggest that acetylcholinesterase (AChE) inhibitors attenuate Meth-seeking behaviour in rats. The investigators conducted this study in order to determine the safety (adverse events, mood changes, cardiovascular effects) and preliminary efficacy (subjective effects) of the AChE inhibitor rivastigmine (Riv) when tested in combination with Meth. Twenty-three non-treatment-seeking Meth-dependent participants resided in an in-patient unit at UCLA for 2 wk, and completed this double-blind, between-subjects, placebo-controlled study. Prior to randomization to study drug, infusions of saline (day 4, 0 mg i.v.) and Meth (day 5, 30 mg i.v.) were given to all participants at 11:30 hours in single-blinded fashion. On day 7 and continuing to day 11, participants were

randomized to receive oral placebo (0 mg, n=7) or Riv (1.5 mg, n=7; 3 mg, n=9). On day 11, the subjects received saline and Meth infusions again (randomized to either 11:30 or 14:30 hours), under double-blind conditions. The data analyses compared across-study measures of adverse events and mood, and a post-randomization analysis of cardiovascular and subjective effects (on day 11). The data reveal that rivastigmine was not associated with increased adverse events or alterations in mood. As expected, acute Meth exposure (30 mg i.v.) increased heart rate and blood pressure, as well as several positive subjective effects, Addiction Research Center Inventory (ARCI) ratings, and reported monetary value ($p<0.05$). The data indicated that Riv, at 3 mg, significantly attenuated Meth-induced increases in diastolic blood pressure, and self-reports of 'anxious' and 'desire' ($p<0.05$). Taken together, the findings in the current report suggest that pharmacological manipulations that enhance brain ACh warrant continued investigation as potential treatments for Meth addiction. De La, G.R., Shoptaw, S., and Newton, T.F. Evaluation of the Cardiovascular and Subjective Effects of Rivastigmine in Combination with Methamphetamine in Methamphetamine-Dependent Human Volunteers. Int. J. Neuropsychopharmacol., pp. 1-13, 2008.

Residual Effects of Intranasal Methamphetamine on Sleep, Mood, and Performance

Although intranasal methamphetamine abuse has increased, there are no published data investigating the residual effects of the drug under controlled conditions. Thus, the current study examined the residual effects of single-dose intranasal methamphetamine administration on a broad range of behavioral and physiological measures. Non-treatment seeking methamphetamine abusers (n=11) completed this two-week, in patient, within-participant, double-blind study. The study consisted of four two-day blocks of sessions; each block was separated by at least 48h. At approximately 10:00h, on the first day of each block, participants received one of four intranasal methamphetamine doses (0, 12, 25, 50mg/70kg). Lights were turned out at 23:00h that evening and sleep measures were assessed. On the morning of the second day of each block, methamphetamine plasma levels, cardiovascular measures, mood, subjective reports of the previous evening's sleep, and psychomotor performance were assessed to determine residual drug effects. The larger methamphetamine doses (25 and 50mg) markedly disrupted subjective measures of that night's sleep and some indices of next-day mood, but only the largest dose (50mg) decreased objective measures of that night's sleep and increased next-day physiological measures. Methamphetamine did not produce any negative residual effects on early next-day performance. Future studies should assess methamphetamine-related residual effects following repeated doses administered over consecutive days. Perez, A.Y., Kirkpatrick, M.G., Gunderson, E.W., Marrone, G., Silver, R., Foltin, R.W. et al. Residual Effects of Intranasal Methamphetamine on Sleep, Mood, and Performance. Drug Alcohol Depend., 94, pp. 258-262, 2008.

Riluzole and D-amphetamine Interactions in Humans

In preclinical studies, medications which decrease glutamate release have been shown to block some of the effects of psychostimulants. One such medication is riluzole, marketed for the treatment of Amyotrophic Lateral Sclerosis (ALS). The goal of this study was to determine riluzole's effects on acute physiological and subjective responses to d-amphetamine in healthy volunteers. Seven male and 5 female subjects participated in an outpatient double-blind, placebo-controlled, crossover study. Across 4 sessions, subjects were randomly assigned to a sequence of 4 oral treatments: placebo, 20 mg D-amphetamine alone, 100 mg riluzole alone, or d-amphetamine plus riluzole. Outcome measures included heart rate, blood pressure, plasma cortisol, performance on the Sustained Attention to Response Test (SART), and subjective measures. D-

amphetamine increased heart rate, blood pressure and plasma cortisol levels while inducing psychostimulant-type subjective effects. On the SART, d-amphetamine enhanced the speed of correct responses but also significantly increased the number of errors of commission. Riluzole at 100 mg did not block the typical subjective and physiological responses to 20 mg D-amphetamine. Riluzole alone induced amphetamine-like subjective responses. On the SART test, riluzole increased the number errors of commission, but unlike d-amphetamine, did not speed reaction time. The mechanism accounting for these findings is unclear, but may involve processes other than decreased glutamate release by riluzole. The effects of glutamate medications on psychostimulant responses need to be further examined. Sofuoglu, M., Waters, A.J., Mooney, M., and Kosten, T. Riluzole and D-amphetamine Interactions in Humans. Prog. Neuropsychopharmacol. Biol. Psychiatry, 32, pp. 16-22, 2008.

Profile of Lifetime Methamphetamine Use Among Homeless Adults in Los Angeles

Although the dramatic rise of methamphetamine use in the general population has been well-documented, little is known about methamphetamine use in the homeless population. This study examines self-reported methamphetamine use and its correlates among a sample of 664 urban homeless adults in Los Angeles. Over one-quarter of the overall sample, and 60% of whites, disclosed lifetime methamphetamine use. Less than 10% of African-Americans reported ever using methamphetamine. Approximately one-tenth of respondents reported current methamphetamine use; almost 90% of current users shared straws to snort methamphetamine and half used it daily. Logistic regression analysis in younger (18-39) and older (40+) respondents revealed that white ethnicity, polydrug use and binge drinking were independently associated with lifetime methamphetamine use, regardless of age. Injection drug use (IDU) was also an important correlate of methamphetamine use for older African-Americans. IDU was not important for the younger group. Findings suggest that there is need for greater surveillance of methamphetamine use among homeless whites and Hispanics, and methamphetamine-use prevention and reduction targeted to younger, polydrug-using, alcohol-binging homeless adults. Nyamathi, A., Dixon, E.L., Shoptaw, S., Marfisee, M., Gelberg, L., Williams, S. et al. Profile of Lifetime Methamphetamine Use Among Homeless Adults in Los Angeles. Drug Alcohol Depend., 92, pp. 277-281, 2008.

Substance Abuse and Schizophrenia: Pharmacotherapeutic Intervention

Substance use disorder is common in patients with schizophrenia and dramatically worsens their outcome. The typical antipsychotic medications, introduced more than 50 years ago, are effective for the treatment of psychosis but may have only limited efficacy in patients with these co-occurring disorders because patients continue to use substances while taking them. In preliminary studies, however, several of the atypical antipsychotic medications have shown promise for reducing alcohol and drug use in patients with schizophrenia. A neurobiological formulation is discussed, suggesting that the use of substances in patients with schizophrenia may be based on a dysfunction within the dopamine-mediated brain reward circuitry and that clozapine, in particular, may potentially ameliorate this dysfunction and lessen the desire for substance use. Medications for the treatment of alcohol use disorders, such as disulfiram, naltrexone, and acamprosate, as well as other adjunctive medications, may also be useful. Further studies are required to establish a solid evidence base of best practices for the use of medications in these patients. Green, A.I., Noordsy, D.L., Brunette, M.F., and O'Keefe, C. Substance Abuse and Schizophrenia: Pharmacotherapeutic Intervention. J. Subst. Abuse Treat., 34, pp. 61-71, 2008.

Controversies in Translational Research: Drug Self-Administration

Laboratory animal and human models of drug self-administration are used to evaluate potential pharmacotherapies for drug abuse, yet the utility of these models in predicting clinically useful medications is variable. The objective of this study was to track how antagonist, agonist, and partial agonist medication approaches influence heroin and cocaine self-administration by rodents, non-human primates, and humans and to compare these results to clinical outcomes. Across species, heroin self-administration was decreased by all three medication approaches, paralleling their demonstrated clinical utility. The heroin data emphasize the importance of assessing a medication's abuse liability preclinically to predict medication abuse and compliance and of considering subject characteristics (e.g., opioid dependence) when interpreting medication effects. For cocaine, the effects of ecopipam, modafinil, and aripiprazole were consistent in the laboratory and clinic, provided that the medications were administered repeatedly before self-administration sessions. Modafinil attenuated cocaine's reinforcing effects in the human laboratory and improved treatment outcome, while ecopipam and aripiprazole increased the reinforcing effects of cocaine and do not appear promising in the clinic. The self-administration model has reliably identified medications to treat opioid dependence, and the recent data with modafinil suggest that the human laboratory model also identifies medications to treat cocaine dependence. There have been numerous false positives when subjective effects are the primary outcome measure, but not when self-administration is the outcome. Factors relevant to the predictive validity of self-administration procedures include medication maintenance and the concurrent assessment of a range of behaviors to determine abuse liability and the specificity of effect. Haney, M. and Spealman, R. Controversies in Translational Research: Drug Self-Administration. Psychopharmacology (Berl). Epub ahead of print, 2008.

ADHD, Substance Use Disorders, and Psychostimulant Treatment: Current Literature and Treatment Guidelines

This review explores the relationship between ADHD and substance use disorder (SUD), factors that determine the abuse potential of psychostimulants, and strategies for identifying and treating at-risk ADHD patients. This study uses a Medline review of literature. Results show that psychostimulants, such as methylphenidate and amphetamines, are effective first-line pharmacotherapy for ADHD and when used appropriately in individuals with ADHD do not appear to be frequently abused by patients. Diversion and misuse of prescription stimulants are growing concerns, especially among young adults and college students. Short-acting psychostimulant formulations may have higher potential for abuse, misuse, and diversion, but more data are needed to substantiate this observation. Nonstimulant treatments for ADHD may be considered for patients at particularly high risk for substance use, misuse, or diversion of stimulants. The authors conclude that in treating patients with ADHD and comorbid substance use, psychostimulants may be a useful pharmacologic alternative. However, the risks of such treatment with high-risk populations must be considered alongside potential benefits. Kollins, S.H., J. Atten. Disord. Jan 11, Epublication ahead of print, 2008.

Cigarette Reduction: An Intervention for Adolescent Smokers

This observational study examined whether adolescents who were not interested in quitting could reduce cigarette smoking and if cigarette reduction led to a corresponding and significant reduction in biomarkers of exposure. The study design was a randomized, open-label trial of nicotine patch and nicotine gum with an added placebo control. Participants (n=103) attended 4 treatment visits over 4 weeks and follow-up visits at 3- and 6-months. Participants were

told to reduce their smoking by 25% of baseline smoking during the 1st week and by 50% of baseline smoking during the subsequent 3 weeks. Of consented participants, 91.3% (n=94/103) completed the study until the end-of-treatment, 85.1% (n=80/94) completed the 3-month follow-up visit and 71.3% (n=67/94) completed the 6-month follow-up visit. Participants had a very high prevalence of co-morbidity. With regard to the percentage of participants who achieved a 50% reduction of baseline smoking, there were no significant differences among treatment groups (p=.89). At the end-of-treatment, 49.4% of participants (n=41) had reduced smoking by at least 50%. Additionally, there was no significant group, visit or interaction effect of a biomarker measure for carcinogen exposure (p>.05). The results suggest that reduction may be a potential aid to engage adolescents who are unable or unwilling to quit, but should not be an end goal. The effect of treatment methods on outcome measures did not differ significantly. Hanson, K., Zylla, E., Allen, S., Li, Z., and Hatsukami, D.K. Cigarette Reduction: An Intervention for Adolescent Smokers. Drug Alcohol Depend., 95, pp. 164-168, 2008.

Smokeless Tobacco Reduction: Preliminary Study of Tobacco-Free Snuff Versus No Snuff

This preliminary study examined the effects of tobacco-free snuff (intervention, n = 52) compared with no snuff (control, n = 54) for reducing tobacco use among smokeless tobacco (ST) users not interested in quitting. Both groups received behavioral instructions, and intervention subjects received tobacco-free snuff for 8 weeks. Participants were required to reduce their intake by 50% during the first 4 weeks and by 75% during the subsequent 4 weeks. Follow-up occurred at 12 weeks. Significant reductions were observed from baseline to week 8 (end of treatment) for both treatment groups in the amount of ST use (tins/week and dips/day, p<.001); mean urinary cotinine (p<.001); and mean urinary total NNAL, a carcinogen biomarker (p<.001). At week 8 the intervention resulted in a lower mean total NNAL (p = .048). Compared with the control condition, the intervention resulted in a higher percentage of subjects achieving at least a 50% reduction in cotinine (p = .046) and total NNAL (p = .002) at the end of treatment, more quit attempts (p = .030), and a longer mean duration of abstinence (p = .013) through follow-up. An ST reduction intervention incorporating tobacco-free snuff could potentially reduce risk for ST-related disease beyond that achieved with no snuff by increasing the number of patients who achieve significant reductions in carcinogen exposure and, more important, by facilitating tobacco abstinence by increasing quit attempts and abstinence duration. Hatsukami, D.K., Ebbert, J.O., Edmonds, A., Li, C., Lin, H., Le, C. et al. Smokeless Tobacco Reduction: Preliminary Study of Tobacco-free Snuff Versus No Snuff. Nicotine. Tob. Res., 10, pp. 77-85, 2008.

Smoking Reduction Fails to Improve Clinical and Biological Markers of Cardiac Disease: A Randomized Controlled Trial

Cigarette reduction has been proposed as a treatment goal for smokers who are not interested in stopping completely. This randomized controlled trial was designed to determine the effect of a smoking reduction intervention on smoking behavior, symptoms of heart disease, and biomarkers of tobacco exposure. It included 152 patients with heart disease who did not intend to stop smoking in the next 30 days. Participants were randomly assigned to smoking reduction (SR) or usual care (UC). SR subjects received counseling and nicotine replacement therapy to encourage >/=50% reduction in cigarettes per day (CPD). They were followed at 1, 3, 6, 12 and 18 months to assess smoking, heart disease symptoms, quality of life and nicotine, cotinine, carbon monoxide (CO), white blood cell (WBC) count, fibrinogen, hs-C-reactive protein (hs-CRP), F(2)-isoprostane, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL), and 1-hydroxypyrene (1-HOP). At 6 months SR

participants reduced by 10.9 CPD, compared with 7.4 CPD in UC (difference NS). At 18 months, 9/78 SR vs. 9/74 UC participants quit smoking. There were no significant differences between treatment groups in angina, quality of life or adverse events, nicotine, cotinine, CO, WBC count, fibrinogen, hs-CRP, F(2)-isoprostane, total NNAL or 1-HOP levels at any time point. To determine if smoking reduction, regardless of treatment condition, was associated with improved outcomes, the investigators compared all subjects at 6 months to baseline (mean reduction in CPD from 27.4 to 18.1, p<.01). There were no significant changes in outcome variables except CO, which decreased by 5.5 ppm (p<.01). There were also no significant improvements considering only subjects who reduced by >/=50%, or those who had no history of reduction prior to enrollment in the study. The SR intervention did not significantly reduce CPD or toxin exposure, or improve smoking cessation or clinical outcomes compared to UC. These results emphasize the importance of abstinence for smokers with heart disease to minimize health risks from tobacco. Joseph, A.M., Hecht, S.S., Murphy, S.E., Lando, H., Carmella, S.G., Gross, M. et al. Smoking Reduction Fails to Improve Clinical and Biological Markers of Cardiac Disease: A Randomized Controlled Trial. Nicotine. Tob. Res., 10, pp. 471-481, 2008.

Therapeutic Drug Monitoring of Nortriptyline in Smoking Cessation: A Multistudy Analysis

Multiple, controlled clinical trials support the efficacy of nortriptyline as a smoking cessation agent. Although therapeutic plasma nortriptyline concentrations (PNCs) are known for the treatment of depression, little is known about PNCs in smoking cessation treatment. PNCs from three randomized, placebo-controlled smoking cessation trials (N=244) were analyzed both separately and pooled. PNCs normalized for dose and weight were associated with cigarettes per day and race, but not with sex or age. Greater smoking was associated with decreased normalized PNCs. In addition, both Asian and black populations had significantly higher normalized PNCs than the white populations. Weak and inconsistent associations between PNCs and self-reported side effects were observed. PNCs were linearly related to end of treatment and long-term biochemically verified smoking abstinence. Maximum therapeutic effects were observed over a range of plasma concentrations somewhat lower than those found effective for the treatment of depression. Mooney, M.E., Reus, V.I., Gorecki, J., Hall, S.M., Humfleet, G.L., Munoz, R.F. et al. Therapeutic Drug Monitoring of Nortriptyline in Smoking Cessation: A Multistudy Analysis. Clin. Pharmacol. Ther., 83, pp. 436-442, 2008.

Uses of Coercion in Addiction Treatment: Clinical Aspects

Coerced or involuntary treatment comprises an integral, often positive component of treatment for addictive disorders. By the same token, coercion in health care raises numerous ethical, clinical, legal, political, cultural, and philosophical issues. In order to apply coerced care effectively, health care professionals should appreciate the indications, methods, advantages, and liabilities associated with this important clinical modality. An expert panel, consisting of the Addiction Committee of the Group for the Advancement of Psychiatry, listed the issues to be considered by clinicians in considering coerced treatment. In undertaking this task, they searched the literature using Pubmed from 1985 to 2005 using the following search terms: addiction, alcohol, coercion, compulsory, involuntary, substance, and treatment. In addition, they utilized relevant literature from published reports. In the treatment of addictions, coercive techniques can be effective and may be warranted in some circumstances. Various dimensions of coercive treatment are reviewed, including interventions to initiate treatment; contingency contracting and urine testing in the context of psychotherapy; and pharmacological methods of coercion such as disulfiram, naltrexone, and the

use of a cocaine vaccine. The philosophical, historical, and societal aspects of coerced treatment are considered. Sullivan, M.A., Birkmayer, F., Boyarsky, B.K., Frances, R.J., Fromson, J.A., Galanter, M. et al. Uses of Coercion in Addiction Treatment: Clinical Aspects. Am. J. Addict., 17, pp. 36-47, 2008.

Imputation-Based Strategies for Clinical Trial Longitudinal Data with Nonignorable Missing Values

Biomedical research is plagued with problems of missing data, especially in clinical trials of medical and behavioral therapies adopting longitudinal design. After a literature review on modeling incomplete longitudinal data based on full-likelihood functions, this paper proposes a set of imputation-based strategies for implementing selection, pattern-mixture, and shared-parameter models for handling intermittent missing values and dropouts that are potentially nonignorable according to various criteria. Within the framework of multiple partial imputation, intermittent missing values are first imputed several times; then, each partially imputed data set is analyzed to deal with dropouts with or without further imputation. Depending on the choice of imputation model or measurement model, there exist various strategies that can be jointly applied to the same set of data to study the effect of treatment or intervention from multi-faceted perspectives. For illustration, the strategies were applied to a data set with continuous repeated measures from a smoking cessation clinical trial.. Yang, X., Li, J., and Shoptaw, S. Imputation-Based Strategies for Clinical Trial Longitudinal Data with Nonignorable Missing Values. Stat. Med., Epub ahead of print, 2008.

Role of CYP2B6 in Stereoselective Human Methadone Metabolism

Metabolism and clearance of racemic methadone are stereoselective and highly variable, yet the mechanism remains largely unknown. CYP3A4 was assumed responsible for methadone clearance in vivo. Nevertheless, recent clinical data do not support a primary role for CYP3A4 and suggest that CYP2B6 may mediate methadone clearance. A crossover clinical investigation (control, CYP2B6 and CYP3A4 induction by rifampin, CYP3A inhibition by troleandomycin and grapefruit juice) evaluated stereoselective methadone disposition. Rifampin diminished both R- and S-methadone plasma concentrations, but troleandomycin and grapefruit juice altered neither R- nor S-methadone concentrations. Plasma R/S-methadone ratios were increased by rifampin but unchanged by CYP3A inhibition. These results suggest a significant role for CYP2B6, but not CYP3A, in stereoselective human methadone metabolism and disposition. Totah, R.A., Sheffels, P., Roberts, T., Whittington, D., Thummel, K., and Kharasch, E.D. Anesthesiology. 108(3), pp. 351-352, 2008.

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

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

Long-Term Cocaine Use and Antiretroviral Therapy Are Associated with Silent Coronary Artery Disease in African Americans with HIV Infection Who Have No Cardiovascular Symptoms

Long-term use of cocaine (>/=15 years) and antiretroviral therapy (ART) have been implicated in cardiovascular complications. Nevertheless, the individual and combined effects of ART and cocaine use on silent coronary artery disease have not been fully investigated. Computed tomography coronary angiography was performed for 165 human immunodeficiency virus (HIV)-infected African American study participants aged 25-54 years in Baltimore, Maryland, with contrast-enhanced 64-slice multidetector computed tomography imaging. Significant (>/=50%) coronary stenosis was detected in 24 (15%) of 165 participants. The prevalence of significant stenosis among those who had used cocaine for >/=15 years and had received ART for >/=6 months was 42%. Exact logistic regression analysis revealed that long-term cocaine use (adjusted odds ratio, 7.75; 95% confidence interval, 2.26-31.2) and exposure to ART for >/=6 months (adjusted odds ratio, 4.35; 95% confidence interval, 1.30-16.4) were independently associated with the presence of significant coronary stenosis. In addition, after controlling for confounding factors, both stavudine use for >/=6 months or combivir use for >/=6 months were independently associated with the presence of significant coronary stenosis. The authors conclude that long-term exposure to ART may be associated with silent coronary artery disease; however, the magnitude of increased risk associated with ART was much lower than the risk associated with cocaine use or traditional risk factors. Cardiovascular monitoring and aggressive modification of cardiovascular risk factors are essential for reducing the risk of coronary artery disease in HIV-infected individuals. Extensive efforts should also be made to develop effective cocaine use cessation programs for HIV-infected cocaine users. Lai, S., Fishman, E.K., Lai, H., Moore, R., Cofrancesco, Jr J., Pannu, H., Tong, W., Du, J., Bartlett, J. Clin. Infect. Dis. January 14, 2008 Epub ahead of print.

Impact of Drug Abuse Treatment Modalities on Adherence to ART/HAART Among a Cohort of HIV Seropositive Women

Methadone maintenance is associated with improved adherence to antiretroviral therapies among HIV-positive illicit drug users; however, little information exists on whether adherence is associated with different drug abuse treatment modalities. Using longitudinal data from the Women's Interagency HIV Study, the authors evaluated the relationship between drug abuse treatment modality and adherence to antiretroviral therapies. In prospective analyses, individuals who reported accessing any drug abuse

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treatment program were more likely to report adherence to antiretroviral regimens > or = 95% of the time (AOR = 1.39, 95% CI =1.01-1.92). Involvement in either a medication-based or medication-free program was similarly associated with improved adherence. Drug abuse treatment programs, irrespective of modality, are associated with improved adherence to antiretroviral therapies among drug users. Concerted efforts to enroll individuals with drug use histories in treatment programs are warranted to improve HIV disease outcomes. Kapadia, F., Vlahov, D., Wu, Y., Cohen, M.H., Greenblatt, R.M., Howard, A.A., Cook, J.A., Goparaju, L., Golub, E., Richardson, J., and Wilson, T.E. Am. J. Drug Alcohol Abuse. 34(2), pp. 161-170, 2008.

Attribution of Menopause Symptoms in Human Immunodeficiency Virus-Infected or At-Risk Drug-Using Women

The objective of this study was to examine the relationship of human immunodeficiency virus (HIV) and attribution of menopausal symptoms. Peri- and postmenopausal women participating in a prospective study of HIV-infected and at-risk midlife women (the Ms. Study) were interviewed to determine whether they experienced hot flashes and/or vaginal dryness and to what they attributed these symptoms. Of 278 women, 70% were perimenopausal; 54% were HIV-infected; and 52% had used crack, cocaine, heroin, and/or methadone within the past 5 years. Hot flashes were reported by 189 women and vaginal dryness was reported by 101 women. Overall, 69.8% attributed hot flashes to menopause and 28.7% attributed vaginal dryness to menopause. In bivariate analyses, age 45 years and older was associated with attributing hot flashes and vaginal dryness to menopause, and postmenopausal status and at least 12 years of education were associated with attributing vaginal dryness to menopause, but HIV status was not associated with attribution to menopause. In multivariate analysis, significant interactions between age and menopause status were found for both attribution of hot flashes (P = 0.019) and vaginal dryness (P = 0.029). Among perimenopausal women, older age was independently associated with attribution to menopause for hot flashes (adjusted odds ratio = 1.2, 95% CI: 1.1-1.4, P = 0.001) and vaginal dryness (adjusted odds ratio = 1.3, 95% CI: 1.1-1.6, P = 0.011). None of the tested factors were independently associated with attribution to menopause among postmenopausal women. The authors conclude that tailored health education programs may be beneficial in increasing the knowledge about menopause among HIV-infected and drug-using women, particularly those who are perimenopausal. Johnson, T.M., Cohen, H.W., Howard, A.A., Santoro, N., Floris-Moore, M., Arnsten, J.H., Hartel, D.M., and Schoenbaum, E.E. Menopause, January 9, 2008 Epub ahead of print.

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

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

hepatitis B and hepatitis C co-infections, cigarette smoking and depression were not associated with BMI in the final model. In conclusion, BMI was lower in drug users than non-drug users, and was lowest in cocaine users. BMI was also directly associated with CD4 count and inversely related to age more than 55 years old. HIV-infected cocaine users may be at higher risk of developing malnutrition, suggesting the need for anticipatory nutritional support. Quach, L.A., Wanke, C.A., Schmid, C.H., Gorbach, S.L., Mkaya Mwamburi, D., Mayer, K.H., Spiegelman, D., and Tang, A.M. Drug Alcohol Depend. 95(1-2), pp. 30-36. Epub February 19, 2008.

The Challenge of Hepatitis C in the HIV-Infected Person

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

Limited Uptake of Hepatitis C Treatment Among Injection Drug Users

The authors characterized hepatitis C virus (HCV) treatment knowledge, experience and barriers in a cohort of community-based injection drug users (IDUs) in Baltimore, MD. In 2005, a questionnaire on HCV treatment knowledge, experience and barriers was administered to HCV-infected IDUs. Self-reported treatment was confirmed from medical records. Of 597 participants, 71% were male, 95% African-American, 31% HIV co-infected and 94% were infected with HCV genotype 1; 70% were aware that treatment was available, but only 22% understood that HCV could be cured. Of 418 who had heard of treatment, 86 (21%) reported an evaluation by a provider that included a discussion of treatment of whom 30 refused treatment, 20 deferred and 36 reported initiating treatment (6% overall). The most common reasons for refusal were related to treatment-related perceptions and a low perceived need of treatment. Compared to those who had discussed treatment with their provider, those who had not were more likely to be injecting drugs, less likely to have health insurance, and less knowledgeable about treatment. Low HCV treatment effectiveness was observed in this IDU population. Comprehensive integrated care strategies that incorporate education, case-management and peer support are needed to improve care and treatment of HCV-infected IDUs. Mehta, S.H., Genberg, B.L., Astemborski, J., Kavasery, R., Kirk, G.D., Vlahov, D., Strathdee, S.A., and Thomas, D.L. J. Community Health. 33(3), pp. 126-133, 2008.

Rapid Fibrosis Progression Among HIV/Hepatitis C Virus-Co-Infected Adults

The objectives of this study were to define the incidence of fibrosis progression among hepatitis C virus (HCV)/HIV-co-infected adults, to assess whether HCV or HIV treatment alters the risk of progression, and to determine the utility of liver biopsy to predict future disease. This prospective cohort evaluated 184 HIV/HCV-co-infected individuals who had at least two liver biopsies (median interval 2.9 years). Biopsies were scored according to the Ishak modified histological activity index scoring system by a single pathologist blind to biopsy sequence. Significant fibrosis progression was defined as an increase of at least

two Ishak fibrosis units between the first and second liver biopsy. Logistic regression analysis was used to assess determinants of fibrosis progression. A total of 174 non-cirrhotic patients were eligible; the majority were African-American men undergoing HIV treatment. On initial biopsy, no or minimal fibrosis was identified in 136 patients (77%). Significant fibrosis progression occurred in 41 patients (24%). Measures of HIV disease and its treatment before and after initial biopsy were not significantly different in progressors and non-progressors. Fibrosis progression was not associated with HCV treatment, which was received by 37 patients (21%) but only three sustained HCV-RNA suppression. In adjusted analysis, only an elevated serum aspartate aminotransferase level between biopsies was associated with progression (odd ratio 3.4, 95% confidence interval 1.4-7.9). The authors conclude that over a 3-year interval, significant fibrosis progression can occur in co-infected individuals even if minimal disease was detected on initial biopsy. In this context, factors other than treatment for HIV or HCV modify the risk of fibrosis progression. Sulkowski, M.S., Mehta, S.H., Torbenson, M.S., Higgins, Y., Brinkley, S.C., de Oca, R.M., Moore, R.D., Afdhal, N.H., and Thomas, D.L. AIDS. 21(16), pp. 2209-2216, 2007.

Co-Morbid Medical and Psychiatric Illness and Substance Abuse in HCV-Infected and Uninfected Veterans

Comorbidities may affect the decision to treat chronic hepatitis C virus (HCV) infection. The authors undertook this study to determine the prevalence of these conditions in the HCV-infected persons compared with HCV-uninfected controls. Demographic and comorbidity data were retrieved for HCV-infected and -uninfected subjects from the VA National Patient Care Database using ICD-9 codes. Logistic regression was used to determine the odds of comorbid conditions in the HCV-infected subjects. HCV-uninfected controls were identified matched on age, race/ethnicity and sex. The authors identified 126,926 HCV-infected subjects and 126,926 controls. The HCV-infected subjects had a higher prevalence of diabetes, anemia, hypertension, chronic obstructive pulmonary disease (COPD)/asthma, cirrhosis, hepatitis B and cancer, but had a lower prevalence of coronary artery disease and stroke. The prevalence of all psychiatric comorbidities and substance abuse was higher in the HCV-infected subjects. In the HCV-infected persons, the odds of being diagnosed with congestive heart failure, diabetes, anemia, hypertension, COPD/asthma, cirrhosis, hepatitis B and cancer were higher, but lower for coronary artery disease and stroke. After adjusting for alcohol and drug abuse and dependence, the odds of psychiatric illness were not higher in the HCV-infected persons. The prevalence and patterns of comorbidities in HCV-infected veterans are different from those in HCV-uninfected controls. The association between HCV and psychiatric diagnoses is at least partly attributable to alcohol and drug abuse and dependence. These factors should be taken into account when evaluating patients for treatment and designing new intervention strategies. Butt, A.A., Khan, U.A., McGinnis, K.A., Skanderson, M., and Kent Kwoh, C. J. Viral Hepat. 14(12), pp. 890-896, 2007.

Impact of Hepatitis C Virus Infection and other Comorbidities on Survival in Patients on Dialysis

The impact of hepatitis C virus (HCV) and other comorbid conditions upon survival is not well quantified in patients on dialysis. The authors identified HCV-infected and uninfected persons in the USRDS using claims data in 1997-1998 and followed until September 22, 2002 or death. They used Gray's time-varying coefficients model to examine factors associated with survival. Subjects with a renal transplant were excluded. A total of 5737 HCV-infected and 11 228 HCV-uninfected persons were identified. HCV-infected subjects were younger (mean age 57.8 vs 65.3 years), more likely to be male (57.6%vs 49.6%) and black (54.0%vs 36.4%). They were more likely to have a diagnosis of drug

(16.5%vs 4.6%) and alcohol use (14.0%vs 3.1%), and to be human immunodeficiency virus (HIV) co-infected (7.4%vs 1.8%) (all comparisons, P < 0.0005). In an adjusted Gray's time-varying coefficient model, HCV was associated with an increased risk of mortality (P < 0.0005). The hazards were highest at the time of HCV diagnosis and decreased to a stable level 2 years after diagnosis. Other factors associated with increased risk of mortality were (P < 0.0005 unless stated) HIV coinfection; diagnosis of drug use (P = 0.001); coronary artery disease (P = 0.006); stroke; diabetes as the primary cause for renal failure; peripheral vascular disease; depression and presence of anemia. HCV was associated with higher risk of death in patients on dialysis, even after adjusting for concurrent comorbidities. The risk was highest at the time of HCV diagnosis and stabilized over time. Clinical trials of HCV screening and treatment to reduce mortality in this population are warranted. Butt, A.A., Skanderson, M., McGinnis, K.A., Ahuja, T., Bryce, C.L., Barnato, A.E., and Chang, C.C. J. Viral Hepat. 14(10), pp. 688-696, 2007.

Biochemical and Virologic Parameters in Patients Co-Infected with Hepatitis C and HIV Versus Patients with Hepatitis C Mono-Infection

Previous studies of patients with hepatitis C virus (HCV) infection looking at the effect of human immunodeficiency virus (HIV) co-infection on biochemical parameters and HCV RNA level have shown conflicting results. Accurate characterization of the effect of HIV is important for evaluation and treatment of HCV in co-infected persons. The authors studied 315 HCV mono-infected and 75 HCV-HIV co-infected subjects to determine the effect of HIV on biochemical parameters and HCV RNA and to determine the predictors of elevated serum alanine aminotransferase (ALT) levels and HCV RNA levels. Results showed that the co-infected subjects were more likely to be African-American (55% vs 26%, P < 0.0005), have used injection drugs (68% vs 60%, P = 0.02), have detectable HCV RNA (84% vs 70.5%, P = 0.018), have HCV RNA levels >6 log10 IU/mL (60% vs 38%, P = 0.001), and have lower mean serum ALT levels (50.4 IU/mL vs 73.7 IU/mL, P = 0.006). In multivariable analyses, the following factors predicted an ALT level >50 IU/mL: log10 HCV RNA (OR, 1.15; 95% CI, 1.00 to 1.32); HIV co-infection (OR, 0.48; 95% CI, 0.25 to 0.89); and having ever been treated for HCV (OR, 1.92; 95% CI, 1.16 to 3.18). The only significant predictor of HCV RNA level >6 log10 IU/mL was HIV co-infection (OR, 2.75; 95% CI, 1.46 to 5.15). Significant predictors of having a detectable HCV RNA level were female sex (OR, 3.81; 95% CI, 1.18 to 12.25); HIV co-infection (2.45; 95% CI, 1.14 to 5.26); and ever being treated for HCV (OR, 1.96; 95% CI, 1.10 to 3.48). The authors conclude that HCV-HIV co-infected persons have higher HCV RNA levels but lower serum ALT levels than HCV mono-infected patients. Criteria for performing liver biopsy and treating HCV infection in co-infected patients may need to be revisited. Butt, A.A., Tsevat, J., Ahmad, J., Shakil, A.O., Mrus, J.M. Am. J. Med. Sci. 333(5), pp. 271-275, 2007.

Molecular and Bioinformatic Evidence of Hepatitis C Virus Evolution in Brain

Neurocognitive deficits in patients with hepatitis C virus (HCV) infection prompted a search for HCV in brain. HCV was present in the brains of 7 (54%) of 13 patients with viremia, as determined by 5' UTR and E1 (envelope 1) gene analysis. Brain HCV RNA consensus sequences differed from those in plasma and liver in 4 (57%) of 7 patients. The quality of HCV RNA from postmortem brain and liver was assessed and demonstrated to be suitable for sequence analysis. Quasispecies analysis revealed that several mutations present in clones from >1 brain region were absent in clones from liver and plasma. Brain-specific mutations defined several families of related sequences. The patterns of brain-specific mutations in these families were consistent with the

evolution of HCV RNA from a common ancestor. Single-nucleotide-polymorphism analysis confirmed that a prominent brain-specific mutation constituted approximately 10% of HCV RNA in cerebellum and medulla but that this mutation was undetectable in the liver and plasma of the same patient. This study introduces novel methods for assessing RNA from postmortem samples. It increases the reported cases of HCV in the brain, provides the first E1 sequences from the brain, and contributes to the growing evidence that HCV replicates and evolves within the brain. Fishman, S.L., Murray, J.M., Eng, F.J., Walewski, J.L., Morgello, S., and Branch, A.D. J. Infect. Dis. 197(4), pp. 597-607, 2008.

Evidence for a Functional RNA Element in the Hepatitis C Virus Core Gene

In the core protein-coding region of hepatitis C virus (HCV), evidence exists for both phylogenetically conserved RNA structures and a +1 alternative reading frame (ARF). To investigate its role in HCV infection, the authors introduced four stop codons into the ARF of a genotype 1a H77 molecular clone. The changes did not alter the core protein sequence, but were predicted to disrupt RNA secondary structures. An attenuated infection was established after inoculation of the mutant HCV RNA into an HCV naive chimpanzee. The acute infection was atypical with low peak viremia, minimal alanine aminotransferase elevation, and early virus control by a diverse adaptive immune response. Sequencing circulating virus revealed progressive reversions at the third and then fourth stop codon. In cell culture, RNA replication of a genome with four stop codons was severely impaired. In contrast, the revertant genome exhibited only a 5-fold reduction in replication. Genomes harboring only the first two stop codons replicated to WT levels. Similarly, reversions at stop codons 3 and 4, which improved replication, were selected with recombinant, infectious HCV in cell culture. The authors conclude that ARF-encoded proteins initiating at the polyprotein AUG are not essential for HCV replication in cell culture or in vivo. Rather, these results provide evidence for a functionally important RNA element in the ARF region. McMullan, L.K., Grakoui, A., Evans, M.J., Mihalik, K., Puig, M., Branch, A.D. Feinstone, S.M., and Rice, C.M. Proc. Natl. Acad. Sci. U S A. 104(8), pp. 2879-2884, 2007. Epub 2007 February 13, 2007.

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

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

for HIV monoinfected patients 43.2 (7.3), for liver-only HCV 39.5 (9.0), and for those with HCV in brain and liver 33.2 (5.1) (P = .0927). Predominant brain HCV sequences did not match those of the plasma or liver in 4 of the 6 coinfected patients analyzed. The authors conclude that in the setting of HIV/HCV coinfection, brain HCV is a common phenomenon unrelated to the magnitude of HCV viremia, but related to active HIV disease and detectable CSF HIV. Furthermore, there is sequence evidence of brain compartmentalization. Differences in abstraction/executive function of HCV/HIV coinfected patients compared to HIV monoinfected warrant further studies to determine if neuropsychiatric effects are predicated upon brain infection. Murray, J., Fishman, S.L., Ryan, E., Eng, F.J., Walewski, J.L., Branch, A.D., and Morgello, S. J. Neurovirol. 14(1), pp. 17-27, 2008.

The Insulin-like Growth Factor Axis and Risk of Liver Disease in Hepatitis C Virus/HIV-Co-Infected Women

Insulin-like growth factor (IGF) I stimulates the proliferation of hepatic stellate cells (HSC), the primary source of extracellular matrix accumulation in liver fibrosis. In contrast, insulin-like growth factor binding protein (IGFBP) 3, the most abundant IGFBP in circulation, negatively modulates HSC mitogenesis. To investigate the role of the IGF axis in hepatitis C virus (HCV)-related liver disease among high-risk patients, the authors prospectively evaluated HCV-viremic/HIV-positive women. This study comprised a cohort investigation in which total IGF-I and IGFBP-3 were measured in baseline serum specimens obtained from 472 HCV-viremic/HIV-positive subjects enrolled in the Women's Interagency HIV Study, a large multi-institutional cohort. The aspartate aminotransferase to platelet ratio index (APRI), a marker of liver fibrosis, was assessed annually. Normal APRI levels (< 1.0) at baseline were detected in 374 of the 472 HCV-viremic/HIV-positive subjects tested, of whom 302 had complete liver function test data and were studied. IGF-I was positively associated [adjusted odds ratio comparing the highest and lowest quartiles (AORq4-q1), 5.83; 95% confidence interval (CI) 1.17-29.1; Ptrend = 0.03], and IGFBP-3 was inversely associated (AORq4-q1, 0.13; 95% CI 0.02-0.76; Ptrend = 0.04), with subsequent (incident) detection of an elevated APRI level (> 1.5), after adjustment for the CD4 T-cell count, alcohol consumption, and other risk factors. The authors conclude that high IGF-I may be associated with increased risk and high IGFBP-3 with reduced risk of liver disease among HCV-viremic/HIV-positive women. Strickler, H.D., Howard, A.A., Peters, M., Fazzari, M., Yu, H., Augenbraun, M., French, A.L., Young, M., Gange, S., Anastos, K., and Kovacs, A. AIDS. 22(4), pp. 527-531, 2008.

Hepatitis C Infection is Associated with Lower Lipids and High-Sensitivity C-Reactive Protein in HIV-Infected Men

Increased cardiovascular risk has been linked to HIV infection and combination antiretroviral therapy, but the impact of hepatitis C virus (HCV) status on indices of cardiovascular risk has not been routinely assessed in the HIV-infected population. The objective of this study was to analyze associations of HCV, HIV, and combination antiretroviral therapy with lipid levels and C-reactive protein (CRP) among older men. The authors measured fasting total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride, and high-sensitivity CRP serum levels in a cross-sectional study of 108 HIV-infected and 74 HIV-uninfected at-risk older men. One hundred ten men (60%) had detectable HCV RNA, with no difference by HIV status (p = 0.25). The majority (88%) of men with HCV infection had a history of injection drug use. Among all men, HCV infection was independently associated with lower total cholesterol (p < 0.001), LDL-C (p < 0.001), triglycerides (p = 0.01), and CRP (p = 0.001). Among HIV-infected men, HCV infection was associated with lower total cholesterol (p < 0.001), LDL-C (p < 0.001), and CRP (p = 0.004). HCV infection was associated with

lower triglycerides among men on protease inhibitors (PI) (p = 0.02) and non-PI combination antiretroviral therapy (p=0.02), but not among antiretroviral-naive men. These findings demonstrate an association of lower serum lipid and CRP levels with HCV infection and suggest that HCV status should be assessed as an important correlate of cardiovascular risk factors in studies of older men with or at risk for HIV. Floris-Moore, M., Howard, A.A., Lo, Y., Schoenbaum, E.E., Arnsten, J.H., and Klein, R.S. AIDS Patient Care STDS. 21(7), pp. 479-491, 2007.

Immune Status at Presentation to Care Did not Improve among Antiretroviral-Naive Persons from 1990 to 2006

Human immunodeficiency virus (HIV) prevention initiatives to improve access to HIV services have increased over time. Despite this, >250,000 cases of HIV infection in the US are undiagnosed, and many infected persons do not present for care until their HIV infection is advanced. Late presentation may increase the risk of HIV transmission and make HIV infection more difficult to treat effectively. With more effective HIV therapy, it has been the hope that patients might present earlier in their disease course. To assess immune status and time of HIV diagnosis in patients who newly presented for care, researchers analyzed data for the period 1990-2006 from patients who were antiretroviral naive at presentation to the Johns Hopkins HIV Clinic in Baltimore, Maryland. They compared CD4 (+) cell count and time from HIV diagnosis at presentation by demographic characteristics at enrollment. The median presenting CD4(+) cell count decreased from 371 cells/mm(3) during 1990-1994 to 276 cells/mm(3) during 2003-2006 (P<.01) overall and decreased within individual demographic groups. There was also a decrease in the median time from HIV diagnosis to presentation for care (271 days in 1990-1994 to 196 days in 2003-2006; P<.01). Multivariate analysis revealed that, in addition to CD4(+) cell count at presentation, male sex was associated with lower CD4(+) cell counts (-93 cells/mm(3)), as was black race (-71 cells/mm(3)) and older age (-20 cells/mm(3) per 10 years). These findings show that there has been a decrease in time from diagnosis of HIV infection to presentation for care, coupled with an increase in the severity of immunodeficiency at time of presentation, over the past 16 years in Maryland. The findings highlight the urgent need to develop effective strategies for providing earlier HIV testing and referral into care. Keruly, J., and Moore, R. Immune Status at Presentation to Care Did not Improve among Antiretroviral-Naive Persons from 1990 to 2006. Clin. Infect. Dis., 45(10), pp. 1369-1374, 2007.

Herpes Simplex Virus-2 and HIV among Noninjecting Drug Users in New York City

This study sought to examine the relationship between herpes simplex virus 2 (HSV-2) seroprevalence and HIV seroprevalence among noninjecting heroin and cocaine users in New York City. Four hundred sixty-two noninjecting cocaine and heroin users were recruited from a drug detoxification program in New York City. Smoking crack cocaine, intranasal use of heroin, and intranasal use of cocaine were the most common types of drug use. A structured interview was administered and a serum sample was collected for HIV and HSV testing. HIV prevalence was 19% (95% CI 15%-22%) and HSV-2 seroprevalence was 60% (95% CI 55%-64%). The adjusted risk ratio for the association between HSV-2 and HIV was 1.9 (95% CI 1.21%-2.98%). The relationship between HSV-2 and HIV was particularly strong among females, among whom 86% were HSV-2 seropositive, 23% were HIV seropositive, and all HIV seropositives were also HSV-2 seropositive. The findings suggest that HSV-2 is an important factor in sexual transmission of HIV among noninjecting cocaine and heroin users in New York City, especially among females. The estimated population attributable risk for HIV infection attributable to HSV-2 infection in this sample was 38%, underscoring the importance of programs to

manage HSV-2 infection as part of comprehensive HIV prevention for noninjecting drug users. Des Jarlais, D., Hagan, H., Arasteh, K., McKnight, C., Perlman, D., and Friedman, S. Herpes Simplex Virus-2 and HIV among Non Injecting Drug Users in New York City. Sex Transm. Dis., 34(11), pp. 923-927, 2007.

Factors Associated with the Prevalence and Incidence of Trichomonas Vaginalis Infection among African American Women in New York City Who Use Drugs

Trichomoniasis vaginalis, the most prevalent nonviral sexually transmitted infection, is associated with negative reproductive outcomes and increased HIV transmission and may be overrepresented among African Americans. A total of 135 African American women who used drugs were screened for Trichomonas vaginalis on >/=2 occasions between March 2003 and August 2005. Women were administered a structured questionnaire in a community-based research center, underwent serological testing for HIV and HSV-2, and were screened for Neisseria gonorrhoeae and Chlamydia trachomatis. Fifty-one women (38%) screened positive for T. vaginalis at baseline. Twenty-nine (31%) of 95 women with negative results of baseline tests became infected, for an incidence of 35.1 cases per 100 person-years at risk (95% confidence interval [CI], 23.5-49.0). Prevalent infection was associated with drug use in the past 30 days, and incident infection was associated with sexual behavior in the past 30 days, namely having >1 male sex partner. Women who reported having >1 partner were 4 times as likely as women with fewer partners to acquire T. vaginalis (hazard ratio, 4.3; 95% CI, 2.0-9.4). These findings suggest that T. vaginalis may be endemic in this community of African American women. A control strategy that includes T. vaginalis screening in nonclinical settings and rapid point-of-care testing could contribute to the disruption of transmission of this pathogen. Miller, M., Liao, Y., Gomez, A. M., Gaydes, C., and D'Mellow, D. Factors Associated with the Prevalence and Incidence of Trichomonas Vaginalis Infection Among African American Women in New York City Who Use Drugs. J. Infect. Dis., 197(4), pp. 503-509, 2008.

Risk Factors for Methadone Outside Treatment Programs: Implications for HIV Treatment among Injection Drug Users

Diversion of methadone outside treatment programs occurs, yet reasons for use of ''street methadone '' are characterized poorly. Self-medication for withdrawal symptoms is one plausible hypothesis. Among HIV-infected drug users, some antiretroviral medications can reduce potency of methadone, yet any association between such effects and the use of supplemental methadone sources remains undetermined. This study sought to estimate the frequency and risk factors for use of street methadone. Injection drug users (IDUs) recruited through extensive community outreach in 1988-89 and 1994 were followed semi-annually with questionnaires about health history, use of licit and illicit drugs including methadone and HIV-related assays. Analyses were performed using generalized estimating equation logistic regression. Of 2811 IDUs enrolled and eligible for analysis, 493 people reported use of street methadone over 12,316 person-years of follow-up (4.0/100 person-years). In multivariate analyses, street methadone use was more common among women, whites, those 40-59 years old, those who reported withdrawal symptoms, past methadone program attendance (6-12 months before visit), recent heroin injection with or without cocaine (but not cocaine alone), smoking or sniffing heroin and reported trading sex. Street methadone was not associated with HIV infection or treatment. The results suggest that older IDUs still using heroin may be using street methadone to treat signs of withdrawal. The absence of a higher rate of street methadone use in HIV seropositive IDUs reveals that antiretroviral/methadone interactions are not a primary determinant of use outside of treatment settings. Vlahov, D., O 'Driscoll, P.,

Mehta, S., Ompad, D., Gern, R., Galai, N., and Kirk, G. Risk Factors for Methadone Outside Treatment Programs: Implications for HIV Treatment among Injection Drug Users. Addiction, 102(5), pp. 771-777, 2007.

Early Immunologic and Virologic Responses to Highly Active Antiretroviral Therapy and Subsequent Disease Progression among HIV-Infected Injection Drug Users

Researchers examined the prevalence and prognostic value of early responses to highly active antiretroviral therapy (HAART) among community-based injection drug users (IDUs) in Baltimore. Virologic (HIV RNA <1000 copies/ml) and immunologic (CD4 >500 cells/ul or increase of 50 cells/ul from the pre-HAART level) responses were examined in the 1st year of HAART initiation. Cox regression was used to examine the effect of early response on progression to new AIDS diagnosis or AIDS-related death. Among 258 HAART initiators, 75(29%) had no response, 53(21%) had a virologic response only, 38(15%) had an immunologic response only and 92(36%) had a combined immunologic and virologic response in the first year of therapy. Poorer responses were observed in those who were older, had been recently incarcerated, reported injecting drugs, had not had a recent outpatient visit and had some treatment interruption within the 1st year of HAART. In multiple Cox regression analysis, the risk of progression was lower in those with combined virologic and immunologic response than in non-responders, (relative hazard [RH], 0.32; 95% confidence interval [CI], 0.17-0.60). Those with discordant responses had reduced risk of progression compared to non-responders but experienced faster progression than those with a combined response, although none of these differences was statistically significant. Early discordant and non response to HAART was common, often occurred in the setting of injection drug use and treatment interruption and was associated with poorer survival. Interventions to reduce treatment interruptions and to provide continuity of HIV care during incarceration among IDUs are needed to improve responses and subsequent survival. Mehta, S., Lucas, G., Astemborski, J., Kirk, G., Vlahov, D., and Galai, N. Early Immunologic and Virologic Responses to Highly Active Antiretroviral Therapy and Subsequent Disease Progression among HIV-Infected Injection Drug Users. AIDS Care, 19(5), pp. 637-645, 2007.

A Ten-Year Analysis of the Incidence and Risk Factors for Acute Pancreatitis Requiring Hospitalization in an Urban HIV Clinical Cohort

To assess the incidence of and risk factors for acute pancreatitis in HIV-infected patients in the contemporary highly active antiretroviral therapy (HAART) era, researchers evaluated all cases of acute pancreatitis requiring hospitalization between 1996 and 2006 in a cohort receiving care from Johns Hopkins Hospital's HIV clinic. A nested, case-control analysis was employed for initial episodes of acute pancreatitis, and conditional logistic regression was used to assess risk factors. Of 5970 patients followed for 23,460 person-years (PYs), there were 85 episodes of acute pancreatitis (incidence: 3.6 events/1000 PYs). The incidence of pancreatitis from 1996 to 2000 was 2.6 events/1000 PYs; the incidence from 2001 to 2006 was 5.1 events/1000 PYs (p = 0.0014, comparing rates in two time periods). In multivariate regression, factors associated with pancreatitis included female gender (adjusted odds ratio [AOR] 2.96 [1.69, 5.19]; p < 0.001); stavudine [an antiretroviral therapy} use (AOR 2.19 [1.16, 4.15]; p = 0.016); aerosolized pentamidine use (OR 6.27; [1.42, 27.63]; p = 0.015); and a CD4 count <50 cells/mm(3) (AOR 10.47 [3.33, 32.90]; p < 0.001). Race/ethnicity, primary HIV risk factor, HIV-1 RNA, and newer HAART regimens were not associated with an increased risk of pancreatitis after adjustment for the above factors. Pancreatitis remains a significant cause of morbidity in the HIV population in the HAART era. Acute pancreatitis is

associated with female gender, severe immunosuppression, and stavudine and aerosolized pentamidine usage. Of note, newer antiretrovirals were not associated with an increased risk of pancreatitis. Riedel, D., Gebo, K., Moore, R., and Lucas, G. A Ten-Year Analysis of the Incidence and Risk Factors for Acute Pancreatitis Requiring Hospitalization in an Urban HIV Clinical Cohort. AIDS Patient Care STDS, 22(2), pp. 113-121, 2008.

End-Stage Renal Disease and Chronic Kidney Disease in a Cohort of African-American HIV-Infected and At-Risk HIV-Seronegative Participants Followed between 1988 and 2004

HIV-infected African-Americans are at increased risk of end-stage renal disease requiring renal replacement therapy (RRT). This study sought to compare the incidence of RRT in a cohort of 4509 HIV-infected and 1746 HIV-seronegative African-Americans and describe temporal trends in RRT and chronic kidney disease (CKD) in HIV infection. Incident RRT was defined by matching participant identifiers with the US Renal Data System; CKD was defined as an estimated glomerular filtration rate < 60 ml/min per 1.73m for >/= 3 months. Standardized incidence ratios (SIR) and 95% confidence intervals (CI) were calculated by indirect adjustment. Risk factors for RRT were assessed by person-time methods and Poisson regression. RRT was initiated in 24 HIV-seronegative subjects over 13415 person-years of follow-up (SIR, 2.3; 95% CI, 1.5-3.4), in 51 HIV-infected participants without AIDS over 10780 person-years (SIR, 6.9; 95% CI, 5.1-9.0), and in 125 participants with AIDS over 9833 person-years. SIR, 16.1; 95% CI, 13.4-19.2). In HIV-infected African-Americans, RRT incidences were 5.8 and 9.7/1000 person-years in the pre-HAART and HAART eras, respectively (adjusted rate ratio 1.2; 95% CI, 0.8-1.9). In supplementary analyses, CKD incidence declined significantly in the HAART era compared with pre-HAART, but the CKD period prevalence increased. Nearly 1% of HIV-infected African-Americans initiated RRT annually, a rate that was similar in the HAART and pre-HAART eras. However, while new cases of CKD decreased, the prevalence of CKD increased in the HAART era. This increase reflects improvements in survival among individuals with HIV-associated CKD. Lucas, G., Mehta, S., Atta, M., Kirk, G., Galai, N., Vlahov, D., and Moore, R. End-Stage Renal Disease and Chronic Kidney Disease in a Cohort of African-American HIV-Infected and At-Risk HIV-Seronegative Participants Followed between 1988 and 2004. AIDS, 21(18), pp. 2435-2443, 2007.

Incidence and Outcomes of Malignancy in the HAART Era in an Urban Cohort of HIV-infected Individuals

This study sought to investigate trends, patient characteristics, and survival associated with AIDS-defining cancer (ADC) and non-AIDS defining cancer (NADC) in the HAART era. Retrospective analysis was conducted of all incident malignancies occurring in 1996-2005 among 2566 patients in an urban HIV clinic. Clinical profiles of NADC were compared with ADC and the general cohort. Incidence was examined by Poisson analysis. Standardized incidence ratios (SIR) compared cancer risk with that in the general population. Survival was analyzed by Kaplan-Meier and Cox proportional hazards models. Between 1996 and 2005, 138 ADC and 115 NADC were diagnosed. ADC rates decreased from 12.5 to 3.5 cases/1000 person-years (P < 0.001 for trend) while NADC rates increased from 3.9 to 7.1 cases/1000 person-years (P = 0.13 for trend). Incidence of the most common NADC was higher than expected, including cancers of the lung [n = 29; SIR, 5.5; 95% confidence interval (CI), 3.7-8.0], liver (n = 13, SIR, 16.5; 95% CI, 8.8-28.2), anus (n = 10; SIR, 39.0; 95% CI, 18.7-71.7), head and neck (n = 14; SIR, 5.1; 95% CI, 2.8-8.6), and Hodgkin's lymphoma (n = 8; SIR, 9.8; 95% CI, 4.2-19.2). Survival after cancer diagnosis did not differ between ADC and NADC. Advanced age was associated with NADC (P < 0.01 for trend) and increased mortality in ADC (age > or = 50 years adjusted hazard ratio, 2.21; 95% CI, 1.00-4.89). These findings show

that rates of ADC decreased while NADC increased within this cohort. Several NADC occurred at rates significantly higher than expected, indicating that screening and suspicion for NADC should increase in care for HIV-infected patients. Long, J., Engels, E., Moore, R., and Gebo, K. Incidence and Outcomes of Malignancy in the HAART Era in an Urban Cohort of HIV-Infected Individuals. AIDS, 22(4), pp. 489-496, 2008.

Burden of HIV Infection among Aboriginal Injection Drug Users in Vancouver, British Columbia

Researchers sought to examine whether there were differential rates of HIV incidence among Aboriginal and non-Aboriginal IDU in a Canadian setting. Data were derived from 2 prospective cohort studies of IDU in Vancouver, British Columbia. Using the Kaplan-Meier method and Cox proportional hazards regression, the HIV incidence was compared among Aboriginal and non-Aboriginal participants. Overall, 2496 individuals were recruited between May 1996 and December 2005. Compared with that of non-Aboriginal persons, the baseline HIV prevalence was higher among Aboriginal persons (16.0% vs 25.1%; P<.001). Among participants who were HIV negative at baseline, the cumulative HIV incidence at 48 months was higher among Aboriginal persons (18.5% vs 9.5%; P<.001). In multivariate analyses, Aboriginal ethnicity was independently associated with elevated HIV incidence (relative hazard=1.59; 95% confidence interval=1.12, 2.26; P=.009). Aboriginal persons in Vancouver had a significantly elevated burden of HIV infection, which highlights the need for a culturally sensitive and evidence-based response that is proactive with HIV-prevention programs. Wood, E., Montaner, J., Li, K., Zhang, R., Barney, L., Strathdee, S., Tyndall, M., and Kerr, T. Burden of HIV Infection among Aboriginal Injection Drug Users in Vancouver, British Columbia. Am. J. Public Health, 98(3), pp. 515-519, 2008.

HIV Rates and Risk Behaviors are Low in the General Population of Men in Southern India but High in Alcohol Venues: Results from Two Probability Surveys

As the HIV epidemic continues to expand in India, empirical data are needed to determine the course of the epidemic for high-risk populations and the general population. Two probability surveys were conducted in Chennai slums among a household sample of men and alcohol venue patrons ("wine shops") to compare HIV and other sexually transmitted disease (STD) prevalence and to identify STD behavioral risk factors. The wine shop sample (n = 654) had higher rates of HIV and prevalent STDs (HIV, herpes simplex virus 2 [HSV-2], syphilis, gonorrhea, or Chlamydia) compared with the household sample (n = 685) (3.4% vs. 1.2%, P = 0.007 and 21.6% vs. 11.8%, P < 0.0001, respectively). High-risk behaviors in the household sample were rare (<4%), but 69.6% of wine shop patrons had >2 partners, 58.4% had unprotected sex with a casual partner, and 54.1% had exchanged sex for money in the past 3 months. A multivariate model found that older age, ever being married, ever being tested for HIV, and having unprotected sex in the past 3 months were associated with STD prevalence in wine shop patrons. Prevalent HIV and STDs, and sexual risk behaviors are relatively low among the general population of men; however, men who frequent alcohol venues practice high-risk behaviors and have high rates of STDs, including HIV, and are likely to have an important role in expanding the Indian epidemic. Go, V., Solomon, S., Srikrishnan, A., Sivaram, S., Johnson, S., Sripaipan, T., Murugavel, K., Latkin, C., Mayer, K., and Celentano, D. HIV Rates and Risk Behaviors are Low in the General Population of Men in Southern India but High in Alcohol Venues: Results from Two Probability Surveys. J. Acquir. Immune Defic. Syndr., 46(4), pp. 491-497, 2007.

Hepatitis C in Puerto Rico: A Time for Public Health Action

Studies investigating the seroprevalence of HCV infection have been carried out in diverse populations, showing an estimated worldwide prevalence of 3%. A seroprevalence survey conducted among randomly selected non-institutionalized adults aged 21-64 years in San Juan, Puerto Rico in 2001-2002 revealed that 6.3% were positive for HCV antibodies. These data suggest that Puerto Ricans are burdened with a significantly greater prevalence of HCV infection compared to the general United States population aged 20-69 years (0.9%-4.3%). This article reviews data from multiple studies and sources that, taken together, establish the need to address HCV infection in Puerto Rico with prompt and decisive public health actions. Some of these actions include (1) establish hepatitis C prevention as a priority for state and municipal public health authorities, (2) raise awareness and educate target populations about HCV transmission and prevention, (3) increase clinician awareness of the HCV reporting system and the epidemiology and management of hepatitis C, (4) increase availability of diagnosis and treatment facilities, (5) increase access to effective drug treatment services, and (6) develop appropriate control measures to help reduce continued transmission in correctional settings. Perez, C., Albizu, C., Pena, M., Torres, E., Reyes, J., Colon, H., Ortiz, A., and Suarez, E. Hepatitis C in Puerto Rico: A Time for Public Health Action. P. R. Health Sci. J., 26(4), pp. 395-400, 2007.

HIV Risks Among Gay- and Non-Gay-Identified Migrant Money Boys in Shanghai, China

Men having sex with men (MSM) now account for 7% of all HIV/AIDS cases in China and there is growing awareness that internal rural-to-urban migration might shift the HIV epidemic within China by broadening social and sexual mixing. About 70% of HIV/AIDS infections are among rural residents, of whom 80% are males and 60% aged 16-29. This young, male, rural-to-urban migrant population has been identified as the tipping point for the AIDS epidemic in China. A subgroup of these migrants is the ''money boy'' population, i.e. those who engage in same-sex transactional sex for economic survival. However, the literature addressing money boys is very limited. This study examined factors for preventing substance abuse and HIV among two types of money boys ''gay-identified'' and ''non-gay-identified'' living in the Shanghai metropolitan area. Results reveal gay and non-gay money boys were not significantly different in terms of age, income, marriage status and education. Both groups shared similar patterns of substance use. Both groups had high self-reported depressive symptoms and low HIV knowledge. However, sexual orientation differentially predicted HIV testing, with gay money boys more likely to be tested for HIV. Non-gay money boys showed fewer sexual risks. Additional HIV prevention strategies are needed which target MSM (including money boys) within rapidly changing China. Wong, F., Huang, Z., He, N., Smith, B., Ding, Y., Fu, C., and Young, D. HIV Risks among Gay- and Non-Gay-Identified Migrant Money Boys in Shanghai, China. AIDS Care, 20(2), pp. 170-180, 2008.

Substance Use and HIV Risks Among Male Heterosexual and 'Money Boy' Migrants in Shanghai, China

There is a growing awareness that internal migration in China might shift the HIV epidemic by broadening the social and sexual mixing of its population. However, little is known about how drug use/abuse might contribute to the spread of HIV. This qualitative study examined factors for preventing substance abuse and HIV among two types of male migrants living in the Shanghai metropolitan area; the general migrant population and so-called "money boys" (those who engaged in same-sex activities for money). Compared to most male migrants, the ''money boys'' had a slightly better economic situation;

rarely visited their hometowns; used alcohol less but drugs more; had more knowledge about HIV and sexually transmitted diseases; higher HIV/ STD testing rates and fewer HIV risk behaviors. The general male migrants had more misconceptions about HIV (e.g. the need to pay for HIV testing) than the ''money boys". However, it was noted that ''money boys'' who were new to the enterprise and men who have sex with men but did not engage in commercial sex often lacked HIV knowledge and protective skills. Given the needs of various sub-types of ''migrants'', differential approaches to HIV prevention are needed. He, N., Wong, F., Huang, Z., Thompson, E., and Fu, C. Substance Use and HIV Risks Among Male Heterosexual and 'Money Boy ' Migrants in Shanghai, China. AIDS Care, 19(1), pp. 109-115, 2007.

HIV Risks Among Two Types of Male Migrants in Shanghai, China: Money Boys vs. General Male Migrants

This study examined HIV/AIDS-related knowledge, attitudes and behaviours among ''money boys'' (men who engage in same-sex transactional sex) and general male migrants in Shanghai, China. A quantitative cross-sectional design with self-administered paper-and-pencil instruments was used. A total of 239 money boys were enrolled using community popular opinion leader and respondent-driven sampling methods, and 100 general male migrants were enrolled through venue-based sampling. Compared to general male migrants, money boys were significantly younger, better educated, more likely to be single, earned a higher income, suffered greater stress, and were less satisfied with life in Shanghai. Both groups had substantial misconceptions about HIV/AIDS, although general male migrants were less well informed. Furthermore, both groups reported low rates of condom use, regardless of who their sexual partners were. Money boys were more likely to use alcohol, had more sexual partners and more casual sex partners, and were more likely to engage in other sexual risks. Moreover, they were likely to be the victims of sexual violence at the hands of their clients. More than half of the money boys had been tested for HIV and 3% self-reported to be HIV-positive, whereas only 1% of the general male migrants had ever been tested and all self-reported to be HIV-negative. Infection with other sexually transmitted diseases was also reported by money boys. This study suggests an urgent need to implement HIV/AIDS prevention and intervention programs targeting male migrants, especially money boys and their clients. He, N., Wong, F., Huang, Z., Ding, Y., Fu, C., Smith, B., Young, D., and Jiang, Q. HIV Risks Among Two Types of Male Migrants in Shanghai, China: Money Boys vs. General Male Migrants. AIDS, 21 Suppl 8, pp. S73-S79, 2007.

Oral Direct Renin Inhibition: Premise, Promise, and Potential Limitations of a New Antihypertensive Drug

The first oral direct renin inhibitor, aliskiren, recently received approval for the treatment of hypertension. This article addresses the premise, promise, and potential limitations of this new class of renin-angiotensin system inhibitor. Although aliskiren adds to a list of more than 100 drugs approved for the treatment of hypertension, its introduction into clinical medicine is of particular interest because of the novel mechanism of action: inhibition of renin's catalytic activity, the most proximal and rate-limiting step in renin-angiotensin system activation. By producing more complete renin-angiotensin system inhibition than with existing agents, direct renin inhibitors may afford greater protection from hypertensive complications. Other potential advantages include additional blood pressure reduction when used in combination therapy, a placebo-like side-effect profile, avid renal concentration, and long duration of action. Potential limitations include modest levels of blood pressure reduction that are equivalent to but not greater than angiotensin receptor blockers, reduced gastrointestinal absorption with a high-fat meal, and large reactive increases in renin secretion--the functional importance of which is under

intense investigation. The results of outcomes trials are eagerly awaited.
Shafiq, M.M., Menon, D.V., and Victor, R.G. Am. J. Med. 121(4), pp. 265-271, 2008.

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

Research Findings - Services Research

Screening, Brief Intervention, and Referral to Treatment (SBIRT): Toward a Public Health Approach to the Management of Substance Abuse

Screening, Brief Intervention, and Referral to Treatment (SBIRT) is a comprehensive and integrated approach to the delivery of early intervention and treatment services through universal screening for persons with substance use disorders and those at risk. This paper by Dr. Babor describes research on the components of SBIRT conducted during the past 25 years, including the development of screening tests, clinical trials of brief interventions and implementation research. Beginning in the 1980s, concerted efforts were made in the US and at the World Health Organization to provide an evidence base for alcohol screening and brief intervention in primary health care settings. With the development of reliable and accurate screening tests for alcohol, more than a hundred clinical trials were conducted to evaluate the efficacy and cost effectiveness of alcohol screening and brief intervention in primary care, emergency departments and trauma centers. With the accumulation of positive evidence, implementation research on alcohol SBI was begun in the 1990s, followed by trials of similar methods for other substances (e.g., illicit drugs, tobacco, prescription drugs) and by national demonstration programs in the US and other countries. The results of these efforts demonstrate the cumulative benefit of translational research on health care delivery systems and substance abuse policy. It is shown that SBIRT yields short-term improvements in individual's health, however long-term effects on population health have not yet been demonstrated, but simulation models suggest that the benefits could be substantial. Babor, T., McRee, B., Kassebaum, P., Grimaldi, P., Ahmed, K., and Bray, J. Screening, Brief Intervention, and Referral to Treatment (SBIRT): Toward a Public Health Approach to the Management of Substance Abuse. Subst. Abuse, 28(3), pp. 7-30, 2007.

Discovery of Three Distinct Life Course Trajectories for Heroin Addicts Show Delayed Treatment Results in High Morbidity and Early Mortality

This study investigates trajectories of heroin use and subsequent consequences in a sample of 471 male heroin addicts who were admitted to the California Civil Addict Program in 1964-1965 and followed over 33 years. Applying a two-part growth mixture modeling strategy to heroin use level during the first 16 years of the addiction careers since first heroin use, the authors identified three groups with distinctive profiles: stably high-level heroin users (n = 278), late decelerated users (n = 149), and early quitters (n = 44). Study findings empirically demonstrate the chronic nature of heroin addiction. Early treatment seekers are more likely to have periods of recovery, fewer medical problems,

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and longer survival than those delaying treatment beyond 16 years (X2=11.0, df=2, p<.004). Hser, Y., Huang, D., Chou, C., and Anglin, M. Trajectories of heroin addiction: growth mixture modeling results based on a 33-year follow-up study. Eval. Rev., 31(6), pp. 548-563, 2007.

Primary Medical Care Reduces HIV Risk Behaviors in Adults with Addictions

Human immunodeficiency virus (HIV) risk behaviors are prevalent in persons with addictions. This study assessed whether exposure to primary medical care is associated with decreases in HIV risk behaviors. This was a prospective 2-year cohort study of 298 adults with addictions. Outcomes evaluated were sex and drug-related HIV risk behaviors, measured by the Risk Assessment Battery. The predictor variables were the cumulative number of primary care visits (0, 1, > or = 2). Associations were tested using regression models for correlated data. It was found that in women, receipt of primary care was associated with less sex risk behavior (mean decrease 2.1, p < or = 0.1). Among women and men, > or = 2 primary care visits was associated with lower odds of any drug risk behavior (OR = 0.37, p = 0.03). From this study it is shown that exposure to primary care can impact HIV risk behavior favorably among adults with addictions. Takizawa, C., Cheng, D., Samet, J., Winter, M., Larson, M., and Saitz, R. Primary Medical Care and Reductions in HIV Risk Behaviors in Adults with Addictions. J. Addict. Dis., 26(3), pp. 17-25, 2007.

Methadone Maintenance at Release for Male Prisoners: 3 Month Outcomes

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

Buprenorphine-Naloxone Treatment for Prerelease Opioid-dependent Inmates in Puerto Rico

This study examined the feasibility of providing daily buprenorphine-naloxone (bup-nx) in prison and on release to 45 male inmates with histories of heroin addiction in Puerto Rico. Participants were assessed at study entry and at 1 month after release (N = 42; 93.3% follow-up rate). Treatment completers compared with non-completers had significantly greater reductions in self-reported heroin use, cocaine use, and crime and were less likely to be opioid-positive according to urine drug testing. The short-term outcomes of this study suggest that bup-nx may contribute to reductions in re-addiction to heroin and in criminal activities among re-entering male prisoners. Garcia, C.A., Correa, G.C., Hernandez, A.D., Kinlock, T.W., Gordon, M.S., Avila, C.A., Reyes, I.C., and Schwartz, P. Buprenorphine-Naloxone Treatment for Pre-Release Opioid-Dependent Inmates in Puerto Rico. J. Addiction Medicine, 1(3), pp. 126-132,

Planned Meetings

Publications

Staff Highlights

Grantee Honors

2007.

A New Tobacco Threat: Characteristics of U.S. Waterpipe Users

Waterpipe smoking, a traditional method of tobacco use, has experienced resurgence in the Middle East and Indian subcontinent in recent years. Despite growing evidence of its dependence potential and health-damaging effects, waterpipe use has spread beyond these regions to many other countries, including the United States. Because little is known about waterpipe use in the United States, the authors surveyed convenience samples of users from two U.S. cities, Richmond, Virginia (n = 109), and Memphis, Tennessee (n = 34). Respondents in both cities were primarily young adults, a majority (75%) was men, and most were college students or had a college degree. Initial and current use usually occurred in a social context, with a group of friends in a cafe or restaurant or at home. Most respondents had smoked a waterpipe for 2 or fewer years, and 67% currently smoked at least once a month (22% smoked at least once per week and 10% smoked daily). Most believed waterpipe use to be less addictive and harmful than cigarette smoking, believed they could quit use at any time, but had no plans or desire to quit. A majority of respondents used other tobacco products such as cigarettes, and 35% of those who did not smoke cigarettes said they would "probably" or "definitely" smoke one in the next year. Multivariate correlates of greater frequency of use included younger age at first use, ownership of a waterpipe, use occurring primarily with groups of friends, and the perception of being "hooked." Waterpipe users were young and educated, tended to experiment with multiple forms of tobacco, were unaware of the potentially harmful and addictive properties of waterpipe use, and planned to continue use in the future. Educational efforts are needed to increase awareness of the potential hazards of this increasingly popular form of tobacco use. Ward, K., Eissenberg, T., Gray, J., Srinivas, V., Wilson, N., and Maziak, W. Characteristics of U.S. Waterpipe Users: A Preliminary Report. Nicotine Tob. Res., 9(12), pp. 1339-1346, 2007.

Waterpipe Tobacco Smoking in the United States: Knowledge, Attitudes, Beliefs, and Behavior

Despite evidence of increasing waterpipe tobacco smoking prevalence among U.S. young adults little is known about the knowledge, attitudes, beliefs, and smoking patterns of waterpipe users in this population. To address this lack of knowledge, two convenience samples of U.S. waterpipe users were surveyed - one from a Richmond, Virginia, waterpipe cafe (n = 101), the other from an Internet forum called HookahForum.com (n = 100). Sixty percent reported first-time waterpipe use at or before age 18. Daily waterpipe use was reported by 19%, weekly use by 41%, and monthly use by 29%. Waterpipe use was more common during the weekend (75%) than during weekdays (43%). Many waterpipe users smoked the sweetened and flavored tobacco (i.e., maassel), and fruit flavors were the most popular (54%). Past month use of cigarettes, tobacco products other than cigarettes or waterpipe, and alcohol was 54%, 33%, and 80% respectively, and 36% reported past-month marijuana use. Most waterpipe users were confident about their ability to quit (96%), but only a minority (32%) intended to quit. Most waterpipe users believed waterpipe tobacco smoking was less harmful and addictive than cigarettes. More detailed study of a larger group of randomly sampled U.S. waterpipe tobacco smokers will be valuable in understanding this behavior and developing effective strategies to prevent it. Smith-Simone, S., Maziak, W., Ward, K., and Eissenberg, T. Waterpipe Tobacco Smoking: Knowledge, Attitudes, Beliefs, and Behavior in Two U.S. Samples. Nicotine Tob. Res., 10(2), pp. 393-398, 2008.

Blacks and Hispanics Received Alcohol and Employment Services

That Were Not Commensurate With their Greater Need

This study examined whether ethnic differences exist in access to care, receipt of services, and associated outcomes of 1,057 offenders participating in California's Proposition 36. Data are based on intake and 3-month follow-up interviews conducted as part of a multisite prospective treatment outcome study. Logistic regressions were conducted to examine ethnicity and other predictors of treatment placement and services intensity. Across ethnic groups, services intensity in several domains was inadequately matched to need, and few services besides substance abuse treatment were provided. Blacks and Hispanics received alcohol and employment services that were not commensurate with their greater need (O.R. = 0.59, $p<.05$). Although Blacks were more likely to be placed in residential programs, their employment status worsened from intake to follow-up (11% vs. 26% for Hispanics and 23% for Whites, $p<.05$). There were few other ethnic differences in outcomes. Assessing and eliminating ethnic-associated differences in health service delivery may improve program processes and outcomes. Fosados, R., Evans, E., and Hser, Y. Ethnic Differences in Utilization of Drug Treatment Services and Outcomes Among Proposition 36 Offenders in California. J. Subst. Abuse Treat., 33(4), pp. 391-399, 2007.

Trends in Opioid Prescribing by Race/Ethnicity for Patients Seeking Care in US Emergency Departments

National quality improvement initiatives implemented in the late 1990s were followed by substantial increases in opioid prescribing in the United States, but it is unknown whether opioid prescribing for treatment of pain in the emergency department has increased and whether differences in opioid prescribing by race/ethnicity have decreased. The objective of this study was to determine whether opioid prescribing in emergency departments has increased, whether non-Hispanic white patients are more likely to receive an opioid than other racial/ethnic groups, and whether differential prescribing by race/ethnicity has diminished since 2000. Pain-related visits to US emergency departments were identified using reason-for-visit and physician diagnosis codes from 13 years (1993-2005) of the National Hospital Ambulatory Medical Care Survey. Pain-related visits accounted for 156,729 of 374,891 (42%) emergency department visits. Opioid prescribing for pain-related visits increased from 23% (95% confidence interval [CI], 21%-24%) in 1993 to 37% (95% CI, 34%-39%) in 2005 ($P < .001$ for trend), and this trend was more pronounced in 2001-2005 ($P = .02$). Over all years, white patients with pain were more likely to receive an opioid (31%) than black (23%), Hispanic (24%), or Asian/other patients (28%) ($P < .001$ for trend), and differences did not diminish over time ($P = .44$), with opioid prescribing rates of 40% for white patients and 32% for all other patients in 2005. Differential prescribing by race/ethnicity was evident for all types of pain visits, was more pronounced with increasing pain severity, and was detectable for long-bone fracture and nephrolithiasis as well as among children. Statistical adjustment for pain severity and other factors did not substantially attenuate these differences, with white patients remaining significantly more likely to receive an opioid prescription than black patients (adjusted odds ratio, 0.66; 95% CI, 0.62-0.70), Hispanic patients (0.67; 95% CI, 0.63-0.72), and Asian/other patients (0.79; 95% CI, 0.67-0.93). Opioid prescribing for patients making a pain-related visit to the emergency department increased after national quality improvement initiatives in the late 1990s, but differences in opioid prescribing by race/ethnicity have not diminished. Fletcher, M., Kertesz, S., Kohn, M., and Gonzales, R. Trends in Opioid Prescribing by Race/ethnicity for Patients Seeking Care in US Emergency Departments. JAMA, 299(1), pp. 70-78, 2008.

On-Site 12-Step Meetings Are Associated With Abstinence One Year After Discharge

Rates of return to active substance use after addiction treatment tend to be high; participation in 12-step fellowships (e.g., Alcoholics Anonymous) reduces relapse rates but many clients do not attend or attend for a short period only. The authors of this quasi-experimental study used repeated measurement to explore the role of presence/absence of on-site 12-step meetings during treatment on post-treatment outcomes. Polysubstance-dependent clients (N = 219) recruited at a program with and one without 12-step on-site, were followed for one year post-treatment. On-site 12-step enhanced 12-step attendance, especially during treatment, and predicted continuous abstinence for the post-treatment year. Holding 12-step meetings on-site is a low-cost strategy that programs should consider to foster post-treatment remission maintenance. Laudet, A., Stanick, V., and Sands, B. An Exploration of the Effect of On-Site 12-Step Meetings on Post-Treatment Outcomes among Polysubstance-Dependent Outpatient Clients. Eval. Rev., 31(6), pp. 613-646, 2007.

Unprotected Sex Among Ukrainian Addicts Forecasts Escalated HIV Infection Rates

From June 2004 through November 2006, outreach workers recruited 1557 Ukrainian IDUs, including 526 from Kiev, 494 from Odessa, and 537 from Makeevka/Donesk. Participants were administered a standardized computer-assisted interview assessing HIV-related drug and sex risk behaviors, self-efficacy for practicing safe sex, and HIV knowledge. Overall, 80% of the participants were sexually active in the 30-day period before their interview. They also engaged in high-risk sex behavior with 53% reporting anal or vaginal sex without a condom, 27% having sex with more than 1 partner, 41% having an IDU sex partner, and 37% having an HIV-positive sex partner or a partner whose HIV status they did not know. Overall, serology found significantly more women (40%) compared to men (32%) were HIV-positive. Men were twice as likely to have multiple sex partners ($X2 = 33.42$, $df = 1$; $p < .001$). The extremely high HIV prevalence rate in Ukraine and in this cohort, combined with their recent high-risk sex behaviors, forecasts not only a continuance of the AIDS epidemic in the region but an escalation. Booth, R., Lehman, W., Brewster, J., Sinitsyna, L., and Dvoryak, S. Gender Differences in Sex Risk Behaviors among Ukraine Injection Drug Users. J. Acquir. Immune Defic. Syndr., 46(1), pp. 112-117, 2007.

Long-term Drug Abstinence Is Related to Psychiatric Trajectory

This study examines psychiatric trajectories of individuals entering chemical dependency treatment in a private, managed care health plan, and estimates relationships among those trajectories, individual characteristics, and abstinence (in the 30 days prior to follow-up) from drugs over 9 years. The original sample consisted of 1,204 adult men and women who met criteria for alcohol or other drug dependence or abuse and were admitted to treatment between April 1994 and April 1996. Interview data were collected at 6 mo., and 1, 5, 7, and 9 years after intake. This study is based on the 934 clients who had at least one follow-up interview within in 1 year and another between years 1 and 9. Psychiatric outcomes were measured using the ASI Psychiatric Composite scale. Other variables included age, gender, race/ethnicity, income, education, marital status, employment status, all seven ASI composite scores, and dependence and abuse measures based on the Diagnostic Interview Schedule for Psychoactive Substance Dependence. Four discrete trajectory groups of clients with homogenous longitudinal traits based on their patterns of psychiatric status over time were identified: consistent low-severity, deteriorating, improving, and consistent high-severity. Results, reported as odds ratios (OR), indicate that compared to clients in low severity groups, those in the deteriorating (OR = 0.61, 95% CI: 0.42 - 0.87), improving (OR =

0.61, 95% CI = 0.40-0.93) and high-severity (OR = 0.43, 95% CI: 0.29-0.66) all had lower levels of abstinence at follow-up. A higher ASI Drug Composite score was also negatively associated with attaining abstinence at follow-up. Variables associated with higher follow-up abstinence rates included higher index treatment length of stay, higher ASI Medical Composite score, being female, being married at follow-up, and being employed at follow-up. Age demonstrated a non-linear effect, with those aged 30-39 years and 50 to 59 years experiencing better outcomes than those aged 40-49 years in comparison to those younger than 30 years of age. These results suggest that careful attention be paid to client's psychiatric status during treatment assessment, treatment, and aftercare. Chi, F.W., and Weisner, C.M. Nine-Year Psychiatric Trajectories and Substance Use Outcomes. Eval. Rev., 32(1), pp. 39-58, 2008.

Pain Medication Agreements are Found Useful by Internal Medicine Residents

Little is known about whether internal medicine residents find pain management agreements (PMAs) useful or whether PMA use is associated with more positive attitudes toward patients with chronic noncancer pain (CNCP). The authors surveyed all internal medicine residents at Rhode Island Hospital regarding whether they found PMAs useful, what percentage of their patients taking chronic opioids had a signed PMA, and their attitudes toward and experiences with managing CNCP. The survey response rate was 89% (110/124). Ninety percent of respondents reported finding PMAs useful. A majority of respondents reported that PMAs were at least somewhat helpful for reducing multiple prescribers (76%), reducing requests for early refills (67%), reducing calls and pages from patients (57%), making it easier to discuss potential problems associated with chronic opioid use (73%), and making it easier to identify patients who are abusing pain medications (66%). Residents who reported greater use of PMAs reported a greater sense of preparation (r=0.20, P=0.04), greater confidence (r=0.18, P=0.06), and a greater sense of reward (r=0.24, P=0.02) for managing CNCP. In a multivariate analysis, PMA use was significantly associated with a greater sense of preparation and a greater sense of reward for managing CNCP. Overall this study shows that among internal medicine residents, PMA use was associated with more positive attitudes toward CNCP management. Fagan, M., Chen, J., Diaz, J., Reinert, S., and Stein, M. Do Internal Medicine Residents Find Pain Medication Agreements Useful? Clin. J. Pain, 24(1), pp. 35-38, 2008.

When Seeking Care From Free-Standing Drug Abuse Treatment Clinics, Patients Are Less Likely to be Medicated for Their Clinical Depression

This research considers the public-private distinction, organizational compatibility, and inter-organizational referral relationships in the use of selective serotonin reuptake inhibitors (SSRIs) medication for depression, by substance abuse treatment organizations. Using data from nationally representative samples of 363 publicly funded and 403 privately funded substance abuse treatment centers, a four-category typology of public and private organizations initially predicted variation in SSRI use. Controlling for government-ownership and not-for-profit status, results indicate that compared to free-standing drug abuse treatment programs, those affiliated with mental health centers were almost 3 times more likely to offer SSRIs (I.R = 2.97, p<,001). Those affiliated with hospitals were almost 2 times more likely to offer SSRIs (O.R. = 1.85, p<.05). Other factors included program access to contract physicians (O.R. = 2.18, P<.01) or full-time staff physicians (O.R. = 3.94, p<.001). These and other findings indicate that patients with co-morbid conditions do not have an equal likelihood of treatment with psychiatric medication. When seeking care from free-standing clinics, patients are less

likely to be medicated for their clinical depression. Knudsen, H., Ducharme, L., and Roman, P. The Use of Anti-depressant Medications in Substance Abuse Treatment: The Public-Private Distinction, Organizational Compatibility, and the Environment. J. Health Soc. Behav., 48(2), pp. 195-210, 2007.

For-Profit Organizations More Likely To Implement New Treatments or Services Than Non-Profit Organizations

This study used a structured interview survey of directors of a large national sample (n = 200) of mental health service organizations treating children to examine the governance, financing, staffing, services, and implementation practices of these organizations. Descriptive analyses showed private organizations financing services with public (particularly Medicaid) funds are prevalent and that employment of professional staff, clinical supervision and training, productivity requirements, and outcomes monitoring are common. Results of random effects regression models (RRMs) evaluating associations between governance, financing, and organizational characteristics and the use of new treatments and services showed for-profit organizations more likely to implement such treatments, and organizations with more licensed clinical staff and weekly clinical supervision in place less likely to do so. Results of RRMs evaluating relations between director ratings of the importance to new treatment and service implementation of three factors-fit with existing implementation practices, infrastructure support, and organizational mission and support-suggest greater importance to public than private organizations of these factors. Schoenwald, S., Chapman, J., Kelleher, K., Hoagwood, K., Landsverk, J., Stevens, J., Glisson, C., Rolls-Reutz, J., and Rolls-Reutz, J. A Survey of The Infrastructure for Children's Mental Health Services: Implications for The Implementation of Empirically Supported Treatments (ESTs). Adm. Policy Ment. Health, 35(1-2), pp. 84-97, 2008.

Longer Stay in Mutual Help Recovery Homes Associated with Lower Levels of Anxiety and Alcohol Use

Anxiety often co-occurs with alcohol abuse and predicts both the initial development of alcohol abuse problems and relapse among individuals in recovery. Individuals with comorbid substance abuse and anxiety symptoms may benefit from mutual-help environments, as these settings offer an increased amount of social support for individuals in recovery. Because symptoms of anxiety predict higher rates of relapse, mutually-supportive environments that potentially buffer anxiety might be beneficial recovery settings. This study examined anxiety symptoms and alcohol use over a one-year period among a sample of adults in self-governed, communal-living recovery homes for substance abuse (n=163). The authors explored whether staying in a supportive recovery environment for six months or longer was associated with lower levels of anxiety and alcohol use over time. Findings indicated that individuals who remained for at least six months had significantly lower anxiety symptoms and rates of alcohol use over time. The implications of these findings are discussed. Aase, D.M., Jason, L.A., Ferrari, J.R., Groh, D.R., Alvarez, J., Olson, B.D., and Davis, M.I. Anxiety Symptoms and Alcohol Use: A Longitudinal Analysis of Length-of-Time in Mutual-Help Recovery Homes. International Journal of Self Help & Self Care, 4 pp. 19-33, 2007.

Particulate Emissions from Waterpipe-Smoking

Waterpipe tobacco smoking is increasingly common worldwide, and evidence about its harmful effects to smokers is emerging. However, no studies have investigated the potential exposure of nonsmokers to waterpipe smoke. The authors measured particulate matter (PM) emissions (PM(2.5), PM(10)) before and during laboratory sessions in which 20 individuals used a waterpipe to

smoke tobacco and 20 individuals smoked a cigarette (10 for each particle-size/smoking-method), as well as 10 waterpipe and 10 cigarette smoldering sessions (i.e., without a smoker). For the waterpipe smoking method, the indoor air levels of particulate matter build gradually, reaching high levels compared with background. Higher levels of PM are reached during waterpipe use compared with cigarette smoking, likely because of cumulative, yet slower buildup during the longer waterpipe use sessions. Smoldering of waterpipe, however, did not seem to contribute to indoor particulate matter, in sharp contrast to what is witnessed with cigarette smoking, where smoldering can be a substantial source of hazardous PM emissions. Policymakers considering clean air regulations should include waterpipe tobacco smoking, and the public should be warned about this source of smoke exposure. Maziak, W., Rastam, S., Ibrahim, I., Ward, K., and Eissenberg, T. Particulate Emissions from Waterpipe-Smoking. Nicotine Tob. Res., 10(3), pp. 519-523, 2008.

Individual and System Factors Influence Waiting Time for Addition Treatment

The authors of this study assessed waiting time preceding clinical assessment at a centralized intake unit and during the period after the assessment but before treatment entry. The analysis included 577 substance abusers who were enrolled in a large clinical trial of two brief treatment interventions in a midsize metropolitan area in Ohio. Bivariate analyses identified individual and system factors that influenced pre-assessment and post-assessment waiting time, as well as total wait to treatment services. Multivariate analyses demonstrated that longer wait time for an assessment is influenced by being court referred, less belief in having a substance abuse problem, and less desire for change. A shorter wait to actually enter treatment is predicted by having a case manager, being more ready for treatment, and having less severe employment and alcohol problems. The different influences present during the two waiting periods suggest that assessment and treatment programs need to implement system changes and entry enhancement interventions that are specific to the needs of substance abusers at each waiting period. Carr, C.J., Jiangmin, X.U., Redko, C., Lane, T., and Rapp, R. Individual and System Influences on Waiting Time for Substance Abuse Treatment. J. Subst. Abuse Treat., E-Published 2007.

The Ecology of Adolescent Substance Abuse Service Utilization

This paper presents an ecological-community model toward the explanation of variation in patterns of substance abuse (SA) service utilization among adolescents who are enrolled in Tennessee's Medicaid program (TennCare). Guided by a theoretical framework that draws from the social ecology work of Bronfenbrenner and health services utilization models promoted by Aday and Andersen, the researchers applied a social indicators approach toward explaining the impact of community ecology on identification of SA and treatment engagement. Both county-level rates and individual-level treatment utilization are examined and hierarchical linear modeling is incorporated to examine the individual-in-community phenomenon. This study is an expansion of previous service utilization research and suggests that explanations of youth's service utilization must necessarily include not only individual, familial, and service system characteristics, but community factors, as well. Jones, D.L., and Heflinger, C.A. The Ecology of Adolescent Substance Abuse Service Utilization. Am. J. Community Psychol., 40 pp. 345-358, 2007.

Crack Cocaine Trajectories Among Users In a Midwestern American City

Although crack cocaine first appeared in cities in the United States in the mid-

1980s, little is known about its use over long periods of time. This study identified crack cocaine user groups on the basis of long-term trajectories. Following a natural history approach, data were collected periodically from 1996 to 2005. Group-based modeling assessed the probability of a crack smoker becoming abstinent during the observation period. A targeted sampling plan guided the recruitment of a community sample of crack cocaine users in Dayton, Ohio. Subjects on this study were crack smokers (n = 430) 18 years or older whose urine tested positive for cocaine metabolites at the baseline interview. Interviewer-administered and audio computer self-administered, structured questionnaires were used to collect data on a range of variables, including frequency of crack use. Abstinence was defined as not having used crack for at least 6 consecutive months during the study. Three trajectory-based groups were identified: (1) No Change, characterized by a very low probability of abstinence; (2) Some Change, characterized by a low to moderate probability of abstinence; and (3) Dramatic Change, characterized by a high probability of abstinence. The authors also found African Americans and men were significantly less likely to become abstinent. For the majority of the people (63.6%), crack use was uninterrupted by extended periods of abstinence during the study. From this study it appears that crack cocaine use that persists for a decade or longer may well be the norm for a large proportion of people who have experience with the drug. Falck, R., Wang, J., and Carlson, R. Crack Cocaine Trajectories among Users in a Midwestern American City. Addiction, 102(9), pp. 1421-1431, 2007.

Impact of Behavioral Contingency Management Intervention on Coping Behaviors and PTSD Symptom Reduction in Cocaine-addicted Homeless

The purpose of this study was to examine changes in post-trauma symptoms among 118 homeless cocaine-dependent adults participating in a randomly controlled trial studying effective treatments for dually diagnosed homeless individuals. Among those with trauma exposure and PTSD symptoms, the group receiving more behaviorally intensive, contingency management treatment had significantly greater reductions in PTSD symptomatology than did the group receiving less-intensive treatment. Regression analyses revealed that greater positive distraction coping and lower negative avoidance coping at baseline, in addition to changes in avoidance coping over the 6-month study period, were significantly related to greater symptom and severity reductions. The study provides some initial evidence of important treatment outcomes other than abstinence in addiction-related interventions. Lester, K., Milby, J., Schumacher, J., Vuchinich, R., Person, S., and Clay, O. Impact of Behavioral Contingency Management Intervention on Coping Behaviors and PTSD Symptom Reduction in Cocaine-addicted Homeless. J Trauma Stress, 20(4), pp. 565-575, 2007.

Toward Cost-Effective Initial Care for Substance-Abusing Homeless

In a randomized controlled trial, behavioral day treatment, including contingency management (CM (+)), was compared to contingency management components alone (CM). All 206 cocaine-dependent homeless participants received a furnished apartment with food and work training/employment contingent on drug-negative urine tests. CM (+) also received cognitive-behavioral therapy, therapeutic goal management, and other intervention components. Results revealed that CM (+) treatment attendance and abstinence were not significantly different from CM during 24 weeks of treatment. After treatment and contingencies ended, however, CM (+) showed more abstinence than CM, indicating a delayed effect of treatment from 6 to 18 months. CM (+) had more consecutive weeks abstinent across 52 weeks, but not during active treatment. The researchers concluded that 1) CM

alone may be viable as initial care for cocaine-dependent homeless persons; 2) since CM(+) yields more durable abstinence, it may be appropriate as stepped-up care for clients not responding to CM. Milby, J., Schumacher, J., Vuchinich, R., Freedman, M., Kertesz, S., and Wallace, D. Toward Cost-effective Initial Care for Substance-abusing Homeless. J. Subst. Abuse Treat., 34(2), pp. 180-191, 2008.

Provider-Level Effects on Psychiatric Inpatient Length of Stay for Youth with Mental Health and Substance Abuse Disorders

Previous research on inpatient care for children and adolescents with emotional or behavioral problems indicates that patient-level factors predict length of stay (LOS) poorly. This analysis examines whether patient-level factors are poor predictors of LOS, because LOS is primarily determined by facilities rather than patients. This study uses Tennessee Medicaid claims data from 1996 to 2001. The data include information on 14,162 observations related to 8,400 patients (age 12-21) from 163 hospitals. The researchers estimate log LOS using a cross-classified model. Covariates include admission-level characteristics (age, diagnosis, qualification for Medicaid, year), patient-level characteristics (gender, race), and facility characteristics (facility type). Results suggest that variation in LOS is attributable to facility-level factors (51%), time-invariance patient-level factors (5%), factors that vary across admissions (42%), and a correlation between patient-level and facility-level factors (5%). About half of the variation in LOS is explained by facility-level factors. Given the vulnerable nature of youth who are in need of inpatient psychiatric care, it may be particularly important to monitor provider-level processes and outcomes. Gifford, E. J., and Foster, E. M. Provider-level Effects on Psychiatric Inpatient Length of Stay for Youth with Mental Health and Substance Abuse Disorders. Med Care, 46 pp. 240-246, 2008.

Substance Abuse Treatment Provider Views of "Culture": Implications for Behavioral Health Care in Rural Settings

Mandates for culturally competent substance abuse and mental health services call for behavioral health providers to recognize and engage cultural issues. These efforts to incorporate culture typically focus on client culture, but provider views of culture can also influence the provision of services. Analysis of 42 semi-structured interviews with behavioral health providers suggests that culture is considered by many to be an obstacle to help seeking and treatment of substance-abusing youth. Although some providers do not highlight cultural issues, others conceptualize culture in terms of (a) generalized Hispanic cultural attributes, (b) male-dominant gender roles, and (c) the culture of poverty. Quintero, G.A., and Lilliott, E. Substance Abuse Treatment Provider Views of "Culture": Implications for Behavioral Health Care in Rural Settings. Qual. Health Res., 17(9), pp. 1256-1267, 2007.

Exposure to Secondhand Smoke At Home and in Public Places in Syria: A Developing Country's Perspective

This study employs sensitive methods to address the issue of exposure to secondhand smoke among children and women in an understudied developing country setting (Syria). The study combines data collected by the Syrian Center for Tobacco Studies as part of two international studies conducted in 2006: by Johns Hopkins and the Roswell Park Cancer Institute. The authors employed objective measures (hair nicotine, and ambient household nicotine assessed by passive monitors) to assess children's and mother's exposure to secondhand smoke at home, and used the TSI SidePak personal aerosol monitor to sample respirable suspended particles less than 2.5 micron diameter (PM(2.5)) in the air in public places (40 restaurants/cafes in Aleppo). Mean

level of hair nicotine was 11.8 ng/mg among children (n = 54), and was higher if the mother was a smoker (19.4 +/- 23.6 ng/mg) than nonsmoker (5.2 +/- 6.9 ng/mg) ($p < .05$). Children's hair nicotine level was strongly correlated with ambient household nicotine and number of cigarettes smoked daily in the house ($r = .54$ and $r = .50$, respectively, $p < .001$), and also was related to having a father who smoked in the children's presence. In public places, average PM(2.5) in the monitored 40 hospitality venues was 464 microg/m(3) and correlated with smoker density measured as cigarettes-waterpipes/100 m(3) ($r = .31$, $p = 0.049$). Thus, children in Syria are exposed to high levels of secondhand smoke at home, in which mothers smoking plays a major role. Also, levels of respirable hazardous particles are high in public hospitality venues, putting customers and workers at serious health risks. Maziak, W., Ali, R., Fouad, M., Rastam, S., Wipfl, H., Travers, M., Ward, K., and Eissenberg, T. Exposure to Secondhand Smoke at Home and in Public Places in Syria: A Developing Country 's Perspective. Inhal. Toxicol., 20(1), pp. 17-24, 2008.

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

Individuals with a history of injecting drugs are at the highest risk of becoming infected with the hepatitis C virus (HCV), with studies of patients in methadone maintenance treatment programmes (MMTP's) reporting that 60-90 percent of intravenous drug users (IDUs) have the virus. Fortunately, HCV therapy has been shown to be effective in 42-82 percent of all patients with chronic HCV infection, including IDUs. While the decision to start HCV therapy requires significant consideration, little research exists that explores the attitudes of drug users toward HCV therapy. Therefore, this paper examines how drug users perceive the treatment, as well as the processes by which HCV-positive individuals examined the advantages and disadvantages of starting the HCV medications. Interviews were conducted with 164 patients from 14 drug treatment programs throughout the United States, and both uninfected and HCV-positive drug users described a pipeline of communication among their peers that conveys largely negative messages about the medications that are available to treat HCV. Although many of the HCV-positive individuals said that these messages heightened their anxiety about the side effects and difficulties of treatment, some patients said that their peers helped them to consider, initiate HCV treatment or both. Gaining a better understanding of drug users' perceptions of HCV treatment is important, because so many of them, particularly IDUs, are already infected with HCV and may benefit from support in addressing their HCV treatment needs. In addition, currently uninfected drug users will likely remain at high risk for contracting HCV and may need to make decisions about whether or not to start the HCV medical regimen in the future. Munoz-Plaza, C.E., Astone-Twerell, J., Des Jarlais, D., Gwadz, M., Hagan, H., Osborne, A., and Rosenblum, A. Exploring Drug Users Attitudes and Decisions Regarding Hepatitis C (HCV) Treatment in the U.S. Int. J. Drug Policy, 19 pp. 71-78, 2008.

A Behavioral Treatment for Opioid-dependent Patients with Antisocial Personality

Antisocial personality disorder (APD) is associated with increased problem severity in treatment-seeking opioid-dependent patients. Treatment studies have reported mixed results but generally show that patients with APD make progress that is often comparable to drug dependent patients without the personality disorder. Much of this work is based on secondary analyses of studies evaluating responses to a variety of drug abuse treatment interventions. This study reports on a randomized prospective trial evaluating a behavioral approach for managing opioid-dependent patients with APD. Subjects (N = 100) met Diagnostic and Statistical Manual of Mental Disorders criteria for opioid dependence and APD using a structured clinical interview and

were randomly assigned to either an experimental condition (n = 51), which used a highly structured contingency management intervention, or a control condition (n = 49), which reflected standard methadone treatment. Subjects in the experimental group had significantly better counseling attendance and some indication of lower psychosocial impairment compared to the control group. The experimental intervention increased attendance in subjects with low and high levels of psychopathy and with and without other psychiatric comorbidity. These findings support the development of interventions more tailored to drug-dependent patients with APD. Neufeld, K.J., Kidorf, M.S., Kolodner, K., King, V.L., Clark, M., and Brooner, R.K. A Behavioral Treatment for Opioid-dependent Patients with Antisocial Personality. J. Subst. Abuse Treat., 34, pp. 101-111, 2008.

A Ten-Year Analysis of the Incidence and Risk Factors for Acute Pancreatitis Requiring Hospitalization in an Urban HIV Clinical Cohort

To assess the incidence of and risk factors for acute pancreatitis in HIV-infected patients in the contemporary highly active antiretroviral therapy (HAART) era, the researchers evaluated all cases of acute pancreatitis requiring hospitalization between 1996 and 2006 in patients followed at Johns Hopkins Hospital's HIV clinic. A nested, case-control analysis was employed for initial episodes of acute pancreatitis, and conditional logistic regression was used to assess risk factors. Of 5,970 patients followed for 23,460 person-years (PYs), there were 85 episodes of acute pancreatitis (incidence: 3.6 events/1000 PYs). The incidence of pancreatitis from 1996 to 2000 was 2.6 events/1000 PYs; the incidence from 2001 to 2006 was 5.1 events/1000 PYs (p= 0.0014, comparing rates in two time periods). In multivariate regression, factors associated with pancreatitis included female gender (adjusted odds ratio [AOR] 2.96 [1.69, 5.19]; p< 0.001); stavudine use (AOR 2.19 [1.16, 4.15]; p 0.016); aerosolized pentamidine use (OR 6.27; 1.42, 27.63]; p 0.015); and CD4 count less than 50 cells/mm3 (AOR 10.47 [3.33, 32.90]; p<0.001). Race/ethnicity, HIV risk factor, HIV-1 RNA, and newer non-nucleoside reverse transcriptase inhibitors (NNRTI) - and protease inhibitor (PI)-based HAART regimens were not associated with an increased risk of pancreatitis after adjustment for the above factors. Pancreatitis remains a significant cause of morbidity in the HIV population in the HAART era. Acute pancreatitis is associated with female gender, severe immunosuppression, and stavudine and aerosolized pentamidine usage. Newer anti-retrovirals, articularlyatazanavir, lopinivir/ritonavir, tenofovir, abacavir, and efavirenz, were not associated with an increased risk of pancreatitis. Riedel, D.J., Gebo, K.A., Moore, R.D., and Lucas, G.M. A Ten-Year Analysis of the Incidence and Risk Factors for Acute Pancreatitis Requiring Hospitalization in an Urban HIV Clinical Cohort. AIDS Patient Care STDS, 22(2), pp. 113-121, 2008.

Uncovering Patterns of HIV Risk Through Multiple Housing Measures

Understanding the relationships between housing and HIV has been limited by reliance on a single housing indicator based on current living arrangements (e.g., stable, unstable, or homeless). This paper examines the cross-sectional and longitudinal relationships between five housing indicators (objective housing stability, subjective housing stability, supportive housing, number of residences in the last 6 months, and housing services needs) and four HIV risk behaviors (hard drug use, needle sharing, sex exchange, and unprotected intercourse) among women at-risk for HIV and with recent criminal justice system involvement (n = 493). In cross-sectional analyses, each risk behavior was associated with multiple indicators of poor housing, and the patterns of association varied by risk behavior. In the longitudinal analyses, changes in risk behavior were associated with changes in housing status since the

previous assessment. These indicators reflect different aspects of housing and are uniquely associated with different risk behaviors. The relationships between housing and HIV risk are complex, and both constructs must be recognized as multidimensional. Weir, B.W., Bard, R.S., O'Brien, K., Casciato, C.J., and Stark, M.J. Uncovering Patterns of HIV Risk Through Multiple Housing Measures. AIDS Behav., 11 pp. S31-S44, 2007.

It is More Than the Money: Adolescents with Substance Use Problems Have Many Reasons for Participating in Research

The authors of this paper examined reasons why adolescents with substance use problems continued to participate in follow-up interviews. The sample consisted of 145 adolescents between the ages of 12 and 18, who completed an outcome study following outpatient treatment for substance use. Participants were asked to report on 18 possible reasons for continued participation. Adolescents' top reason for continued participation was financial compensation; however, a high percentage of adolescents responded favorably to several other attitudinal questions concerning their follow-up participation, suggesting that the adolescents had a primarily positive view of their research experience and that reasons for research participation are multidimensional. Reasons other than financial compensation that were reported include fulfillment of a commitment, wanting to help others, and the perception that the research was important and credible. Garner, B.R., Passetti, L.L., Orndorff, M.G., and Godley, S.H. Reasons for and Attitudes Toward Follow-Up Research Participation Among Adolescents Enrolled in an Outpatient Substance Abuse Treatment Program. Journal of Child and Adolescent Substance Abuse, 164(4), pp. 45-58, 2007.

Decline in Availability of Tailored Outpatient Care for Women from 1995 to 2005

Tailoring substance abuse treatment to women often leads to better outcomes. This investigation sought to depict recent changes in outpatient substance abuse treatment (OSAT) tailoring to women. Data were from 2 waves of a national OSAT unit survey (N = 618 in 1995, N = 566 in 2005). Multiple logistic regressions with generalized estimating equations test associations between unit and contextual attributes and tailoring to women. Two measures of tailoring to women declined significantly between 1995 and 2005: availability of single sex therapy (from 66% to 44% of units) and percent of staff trained to work with women (from 42% to 32% of units). No aspect of tailoring to women became more common. Methadone treatment (O.R. =2.3; $p<.001$), and private for-profit status (O.R. = .23 to .49; $p<.01$) and government managed care financing (O.R. = 3.64; $p<.001$) were associated with higher odds of tailoring to women. Campbell, C., Wells, R., Alexander, J., Jiang, L., Nahra, T., and Lemak, C. Tailoring of Outpatient Substance Abuse Treatment To Women, 1995-2005. Med. Care, 45(8), pp. 775-780, 2007.

Psychometrics of the Inmate Prerelease Assessment for Reentry Planning

The Inmate Prerelease Assessment (IPASS) was developed specifically as a measure of post-release risk for prison-based treatment graduates. By taking into account historical drug use and criminal activity of inmates as well as their performance during prison-based treatment, the IPASS provides a "priority" score indicating the relative need for more (versus less) intensive treatment services on release. The present study used data from offenders paroling from prisons in a southwest (N = 127) and Midwest (N = 75) state to examine the psychometric properties of the IPASS subscales. With regard to construct validity, psychometric properties ranged from good to excellent. The IPASS

scales also showed strong internal consistency, with coefficient alphas greater than .80 for the Texas Christian University Drug Screen, Client Evaluation of Treatment, and Counselor Evaluation of Client scales. Further research will explore alternatives on how the Client and Counselor scales are optimally incorporated into the IPASS priority score and will examine the score in relation to aftercare participation and post-release outcomes Farabee, D., Knight, K., Garner, B. R., and Calhoun, S. The Inmate Prerelease Assessment for Reentry Planning. Criminal Justice and Behavior, 34(9), pp. 1188-1197, 2007.

A Validation Study of the Co-Occurring Disorders Screening Instrument For Mental Disorders Developed Under the Criminal Justice Drug Abuse Treatment Studies

Three standardized screening instruments--the Global Appraisal of Individual Needs Short Screener, the Mini-International Neuropsychiatric Interview-Modified, and the Mental Health Screening Form (MHSF)--were compared to two shorter instruments, the 6-item Co-Occurring Disorders Screening Instrument for Mental Disorders (CODSI-MD) and the 3-item CODSI for Severe Mental Disorders (CODSI-SMD) for use with offenders in prison substance abuse treatment programs, which was developed as part of the Criminal Justice Drug Abuse Treatment Studies (CJDATS). Results showed that the CODSI screening instruments were comparable to the longer instruments in overall accuracy and that all of the instruments performed reasonably well. The CODSI instruments showed sufficient value to justify their use in prison substance abuse treatment programs and to warrant validation testing in other criminal justice populations and settings. Sacks, S., Melnick, G., Coen, C., Banks, S., Friedmann, P.D., Grella, C., Knight, K., and Zlotnick, C. CJDATS Co-Occurring Disorders Screening Instrument For Mental Disorders: A Validation Study. Criminal Justice and Behavior, 34(9), pp. 1198-1215, 2007.

Screening for Substance Abuse Lags Behind Screening for Mental Health Disorders in Private Managed Care Health Plans

Epidemiological data suggest that mental health and substance use conditions are under-recognized and under-treated. There are several strategies that private health plans can use in their managed care products to increase screening rates for these conditions, and this study examines the extent to which selected strategies were used by health plans in 2003. Data are from a survey of a nationally-representative sample of health plans representing 812 products. Results were weighted to produce national estimates. Plans were asked about whether or not they verify health care providers' screening for these conditions or distribute practice guidelines. (Plans were also asked about their use of screening outside of primary care, for example through member surveys, but the results were not given separately for substance abuse). The study found relatively lower rates of use of these strategies for substance abuse compared with mental health. Overall, 52.4% of the products used no strategies to screen for substance abuse conditions, compared with only 19.2% that used no strategies for mental health screening. Only eight percent of products verify primary care providers' screening for substance abuse, while 34% of products verify it for mental health. Only 33% distributed practice guidelines for substance abuse compared with 78% for mental health. Increases in the use of these strategies may lead to higher rates of identification of these disorders, which may lead to higher rates of entry into treatment, and ultimately, higher rates of recovery. Garnick, D., Horgan, C., Merrick, E., and Hoyt, A. Identification and Treatment of Mental and Substance Use Conditions: Health Plans Strategies. Med. Care, 45(11), pp. 1060-1067, 2007.

Evidence that the Dimensions of Change Instrument (DCI) is Valid

for Monitoring Adult Progress in Therapeutic Communities

The Dimensions of Change Instrument (DCI) measures treatment process in residential therapeutic community (TC) settings. It summarizes eight factors of treatment process from a client perspective. Results present evidence of the reliability of the DCI for assessing both adult (N = 519) and adolescent (N = 474) client perceptions of treatment process. The DCI factors significantly increased over time, with increases consistently seen across all DCI factors for adults. Findings show that clinicians can use the DCI to evaluate adult client progress and target areas for improving quality of care in TC settings. Paddock, S., Edelen, M., Wenzel, S., Ebener, P., Mandell, W., and Dahl, J. Measuring Changes in Client-Level Treatment Process in The Therapeutic Community (TC) with The Dimensions of Change Instrument (DCI). Am. J. Drug Alcohol Abuse, 33(4), pp. 537-546, 2007.

Health Plans Place More Restrictions on Buprenorphine Coverage than on the Coverage of Prescription Drugs for Alcohol Disorders

This paper describes results from a nationally-representative telephone survey of health plan managers (including medical directors) that assessed restrictions on plan member access to prescription medications for substance abuse disorders, including buprenorphine. These restrictions included formulary exclusions, prior authorization requirements, and placing these medications on higher cost-sharing tiers. Information was collected in 2003 on 347 health plans (83% response rate) representing 812 distinct insurance products. Weights were used to generate national estimates. The results reveal that buprenorphine was excluded from the formularies of 31% of health products, although this varied by product type. For example 45% of point of service plans (POS) excluded buprenorphine from their formularies, compared with 38% of health maintenance organizations (HMOs) and 5.9% of preferred provider organizations (PPO's). These proportions also varied by whether or not the health product used a pharmacy benefits manager - only 9.5% of products with a pharmacy benefits manager excluded these prescription drugs from the formulary compared with 55.2% of products without one. The overall rate of formulary exclusion of buprenorphine is much higher than the exclusion rates of disulfiram (1.3%), generic naltrexone (6.2%), and branded naltrexone (6.4%). Among products that include these drugs in their formularies, 79.5% of the products restricted buprenorphine to the most costly cost-sharing tier, compared with 28% for disulfiram, 1.6% for generic naltrexone, and 44% for branded naltrexone (44.2%). Prior authorization was also higher for buprenorphine. Approximately 7% of products covering buprenorphine required prior authorization, compared with 0.4-2.7% of plans covering prescription drugs for alcohol disorders. The authors speculate that coverage of buprenorphine may be restricted either because it is a relatively new drug, having been approved by the FDA only a year before the data were collected, or because the demand for the drug by health plan purchasers and enrollees is low, making restrictions less risky for health plans. Horgan, C., Reif, S., Hodgkin, D., Garnick, D., and Merrick, E. Availability of Addiction Medications in Private Health Plans. J. Subst. Abuse Treat., 34(2), pp. 147-156, 2008.

The Latent Structure of Substance Use Disorders: National Data

To better understand the underlying concepts of substance dependence and abuse, the authors examine the factor structure of DSM-IV lifetime criteria for cannabis and cocaine use disorders. Data for this study were drawn from the National Longitudinal Alcohol Epidemiologic Survey (NLAES), a large nationally representative U.S. sample aged 18 years and older. Exploratory factor analysis (EFA) examined the factor structure for each substance and the factors were related to background covariates using latent variable modeling

techniques. Separate analyses were conducted for lifetime marijuana and cocaine users. A two-factor solution was identified for each substance and was similar to DSM-IV abuse and dependence. The factors were highly correlated for both cannabis (r = 0.73) and cocaine (r = 0.77). Background variables accounted only for a modest amount of factor variance. In conjunction with the findings in alcohol use disorders, these results support the use of consistent criteria across substances in DSM-IV and ICD-10, and suggest that the consistent finding of two correlated factors across substances needs to be better understood. Blanco, C. Harford, T.C., Nunes, E., et al. The Latent Structure of Marijuana and Cocaine Use Disorders: Results from the National Longitudinal Alcohol Epidemiologic Survey (NLAES). Drug and Alcohol Dependence, 91, pp. 91-96, 2007.

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

Many recovering persons report quitting their drug use because they are "sick and tired" of the drug life. Recovery is the path to a better life, but that path is often challenging and stressful. There has been little research on the millions of recovering persons in the United States, and most research has focused on substance use outcomes rather than on broader functioning domains. This study builds on the authors' previous cross-sectional findings that recovery capital (social supports, spirituality, religiousness, life meaning, and 12-step affiliation) enhances the ability to cope with stress and enhances life satisfaction. This study (a) tests the hypothesis that higher levels of recovery capital prospectively predict sustained recovery, higher quality of life, and lower stress one year later, and (b) examines the differential effects of recovery capital on outcomes across the stages of recovery. Recovering persons (N = 312), mostly inner-city ethnic minority members whose primary substance had been crack or heroin, were interviewed twice at a one year interval in New York City between April 2003 and April 2005. Participants were classified into one of four baseline recovery stages: under 6 months, 6-18 months, 18-36 months, and over 3 years. Multiple regression findings generally supported the central hypothesis and suggested that different domains of recovery capital were salient at different recovery stages. The study's limitations are noted and implications of findings for clinical practice and for future research are discussed, including the need for a theoretical framework to elucidate the recovery process. Laudet, A.B., and White, W. Recovery Capital as Prospective Predictor of Sustained Recovery, Life Satisfaction, and Stress among Former Poly-Substance Users. Substance Use & Misuse, 43, pp. 27-54, 2008.

Improving Linkage to Addiction Treatment: Case Management Superior to Motivational Interviewing

Poor linkage with substance abuse treatment remains a problem, negating the benefits that can accrue to both substance abusers and the larger society. Numerous behavioral interventions have been tested to determine their potential role in improving linkage. This study reports the results of a randomized clinical trial of 678 substance abusers that compared the linkage effect of two brief interventions with the referral standard of care (SOC) at a centralized intake unit (CIU). Interventions included five sessions of strengths-based case management (SBCM) or one session of motivational interviewing (MI). A priori hypotheses predicted that both interventions would be better than the standard of care in predicting linkage and that SBCM would be more effective than MI. The authors analyzed the effect of the two interventions on overall treatment linkage rates and by treatment modality. Logistic regression analysis examined predictors of treatment linkage for the sample and each group. Two hypotheses were confirmed in that SBCM (n=222) was effective in improving linkage compared to the SOC (n=230), 55.0% vs. 38.7% (p<.01).

SBCM improved linkage more than MI (55.0% vs. 44.7%, p<.05). Motivational interviewing (n=226) was not significantly more effective in improving linkage than the standard of care (44.7% vs. 38.7%; p>.05). The three trial groups differed only slightly on the client characteristics that predicted linkage with treatment. The results of this study confirm a body of literature that supports the effectiveness of case management in improving linkage with treatment. The role of motivational interviewing in improving linkage was not supported. Results are discussed in the context of other case management and motivational interviewing linkage studies. Rapp, R., Otto, A., Lane, D., Redko, C., McGatha, S., and Carlson, R. Improving Linkage with Substance Abuse Treatment Using Brief Case Management and Motivational Interviewing. Drug Alcohol Depend., 94(1-3), pp. 172-182, 2008.

Substance Abuse Treatment May Be Sufficient for Those with Mild Mental Health Symptoms

This article reviews the literature on the prevalence of co-occurring disorders in the substance abuse treatment system, and on the effects of single and integrated treatments on that population. It suggests that although prevalence of mental disorders is likely substantially higher in the substance abuse treatment population than in the general population, it is not clear that requiring that each individual with a co-occurring disorder receive integrated treatment is necessary, and in fact may not be possible given current funding constraints and scarcity of highly-educated treatment professions who are able to provide integrated treatment. It does suggest that screening for mental health disorders by substance abuse treatment providers may be useful, after clients have become abstinent, so that tailored treatments can be targeted to the more severely mentally ill, which research shows can benefit from the addition of psychotherapy to substance abuse counseling. Screening might also be useful in discharge planning, as those with co-occurring disorders appear to have much higher rates of relapse and may be especially able to benefit from follow-up care that addresses the chronicity of the disorder. Flynn, P.M., and Brown, B.S. Co-occurring Disorders in Substance Abuse Treatment: Issues and Prospects. J Subst. Abuse Treat., 34, pp. 36-47, 2008.

Outcomes in Syria's First Smoking Cessation Trial

This study was undertaken to determine the feasibility of implementing cessation interventions in Syria. The authors randomized 50 smokers to either a brief or intensive behavioral cessation intervention. Adherence to treatment and cessation through 3 months post-cessation were calculated. It was found that adherence in the intensive group was only moderate and was associated with smoking for more years and higher self-efficacy. Cessation rates in the brief and intensive intervention groups were 16% and 4%, respectively. Nicotine dependence predicted abstinence at 3 months. This study shows that important barriers to cessation included perceived dependence, lack of access to pharmacotherapy, poor social support, and water pipe smoking. Asfar, T., Weg, M., Maziak, W., Hammal, F., Eissenberg, T., and Ward, K. Outcomes in Syria's First Smoking Cessation Trial. Am. J. Health Behav., 32(2), pp. 146-156, 2008.

Results of RCTs May Be Externally Valid

This study compared abstinence rates at 6 and 12 months for 4 groups of treatment seeking commercially-insured HMO members meeting most or all of the criteria for ASAM Level III treatment: Those randomized to day hospital (n=154) or community residential treatment (n=139); those self-selected into day hospital (n=321); and those directed to residential treatment because of high environmental risks (n=82). A multivariate random-effects logistic

regression model, which included group dummies, group x time interactions, baseline ASI scores and other measures, yielded no difference in abstinence rates by group. Variables that were significantly associated with lower abstinence rates included ASI drug severity scores and number of lifetime treatment episodes, while age, number of index episode treatment days, and number of 12-step meeting days were associated with higher abstinence rates. These results suggest that concerns in the literature about the external validity of trials that randomize clients to different treatment settings requiring different levels of treatment intensity (e.g. clients who agree to be randomized may have different prognoses than the average client in treatment; having a say in the treatment decisions may affect prognosis) may not be valid for this specific population of clients. Witbrodt, J., Bond, J., Kaskutas, L., Weisner, C., Jaeger, G., Pating, D., and Moore, C. Day Hospital and Residential Addiction Treatment: Randomized and Nonrandomized Managed Care Clients. J. Consult. Clin. Psychol., 75(6), pp. 947-959, 2007.

Co-occurring Mental Health Problems are Common for Both Adolescents and Adults in Addiction Treatment

As the field follows recommendations to introduce standardized assessments on substance, mental and behavioral problems, a consistent picture has emerged that co-occurring disorders are common, that there is heterogeneity in the type of disorder, and that the pattern varies by age. This paper examines the prevalence of self-reported substance use and mental health problems, the pattern of comorbidity, and how both vary by age among people presenting to substance abuse treatment. The authors analyzed data from a sample of 4,939 adolescents and 1,958 adults presenting to substance abuse treatment in multi-site studies who were assessed with the Global Appraisal of Individual Needs (GAIN) and categorized into five age groups: age <15, 15-17, 18-25, 26-39, and 40+. Two thirds of clients had a co-occurring mental problem in the year prior to treatment admission. Across all ages, clients self-reporting criteria for past-year substance dependence were more likely than those who did not to have other co-occurring mental health problems (odd ratios of 2.9 to 8.8). The prevalence and patterns of co-occurring mental health problems however, varied by age. Young adults (age 18-25) were found to be most vulnerable to co-occurring problems. Chan, Y., Dennis, M.L., and Funk, R.R. Prevalence and Comorbidity of Major Internalizing and Externalizing Problems among Adolescents and Adults Presenting to Substance Abuse Treatment. J. Subst. Abuse Treat., 34(1), pp. 14-24, 2008.

Using Mediational Models to Explore the Nature of Tobacco Motivation and Tobacco Treatment Effects

Various theories have proposed mechanisms for drug motivation and relapse. For instance, negative reinforcement theories focus on the alleviation of withdrawal. However, other theories and some data cast doubt on the importance of withdrawal as a motivator of addictive drug use. Using data from a randomized double-blind placebo-controlled smoking cessation treatment study (N=608), this research examined the impact of withdrawal on drug motivation and the ability to maintain abstinence. Withdrawal was experimentally manipulated by randomly assigning participants to receive active bupropion versus placebo. Mediation analyses revealed that active bupropion reduced the amount of withdrawal and craving that individuals reported in the 1st week post quit; modest support was also found for smaller declines in positive affect. These effects, in turn, were all positively associated with post-treatment abstinence. These results implicate withdrawal as an important factor in motivating persistent tobacco use. Piper, M., Federmen, E., McCarthy, D., Bolt, D., Smith, S., Fiore, M., and Baker, T. Using Mediational Models to Explore The Nature of Tobacco Motivation and Tobacco Treatment Effects. J. Abnorm. Psychol., 117(1), pp. 94-105, 2008.

State Level Factors Related to Establishing Tobacco Cessation Quit Line

Quit line services are an effective population-wide tobacco cessation strategy adopted widely in the United States as part of state comprehensive tobacco control efforts. Despite widespread evidence supporting quit lines' effectiveness, many states lack sufficient financial resources to adequately fund and promote this service. Efforts to augment state tobacco control efforts might be fostered by greater knowledge of state level factors associated with the funding and implementation of those efforts. The authors analyzed data from the 2004 North American Quitline Consortium survey and from publicly available sources to identify state level factors related to quitline implementation and funding. Factors included in the analyses were state demographic characteristics, tobacco use variables, state tobacco control spending, and economic and political climate variables. Univariate and multivariate regression analyses were conducted. It was found that the best fitting multivariate model that significantly predicted the presence or absence of a state quitline included only cigarette excise tax rate ($p = 0.020$). In terms of funding levels, states with high rates of cigarette consumption ($p = 0.047$) and with higher per capita expenditures for tobacco control programs ($p = 0$ .0.004) were most likely to spend more on per capita operations budget for quitlines. From this study it is shown that state level factors appear to play a part in whether states had established quitlines by mid-2004 and the amount of per capita quitline funding. It was also shown that only cigarette excise tax predicted the presence or absence of a quitline in a state. Keller, P., Koss, K., Baker, T., Bailey, L., and Fiore, M. Do State Characteristics Matter? State Level Factors Related to Tobacco Cessation Quitlines. Tob. Control, 16 Suppl 1, pp. i75-i80, 2007.

Predictors of Bacterial Infections Among HCV-Negative Injection Drug Users in Rhode Island

The prevalence and risk factors for treated bacterial infections (i.e., skin abscess or cellulitis, osteomyelitis, or endocarditis) were investigated among a community sample of drug users with a history of injection drug use (IDU) who tested negative for Hepatitis C (HCV). Participants were IDUs in an HCV reduction intervention trial followed for 24 months. Among 109 participants, 9.2% reported a bacterial infection during follow-up. Non-Caucasian participants and those who had injected for longer periods at baseline were less likely to experience a bacterial infection at follow-up. IDUs with no history of HCV infection experience bacterial infections, but at lower rates than other IDU cohorts. This paper shows that behavioral interventions should target bacterial infections as well as HCV or HIV prevention outcomes. Phillips, K., Anderson, B., and Stein, M. Predictors of Bacterial Infections Among HCV-Negative Injection Drug Users in Rhode Island. Am. J. Drug Alcohol Abuse, 34(2), pp. 203-210, 2008.

A Rasch Model Analysis of Evidence-Based Treatment Practices Used in the Criminal Justice System

This study used item response theory (IRT) to examine the extent to which criminal justice facilities and community-based agencies are using evidence-based substance abuse treatment practices (EBP's), which EBPs are most commonly used, and how EBP's cluster together. The study used data collected from wardens, justice administrators, and treatment directors as part of the National Criminal Justice Treatment Practices survey (NCJTP), and includes both adult criminal and juvenile justice samples. Results of Rasch modeling demonstrated that a reliable measure can be formed reflecting the extent to

which juvenile and adult correctional facilities, and community treatment agencies serving offenders, have adopted various treatment practices supported by research. Results also demonstrated the concurrent validity of the measure by showing that features of the facilities' organizational contexts were associated with the extent to which facilities were using EBP's, and which EBP's they were using. Researchers, clinicians, and program administrators may find these results interesting not only because they show the program factors most strongly related to EBP use, but the results also suggest that certain treatment practices cluster together, which may help stakeholders plan and prioritize the adoption of new EBP's in their facilities. Henderson, C.E., Taxman, F.S., and Young, D.W. A Rasch Model Analysis of Evidence-Based Treatment Practices Used in the Criminal Justice System. Drug Alcohol Depend., 93 pp. 163-175, 2008.

Drug Use Expectancies Among Non-abstinent Community Cocaine Users

Previous research has shown that one's expectations about the effects of using a particular substance (i.e., substance use expectancies) are associated with the quantity and frequency of actual use. An extensive literature supports the importance of expectancies in predicting alcohol use, but less is known about the association between expectancies and use of other substances. The purpose of the present investigation was to examine the association between cocaine expectancies and frequency of use in a heterogeneous community sample of drug users. Participants were 157 self-identified primary cocaine users recruited from the community as part of a hepatitis prevention study. Participants completed a structured interview that assessed demographic variables, current and past drug use, and drug expectancies. Results from multivariate logistic regression analyses indicated that frequency of cocaine use was positively associated with higher expectation that drug use would increase social and physical pleasure (OR=1.67, $p<0.05$) and inversely associated with higher expectation that drug use would increase cognitive and physical impairment (OR=0.59, $p<0.01$). These findings suggest that drug use expectancies are an important correlate of cocaine use behavior in non-treatment-seeking community users. Hayaki, J., Anderson, B., and Stein, M. Drug Use Expectancies Among Non-abstinent Community Cocaine Users. Drug Alcohol Depend., 94(1-3), pp. 109-115, 2008.

Comparison of Demographic and Clinical Characteristics Between Opioid-dependent Individuals Admitted to a Community-based Treatment Setting and Those Enrolled in a Research-based Treatment Setting

Despite the significant developments in pharmacotherapy and behavioral treatments for addiction, the dissemination of new treatment methods into the community has been slow. It has been pointed out that treatments developed in research settings may be impractical in community treatment settings, which might help explain the transition lag. Screening and recruitment of participants for research studies might partially explain this, as there is evidence that substance-abusing individuals who participate in clinical research are different on a number of measures from treatment seekers. However, no study has directly compared treatment seekers with research participants drawn from similar populations using prospective methods. This study compared the demographic characteristics, drug use and psychosocial problem severity levels, and personality traits of opioid-dependent individuals seeking help in a community setting (n = 502) with those of opioid-dependent individuals in a primarily research-based drug abuse treatment setting (n = 459); both settings offered a similar set of treatment services (opioid agonist medication and counseling). Although the overall findings revealed numerous similarities

between the groups, differences were also observed. Most notably, there were significantly fewer women in the research sample than in the community-based treatment sample. Other differences included a modest but statistically significant increase in psychosocial problem severity levels in the community-based treatment sample and higher drug use problem severity levels in the research sample. Interestingly, many of these differences were strongest in women as compared with men. Carroll, C.P., Kidorf, M., Strain, E.C., and Brooner, R.K. Comparison of Demographic and Clinical Characteristics Between Opioid-dependent Individuals Admitted to a Community-based Treatment Setting and Those Enrolled in a Research-based Treatment Setting. J. Subst. Abuse Treat., 33 pp. 355-361, 2007.

Perceived Need for Substance Abuse Treatment Among Illicit Stimulant Drug users in Rural Areas of Ohio, Arkansas, & Kentucky

Non-medical drug use in rural communities in the United States is a significant and growing public health threat. Understanding what motivates drug users in rural areas to seek substance abuse treatment may help in addressing the problem. Perceived need for treatment, a construct indicative of problem recognition and belief in problem solution, has been identified as an important predictor of help-seeking behavior. This cross-sectional study used data collected through face-to-face interviews to examine factors associated with perceived need for drug abuse treatment among not-intreatment, adult, illicit stimulant drug users (n = 710) in rural areas of Ohio, Kentucky, and Arkansas. More than one-quarter of the sample perceived a need for treatment. Results from a stepwise multiple regression analysis showed that white users, users with better physical and mental health status, and occasional users of methamphetamine were significantly less likely to see a need for treatment. Users with higher Addiction Severity Index composite scores for family/social problems or legal problems, and users with prior drug abuse treatment experience were significantly more likely to perceive a need for treatment. Falck, R.S., Wang, J., Carlson, R.G., Krishnan, L.L., Leukfeld, C., and Booth, B.B. Perceived Need for Substance Abuse Treatment among Illicit Stimulant Drug Users in Rural Areas of Ohio, Arkansas, and Kentucky. Drug Alcohol Depend., 91, pp. 107-114, 2007.

Crack Cocaine Trajectories Among Users in a Midwestern American City

Although crack cocaine first appeared in cities in the United States in the mid-1980s, little is known about its use over long periods of time. This study identified crack cocaine user groups on the basis of long-term trajectories. Following a natural history approach, data were collected periodically from 1996 to 2005. Group-based modeling assessed the probability of a crack smoker becoming abstinent during the observation period. A targeted sampling plan guided the recruitment of a community sample of crack cocaine users in Dayton, Ohio. Participants were crack smokers (n = 430) 18 years or older whose urine tested positive for cocaine metabolites at the baseline interview. Interviewer-administered and audio computer self-administered, structured questionnaires were used to collect data on a range of variables, including frequency of crack use. Abstinence was defined as not having used crack for at least 6 consecutive months during the study. Three trajectory-based groups were identified: (1) No Change, characterized by a very low probability of abstinence; (2) Some Change, characterized by a low to moderate probability of abstinence; and (3) Dramatic Change, characterized by a high probability of abstinence. African Americans and men were significantly less likely to become abstinent. For the majority of the people (63.6%), crack use was uninterrupted by extended periods of abstinence during the study. The authors conclude that crack cocaine use that persists for a decade or longer may well be the norm for

a large proportion of people who have experience with the drug. Falck, R.S., Wang, J., and Carlson, R.G. Crack Cocaine Trajectories among Users in a Midwestern American City. Addiction, 22(1), pp. 47-54, 2007.

Important Differences Between In-Treatment and Out Of Treatment Opioid Dependent Adults

This study compared the characteristics of opioid-addicted adults seeking (n = 169) and not seeking (n = 74) methadone treatment in Baltimore, Maryland. Participants entering treatment were recruited from six methadone treatment programs, while out-of-treatment participants were recruited from the streets using targeted sampling methods. Measures included the Addiction Severity index, a Supplemental Questionnaire, and urine drug test. Data were analyzed using ANOVA, x2, and regression, holding key background variables constant. Despite the lack of differences between the samples in demographic characteristics, the out-of-treatment sample reported significantly more days of heroin, cocaine, and alcohol use and spent significantly more money on drugs and earned more illegal income at baseline. Using ASI Composite Scores, for example, the out-of-treatment group had significantly higher mean composite scores for both drug use (respectively, .34 vs. .30, $p = .008$) and alcohol use (.16 vs. .06, $p < .001$). Finally, in terms of social functioning, the out-of-treatment group had higher composite scores for both employment (.89 vs. .82, $p = .002$) and legal problems (.34 vs. .30, $p < .001$). Schwartz, R.P., Kelly, S.M., and O'Grady, K.E. In-Treatment vs. Out-of-Treatment Opioid Dependent Adults: Drug Use and Criminal History, Am. J. Drug Alcohol Abuse, 34, pp. 17-28, 2008.

A Conceptual Framework for Child and Family Mental Health Systems

This paper describes research undertaken by the MacArthur Foundation-funded Research Network on Youth Mental Health. The authors illustrate the conceptual model that provides a framework for the research network. The project is designed to understand the challenges of implementing evidence-based treatments in community-based mental health practices. This paper describes the impetus and conceptual framework underlying one cluster of the Network's activity- i.e. the Clinic Systems Project (CSP). The CSP studies examined the organizational and service system environments in a large national sample of community mental health and affiliated organizations that provide services to children. The main goal is to identify leverage points for, and barriers to, the adoption and implementation of evidence-based practices for children. Schoenwald, S., Kelleher, K., and Weisz, J. Building Bridges to Evidence-based Practice: The MacArthur Foundation Child System and Treatment Enhancement Projects (Child STEPs). Adm. Policy Ment. Health, 35(1-2), pp. 66-72, 2008.

Opioid Receptors and Legal Highs: Salvia Divinorum and Kratom

Salvia divinorum and Mitragyna speciosa ("Kratom"), two unscheduled dietary supplements whose active agents are opioid receptor agonists, have discrete psychoactive effects that have contributed to their increasing popularity. Salvia divinorum contains the highly selective kappa- opioid receptor agonist salvinorin A; this compound produces visual hallucinations and synesthesia. Mitragynine, the major alkaloid identified from Kratom, has been reported as a partial opioid agonist producing similar effects to morphine. An interesting minor alkaloid of Kratom, 7-hydroxymitragynine, has been reported to be more potent than morphine. Both Kratom alkaloids are reported to activate supraspinal mu- and delta- opioid receptors, explaining their use by chronic narcotics users to ameliorate opioid withdrawal symptoms. Despite their

widespread Internet availability, use of Salvia divinorum and Kratom represents an emerging trend that escapes traditional methods of toxicological monitoring. This article elaborates on current internet trends, and provides information for toxicologists and poison control specialists with these emerging psychoactive dietary supplements. Babu, K., McCurdy, C., and Boyer, E. Opioid Receptors and Legal Highs: Salvia Divinorum and Kratom. Clin. Toxicol. (Phila), 46(2), pp. 146-152, 2008.

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

Clinical Trials Network Research

Addressing Ethnic Disparities in Drug Abuse Treatment in the Clinical Trials Network

Ethnic minorities have significantly higher rates of unmet needs for treatment of substance use disorders and are often underrepresented in clinical trials and treatment research. The National Drug Abuse Treatment Clinical Trials Network (CTN) was established in 1999 to conduct research in a wide variety of community based treatment programs across the United States. Through its size and scope, the CTN provides a unique opportunity to address a variety of underserved populations, and in particular to evaluate access to and effectiveness of treatments for ethnic minorities. The CTN has continually sought to reduce barriers to all its studies and has attended carefully to recruitment and retention of women and ethnic minority groups. This article describes a symposium from the June 2006 CPDD annual meeting that included four presentations on ongoing CTN activities and strategies used to address the issues of ethnic disparities. Kathleen Carroll described a protocol developed specifically to address retention in treatment among Spanish-speaking substance users. Ray Daw described the special issues raised in clinical research among American Indian communities, including those encountered by a CTN protocol that was adapted on site so it could be implemented among American Indian communities. Kathryn Magruder summarized results of a secondary analysis of CTN data, evaluating rates of retention among ethnical minorities. And Lawrence Brown described a secondary analysis of a CTN survey study on national practices regarding the availability of specialized treatment for sexually transmitted diseases in drug abuse treatment, focusing specifically on services for ethnic minorities. Carroll, K.M., Rosa, C., Brown, Jr., L.S., Daw, R., Magruder, K.M., Beatty, L. Addressing Ethnic Disparities in Drug Abuse Treatment in the Clinical Trials Network. Drug Alcohol Depend. 90(1), pp. 101-106, 2007.

Improving the Transition from Residential to Outpatient Addiction Treatment: Gender Differences in Response to Supportive Telephone Calls

Substance use relapse rates are often high in the first months after discharge from inpatient substance abuse treatment, and patient adherence to aftercare plans is often low. Four residential addiction treatment centers participated in a feasibility study designed to estimate the efficacy of a post-discharge telephone intervention intended to encourage compliance with aftercare. A total of 282 participants (100 women, 182 men) with substance use disorders were included in this secondary analysis. The findings revealed that women were more likely than men to attend aftercare. This "gender effect" persisted after adjustment for a number of potential mediators. Carter, R.E., Haynes, L.F.,

Back, S.E., Herrin, A.E., Brady, K.T., Leimberger, J.D., Sonne, S.C., Hubbard, R.L., and Liepman, M.R. Improving the Transition from Residential to Outpatient Addiction Treatment: Gender Differences in Response to Supportive Telephone Calls. Am. J. Drug Alcohol Abuse, 34(1), pp. 47-59, 2008.

No Smoking Allowed: Integrating Smoking Cessation with Treatment

Substance abuse counselors, programs, and treatment systems are considering how to address smoking and nicotine dependence in the populations they serve. This article reports on the results from a survey within the National Drug Abuse Treatment Clinical Trials Network (CTN) that assessed whether the surveyed treatment agency provided smoking cessation treatment as part of their regular services. The survey also assessed the attitudes of staff regarding the feasibility of offering smoking cessation treatment. Analyses explored those factors associated with whether or not smoking cessation services were provided, and factors that predict staff attitudes toward smoking cessation treatment in these drug treatment strategies. Overall, the study found that smoking cessation treatment was more likely to be available in units that offered other ancillary services, including detoxification. Additionally, clinics that provide smoking cessation care were more likely to have a staff with a supportive attitude toward such services. This was especially true in clinics with a high number of pregnant women, but the proportion of youth admissions was neither a predictor for staff attitudes nor for the provision of smoking cessation services. Overall, this study presents some challenges to the treatment field to focus on evidence-based services regarding smoking cessation treatment, and raises some ethical issues as well. Fuller, B.E., and Guydish, J. No Smoking Allowed: Integrating Smoking Cessation with Treatment. Counselor, 9(1), pp. 22-27, 2008.

Cost, Effectiveness, and Cost-Effectiveness of Contingency Management All Vary by Clinic

Results from cost effectiveness analyses are usually reported based on study averages, where results from all study sites are pooled into one sample. This study, in contrast, examined whether, and by how much, the effectiveness, costs, and cost-effectiveness of a prize-based contingency management intervention (CM) varied across the eight outpatient psychosocial community-based clinics with a total of 412 stimulant abusing clients involved in the NIDA CTN's Motivational Incentives for Enhanced Drug Treatment trial (MIEDAR). Results indicated that that the incremental cost of using CM compared to usual care varied by a factor of 1.9 across the clinics, ranging from an additional $306 to an additional $582 per patient. The effect of CM on the longest duration of continuous stimulant abstinence (LDA) varied by a factor of 8.0 across the clinics, ranging from an additional 0.5 to an additional 4.0 weeks. The ICER's for the LDA varied by a factor of 4.6 across the clinics, ranging from $145 to $666. These results show that the cost-effectiveness of CM varied widely among the clinics in the MIEDAR trial. Future research should focus on identifying the sources of this variation, perhaps by identifying clinic-level best practices and/or identifying those subgroups of patients that respond the most cost-effectively, with the ultimate goal of improving the cost-effectiveness of CM overall. Olmstead, T., Sindelar, J., and Petry, N. Clinic Variation in the Cost-Effectiveness of Contingency Management. Am. J. Addict., 16(6), pp. 457-460, 2007.

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

Research Findings - International Research

Publications by Former NIDA INVEST Drug Abuse Research Fellows

Pressure-Assisted Capillary Electrochromatography with Electrospray Ionization-Mass Spectrometry Based on Silica-Based Monolithic Column for Rapid Analysis of Narcotics
INVEST Fellow: Lan Zhang (China, 2004-2005)
A pressure-assisted CEC (pCEC) with ESI-MS based on silica-based monolithic column was developed for rapid analysis of narcotics. Combining the extremely high permeability and separation efficiency of silica-based monolithic column with the high selectivity and sensitivity of pCEC-ESI-MS, the developed system exhibited its prominent advantages in separation and detection. A systematic investigation of the pCEC separation and ESI-MS detection parameters was performed. Experiment results showed that the optimized separation efficiency could be obtained at 8 bar assisted pressure with 25 kV separation voltage, using the solution containing 65% ACN v/v and 20 mmol/L ammonium acetate with pH 6.0 as running buffer. 3 microL/min of sheath liquid was considered as the optimized flow rate since it could provide the maximum signal intensity. Under the optimum conditions, the five tested narcotics could be completely separated within 10 min with the detection limit in the range of 2.0-80 nmol/L. The proposed method has been successfully used for detection of narcotics in real urine samples. Lu, M., Zhang, L., Feng, Q., Xia, S., Chi, Y., Tong, P., and Chen, G. Electrophoresis. January 22, 2008, Epub ahead of print.

Neurokinin-1 Receptors in Cholinergic Neurons of the Rat Ventral Pallidum have a Predominantly Dendritic Distribution that is Affected by Apomorphine when Combined with Startle-Evoking Auditory Stimulation
INVEST Fellow: Elisa Mengual (Spain, 1999-2000)
Cholinergic neurons of the basal forebrain are implicated in startle reflex inhibition by a prior weak stimulus often referred to as prepulse inhibition (PPI) and used as an index of sensorimotor gating deficits in schizophrenia. Gating deficits can be produced in rodent models by acute systemic administration of apomorphine, a non-selective dopamine D1 and D2 receptor agonist that also affects trafficking of neurokinin-1 (NK(1)) receptors induced by startle evoking auditory stimulation (AS) in midbrain neurons. The authors used electron microscopic immunolabeling of NK(1) receptors and the vesicular acetylcholine transporter (VAchT) to test the hypothesis that the subcellular distributions of these receptors in cholinergic neurons of the rat ventral pallidum are subject to a similar regulation. In vehicle controls, NK(1) immunogold was often seen near cytoplasmic endomembranes in somata and large dendrites, but was more equally distributed in cytoplasmic and plasmalemmal compartments of medium dendrites, and principally located on the plasma membrane of small dendrites. These labeling patterns appeared to be largely independent of whether the NK(1) receptor was co-expressed with VAchT, however only the medium and

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small VAchT-labeled dendrites showed significant treatment-specific differences in NK(1) immunogold distributions. The NK(1) receptor immunogold particle density on the plasma membrane of medium cholinergic dendrites was significantly enhanced by combined apomorphine and AS, while neither alone affected either the plasmalemmal density or the equality of the plasmalemmal and cytoplasmic distributions of NK(1) receptors in these dendrites. Small cholinergic dendrites showed a significant AS-induced increase in both the plasmalemmal and cytoplasmic density of NK(1) gold particles, and an apomorphine-induced disruption of the preferential plasmalemmal targeting of the NK(1) receptors. These results provide ultrastructural evidence that NK(1) receptors in cholinergic neurons of the ventral pallidum have subcellular locations and plasticity conducive to active involvement in dopamine-dependent sensorimotor processing. Mengual, E., Chan, J., Lane, D., San Luciano Palenzuela, M., Hara, Y., Lessard, A., and Pickel, V.M. Neuroscience. December 4, 2007, Epub ahead of print.

Role of Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) Receptor Subunit GluR1 in Spinal Dorsal Horn in Inflammatory Nociception and Neuropathic Nociception in Rat

INVEST Fellow: You Wan (China, 1989-1999)

The present study aims to investigate changes of spinal cord AMPA receptor GluR1 and its phosphorylation in inflammatory and neuropathic pain. Complete Freund's adjuvant (CFA) injection into the hind paw produced inflammatory thermal hyperalgesia that was assessed by decreased response latency to radiant heat; spinal nerve ligation (SNL) was used to induce mechanical allodynia that was evaluated with von Frey hairs. By method of Western blot, expression of GluR1 (the main subunit of the AMPA receptor) and its phosphorylated forms at serine 845 (pGluR1-Ser845) and at serine 831 (pGluR1-Ser831) in the spinal dorsal horn was observed. It was found that the expression of pGluR1-Ser845 and pGluR1-Ser831 increased significantly at 1 h after CFA injection, reached peak at 4 h and returned to the normal control level at 24 h, while no significant change was detected in GluR1 itself. In contrast, neither GluR1 nor pGluR1 showed any significant change in rats following SNL. These results suggest that phosphorylated GluR1 (pGluR1-Ser845 and pGluR1-Ser831) might play a role in the induction of inflammatory but not neuropathic pain. Lu, Y., Sun, Y.N., Wu, X., Sun, Q., Liu, F.Y., Xing, G.G., and Wan, Y. Brain Res. January 16, 2008, Epub ahead of print.

Axonal Accumulation of Hyperpolarization-Activated Cyclic Nucleotide-Gated Cation Channels Contributes to Mechanical Allodynia after Peripheral Nerve Injury in Rat

INVEST Fellow: You Wan (China, 1989-1999)

Peripheral nerve injury causes neuropathic pain including mechanical allodynia and thermal hyperalgesia due to central and peripheral sensitization. Spontaneous ectopic discharges derived from dorsal root ganglion (DRG) neurons and from the sites of injury are a key factor in the initiation of this sensitization. Numerous studies have focused primarily on DRG neurons; however, the injured axons themselves likely play an equally important role. Previous studies of neuropathic pain in rats with spinal nerve ligation (SNL) showed that the hyperpolarization-activated cyclic nucleotide-gated cation (HCN) channel in DRG neuronal bodies is important for the development of neuropathic pain. Here, the authors investigate the role of the axonal HCN channel in neuropathic pain rats. Using the chronic constriction injury (CCI) model, they found abundant axonal accumulation of HCN channel protein at the injured sites accompanied by a slight decrease in DRG neuronal bodies. The function of these accumulated channels was verified by local application of ZD7288, a specific HCN blocker, which significantly suppressed the ectopic discharges from injured nerve fibers with no effect on impulse conduction. Moreover, mechanical allodynia, but not thermal hyperalgesia, was relieved significantly by ZD7288. These results suggest that axonal HCN channel accumulation plays an important role in ectopic discharges from injured spinal

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nerves and contributes to the development of mechanical allodynia in neuropathic pain rats. Jiang, Y.Q., Xing, G.G., Wang, S.L., Tu, H.Y., Chi, Y.N., Li, J., Liu, F.Y., Han, J.S., and Wan, Y. Pain, January 5, 2008, Epub ahead of print.

Delay and Failure in Treatment Seeking After First Onset of Mental Disorders in the World Health Organization's World Mental Health Survey Initiative

INVEST Fellow: Guilherme Borges (Mexico, 1997-1998)

Data are presented on patterns of failure and delay in making initial treatment contact after first onset of a mental disorder in 15 countries in the World Health Organization (WHO)'s World Mental Health (WMH) Surveys. Representative face-to-face household surveys were conducted among 76,012 respondents aged 18 and older in Belgium, Colombia, France, Germany, Israel, Italy, Japan, Lebanon, Mexico, the Netherlands, New Zealand, Nigeria, People's Republic of China (Beijing and Shanghai), Spain, and the United States. The WHO Composite International Diagnostic Interview (CIDI) was used to assess lifetime DSM-IV anxiety, mood, and substance use disorders. Ages of onset for individual disorders and ages of first treatment contact for each disorder were used to calculate the extent of failure and delay in initial help seeking. The proportion of lifetime cases making treatment contact in the year of disorder onset ranged from 0.8 to 36.4% for anxiety disorders, from 6.0 to 52.1% for mood disorders, and from 0.9 to 18.6% for substance use disorders. By 50 years, the proportion of lifetime cases making treatment contact ranged from 15.2 to 95.0% for anxiety disorders, from 7.9 to 98.6% for mood disorders, and from 19.8 to 86.1% for substance use disorders. Median delays among cases eventually making contact ranged from 3.0 to 30.0 years for anxiety disorders, from 1.0 to 14.0 years for mood disorders, and from 6.0 to 18.0 years for substance use disorders. Failure and delays in treatment seeking were generally greater in developing countries, older cohorts, men, and cases with earlier ages of onset. These results show that failure and delays in initial help seeking are pervasive problems worldwide. Interventions to ensure prompt initial treatment contacts are needed to reduce the global burdens and hazards of untreated mental disorders. Wang, P.S., Angermeyer, M., Borges, G., Bruffaerts, R., Tat Chiu, W., DE Girolamo, G., Fayyad, J., Gureje, O., Haro, J.M., Huang, Y., Kessler, R.C., Kovess, V., Levinson, D., Nakane, Y., Oakley Brown, M.A., Ormel, J.H., Posada-Villa, J., Aguilar-Gaxiola, S., Alonso, J., Lee, S., Heeringa, S., Pennell, B.E., Chatterji, S., and Ustuen, T.B. World Psychiatry 6(3), pp. 177-185, 2007.

Cross-National Prevalence and Risk Factors for Suicidal Ideation, Plans and Attempts

INVEST Fellow: Guilherme Borges (Mexico, 1997-1998)

Suicide is a leading cause of death worldwide; however, the prevalence and risk factors for the immediate precursors to suicide - suicidal ideation, plans and attempts - are not well known, especially in low- and middle-income countries. The aim of this study was to report on the prevalence and risk factors for suicidal behaviors across 17 countries. A total of 84, 850 adults were interviewed regarding suicidal behaviors and socio-demographic and psychiatric risk factors. Results showed that the cross-national lifetime prevalence of suicidal ideation, plans, and attempts is 9.2% (s.e.=0.1), 3.1% (s.e.=0.1), and 2.7% (s.e.=0.1). Across all countries, 60% of transitions from ideation to plan and attempt occur within the first year after ideation onset. Consistent cross-national risk factors included being female, younger, less educated, unmarried and having a mental disorder. Interestingly, the strongest diagnostic risk factors were mood disorders in high-income countries but impulse control disorders in low- and middle-income countries. The authors conclude that there is cross-national variability in the prevalence of suicidal behaviors, but strong consistency in the characteristics and risk factors for these behaviors. These findings have significant implications for the prediction and prevention of suicidal behaviors. Nock, M.K., Borges, G., Bromet, E.J.,

Alonso, J., Angermeyer, M., Beautrais, A., Bruffaerts, R., Chiu, W.T., de Girolamo, G., Gluzman, S., de Graaf, R., Gureje, O., Haro, J.M., Huang, Y., Karam, E., Kessler, R.C., Lepine, J.P., Levinson, D., Medina-Mora, M.E., Ono, Y., Posada-Villa, J., and Williams, D. Br. J. Psychiatry.192, pp. 98-105, 2008.

The Epidemiology of Suicide-Related Outcomes in Mexico
INVEST Fellow: Guilherme Borges (Mexico, 1997-1998)
Nationally representative data from the Mexican National Comorbidity Survey are presented on the lifetime prevalence and age-of-onset (AOO) distributions of suicide ideation, plan and attempt and on temporally prior demographic and DSM-IV psychiatric risk factors. Lifetime ideation was reported by 8.1% of respondents, while 3.2% reported a lifetime plan and 2.7% a lifetime suicide attempt. Onset of all outcomes was highest in adolescence and early adulthood. The risk of transition from suicide ideation to plan and attempt was highest within the first year of onset of ideation. The presence of one or more temporally prior DSM-IV/CIDI (Composite International Diagnostic Instrument) disorder was strongly related to each suicide-related outcome. Suicidal outcomes are prevalent, have an early AOO, and are strongly related to temporally prior mental disorders in Mexico. Given the early AOO, intervention efforts need to focus more than currently on children and adolescents with mental disorders to be effective in prevention. Borges, G., Nock, M.K., Medina-Mora, M.E., Benjet, C., Lara, C., Chiu, W.T., and Kessler, R.C. Suicide Life Threat. Behav. 37(6), pp. 627-640, 2007.

Suicide Ideation, Plan, and Attempt in the Mexican Adolescent Mental Health Survey
INVEST Fellow: Guilherme Borges (Mexico, 1997-1998)
No representative data among adolescents in Mexico exist on the prevalence and risk factors for suicide ideation, plan, and attempt despite a recent increase in suicide deaths. Data are presented from the Mexican Adolescent Mental Health Survey, a representative household survey of 3,005 adolescents ages 12 to 17 in metropolitan Mexico City who were gathered in 2005, regarding lifetime prevalence and age-of-onset distributions of suicide ideation, plan, and attempt and demographic and psychiatric disorders risk factors. Lifetime ideation was reported by 11.5% of respondents, whereas 3.9% reported a lifetime plan and 3.1% a lifetime suicide attempt. Onset of suicidality started around age 10 and at age 15 showed the highest hazards. Suicide ideators were more likely to report a plan and attempt within the first year of onset of ideation. Suicidality was more likely to occur among females. The presence of one or more mental disorders was strongly related to suicide ideation, plan, and attempt. Among ideators only dysthymia was consistently related to a plan and attempt. The authors conclude that intervention efforts should focus on assessment and target adolescents with mental disorders, particularly mood disorders, to be effective in prevention. Borges, G., Benjet, C., Medina-Mora, M.E., Orozco, R., and Nock, M. J. Am. Acad. Child Adolesc. Psychiatry. 47(1), pp. 41-52, 2008.

Polymorphisms in Human Dopamine D2 Receptor Gene Affect Gene Expression, Splicing, and Neuronal Activity During Working Memory
INVEST Fellow: Danxin Wang (China, 1996-1997)
Subcortical dopamine D2 receptor (DRD2) signaling is implicated in cognitive processes and brain disorders, but the effect of DRD2 variants remains ambiguous. The authors measured allelic mRNA expression in postmortem human striatum and prefrontal cortex and then performed single nucleotide polymorphism (SNP) scans of the DRD2 locus. A previously uncharacterized promoter SNP (rs12364283) located in a conserved suppressor region was associated with enhanced DRD2 expression, whereas previously studied DRD2 variants failed to affect expression. Moreover, two frequent intronic SNPs (rs2283265 and rs1076560) decreased expression of DRD2 short splice variant (expressed mainly presynaptically) relative to DRD2 long (postsynaptic), a finding reproduced in vitro by using minigene constructs. Being in strong

linkage disequilibrium with each other, both intronic SNPs (but not rs12364283) were also associated with greater activity of striatum and prefrontal cortex measured with fMRI during working memory and with reduced performance in working memory and attentional control tasks in healthy humans. These results identify regulatory DRD2 polymorphisms that modify mRNA expression and splicing and working memory pathways. Zhang, Y., Bertolino, A., Fazio, L., Blasi, G., Rampino, A., Romano, R., Lee, M.L., Xiao, T., Papp, A., Wang, D., and Sadee, W. Proc. Natl. Acad. Sci. U S A. 104(51), pp. 20552-20557, 2007.

The Metabotropic Glutamate Receptor 7 (mGluR(7)) Allosteric Agonist AMN082 Modulates Nucleus Accumbens GABA and Glutamate, but not Dopamine, in Rats

INVEST Fellow: Zhengxiong Xi (China, 1995-1996)

The group III metabotropic glutamate receptor 7 (mGluR(7)) has been implicated in many neurological and psychiatric diseases, including drug addiction. However, it is unclear whether and how mGluR(7) modulates nucleus accumbens (NAc) dopamine (DA), l-glutamate or gamma-aminobutyric acid (GABA), important neurotransmitters believed to be involved in such neuropsychiatric diseases. In the present study, the authors found that systemic or intra-NAc administration of the mGluR(7) allosteric agonist N,N'-dibenzyhydryl-ethane-1,2-diamine dihydrochloride (AMN082) dose-dependently lowered NAc extracellular GABA and increased extracellular glutamate, but had no effect on extracellular DA levels. Such effects were blocked by (R,S)-alpha-methylserine-O-phosphate (MSOP), a group III mGluR antagonist. Intra-NAc perfusion of tetrodotoxin (TTX) blocked the AMN082-induced increases in glutamate, but failed to block the AMN082-induced reduction in GABA, suggesting vesicular glutamate and non-vesicular GABA origins for these effects. In addition, blockade of NAc GABA(B) receptors by 2-hydroxy-saclofen itself elevated NAc extracellular glutamate. Intra-NAc perfusion of 2-hydroxy-saclofen not only abolished the enhanced extracellular glutamate normally produced by AMN082, but also decreased extracellular glutamate in a TTX-resistant manner. The authors interpret these findings to suggest that the increase in glutamate is secondary to the decrease in GABA, which overcomes mGluR(7) activation-induced inhibition of non-vesicular glutamate release. In contrast to its modulatory effect on GABA and glutamate, the mGluR(7) receptor does not appear to modulate NAc DA release. Li, X., Gardner, E.L., and Xi, Z.X. Neuropharmacology. November 19, 2007, Epub ahead of print.

Effects of Gabapentin on Cocaine Self-Administration, Cocaine-Triggered Relapse and Cocaine-Enhanced Nucleus Accumbens Dopamine in Rats

INVEST Fellow: Zhengxiong Xi (China, 1995-1996)

Gabapentin is a gamma-aminobutyric acid (GABA) analogue, with GABAmimetic pharmacological properties. Gabapentin is used for the treatment of seizures, anxiety and neuropathic pain. It has been proposed that gabapentin may be useful in the treatment of cocaine dependence. However, clinical trials with gabapentin have shown conflicting results, while preclinical studies are sparse. In the present study, the authors investigated the effects of gabapentin on intravenous cocaine self-administration and cocaine-triggered reinstatement of drug-seeking behavior, as well as on cocaine-enhanced dopamine (DA) in the nucleus accumbens (NAc). They found that gabapentin (25-200mg/kg, i.p., 30min or 2h prior to cocaine) failed to inhibit intravenous cocaine (0.5mg/kg/infusion) self-administration under a fixed-ratio reinforcement schedule or cocaine-triggered reinstatement of cocaine-seeking behavior. In vivo microdialysis showed that the same doses of gabapentin produced a modest increase (approximately 50%, $p<0.05$) in extracellular NAc GABA levels, but failed to alter either basal or cocaine-enhanced NAc DA. These data suggest that gabapentin is a weak GABA-mimic drug. At the doses tested, it has no effect in the addiction-related animal behavioral models here tested. This is in striking contrast to positive findings in the same animal models

shown by another GABAmimetic - gamma-vinyl GABA (see companion piece to present article). Peng, X.Q., Li, X., Li, J., Ramachandran, P.V., Gagare, P.D., Pratihar, D., Ashby, C.R. Jr., Gardner, E.L., and Xi, Z.X. Drug Alcohol Depend. December 5, 2007, Epub ahead of print.

Gamma-Vinyl GABA Inhibits Cocaine-Triggered Reinstatement of Drug-Seeking Behavior in Rats by a Non-Dopaminergic Mechanism

INVEST Fellow: Zhengxiong Xi (China, 1995-1996)

Relapse to drug use is a core feature of addiction. Previous studies demonstrate that gamma-vinyl GABA (GVG), an irreversible GABA transaminase inhibitor, attenuates the acute rewarding effects of cocaine and other addictive drugs. The authors here report that systemic administration of GVG (25-300mg/kg) dose-dependently inhibits cocaine- or sucrose-induced reinstatement of reward-seeking behavior in rats. In vivo microdialysis data indicated that the same doses of GVG dose-dependently elevate extracellular GABA levels in the nucleus accumbens (NAc). However, GVG, when administered systemically or locally into the NAc, failed to inhibit either basal or cocaine-priming enhanced NAc dopamine in either naive rats or cocaine extinction rats. These data suggest that: (1) GVG significantly inhibits cocaine- or sucrose-triggered reinstatement of reward-seeking behavior; and (2) a GABAergic-, but not dopaminergic-, dependent mechanism may underlie the antagonism by GVG of cocaine-triggered reinstatement of drug-seeking behavior, at least with respect to GVG's action on the NAc. Peng, X.Q., Li, X., Gilbert, J.G., Pak, A.C., Ashby, C.R. Jr., Brodie, J.D., Dewey, S.L., Gardner, E.L., and Xi, Z.X. Drug Alcohol Depend. December 4, 2007, Epub ahead of print.

Incidence of Fatal Adverse Drug Reactions: A Population Based Study

INVEST Fellow: Henrik Druid (Sweden, 2000-2001)

Fatal adverse drug reactions are estimated to be the seventh most common cause of death in Sweden. The aim of this study was to determine the incidence of fatal adverse drug reactions (FADRs) in a Swedish population. Every seventh randomly selected deceased in three counties in South-east Sweden during 1 January 2001-31 December 2001 was identified in the Cause of Death Register. Relevant case records (hospitals and/or primary care centers and medicolegal files) were reviewed to identify suspected drug-related fatalities. Of 1574 deceased study subjects, 49 (3.1%; 95% CI 2.2%, 4.0%) were suspected to have died from FADRs. The most common suspected FADRs were gastrointestinal hemorrhages (n = 18; 37%), central nervous system hemorrhages (n = 14; 29%), cardiovascular disorders (n = 5; 10%), other hemorrhages (n = 4; 8%) and renal dysfunction (n = 3; 6%). The drugs most commonly implicated in FADRs were antithrombotic drugs (n = 31; 63%), followed by nonsteroidal anti-inflammatory drugs (NSAIDs) (n = 9; 18%), antidepressants (n = 7; 14%) and cardiovascular drugs (n = 4; 8%). Of all the 639 fatalities in hospital 41 (6.4%; 95% CI 4.5%, 8.3%) were suspected to be due to FADRs. The authors conclude that the medical burden of FADRs is significant. Hemorrhages were seen in a majority of the FADRs; antithrombotic agents or NSAIDs were implicated in most of these events. These results suggest that preventive measures should be taken to reduce the number of deaths caused by drugs. Wester, K., Jnsson, A.K., Spigset, O., Druid, H., and Hgg, S. Br. J. Clin. Pharmacol. December 7, 2007, Epub ahead of print.

A Selective Nav1.8 Sodium Channel Blocker, A-803467, Attenuates Spinal Neuronal Activity in Neuropathic Rats

INVEST Fellow: Steven McGaraughty (Canada, 1995-1996)

The authors have recently reported that systemic delivery of A-803467, a selective Nav1.8 sodium channel blocker, reduces behavioral measures of chronic pain. In the current study, the effects of A-803467 on evoked and spontaneous firing of wide dynamic range (WDR) neurons were measured in uninjured and spinal nerve ligated (SNL) rats. Administration of A-803467 (10-30 mg/kg, i.v.) reduced mechanically evoked (10 g von Frey hair) and

spontaneous WDR neuronal activity in SNL rats. In uninjured rats, A-803467 (20 mg/kg, i.v.) transiently reduced evoked, but not spontaneous firing of WDR neurons. The systemic effects of A-803467 in SNL rats were not altered by spinal transection or by systemic pre-treatment with the TRPV1 receptor agonist, resiniferatoxin, at doses that impair the function of TRPV1-expressing fibers. In order to determine sites of action, A-803467 was administered into spinal tissue, into the uninjured L4 dorsal root ganglion (DRG), or into the neuronal receptive field. Injections of A-803467 into the L4 DRG (30-100 nmol/1 microl) or into the hind paw receptive field (300 nmol/50 microl) reduced evoked but not spontaneous WDR firing. In contrast, intra-spinal (50-150 nmol/ 0.5 microl) injection of A-803467 decreased both evoked and spontaneous discharges of WDR neurons. Thus, Nav1.8 sodium channels on the cell bodies/axons within the L4 DRG as well as on peripheral and central terminals of primary afferent neurons regulate the inflow of low threshold mechanical signals to spinal WDR neurons, but Nav1.8 sodium channels on central terminals appear to be key to the modulation of spontaneous firing in SNL rats. McGaraughty, S., Chu, K.L., Scanio, M.J., Kort, M.E., Faltynek, C.R., and Jarvis, M.F. J. Pharmacol. Exp. Ther. December 18, 2007, Epub ahead of print.

Pharmacological MRI in Awake Rats Predicts Selective Binding of Alpha(4)beta(2) Nicotinic Receptors

INVEST Fellow: Steven McGaraughty (Canada, 1995-1996)

Neuronal nicotinic receptors are the subject of intensive research focused on developing novel therapies for drug abuse, neurocognitive disorders, neurodegenerative diseases, and pain. In this study, the authors have applied pharmacological magnetic resonance imaging (phMRI) in awake rats to map functional brain responses to the selective alpha(4)beta(2) nicotinic receptor agonists, A-85380, and ABT-594. Moreover, they have validated their methods by comparison with autoradiography using [(3)H]-A-85380 and [(3)H]-ABT-594. Under awake conditions (no anesthesia during scanning) where rats were habituated to the imaging environment, both compounds increased regional cerebral blood volume (rCBV) across multiple brain regions that closely matched regional brain receptor distribution with the same tritiated compounds. In addition, regional ABT-594-induced rCBV changes under awake conditions were also derived and characterized using a pharmacological model. Area-under-curve and maximum rCBV changes in brain were found to be dose-related and region-specific, and corresponded well with the known preclinical behavioral profile of this drug. In contrast, under conditions of alpha-chloralose anesthesia where physiological variables were maintained within normal ranges, increases in rCBV induced by ABT-594 were primarily restricted to some cortical areas and did not agree well with autoradiography data. These data demonstrate the utility of using phMRI in awake animals to characterize selective pharmacological action but also highlight an important confound (anesthesia) that is rarely considered in preclinical phMRI studies. Synapse 62:159-168, 2008. (c) 2007 Wiley-Liss, Inc. Chin, C.L., Pauly, J.R., Surber, B.W., Skoubis, P.D., McGaraughty, S., Hradil, V.P., Luo, Y., Cox, B.F., and Fox, G.B. Synapse. 62(3), pp. 159-168, 2007, Epub ahead of print.

Role of Nociceptin/Orphanin FQ and the Pseudopeptide [Phe(1)Psi(CH(2)NH)Gly(2)]-nociceptin(1-13)-NH(2) and Their Interaction with Classic Opioids in the Modulation of Thermonociception in the Land Snail Helix Aspersa

INVEST Fellow: Silvia Cruz (Mexico, 1996-1997)

The role in nociception of nociceptin/orphanin FQ (N/OFQ) and its receptor, the opioid receptor-like 1 (NOP), remains unclear because this peptide has been implicated in both suppression and enhancement of nociception. The present work characterizes the effects of N/OFQ and the NOP receptor antagonist, the pseudopeptide [Phe(1)Psi(CH(2)NH)Gly(2)]-nociceptin(1-13)-NH(2) (Phe(1)Psi), on thermonociception in the snail Helix aspersa using the hot plate assay. Additionally, the possible interaction of each of these compounds with

morphine or dynorphin A(1-17) and naloxone was studied. Compounds were administered into the hemocoel cavity of H. aspersa and the latency to the aversive withdrawal behavior recorded. Dose-response and time course curves were done. N/OFQ and naloxone produced a similar dose-dependent pronociceptive effect; however, N/OFQ reached its peak effect earlier and was 30 times more potent than naloxone. [Phe(1)Psi(CH(2)NH)Gly(2)]-nociceptin(1-13)-NH(2) and the opioid agonists, morphine and dynorphin A(1-17) produced antinociception with a similar efficacy, but [Phe(1)Psi(CH(2)NH)Gly(2)]-nociceptin(1-13)-NH(2) reached its peak effect more rapidly and lasted longer than that of dynorphin A(1-17) and morphine. [Phe(1)Psi(CH(2)NH)Gly(2)]-nociceptin(1-13)-NH(2) was 50 times less potent than dynorphin A(1-17), but 30 times more potent than morphine. N/OFQ significantly reduced morphine and dynorphin A(1-17)-induced antinociception. Combined administration of low doses of [Phe(1)Psi(CH(2)NH)Gly(2)]-nociceptin(1-13)-NH(2) and morphine or dynorphin A(1-17) produced a potent antinociceptive effect. Sub-effective doses of naloxone and N/OFQ also synergized to produce pronociception. Data suggest that these two opioid classes regulate nociception through parallel systems. The H. aspersa model appears as a valuable experimental preparation to continue the study of these opioid receptor systems. Miller-Perez, C., Sanchez-Islas, E., Pellicer, F., Rodriguez-Manzo, G., Cruz, S.L., and Leon-Olea, M. Eur. J. Pharmacol. November 28, 2007, Epub ahead of print.

Publications by Former NIDA Hubert H. Humphrey Drug Abuse Research Fellows

Comparing Serial and Nonserial Sexual Offenders: Alcohol and Street Drug Consumption, Impulsiveness and History of Sexual Abuse
HHH Fellow: Arthur Guerra de Andrade (Brazil, 1991-1992)
The objectivwe of this study was to evaluate the differences between serial and nonserial sexual offenders in terms of alcohol and drug consumption, impulsivity, and personal history of being sexually abused. A sectional and retrospective study was carried out by the team of the outpatient clinic for the treatment of sexual disorders at Faculdade de Medicina do ABC - Santo Andre, Brazil. Three groups of subjects (n = 198) consisting of sexual offenders against one victim, two victims and three or more victims were examined. Convicts sentenced only for sexual crimes were evaluated with the Drug Addiction Screening Test, the CAGE, the Short Alcohol Dependence Data, the Barratt Impulsiveness Scale, the Sexual Addiction Screening Test, and the Static-99. Sexual offenders against three or more victims showed more frequent history of being sexually abused than the sexual offenders against one victim. A one-way analysis of variance indicated that sexual offenders against three or more victims evidenced significantly higher scores on the Barratt Impulsiveness Scale and on the Sexual Addiction Screening Test than did the sexual aggressors against one victim. After a multinomial logistic regression analysis, the Barratt Impulsiveness Scale and the history of being sexually abused were predicting factors for the group of aggressors against three or more victims in relation to the aggressors against one victim. The authors conclude that sexual offenders against three or more victims present different characteristics from other groups of sexual offenders and these findings can help to create proposals for the management of this type of inmates. Baltieri, D.A., and Andrade, A.G. Rev. Bras. Psiquiatr. December 20, 2007, Epub ahead of print.

Urban Rural Differences in Prevalence of Self-Reported Diabetes in India-The WHO-ICMR Indian NCD Risk Factor Surveillance
HHH Fellow: Nimesh Desai (India, 1999-2000)
Recent reports show strikingly high prevalence of diabetes among urban Asian Indians; however, there are very few studies comparing urban, peri-urban and rural prevalence rates of diabetes and their risk factors at the national level. This study is a part of the national non-communicable diseases (NCD) risk

factor surveillance conducted in different geographical locations (North, South, East, West/Central) in India between April 2003 and March 2005. A total of 44,523 individuals (age: 15-64 years) inclusive of 15,239 from urban, 15,760 from peri-urban/slum and 13,524 from rural areas were recruited. Major risk factors were studied using modified WHO STEPS approach. Diabetes was diagnosed based on self-reported diabetes diagnosed by a physician. The lowest prevalence of self-reported diabetes was recorded in rural (3.1%) followed by peri-urban/slum (3.2%) and the highest in urban areas (7.3%, odds ratio (OR) for urban areas: 2.48, 95% confidence interval (CI): 2.21-2.79, $p<0.001$). Urban residents with abdominal obesity and sedentary activity had the highest prevalence of self-reported diabetes (11.3%) while rural residents without abdominal obesity performing vigorous activity had the lowest prevalence (0.7%). In conclusion, this nation-wide NCD risk factor surveillance study shows that the prevalence of self-reported diabetes is higher in urban, intermediate in peri-urban and lowest in rural areas. Urban residence, abdominal obesity and physical inactivity are the risk factors associated with diabetes in this study. Mohan, V., Mathur, P., Deepa, R., Deepa, M., Shukla, D.K., Menon, G.R., Anand, K., Desai, N.G., Joshi, P.P., Mahanta, J., Thankappan, K.R., and Shah, B. Diabetes Res. Clin. Pract. January 29, 2008, Epub ahead of print.

Hypotension Caused by Therapeutic Doses of Venlafaxine: Case Report and Proposed Pathophysiological Mechanisms

HHH Fellow: Arthur Guerra de Andrade (Brazil, 1991-1992)

Although venlafaxine is usually associated with modest increases in blood pressure and not so often clinical hypertension, there are a few reported cases of hypotension related to overdoses of this specific antidepressant. The case study of a young female patient with a history of Major Depressive Disorder who initiated treatment with venlafaxine 75 mg/day and developed hypotension when the dosage was titrated up to 225 mg/day is described. The patient did not present comorbid diseases nor use other medication. A temporal association and a dose-dependent relationship between the hypotension and the use of venlafaxine is shown. To the best of the knowledge of the authors, this is the first case report that specifically associates regular doses of venlafaxine with the presence of hypotension. A pathophysiological mechanism is proposed, involving the participation of presynaptic alpha2-adrenergic receptors and the presence of a possible genetic polymorphism of cytochrome P4502D6, which is associated with lower drug metabolization, to explain the relationship between venlafaxine in regular dosage and development of hypotension. Alexandrino-Silva, C., Maua, F.H., De Andrade, A.G., and De Toledo Ferraz Alves, T.C. J. Psychopharmacol. January 21, 2008, Epub ahead of print.

Drugs and Fatal Traffic Accidents in the Czech Republic

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

The aim of the study was to determine the prevalence of psychotropic drug use in active participants in traffic accidents who died during the accident or shortly after it due to injuries resulting from the accident. A special mortality register containing data of all forensic autopsies was analyzed. The studied sample consisted of persons who died during traffic accidents and were active participants in those ones (pedestrians, cyclists, or drivers), and were toxicologically tested during the forensic examination. The sample consisted of 1,213 cases, 1,039 (85.7%) males and 174 (14.3%) females who died in 2003-2005. Ethanol was found in 34.7% of cases, however a significant declining trend over the years was noted. The proportion of positive detections for any psychotropic drug other than alcohol was 7.2%; benzodiazepines were found most frequently (3.6%), followed by cannabis (2.2%), and stimulants (1.7% of the sample). Positive findings of ethanol were significantly more common among males, whereas positive benzodiazepine tests were more frequent in females. Positive cases were significantly younger than negative ones for ethanol, volatile substances, stimulants, and cannabis; in cases of

positive medicaments tests, the positive cases were significantly older than the negatives. Mravci-k, V., Vorel, F., and Zabransky, T. Cent. Eur. J. Public Health. 15(4), pp. 158-162, 2007.

Stimulant Injectors in Ukraine: The Next Wave of the Epidemic?
HHH Fellow: Sergey Dvoryak (Ukraine, 1999-2000)
This study was designed to assess differences in drug and sex-related risk behaviors between injectors of opiates only, opiate/sedative mix only and stimulants only. Participants were current out-of-treatment injection drug users (IDUs), unaware of their HIV status, recruited through street outreach in Kiev, Odessa and Makeevka/Donetsk, Ukraine. Overall, 22% tested positive for HIV, including 39% among opiate/sedative injectors, 19% among opiate injectors and 17% among stimulant injectors. Despite these differences, stimulant injectors were at higher risk than other IDUs in sharing a used needle/syringe, always injecting with others, injecting a drug solution drawn from a common container, having an IDU sex partner, not using condoms during vaginal or anal sex and on composite measures of injection and sex risks. After controlling for age differences, stimulant injectors remained at higher risk in their needle and sex risk behaviors. The authors conclude that without intervention, it is likely that HIV will increase among stimulant injectors. Booth, R.E., Lehman, W.E., Kwiatkowski, C.F., Brewster, J.T., Sinitsyna, L., and Dvoryak, S. AIDS Behav. February 9, 2008, Epub ahead of print.

Socio-Cultural, Psychosexual and Biomedical Factors Associated with Genital Symptoms Experienced by Men in Rural India
HHH Fellow: Nimesh Desai (India, 1999-2000)
Biomedical, anthropological and psychiatric frameworks have been used to research different elements of men's sexual health - sexually transmitted infections, psychosexual concerns and psychological distress - but rarely within the same study. The authors combined these in a study in rural north India. In Tehri Garhwal and Agra districts, they explored male perceptions of genital and sexual symptoms through focus group discussions and then conducted a clinic-based survey of 366 symptomatic men who presented at rural private provider clinics. Men's urine specimens were tested for gonorrhea and chlamydia infection using polymerase chain reaction techniques. Researchers screened them for probable psychological distress by administering the General Health Questionnaire (12- items). Results revealed that local and traditional notions of health influenced men's symptom perceptions, with semen loss their predominant concern. Dhat, commonly perceived as an involuntary semen loss, corresponded most closely with the symptom of urethral discharge, but was attributed mainly to non-infectious causes. It could also manifest as a syndrome with physical weakness and mental lethargy. FGD participants lacked correct and complete information on reproductive health. Around 75% of the symptomatic men presented with dhat, but only 5.5% tested positive for gonorrhea or chlamydia. Application of syndromic sexually transmitted infection (STI) guidelines in these settings could result in over diagnosis and over treatment with antibiotics. In contrast, there was a significant association between dhat and probable psychological distress as detected by the GHQ (Adjusted OR, GHQ case positive: 2.66, 95% CI: 1.51-4.68). This study confirms the existence of a dhat syndrome in rural India, which is culturally influenced and reflects heightened psychosexual concerns as well as mental distress states. Comprehensive health services for men should include assessments of their psychosexual needs and be supported by reproductive/sexual health education. STI treatment guidelines for urethral symptoms should be revised and be based on epidemiological data. Gautham, M., Singh, R., Weiss, H., Brugha, R., Patel, V., Desai, N.G., Nandan, D., Kielmann, K., and Grosskurth, H. Trop. Med. Int. Health February 19, 2008, Epub ahead of print.

Methylphenidate DAT Binding in Adolescents with Attention-Deficit/ Hyperactivity Disorder Comorbid with Substance Use Disorder - a

Single Photon Emission Computed Tomography with [Tc(99m)]TRODAT-1 Study

HHH Fellow: Flavio Pechansky (Brazil, 1993-1994)

Background: Attention-Deficit/Hyperactivity Disorder (ADHD) is highly prevalent among adolescents with Substance Use Disorders (SUD). Effects of methylphenidate (MPH) on ADHD are attributed to its properties of blocking the dopamine transporter (DAT) in the striatum. However, it has been demonstrated that drug addiction is associated with dopaminergic system changes that may affect MPH brain effects, emphasizing the need to better understand MPH actions in subjects with ADHD+SUD. The objective of this study was to evaluate the effect of an extended release formulation of MPH (MPH-SODAS) on DAT availability in 17 stimulant-naive ADHD adolescents with comorbid SUD (cannabis and cocaine). Subjects underwent two single photon emission computed tomography (SPECT) scans with [Tc(99m)]TRODAT-1, at baseline and after 3 weeks on MPH-SODAS. Clinical assessment for ADHD relied on the Swanson, Nolan and Pelham Scale - version IV (SNAP-IV). Caudate and putamen DAT binding potential (BP) was calculated. After 3 weeks on MPH-SODAS, there was a significant reduction of SNAP-IV total scores ($p<0.001$), and approximately 52% reductions of DAT BP at the left and right caudate. Similar decreases were found at the left and right putamen ($p<0.001$ for all analyses). This study shows that the magnitude of DAT blockade induced by MPH in this population is similar to what is found in ADHD patients without SUD comorbidity, providing neurobiological support for trials with stimulants in adolescents with ADHD+SUD, an important population excluded from studies. Szobot, C.M., Shih, M.C., Schaefer, T., Junior, N., Hoexter, M.Q., Fu, Y.K., Pechansky, F., Bressan, R.A., and Rohde, L.A. Neuroimage. January 10, 2008, Epub ahead of print.

Schizophrenia Modifying the Expression of Gender Identity Disorder

HHH Fellow: Arthur Guerra de Andrade (Brazil, 1991-1992)

According to the Brazilian Federal Medical Association, transsexualism is recognized as a gender identity disorder if a long-term diagnostic therapeutic process has demonstrated that the transposition of gender roles is irreversible, and if only hormonal and surgical procedures are appropriate to relieve the stress associated with the gender identity. Although such treatment will only be initiated with caution and after a long phase of intense diagnostic screening, the differentiation between pure identity disorders and transsexual feelings secondary to an ongoing psychopathologic process, such as schizophrenia, can be arduous for many health professionals. The aim of this article was to report a case of a female patient with schizophrenia and transsexualism and the risks of a potential diagnostic confusion. A 19-year-old black woman, with an 8-year history of undifferentiated schizophrenia and intense gender dysphoria, was referred for sex reassignment surgery evaluation in the Ambulatory for the Treatment of Sexual Disorders of the ABC Medical School. After a more adequate antipsychotic treatment, her masculine behavior has persisted, but her desire to change her own genital organs has decreased. A better acceptance of the multiplicity of possible genders should neither contribute to inadequate interpretations of the signs and symptoms of our patients nor facilitate dangerous clinical or surgical recommendations. Baltieri, D.A., and De Andrade, A.G. J. Sex Med. December 7, 2007, Epub ahead of print.

Outcomes and Adherence in Syria's First Smoking Cessation Trial

HHH Fellow: Fadi Hammal (Syria, 2005-2006)

The objective of this study was to determine the feasibility of implementing cessation interventions in Syria. The authors randomized 50 smokers to either a brief or intensive behavioral cessation intervention. Adherence to treatment and cessation through 3 months postcessation were calculated. Adherence in the intensive group was only moderate and was associated with smoking for more years and higher self-efficacy. Cessation rates in the brief and intensive intervention groups were 16% and 4%, respectively. Nicotine dependence predicted abstinence at 3 months. Important barriers to cessation included

perceived dependence, lack of access to pharmacotherapy, poor social support, and water pipe smoking. Asfar, T., Weg, M.V., Maziak, W., Hammal, F., Eissenberg, T., and Ward, K.D. Am. J. Health Behav. 32(2), pp. 146-156, 2008.

Tobacco Control in Developing Countries: Tanzania, Nepal, China, and Thailand as Examples

HHH Fellow: Stephen Nsimba (Tanzania, 2005-2006)

This paper illustrates case studies of four developing countries and compares them as to relative advancement in tobacco control as prescribed by the Framework Convention on Tobacco Control. Tobacco-control efforts first seem to involve assessment of tobacco use prevalence and passage of tobacco-control legislation (e.g., warning labels). Tanzania, Nepal, and China serve as examples. Eventually, an integrated tobacco-control stance that demonstrates several cycles of tobacco-control activities occurs, as is shown in Thailand. Through these case studies, one can achieve a sense of the direction of progress in tobacco control in developing countries. Sussman, S., Pokhrel, P., Black, D., Kohrman, M., Hamann, S., Vateesatokit, P., and Nsimba, S.E. Nicotine Tob. Res. 9 Suppl 3, pp. 447-457, 2007.

The Association between Disability and Residual Symptoms in Depressive Patients: A 3-Month Follow-Up

HHH Fellow: Berna Ulug (Turkey, 1995-1996)

In this 3-month naturalistic follow-up the authors aimed to investigate depression treatment outcome and the correlation between improvement of depressive symptoms and level of disability. The study included 104 patients with depression that presented to the Hacettepe Psychiatry Outpatient Clinic. The course was defined operationally using the Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale, and Structured Clinical Interview for DSM-IV Axis I Disorders. The World Health Organization Disability Assessment Schedule (WHO-DAS II) was administered to determine level of disability. Patients received follow-up assessments using the same instruments 3 months after receiving antidepressant treatment. Follow-up assessments showed that improvement in Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale total scores was statistically significant, and lower anxiety and depression ratings were correlated with lower disability levels. The patients that had severe depression and anxiety at the beginning of the course had residual depressive symptoms. The results showed that severity of depression was a predictor of residual symptoms in this cohort. Psychological anxiety was the most common residual symptom (consistent with other studies) and the patients with a psychological anxiety score >/= 2 had higher disability levels ($Z = -3.570$, $P < 0.05$). Severity of depression was a predictor of residual symptoms and partial remission after a depressive episode appeared to be strongly associated with disability. These findings highlight the importance of adequate treatment of depression. Ozyuksel, B., and Ulug, B. Turk. Psikiyatri. Derg.18(4), pp. 323-332, 2007 (Turkish).

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

Research Findings - Intramural Research

Chemistry and Drug Metabolism, CPTRB

Methadone Maintenance and Breastfeeding in the Neonatal Period
Lactation among methadone-maintained women is frequently challenged due to lack of knowledge and guidelines regarding this practice. In methadone-maintained breastfeeding women and a matched group of formula-feeding women, IRP scientists evaluated breast milk methadone concentrations and concentrations of methadone in maternal and infant plasma in both groups. Eight methadone-maintained (dose range 50-105 mg/day), lactating women provided blood and breast milk on days 1, 2, 3, 4, 14 and 30 after delivery at expected trough and peak times. Paired foremilk and hindmilk specimens were obtained at each sampling time. Eight matched formula-feeding subjects had blood drawn the same days. Infant blood for both groups was obtained on day 14. Urine toxicology between 36 weeks gestation and 30 days post-partum confirmed that subjects were not using illicit substances in the perinatal period. Concentrations of methadone in breast milk were low (range 21.0-462.0 ng/mL) and not related to maternal dose. There was a significant increase in methadone concentrations in breast milk over time for all six sampling times. Maternal methadone plasma concentrations were not different between groups and unrelated to maternal dose. Infant methadone plasma concentrations were low in all specimens (range 2.2 - 8.1 ng/mL). Infants in both groups had neurobehavioral assessments on days 3, 14 and 30; there were no significant effects of breastfeeding on neurobehavioral outcomes. Fewer infants in the breastfed group required pharmacotherapy for neonatal abstinence syndrome, but this was not a statistically significant finding. Results contribute to the recommendation of breastfeeding for methadone-maintained women. Jansson, L.M., Choo, R.E., Velez, M., Harrow, C., Schroeder, J., Shakleya, D.M. and Huestis, M.A. Pediatrics, 121, pp. 106-114, 2008.

Validation and Application of a Novel Method for the Determination of Buprenorphine, Norbuprenorphine and Their Glucuronide Conjugates in Human Meconium
A novel liquid chromatography tandem mass spectrometry (LCMSMS) method for buprenorphine, norbuprenorphine, and glucuronidated conjugates' quantification in meconium was developed and fully validated. Maternal self-report, the most common mechanism for identifying drug-exposed neonates is less reliable than biological monitoring of maternal and infant specimens. Meconium, the highly complex neonatal fecal material, is easy and non-invasive to collect and has higher sensitivity and specificity than urine to detect in utero drug exposure. Controlled administration of illicit drugs during pregnancy is unethical and unsafe, and administration of licit medications is recommended only as needed. Buprenorphine administration to pregnant opiate addicts to reduce illicit drug use and craving provides an important opportunity to study disposition of this drug in the maternal-fetal dyad. It is

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unknown whether buprenorphine dose is correlated to buprenorphine and/or metabolite concentrations in meconium, and if meconium concentrations predict neonatal outcomes. This research has not been possible due to the lack of a validated, quantitative chromatographic method for measuring buprenorphine in this neonatal matrix. This method will enable the question of whether drug doses predict meconium drug concentrations, and whether drug concentrations correlate with onset, magnitude and duration of neonatal abstinence syndrome and other outcomes. These findings could improve clinical care in this vulnerable population. Development of this new biomarker assay for buprenorphine and metabolites in meconium is a critical step for conducting this research. This sensitive and specific method will monitor in utero buprenorphine exposure and determine if correlations exist between buprenorphine exposure and neonatal outcomes. Kacinko, S.L., Shakleya, D.M. and Huestis, M.A. Analytical Chemistry, 80, pp. 246-252, 2008.

MDMA, HMMA, MDA, and HMA Plasma Pharmacokinetics in Humans Following Controlled MDMA Administration

An extended pharmacokinetic analysis of MDMA or Ecstasy and three metabolites, HMMA, MDA and HMA, characterizing Cmax, Tmax, AUC()(), detection windows, t1/2, Vd/F, CL/F, and metabolite ratios for up to 143 h after oral MDMA dosing in young adults was performed. The aim of the study was to document whether non-linearity in MDMA pharmacokinetics occurred at recreational doses, and to characterize MDMA pharmacokinetics in African-Americans and women for the first time. Seventeen female and male participants received placebo, low (1.0 mg/kg), and high (1.6 mg/kg) oral MDMA doses in a double blind, randomized, balanced, within-subject design. Study strengths included metabolite measurements, concentrations after low and high doses, frequent and extended plasma sampling, and residence of participants on a closed research unit with 24-h monitoring to prevent self-administration of MDMA or other drugs. A fully validated 2D-GC/MS method simultaneously quantified MDMA and metabolites. Mean +/- SD maximum plasma concentrations (Cmax) were 162.9+/-39.8 and 171.9+/-79.5 ng/mL for MDMA and HMMA, respectively, after low and 291.8+/-76.5 and 173.5+/-66.3 ng/mL after high MDMA doses, demonstrating non-linear MDMA pharmacokinetics. Mean MDMA volume of distribution was constant for low and high doses; clearance was significantly higher after the low dose. MDMA primarily affects the serotonergic system, acting as an indirect monoaminergic agonist; however, the mechanism(s) by which MDMA causes toxicity are not fully understood. Non-linearity in MDMA dose-concentration relationships and wide variability between subjects at typical recreational doses could contribute to observed MDMA toxicity. Preliminary data on gender differences in drug elimination also were noted. Kolbrich, E.A., Goodwin, R.S., Gorelick, D.A., Hayes, R.J., Stein, E.A., and Huestis, M.A. Presentation, 2008. American Academy of Forensic Sciences (AAFS) Annual Meeting, Washington, DC, February 18-22, 2008.

Office of the Scientific Director

Longitudinal ECG Changes in Cocaine Users During Extended Abstinence

Cocaine causes acute changes in the human electrocardiogram (ECG), such as lengthened QTc interval, which can be a marker for cardiac arrhythmias, but the effects of extended abstinence after chronic cocaine use are not well understood. The authors are not aware of any prospective, longitudinal study addressing this issue. This study recorded weekly ECGs from 25 physically healthy, adult, chronic cocaine users during up to 3 months of monitored abstinence on a closed research ward. The first (baseline) ECG was recorded a mean of 20.5 hours after last cocaine use. The greater the total amount of cocaine used and amount used per day in the 2 weeks prior to ward admission, the longer the baseline QTc interval, consistent with an effect of cocaine use.

Planned Meetings

Publications

Staff Highlights

Grantee Honors

There was a significant shortening of QTc interval during the first week of abstinence, with no further significant changes thereafter. There were no significant changes in other ECG parameters. These findings suggest that cocaine-associated QTc prolongation (and possibly risk for cardiac arrhythmia) returns toward normal during the first week of cocaine abstinence. Levin K.H., Copersino M.L., Epstein D.H., Boyd S.J., and Gorelick D.A. Drug and Alcohol Dependence, 95, pp. 160-163, 2008.

Molecular Neuropsychiatry Branch

Differential Neurochemical Consequences of an Escalating Dose-binge Regimen Followed by Single-day Multiple-dose Methamphetamine Challenges

Chronic intake of methamphetamine (METH) causes tolerance to its behavioral and subjective effects. To better mimic human patterns of drug abuse, the present study used a rodent model that took into account various facets of human drug administration and measured METH-induced effects on brain monoamine levels. Adult male Sprague-Dawley rats were injected with METH or saline according to an escalating dose schedule for 2 weeks. This was followed by a challenge regimen of either saline or one of two doses of METH (3 x 10 mg/kg every 2 h or 6 x 5 mg/kg given every hour, both given within a single day). Both challenge doses of METH caused significant degrees of depletion of dopamine in the striatum and norepinephrine and serotonin in the striatum, cortex, and hippocampus. Animals pre-treated with METH showed significant attenuation of METH-induced striatal dopamine depletion but not consistent attenuation of norepinephrine and serotonin depletion. Unexpectedly, METH pre-treated animals that received the 3 x 10 mg/kg challenge showed less increases in tympanic temperatures than saline pre-treated rats whereas METH pre-treated animals that received the 6 x 5 mg/kg METH challenge showed comparable increases in temperatures to saline pre-treated rats. Therefore, pre-treatment-induced partial protection against monoamine depletion is probably not because of attenuated METH-induced hyperthermia in those rats. Graham, D.L., Noailles, P.A. and Cadet, J.L. J. Neurochem., 2008, Epub ahead of print.

Transcriptional Responses to Reinforcing Effects of Cocaine in the Rat Hippocampus and Cortex

The psychostimulant effects of cocaine are thought to result from its ability to block dopamine (DA) uptake and increase DA levels in ventral striatum. In addition, cocaine causes biochemical changes in the brain areas involved in learning and memory, including hippocampus and cortex, whose role in drug reinforcement is now being actively investigated. Thus, IRP researchers studied molecular events in the hippocampus and frontal cortex of rats treated with cocaine conditioned place preference (CPP) paradigm. After exposure to cocaine conditioning (cocaine paired), cocaine alone (cocaine non-paired) or saline rats were tested for place conditioning. Cocaine (10 mg/kg) caused increases in time spent in the drug-paired compartment. By using microarray analyses, the authors examined gene expression in the hippocampi and frontal cortices of cocaine-paired rats, cocaine non-paired and saline-treated controls. Their study revealed that 214 transcripts were differentially regulated in the hippocampi of cocaine-paired rats. These include genes that play roles in protein phosphorylation, RNA processing and protein synthesis, ubiquitin-dependent protein degradation and cytoskeleton organization. In contrast, 39 genes were differently expressed in the frontal cortex. These data support the possibility that molecular changes in the hippocampus might participate in the formation and maintenance of memory patterns induced by cocaine in the brain. Differences in the transcriptional responses in the hippocampus and cortex suggest the primary importance of the hippocampus for recent memory processing associated with cocaine-induced CPP. Krasnova, I.N., Li, S.M., Wood, W.H., McCoy, M.T., Prabhu, V.V., Becker, K.G., Katz, J.L. and Cadet, J.L.

Genes Brain Behavior 7(2), pp. 193-202, 2008.

EEG of Chronic Marijuana Users During Abstinence: Relationship to Years of Marijuana Use, Cerebral Blood Flow and Thyroid Function

Marijuana abuse is associated with neurological changes including increases in frontal EEG alpha during abstinence. Research is needed to assess to what extent these EEG patterns are indicative of cerebral perfusion deficits. IRP scientists recorded the resting eyes closed EEG of 75 abstinent marijuana users and 33 control subjects. Fifty-six marijuana users used marijuana for less than eight years and 19 used for eight years or more. The EEG evaluation occurred within 72h of admission to an inpatient unit. Fifty-nine marijuana users remained abstinent for a month and were tested twice. Supplemental psychological and physiological data were also collected. Log alpha2 and beta2 power at posterior sites were significantly lower for the marijuana abusers that used eight years or more than the other marijuana abusers and the control subjects. These EEG changes continued for the month of abstinence. The marijuana users who used marijuana for more than eight years, also, had lower heart rates and thyroid function (T4) compared to the other marijuana users and the control subjects. Chronic marijuana use was also associated with reduced EEG power in alpha and beta bands at posterior sites. These reductions in EEG power appear to be related to cerebral perfusion deficits and/or thyroid function in marijuana abusers. These results suggest EEG, cerebral blood flow velocity, cardiovascular and thyroid function alterations in marijuana abusers with an extended period of use. These alterations reflect under arousal in these systems. Herning, R., Better, W. and Cadet, J.L. Clin. Neurophysiol. 119(2), pp. 321-331, 2008.

Development and Plasticity Section, Cellular Neurobiology Research Branch

Postmortem Diagnosis and Toxicological Validation of Illicit Substance Use

The present study examines the diagnostic challenges of identifying ante-mortem illicit substance use in human postmortem cases. Substance use, assessed by clinical case history reviews, structured next-of-kin interviews, by general toxicology of blood, urine and/or brain, and by scalp hair testing, identified 33 cocaine, 29 cannabis, 10 phencyclidine and nine opioid cases. Case history identified 42% cocaine, 76% cannabis, 10% phencyclidine and 33% opioid cases. Next-of-kin interviews identified almost twice as many cocaine and cannabis cases as Medical Examiner (ME) case histories, and were crucial in establishing a detailed lifetime substance use history. Toxicology identified 91% cocaine, 68% cannabis, 80% phencyclidine and 100% opioid cases, with hair testing increasing detection for all drug classes. A cocaine or cannabis use history was corroborated by general toxicology with 50% and 32% sensitivity, respectively, and with 82% and 64% sensitivity by hair testing. Hair testing corroborated a positive general toxicology for cocaine and cannabis with 91% and 100% sensitivity, respectively. Case history corroborated hair toxicology with 38% sensitivity for cocaine and 79% sensitivity for cannabis, suggesting that both case history and general toxicology underestimated cocaine use. Identifying ante-mortem substance use in human postmortem cases are key considerations in case diagnosis and for characterization of disorder-specific changes in neurobiology. The sensitivity and specificity of substance use assessments increased when ME case history was supplemented with structured next-of-kin interviews to establish a detailed lifetime substance use history, while comprehensive toxicology, and hair testing in particular, increased detection of recent illicit substance use. Lehrmann, E., Afanador, Z.R., Deep-Soboslay, A., Gallegos, G., Darwin, W.D., Lowe, R.H., Barnes, A.J., Huestis, M.A., Cadet, J.L., Herman, M.M., Hyde, T.M., Kleinman, J.E., and Freed, W.J. Addiction Biology, 13(1), pp. 105-117, 2008.

An Immortalized Rat Ventral Mesencephalic Cell Line, RTC4, is Protective in a Rodent Model of Stroke

One therapeutic approach to stroke is the transplantation of cells capable of trophic support, reinnervation, and/or regeneration. Previously, IRP researchers have described the use of novel truncated isoforms of SV40 large T antigen to generate unique cell lines from several primary rodent tissue types. Here they describe the generation of two cell lines, RTC3 and RTC4, derived from primary mesencephalic tissue using a fragment of mutant T antigen, T155c (cDNA) expressed from the RSV promoter. Both lines expressed the glial markers vimentin and S100beta, but not the neuronal markers NeuN, MAP2, or beta-III-tubulin. A screen for secreted trophic factors revealed substantially elevated levels of platelet-derived growth factor (PDGF) in RTC4, but not RTC3 cells. When transplanted into rat cortex, RTC4 cells survived for at least 22 days and expressed PDGF. Because PDGF has been reported to reduce ischemic injury, the authors examined the protective functions of RTC4 cells in an animal model of stroke. RTC4 or RTC3 cells, or vehicle, were injected into rat cortex 15-20 min prior to a 60-min middle cerebral artery ligation. Forty-eight hours later, animals were sacrificed and the stroke volume was assessed by triphenyl-tetrazolium chloride (TTC) staining. Compared to vehicle or RTC3 cells, transplanted RTC4 cells significantly reduced stroke volume. Overall, the authors generated a cell line with glial properties that produces PDGF and reduces ischemic injury in a rat model of stroke. Harvey, B.K., Chen, G.J., Schoen, C.J., Lee, C.T., Howard, D.B., Dillon-Carter, O., Coggiano, M., Freed, W.J., Wang, Y., Hoffer, B.J., and Sanchez, J.F. Cell Transplantation, 16(5), pp. 483-491, 2007.

Gene Expression Profile of Neuronal Progenitor Cells Derived from hESCs: Activation of Chromosome 11p15.5 and Comparison to Human Dopaminergic Neurons

IRP scientists initiated differentiation of human embryonic stem cells (hESCs) into dopamine neurons, obtained a purified population of neuronal precursor cells by cell sorting, and determined patterns of gene transcription. Dopaminergic differentiation of hESCs was initiated by culturing hESCs with a feeder layer of PA6 cells. Differentiating cells were then sorted to obtain a pure population of PSA-NCAM-expressing neuronal precursors, which were then analyzed for gene expression using Massive Parallel Signature Sequencing (MPSS). Individual genes as well as regions of the genome which were activated were determined. A number of genes known to be involved in the specification of dopaminergic neurons, including MSX1, CDKN1C, Pitx1 and Pitx2, as well as several novel genes not previously associated with dopaminergic differentiation, were expressed. Notably, the authors found that a specific region of the genome located on chromosome 11p15.5 was highly activated. This region contains several genes which have previously been associated with the function of dopaminergic neurons, including the gene for tyrosine hydroxylase (TH), the rate-limiting enzyme in catecholamine biosynthesis, IGF2, and CDKN1C, which cooperates with Nurr1 in directing the differentiation of dopaminergic neurons. Other genes in this region not previously recognized as being involved in the functions of dopaminergic neurons were also activated, including H19, TSSC4, and HBG2. IGF2 and CDKN1C were also found to be highly expressed in mature human TH-positive dopamine neurons isolated from human brain samples by laser capture. The present data suggest that the H19-IGF2 imprinting region on chromosome 11p15.5 is involved in the process through which undifferentiated cells are specified to become neuronal precursors and/or dopaminergic neurons. Freed, W.J., Chen, J., Baeckman, C.M., Schwartz, C.M., Vazin, T., Cai, J., Spivak, C.E., Lupica, C.R., Rao, M.S., and Zeng, X. Public Library of Science One, 3(1), pp. e1422, 2008.

Cellular Pathobiology Section, Cellular Neurobiology Research Branch

An Update on the Development of Drugs for Neuropsychiatric Disorders: Focusing on the Sigma1 Receptor Ligand

The sigma1 receptor is an intracellular molecule that shares no homology with any mammalian proteins. Sigma1 receptors normally localize at the endoplasmic reticulum and regulate a variety of signal transductions including intracellular Ca2+ dynamics and neurotrophic factor signaling. In the brain, sigma1 receptors are known to regulate the activity of diverse ion channels via protein-protein interactions. Accumulated evidence strongly indicates that the activation/upregulation of sigma1 receptors promotes the neuronal differentiation as well as a robust antiapoptotic action. In animals, sigma1 receptor agonists exhibit an antidepressant-like action. Furthermore, the agonists enhanced neuronal survival even though they were administered several hours after a brain ischemia. Thus, primary clinical targets of sigma1 receptor ligands are proposed to include stroke, neurodegenerative disorders and depression. Ligands for the sigma1 receptor may constitute a new class of therapeutic drugs targeting an endoplasmic reticular protein. Hayashi T., and Su, T.P. Expert Opinion on Therapeutic Targets, 12(1), pp. 45-58, 2008.

Sigma-1 Receptor Chaperones at the ER-Mitochondrion Interface Regulate Ca(2+) Signaling and Cell Survival

Communication between the endoplasmic reticulum (ER) and mitochondrion is important for bioenergetics and cellular survival. The ER supplies Ca(2+) directly to mitochondria via inositol 1,4,5-trisphosphate receptors (IP3Rs) at close contacts between the two organelles referred to as mitochondrion-associated ER membrane (MAM). IRP scientists found here that the ER protein sigma-1 receptor (Sig-1R), which is implicated in neuroprotection, carcinogenesis, and neuroplasticity, is a Ca(2+)-sensitive and ligand-operated receptor chaperone at MAM. Normally, Sig-1Rs form a complex at MAM with another chaperone, BiP. Upon ER Ca(2+) depletion or via ligand stimulation, Sig-1Rs dissociate from BiP, leading to a prolonged Ca(2+) signaling into mitochondria via IP3Rs. Sig-1Rs can translocate under chronic ER stress. Increasing Sig-1Rs in cells counteracts ER stress response, whereas decreasing them enhances apoptosis. These results reveal that the orchestrated ER chaperone machinery at MAM, by sensing ER Ca(2+) concentrations, regulates ER-mitochondrial interorganellar Ca(2+) signaling and cell survival. Hayashi T., and Su, T.P. Cell, 131(3), pp. 596-610, 2007.

Electrophysiology Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

MPTP-Induced Deficits in Striatal Synaptic Plasticity are Prevented by Glial Cell Line-Derived Neurotrophic Factor Expressed Via an Adeno-Associated Viral Vector

This study determined the consequences of dopamine denervation of the striatum on synaptic plasticity and prevention of these changes with gene therapy using an adeno-associated viral vector (AAV) expressing glial cell line-derived neurotrophic factor (GDNF). C57BL6/J mice were injected with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine(MPTP); long-term depression (LTD) or potentiation (LTP) were measured in vitro. Fast-scan cyclic voltammetry measured electrically released dopamine from a functionally relevant pool in these same striatal slices. After MPTP, dopamine release and uptake were greatly diminished, and LTP and LTD were blocked in the striatal slices. The loss of plasticity resulted directly from the loss of dopamine since its application rescued synaptic plasticity. Striatal GDNF expression via AAV, before MPTP, significantly protected against the loss of dopamine and prevented the blockade of corticostriatal LTP. These data demonstrate that dopamine plays a role in supporting several forms of striatal plasticity and that GDNF expression via AAV prevents the loss of dopamine and striatal plasticity caused by MPTP. The authors propose that impairment of striatal plasticity after dopamine denervation plays a role in the symptomology of Parkinson's

disease and that AAV expression of neurotrophic factors represents a tenable approach to protecting against or slowing these neurobiological deficits. Chen, Y.H., Harvey, B.K., Hoffman, A.F., Wang, Y., Chiang, Y.H., and Lupica, C.R. Federation of American Societies for Experimental Biology, 22(1), pp. 261-275, 2008.

The Endocannabinoid Anandamide Inhibits the Function of Alpha4beta2 Nicotinic Acetylcholine Receptors

The effects of the endocannabinoid anandamide (arachidonylethanolamide, AEA) on the function of alpha4beta2 nicotinic acetylcholine receptors (nAChR) stably expressed in SH-EP1 cells were investigated using the whole-cell patch-clamp technique. In the concentration range of 200 nM to 2 microM, AEA significantly reduced the maximal amplitudes and increased the desensitization of acetylcholine (ACh)-induced currents. The effects of AEA could be neither replicated by the exogenous cannabinoid Delta(9)-tetrahydrocannabinol (1 microM) nor reversed by the selective CB1 receptor antagonist 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide (SR-141716A) (1 microM). The actions of AEA were apparent when applied extracellularly but not during intracellular dialysis. Furthermore, the effects of AEA ACh currents were not altered by the calcium chelator 1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid. The onset and washout of the AEA effects required several minutes (10-30 min), but the latter was significantly decreased in the presence of lipid-free bovine serum albumin (BSA). Moreover, BSA alone increased peak ACh current amplitudes and diminished desensitization rates in naive cells, suggesting a tonic modulation of alpha4beta2 nAChR function by an endogenous AEA-like lipid. Further analysis of AEA effects on alpha4beta2 nAChR-mediated currents, using a two-stage desensitization model, indicated that the first forward rate constant leading to desensitization, k(1), increased nearly 30-fold as a linear function of the AEA concentration. In contrast, the observation that the other three rate constants were unaltered by AEA suggested that AEA raised the energy of the activated state. These results indicate that AEA directly inhibits the function of alpha4beta2 nAChRs in a CB1 receptor-independent manner. Spivak, C.E., Lupica, C.R., and Oz, M. Molecular Pharmacology, 72(4), pp. 1024-1032, 2007.

Proteomics Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Volatile Anesthetics and Endogenous Cannabinoid Anandamide have Additive and Independent Inhibitory Effects on Alpha(7)-Nicotinic Acetylcholine Receptor-Mediated Responses In Xenopus Oocytes

In earlier studies, the volatile anesthetics and the endogenous cannabinoid anandamide have been shown to inhibit the function of alpha(7)-nicotinic acetylcholine receptors. In the present study, interactions between the effects of volatile anesthetics and anandamide on the function of alpha(7)-nicotinic acetylcholine receptors expressed in Xenopus oocytes were investigated using the two-electrode voltage-clamp technique. Anandamide and volatile anesthetics isoflurane and halothane inhibited currents evoked with acetylcholine (100 muM) in a reversible and concentration-dependent manner. Coapplication of anandamide and volatile anesthetics caused a significantly greater inhibition of alpha(7)-nicotinic acetylcholine receptor function than anandamide or volatile anesthetics alone. Analyses of oocytes by matrix-assisted laser desorption/ionization mass spectroscopy indicated that volatile anesthetics did not alter the lipid profile of oocytes. Results of studies with chimeric alpha(7)-nicotinic acetylcholine-5-HT(3) receptors comprised of the N-terminal domain of the alpha(7)-nicotinic acetylcholine receptor and the transmembrane and carboxyl-terminal domains of 5-HT(3) receptors suggest that while isoflurane inhibition of the alpha(7)-nicotinic acetylcholine receptor is likely to involve the N-terminal region of the receptor, the site of action for anandamide involves transmembrane and carboxyl-terminal domains of the

receptors. These data indicate that endocannabinoids and isoflurane have additive inhibitory effects on alpha(7)-nicotinic acetylcholine receptor function through allosteric binding sites located on the distinct regions of the receptor. Jackson, S.N., Singhal, S.K., Woods, A.S., Morales, M., Shippenberg, T., Zhang, L., and Oz. M. European Journal of Pharmacology, 582(1-3), pp. 42-51, 2008.

A Snapshot of Tissue Glycerolipids

The lipid membrane is the portal to the cell and its first line of defense against the outside world. Its plasticity, diversity and powers of accommodation in a myriad of environments, mirrored by the varied make up of the cells it protects, are unparalleled. Glycerophospholipids are one of its major components. In cell membranes the extracellular layer is mainly made up of positively charged glycolipids, while the intracellular one's main components are negatively charged. Advances in mass spectrometry have allowed the direct probing of tissues, and thus a direct approach to probing membranes make up was developed. Until recently most studies have focused on proteins. An overview of the use of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOFMS) for the direct analysis of phospholipids in various tissue is presented. Molecular ions corresponding to phosphatidlycholines, sphingomyelin, phosphatidylethanolamines, phosphatidylserines, phosphatidylinositols and sulfatides were mapped. Woods, A.S., Wang, H.Y., and Jackson, S.N. Current Pharmaceutical Design, 13(32), pp. 3344-3356, 2007.

A Stargardt Disease-3 Mutation in the Mouse Elovl4 Gene Causes Retinal Deficiency of C32-C36 Acyl Phosphatidylcholines

Stargardt disease-3 (STGD3) is a juvenile dominant macular degeneration caused by mutations in elongase of very long chain fatty acid-4. All identified mutations produce a truncated protein which lacks a motif for protein retention in endoplasmic reticulum, the site of fatty acid synthesis. In these studies of Stgd3-knockin mice carrying a human pathogenic mutation, IRP scientists examined two potential pathogenic mechanisms: truncated protein-induced cellular stress and lipid product deficiency. Analysis of mutant retinas detected no cellular stress but demonstrated selective deficiency of C32-C36 acyl phosphatidylcholines. The authors conclude that this deficit leads to the human STGD3 pathology. McMahon, A., Jackson, S.N., Woods, A.S., and Kedzierski, W. FEBS Letters, 581(28), pp. 5459-5463, 2007.

Adenosine Receptor Heteromers and Their Integrative Role in Striatal Function

By analyzing the functional role of adenosine receptor heteromers, IRP investigators review a series of new concepts that should modify our classical views of neurotransmission in the central nervous system (CNS). Neurotransmitter receptors cannot be considered as single functional units anymore. Heteromerization of neurotransmitter receptors confers functional entities that possess different biochemical characteristics with respect to the individual components of the heteromer. Some of these characteristics can be used as a "biochemical fingerprint" to identify neurotransmitter receptor heteromers in the CNS. This is exemplified by changes in binding characteristics that are dependent on coactivation of the receptor units of different adenosine receptor heteromers. Neurotransmitter receptor heteromers can act as "processors" of computations that modulate cell signaling, sometimes critically involved in the control of pre- and postsynaptic neurotransmission. For instance, the adenosine A1-A2A receptor heteromer acts as a concentration-dependent switch that controls striatal glutamatergic neurotransmission. Neurotransmitter receptor heteromers play a particularly important integrative role in the "local module" (the minimal portion of one or more neurons and/or one or more glial cells that operates as an independent integrative unit), where they act as processors mediating computations that convey information from diverse volume-transmitted signals. For instance, the

adenosine A2A-dopamine D2 receptor heteromers work as integrators of two different neurotransmitters in the striatal spine module. Ferre, S., Ciruela, F., Quiroz, C., Lujan, R., Popoli, P., Cunha, R.A., Agnati, L.F., Fuxe, K., Woods, A.S., Lluis, C., and Franco, R. Scientific World Journal, 7, pp. 74-85, 2007.

Anatomy and Cell Biology Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Hippocampal Interneurons Co-Express Transcripts Encoding the Alpha7 nicotinic Receptor Subunit and the Cannabinoid Receptor 1

The notion of functional interactions between the alpha7 nicotinic acetylcholine (alpha7 nACh) and the cannabinoid systems is emerging from recent in vitro and in vivo studies. Both the alpha7 nACh receptor and the cannabinoid receptor 1 (CB1) are highly expressed in the hippocampus. To begin addressing possible anatomical interactions between the alpha7 nACh and the cannabinoid systems in the rat hippocampus, IRP scientists investigated the distribution of neurons expressing alpha7 nACh mRNA in relation to those containing CB1 mRNA. By in situ hybridization the authors found that the alpha7 nACh mRNA is diffusely expressed in principal neurons and is highly expressed in a subset of interneurons. They observed that the pattern of distribution of hippocampal interneurons co-expressing transcripts encoding alpha7 nACh and glutamate decarboxylase (GAD; synthesizing enzyme of GABA) closely resembles the one displayed by interneurons expressing CB1 mRNA. By double in situ hybridization the authors established that the majority of hippocampal interneurons expressing alpha7 nACh mRNA have high levels of CB1 mRNA. As CB1 interneurons contain cholecystokinin (CCK), they investigated the degree of cellular co-expression of alpha7 nACh mRNA and CCK, and found that the cellular co-existence of alpha7 nACh and CCK varies within the different layers of the hippocampus. In summary, the authors established that most of the hippocampal alpha7 nACh expressing interneurons are endowed with CB1 mRNA. They found that these alpha7 nACh/CB1 interneurons are the major subpopulation of hippocampal interneurons expressing CB1 mRNA. The alpha7 nACh expressing interneurons represent half of the detected population of CCK containing neurons in the hippocampus. Since it is well established that the vast majority of hippocampal interneurons expressing CB1 mRNA have 5-HT type 3 (5-HT(3)) receptors, we conclude that these hippocampal alpha7 nACh/5HT(3)/CB1/CCK interneurons correspond to those previously postulated to relay inputs from diverse cortical and subcortical regions about emotional, motivational, and physiological states. Morales, M., Hein, K., and Vogel, Z. Neuroscience, 152(1), pp. 70-81, 2008.

Synapses Between Corticotropin-Releasing Factor-Containing Axon Terminals and Dopaminergic Neurons in the Ventral Tegmental Area are Predominantly Glutamatergic

Interactions between stress and the mesocorticolimbic dopamine (DA) system have been suggested from behavioral and electrophysiological studies. Because corticotropin-releasing factor (CRF) plays a role in stress responses, IRP scientists investigated possible interactions between neurons containing CRF and those producing DA in the ventral tegmental area (VTA). They first investigated the cellular distribution of CRF in the VTA by immunolabeling VTA sections with anti-CRF antibodies and analyzing these sections by electron microscopy. They found CRF immunoreactivity present mostly in axon terminals establishing either symmetric or asymmetric synapses with VTA dendrites. They established that nearly all CRF asymmetric synapses are glutamatergic, insofar as the CRF-immunolabeled axon terminals in these synapses coexpressed the vesicular glutamate transporter 2, and that the majority of CRF symmetric synapses are GABAergic, insofar as the CRF-immunolabeled axon terminals in these synapses coexpressed glutamic acid decarboxylase, findings that are of functional importance. The authors then looked for synaptic interactions between CRF- and DA-containing neurons, by

using antibodies against CRF and tyrosine hydroxylase (TH; a marker for DA neurons). They found that most synapses between CRF-immunoreactive axon terminals and TH neurons are asymmetric (in the majority likely to be glutamatergic) and suggest that glutamatergic neurons containing CRF may be part of the neuronal circuitry that mediates stress responses involving the mesocorticolimbic DA system. The presence of CRF synapses in the VTA offers a mechanism for interactions between the stress-associated neuropeptide CRF and the mesocorticolimbic DA system. Tagliaferro, P., and Morales, M. The Journal of Comparative Neurology, 506 (4), pp. 616-626, 2008.

Clinical Psychopharmacology Section, Chemical Biology Research Branch

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

Large elevations in blood serotonin (5-HT) can produce valvular heart disease in humans and laboratory animals. Accordingly, one prevailing hypothesis (i.e., the "5-HT hypothesis") suggests 5-HT transporter substrates like fenfluramine increase the risk for valvular heart disease by elevating plasma 5-HT, secondary to the release of 5-HT from platelets. The main purpose of this study was to determine if chronic administration of fenfluramine increases plasma 5-HT to concentrations that are associated with the development of valvular heart disease. To the best of the authors' knowledge, this is the first study to address this issue using an in vivo microdialysis method that measures plasma 5-HT in non-hypoxic rats. The IRP scientists examined the effects of chronic (+/-)-fenfluramine and fluoxetine on plasma levels of 5-HT and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in blood samples from conscious catheterized rats. Plasma indoles were measured by HPLC-ECD in dialysates of whole blood. Baseline plasma 5-HT was < 1.0 nM. Chronic fenfluramine (14-day minipump infusion) produced small increases in baseline plasma 5-HT (~2-to-4-fold), while chronic fluoxetine had no effect. Chronic fenfluramine and fluoxetine markedly decreased whole blood 5-HT, and reduced the ability of acute fenfluramine to evoke 5-HT release. Elevations in baseline plasma 5-HT produced by chronic fenfluramine are far below M levels necessary to produce valvular heart disease. Furthermore, chronic fenfluramine reduces the ability of acute fenfluramine to increase plasma 5-HT, suggesting the "5-HT hypothesis" can not explain the increased risk of valvular heart disease in patients treated with fenfluramine. Zolkowska, D., Baumann M.H., and Rothman R.B. J. Pharmacol. Exp. Ther., 324, pp. 791-797, 2008.

Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch

Blockade of THC-seeking Behavior and Relapse in Monkeys by the Cannabinoid CB(1)-receptor Antagonist Rimonabant

Accumulating evidence suggests the endocannabinoid system modulates environmental cues' ability to induce seeking of drugs, including nicotine and alcohol. However, little attention has been directed toward extending these advances to the growing problem of cannabis use disorders. Therefore, IRP researchers studied intravenous self-administration of delta(9)-tetrahydrocannabinol (THC), the main psychoactive constituent of marijuana, using a second-order schedule of drug seeking. Squirrel monkeys' lever responses produced only a brief cue light until the end of the session, when the final response delivered THC along with the cue. When a reinstatement procedure was used to model relapse following a period of abstinence, THC-seeking behavior was robustly reinstated by the cue or by pre-session administration of THC, other cannabinoid agonists, or morphine, but not cocaine. The cannabinoid antagonist rimonabant blocked cue-induced drug seeking, THC-induced drug seeking, and the direct reinforcing effects of THC. Thus, rimonabant and related medications might be effective as treatments for

cannabis use disorders. Justinova, Z., Munzar, P., Panlilio, L. V., Yasar, S., Redhi, G. H., Tanda, G. and Goldberg, S. R. Neuropharmacology, February 27, 2008, Epubmed ahead of print.

Blocking Striatal Adenosine A2A Receptors: A New Strategy for Basal Ganglia Disorders

Adenosine A(2A) receptors are highly concentrated in the striatum, where they play an important modulatory role of glutamatergic transmission to the GABAergic enkephalinergic neuron, which function is particularly compromised in Parkinson's disease and in the early stages of Huntington's disease. An important amount of preclinical data suggested the possible application of A(2A) receptor antagonists in Parkinson's disease, particularly as adjuvant therapy to the currently used dopaminergic agonists. Several A(2A) receptor antagonists are currently in clinical trials in patients with Parkinson's disease and initial results have been promising. In recent years, many pharmaceutical companies have started programs to develop A(2A) antagonists for Parkinson's disease and for other indications, such as neurodegenerative diseases in general, depression and restless legs syndrome. Antagonists with high A(2A) receptor affinity and selectivity have been developed from various chemical classes of compounds, including xanthenes, adenines and other amino-substituted heterocyclic compounds. Novel structures include benzothiazole and thiazolopyridine derivatives. The present review describes properties of standard A(2A) receptor antagonists including those in clinical development. Furthermore, the different chemical classes of A(2A) receptor antagonists that have been described in the literature, including recent patent literature, will be presented. Muller, C.E. and Ferre, S. Recent Patents CNS Drug Discoveries, 2, pp. 1-21, 2007.

An Update on the Mechanisms of the Psychostimulant Effects of Caffeine

There has been a long debate about the predominant involvement of the different adenosine receptor subtypes and the preferential role of pre- versus post-synaptic mechanisms in the psychostimulant effects of the adenosine receptor antagonist caffeine. Both striatal A(1) and A(2A) receptors are involved in the motor-activating and probably reinforcing effects of caffeine, although they play a different role under conditions of acute or chronic caffeine administration. The present review emphasizes the key integrative role of adenosine and adenosine receptor heteromers in the computation of information at the level of the striatal spine module (SSM). This local module is mostly represented by the dendritic spine of the medium spiny neuron with its glutamatergic and dopaminergic synapses and astroglial processes that wrap the glutamatergic synapse. In the SSM, adenosine acts both pre- and post-synaptically through multiple mechanisms, which depend on heteromerization of A(1) and A(2A) receptors among themselves and with D(1) and D(2) receptors, respectively. A critical aspect of the mechanisms of the psychostimulant effects of caffeine is its ability to release the pre- and post-synaptic brakes that adenosine imposes on dopaminergic neurotransmission by acting on different adenosine receptor heteromers localized in different elements of the SSM. Ferre, S. Journal of Neurochemistry, January 17, 2008, Epubmed ahead of print.

Topiramate Does Not Alter Nicotine or Cocaine Discrimination in Rats

Two groups of rats trained to discriminate the administration of either 0.4 mg/kg nicotine or 10 mg/kg cocaine from that of saline, under a fixed-ratio 10 schedule of food delivery. Topiramate (1-60 mg/kg, intraperitoneal) did not produce any nicotine-like or cocaine-like discriminative effects by itself and did not produce any shift in the dose-response curves for nicotine or cocaine discrimination. Furthermore, topiramate, given either alone or in combination with nicotine or cocaine, did not depress rates of responding. These experiments indicate that topiramate does not enhance or reduce the ability of rats to discriminate the effects of nicotine or cocaine. Le Foll, B., Justinova, Z.,

Wertheim, C.E., Barnes, C. and Goldberg, S.R. Behavioral Pharmacology, 19, pp. 13-20, 2008.

Light Resonance Energy Transfer-based Methods in the Study of G protein-coupled Receptor Oligomerization

Oligomerization Since most of the functions in cells are mediated by multimeric protein complexes, the determination of protein-protein interactions is an important step in the study of cellular mechanisms. Traditionally, after screening for possible target interactors by means of a yeast two-hybrid screen, several methods are used to validate the initial result before carrying out functional experiments. Nowadays, non-invasive fluorescence-based methods like Bioluminescence Resonance Energy Transfer (BRET) and Fluorescence Resonance Energy Transfer (FRET) are widely used in the study of protein-protein interactions in living cells. In the present review, the authors address the individual strengths and weaknesses of both RET approaches, providing information on their possible future use in the study of G protein-coupled receptor oligomerization. Gandia, J., Lluis, C., Ferre, S., Franco, R. and Ciruela, F. Bioessays, 30, pp. 82-89, 2008.

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

Nicotine Enhances Mood and Cognition in Smokers

The discovery of the role of nicotinic receptors in attention and memory has led to the testing of nicotinic analogs as cognitive enhancing agents in patient populations. Empirical information about nicotine's ability to enhance elements of attention and memory in normal individuals might guide development of therapeutic uses of nicotine in cognitively-impaired populations. The purpose of this study was to determine the effect of nicotine on continuous attention, working memory, and computational processing in tobacco-deprived and nondeprived smokers. A total of 28 smokers (14 men, 14 women) participated in a double-blind, placebo-controlled, within-subject study, in which they were overnight (12 h) tobacco deprived at one session and smoked ad libitum before the other session. At each session, participants received 0, 1, and 2 mg nicotine via nasal spray in random order at 90-min intervals. Before and after each dose, a battery of cognitive, subjective, and physiological measures was administered, and blood samples were taken for plasma nicotine concentration. Overnight tobacco deprivation resulted in impaired functioning on all cognitive tests and increased self-reports of tobacco craving and negative mood; nicotine normalized these deficits. In the nondeprived condition, nicotine enhanced performance on the Continuous Performance Test and Arithmetic Test in a dose-related manner, but had no effect on working memory. In general, women were more sensitive than men to the subjective effects of nicotine. These results provide an unequivocal determination that nicotine enhanced attentional and computational abilities in nondeprived smokers and suggest these cognitive domains as substrates for novel therapeutic indications. Myers, C.S., Taylor, R.C., Moolchan, E.T., and Heishman, S.J. Neuropsychopharmacology, 33, pp. 588-598, 2008.

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

Program Activities

PAs and RFAs Issued with Other NIH Components/Agencies

On March 4, 2008, NIDA, in collaboration with a number of other NIH components, issued a Program Announcement (PA) entitled **Functional Links between the Immune System, Brain Function and Behavior (R01) (PA-08-097)**. This Funding Opportunity Announcement (FOA) solicits research grant applications to study neuroimmune molecules and mechanisms involved in regulating normal and pathological functions of the central nervous system (CNS).

On March 18, 2008, NIDA, in collaboration with several other NIH Institutes, issued a PA entitled **Prevention Research with HIV Positive Individuals (R01) (PA-08-107)**. This Funding Opportunity Announcement (FOA) invites interdisciplinary studies addressing the psychosocial and behavioral consequences of HIV disease. Over the past decade, secondary prevention in HIV disease, or "positive prevention", has received a much needed increase in attention. Gains have been made toward the aim of decreasing HIV transmission behaviors and improving quality of life among individuals living with HIV/AIDS, as well as understanding factors that are important to healthy coping. In this program announcement, further opportunities for innovation in this field are indicated.

On March 18, 2008, NIDA, in collaboration with several other NIH Institutes, issued a PA entitled **Prevention Research with HIV Positive Individuals (R03) (PA-08-108)**. This Funding Opportunity Announcement (FOA) invites interdisciplinary studies addressing the psychosocial and behavioral consequences of HIV disease. Over the past decade, secondary prevention in HIV disease, or "positive prevention", has received a much needed increase in attention. Gains have been made toward the aim of decreasing HIV transmission behaviors and improving quality of life among individuals living with HIV/AIDS, as well as understanding factors that are important to healthy coping. In this program announcement, further opportunities for innovation in this field are indicated.

On March 18, 2008, NIDA, in collaboration with several other NIH Institutes, issued a PA entitled **Prevention Research with HIV Positive Individuals (R21) (PA-08-109)**. This Funding Opportunity Announcement (FOA) invites interdisciplinary studies addressing the psychosocial and behavioral consequences of HIV disease. Over the past decade, secondary prevention in HIV disease, or "positive prevention", has received a much needed increase in attention. Gains have been made toward the aim of decreasing HIV transmission behaviors and improving quality of life among individuals living with HIV/AIDS, as well as understanding factors that are important to healthy coping. In this program announcement, further opportunities for innovation in

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this field are indicated.

On March 18, 2008, NIDA, in collaboration with a number of other NIH components, the Canadian Institutes of Health Research (CIHR) and Autism Speaks, issued a PA entitled **Brain Disorders in the Developing World: Research Across the Lifespan (R01) (PAR-08-112)**. This Funding Opportunity Announcement (FOA) encourages grant applications proposing the development and conduct of innovative, collaborative research and research training projects, between High Income country (HIC) and low- to middle-income country (LMIC) scientists, on nervous system function and disorders throughout life, relevant to LMICs. The collaborative research programs are expected to contribute to the long-term goals of building sustainable research capacity in LMICs to address nervous system development, function and impairment throughout life and to lead to diagnostics, treatment and prevention strategies that are applicable worldwide.

On March 18, 2008, NIDA, in collaboration with a number of other NIH components, the Canadian Institutes of Health Research (CIHR) and Autism Speaks, issued a PA entitled **Brain Disorders in the Developing World: Research Across the Lifespan (R21) (PAR-08-113)**. This Funding Opportunity Announcement (FOA) encourages grant applications proposing the development and conduct of innovative, collaborative research and research training projects, between High Income country (HIC) and low- to middle-income country (LMIC) scientists, on nervous system function and disorders throughout life, relevant to LMICs. The collaborative research programs are expected to contribute to the long-term goals of building sustainable research capacity in LMICs to address nervous system development, function and impairment throughout life and to lead to diagnostics, treatment and prevention strategies that are applicable worldwide.

On April 3, NIDA, in collaboration with NIMH, issued a PA entitled **Prescription Drug Misuse (R01) (PA-08-127)**. This PA invites research applications to reduce prescription drug misuse while supporting the appropriate medical use of therapeutic agents that carry an abuse liability. A range of research is being solicited to combat prescription drug misuse--from epidemiologic research specifying the extent and nature of the problem (including physical and mental health and social consequences) as it relates to each specific drug and identifying determinants and trajectories of use. Basic science applications to determine mechanisms of action at the cellular level and possible mechanisms or medications to block or lessen the abuse potential are encouraged, as are health services applications with the goal of discovering effective clinical practices that identify those at risk and designing and disseminating prevention and treatment interventions.

On April 3, NIDA, in collaboration with NIMH, issued a PA entitled **Prescription Drug Misuse (R21) (PA-08-128)**. This PA invites research applications to reduce prescription drug misuse while supporting the appropriate medical use of therapeutic agents that carry an abuse liability. A range of research is being solicited to combat prescription drug misuse--from epidemiologic research specifying the extent and nature of the problem (including physical and mental health and social consequences) as it relates to each specific drug and identifying determinants and trajectories of use. Basic science applications to determine mechanisms of action at the cellular level and possible mechanisms or medications to block or lessen the abuse potential are encouraged, as are health services applications with the goal of discovering effective clinical practices that identify those at risk and designing and disseminating prevention and treatment interventions.

On April 3, NIDA, in collaboration with NIMH, issued a PA entitled **Prescription Drug Misuse (R03) (PA-08-129)**. This PA invites research applications to reduce prescription drug misuse while supporting the appropriate medical use of therapeutic agents that carry an abuse liability. A range of research is being

Planned Meetings

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Grantee Honors

solicited to combat prescription drug misuse--from epidemiologic research specifying the extent and nature of the problem (including physical and mental health and social consequences) as it relates to each specific drug and identifying determinants and trajectories of use. Basic science applications to determine mechanisms of action at the cellular level and possible mechanisms or medications to block or lessen the abuse potential are encouraged, as are health services applications with the goal of discovering effective clinical practices that identify those at risk and designing and disseminating prevention and treatment interventions.

On April 9, 2008, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Genetic Screens to Enhance Zebrafish Research (R01) (PAR-08-138)**. This FOA encourages investigator-initiated applications designed to exploit the power of the zebrafish as a vertebrate model for biomedical and behavioral research. Applications proposing to develop new genetic screens of high priority to the zebrafish community that will advance the detection and characterization of genes, pathways, and phenotypes of interest in development and aging, organ formation, neural processes, behavior, sensory processes, physiological processes, and disease processes are welcome. This effort stems from an NIH initiative developed by the Institutes and Centers of the Trans-NIH Zebrafish Coordinating Committee (TZCC) under the co-chairmanship of NICHD and NIDDK.

On April 9, 2008, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Enhancing Zebrafish Research with Research Tools and Techniques (R01) (PAR-08-139)**. This FOA encourages investigator-initiated applications designed to exploit the power of the zebrafish as a vertebrate model for biomedical and behavioral research. Applications proposing to develop new research tools or techniques that are of high priority to the zebrafish community and that will advance the detection and characterization of genes, pathways, and phenotypes of interest in development and aging, organ formation, neural processes, behavior, sensory processing, physiological processes, and disease processes are welcome. This effort stems from an NIH initiative developed by the Institutes and Centers of the Trans-NIH Zebrafish Coordinating Committee (TZCC) under the co-chairmanship of NICHD and NIDDK.

On April 16, 2008, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **NIH Support for Conferences and Scientific Meetings (Parent R13/U13) (PA-08-149)**. The purpose of the NIH Research Conference Grant Program (R13 and U13) is to support high quality conferences/scientific meetings that are relevant to the scientific mission of the NIH and to the public health. A conference/scientific meeting is defined as a gathering, symposium, seminar, scientific meeting, workshop or any other organized, formal meeting where persons assemble to coordinate, exchange, and disseminate information or to explore or clarify a defined subject, problem, or area of knowledge.

On April 18, 2008, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Midcareer Investigator Award in Patient-Oriented Research (K24) (PA-08-151)**. The purpose of the Midcareer Investigator Award in Patient-Oriented Research is to provide support to mid-career health-professional doctorates or equivalent who are typically at the Associate Professor level or the equivalent (see Section III. Eligible Individuals) for protected time to devote to patient-oriented research (POR) and to act as research mentors primarily for clinical residents, clinical fellows and/or junior clinical faculty. The intent of this award is two-fold: 1) to enable mid-career clinician scientists to devote more time and to augment their capabilities in patient-oriented research; and 2) to enable mid-career clinical scientists to mentor new clinical investigators in the conduct of patient-oriented research. An award recipient who continues to have an independent peer-reviewed

patient-oriented research program and continues to provide mentoring to new investigators can continue to contribute to the overall goals of the program after being promoted to Full professor.

On April 22, 2008, NIDA, in collaboration with several other NIH components, issued a PA entitled **PHASE II Comprehensive ICOHRTA AIDS/TB (U2R) (PAR-08-155)**. This Funding Opportunity Announcement (FOA) solicits renewal (re-competing) and new Phase II applications in the International Clinical, Operations and Health Services Research Training Award for AIDS and TB (ICOHRTA AIDS TB) program. The applications from a Research Training Unit, composed of a Phase I ICOHRTA AIDS TB (planning grant) recipient and the U.S. partner institution chosen by the Phase I recipient, must propose, in an integrated manner, a comprehensive training program that will strengthen the capacity in the foreign country to conduct clinical research and implementation science, including operations and health services research focused on HIV infection, TB, and, where relevant, HIV/TB co-infection prevention, care and treatment.

On April 24, 2008, NIDA, in collaboration with NIMH, NIA and NIAAA, issued a PA entitled **Mouse Models Containing Human Alleles: Novel Tools to Study Brain Function (R21/R33) (PAR-08-158)**. This Funding Opportunity Announcement (FOA) invites Phased Innovation (R21/R33) grant applications from organizations/institutions that propose the development and characterization of novel mouse models that express human genes or human genetic elements that can aid in understanding the molecular mechanisms underlying brain function and the physiological function/significance of gene variants and gene dosage abnormalities that have been identified as possibly being involved in mental disorders, addiction, neurodegenerative disorders of aging, and alcoholism as well as related comorbid conditions.

On March 19, 2008, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Probes and Instrumentation for Monitoring and Manipulating Nervous System Plasticity (R01) (RFA-MH-09-030)**. This Funding Opportunity Announcement (FOA) is issued as an initiative of the NIH Blueprint for Neuroscience Research, a collaborative framework through which 16 NIH Institutes, Centers and Offices jointly support neuroscience-related research, with the aim of accelerating discoveries and reducing the burden of nervous system disorders (for further information, see http://neuroscienceblueprint.nih.gov/). Applications are solicited for support of projects that will develop probes, instrumentation, and other tools for understanding, monitoring, and manipulating nervous system plasticity. This FOA will focus on the development of tools or techniques that will significantly advance the current state of the art in neuroplasticity research. Although applications will not be restricted to a particular type of technology, the NIH is especially interested in applications that seek to harness the ability to assess and manipulate activity with exquisite subcellular resolution, and in cells specified by their circuit connectivity and/or transmitter phenotype.

On April 24, 2008, NIDA participated in the issuance of an RFA entitled **Functional Characterization of Genetic Variants and Interactions: The Genes, Environment and Health Initiative (R21) (RFA-DA-09-003)**. This FOA is developed as part of the NIH-wide Genes, Environment, and Health Initiative (GEI). All NIH Institutes and Centers participate in NIH-wide initiatives. This FOA will be administered by NIDA (http://www.nida.nih.gov) on behalf of the NIH (http://www.nih.gov). This RFA encourages functional characterization of genetic variants that have been statistically nominated to be associated with a particular outcome through common, complex disease gene discovery approaches, such as genome-wide association studies, candidate gene approaches, or sequencing studies. This FOA supports research relating genetic variation to biological mechanism, or disease causality. Areas of interest include, but are not limited to, relatively low throughput approaches

(e.g. transgenic mouse approaches) to test some of the most promising variants for changes in function; or exploit high-throughput tests (e.g. yeast, C. elegans, cell culture systems, or computational approaches) to look at different aspects of variant function.

On April 24, 2008, NIDA participated in the issuance of an RFA entitled **Functional Characterization of Genetic Variants and Interactions: The Genes, Environment and Health Initiative (R03) (RFA-DA-09-004)**. This FOA is developed as part of the NIH-wide Genes, Environment, and Health Initiative (GEI). All NIH Institutes and Centers participate in NIH-wide initiatives. This FOA will be administered by NIDA (http://www.nida.nih.gov) on behalf of the NIH (http://www.nih.gov). This RFA encourages functional characterization of genetic variants that have been statistically nominated to be associated with a particular outcome through common, complex disease gene discovery approaches, such as genome-wide association studies, candidate gene approaches, or sequencing studies. This FOA supports research relating genetic variation to biological mechanism, or disease causality. Areas of interest include, but are not limited to, relatively low throughput approaches (e.g. transgenic mouse approaches) to test some of the most promising variants for changes in function; or exploit high-throughput tests (e.g. yeast, C. elegans, cell culture systems, or computational approaches) to look at different aspects of variant function.

On March 6, 2008, NIDA, in conjunction with other neuroscience NIH components, reissued the **Jointly Sponsored Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Predoctoral Training Program in the Neurosciences (T32) PAR-08-101**. The purpose of the NRSA research training program is to help ensure that a diverse and highly trained workforce is available to assume leadership roles related to the Nation's biomedical and behavioral research agenda. This joint program encourages and supports early-stage predoctoral training in the neurosciences. The primary objective is to prepare qualified individual for careers in neuroscience that have a significant impact on the health-related research needs of the Nation.

Other Program Activities

Clinical Trials Network (CTN) Update

SBIR: The CCTN received proposals in response to a NIH SBIR Contract Solicitation for, "Development of Web-based Training on Addiction Medicine for Pain Management Providers" and "Development of Web-based Skills Training for Primary Care Physicians on Screening, Brief Intervention, Referral and Treatment of Substance Abuse." The review meeting was held January 11, 2008. There are plans to award up to four proposals.

Protocols: A total of 31 protocols have been initiated since 2001. Nearly 9,000 participants have enrolled in studies. Of these studies, 20 have completed data lock; two are in the data-lock phase; and four are currently enrolling. Five new protocols are in the development phase.

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

Protocol CTN 0001, Buprenorphine/Naloxone versus Clonidine for Inpatient Opiate Detoxification

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

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

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

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

Primary outcome papers are published or in press for:

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

Protocol CTN 0008, A Baseline for Investigating Diffusion of Innovation

Protocol CTN 0009, Smoking Cessation Treatment with Transdermal Nicotine Replacement Therapy in Substance Abuse Rehabilitation Programs

Protocol CTN 0011, A Feasibility Study of a Telephone Enhancement Procedure (TELE) to Improve Participation in Continuing Care Activities

Protocol CTN 0012, Characteristics of Screening, Evaluation, and Treatment of HIV/AIDS, Hepatitis C Viral Infection, and Sexually Transmitted Infections in Substance Abuse Treatment Programs

Protocol CTN 0013, Motivational Enhancement Therapy to Improve Treatment Utilization and Outcome In Pregnant Substance Abusers

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

In addition, the following protocols have submitted primary papers:

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

Protocol CTN 0010, Buprenorphine/Naloxone Facilitated Rehabilitation for Opioid Dependent Adolescents/Young Adults

Protocol CTN 0015, Women's Treatment for Trauma and Substance Use Disorder: A Randomized Clinical Trial

Protocol CTN 0018, Reducing HIV/STD Risk Behaviors: A Research Study for Men in Drug Abuse Treatment

Protocol CTN 0019, Reducing HIV/STD Risk Behaviors: A Research Study for Women in Drug Abuse Treatment

Protocol CTN 0021, Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome for Spanish-Speaking Individuals Seeking Treatment for Substance Abuse. This is the first Spanish-only protocol in the CTN

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

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

Protocol CTN 0029, A Pilot Study of Osmotic-Release Methylphenidate (OROS MPH) in Initiating and Maintaining Abstinence in Smokers with Attention Deficit Hyperactivity Disorder (ADHD)

Four protocols are currently enrolling:

Protocol CTN 0027, Starting Treatment with Agonist Replacement Therapies (START) is a randomized, open-label, multi-center study that was developed in collaboration with the Division of Pharmacotherapies & Medical Consequences of Drug Abuse (DPMCDA). Enrollment began in April 2006. As of March 31, 2008, there were 681 randomized participants.
CCTN 0027A, START Pharmacogenetics: Exploratory Genetic Studies In Starting Treatment With Agonist Replacement Therapies.

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 is now open at 11 sites. As of March 31, 2008, 272 participants have been randomized.
CTN 0028A, Does Methylphenidate Treatment for ADHD Increase the Rate of Smoking in Adolescents with Comorbid ADHD, SUD, and nicotine dependence?

Protocol CTN 0030, Prescription Opioid Addiction Treatment Study (POATS) is a randomized 2-phase, open-label, multi-center study in outpatient treatment settings. Pre-screening began in May 2006. The study is being carried out in 9 sites. As of March 31, 2008, there were 448 randomized participants.
CTN 0030A, Collection of Economic Data for the Prescription Opioid Addiction Treatment Study. This ancillary study is conducted in collaboration and support with NIDA DESPR.
CTN 0030B, Effects of Chronic Opioids is conducted in collaboration and support with NIDA DCNBR to obtain anatomical MR scans in subjects with a history of opioid use to evaluate neural changes that may occur with such use and compare with age/gender healthy controls.

Protocol CTN 0031, Stimulant Abuser Groups to Engage in 12-Step (STAGE-12): Evaluation of a Combined Individual-Group Intervention to Reduce Stimulant and Other Drug Use by Increasing 12-Step Involvement. As of April 4, 2008, 20 participants have been randomized at the 3 Wave 1 sites. Staff from the Wave 2 sites will be trained in Bethesda, MD during August 2008, and Wave 2 recruitment is expected to commence in September 2008.
CTN 0031A, An Evaluation of Neurocognitive Function, Oxidative Damage, and Their Association with Treatment Outcomes in Methamphetamine and Cocaine Abusers. Ten participants have been enrolled.
CTN 0031B, The Role of Alcohol Consumption in Classifications of Alcohol Use Disorders: A Clinical Study is being led by Dr. Deborah Hasin (Long Island Node). This study is funded by an MOU between NIDA and NIAAA.
CTN 0031C, Organizational and Practitioner Influences on Implementation of STAGE-12.

Five protocols are in the development phase:

Protocol CTN 0032, HIV Rapid Testing and Counseling in Drug Abuse Treatment Programs in the U.S. This study seeks to evaluate the most effective strategy to ensure that persons in drug treatment programs are tested for HIV and receive their HIV test results. The protocol seeks to enroll more than 1,200 participants

across approximately 12 sites in the US. A final site selection decision is expected to be done by the middle of summer. The goal is to start enrolling patients by fall 2008.
CTN 0032A, Economic Analysis of HIV Rapid Testing in Drug Abuse Treatment Programs. This is an ancillary study to protocol CTN 0032, to conduct an assessment of the cost-effectiveness of on-site HIV testing in drug abuse treatment settings vs referral for off-site testing. The PI is Dr. Bruce Schakman. The project is being conducted in collaboration with NIDA's DESPR.

Protocol CTN 0033, Methamphetamine Use among American Indians. The first area of research emphasis in the National Institute on Drug Abuse's Strategic Plan on Reducing Health Disparities (2004 Revision) is the epidemiology of drug abuse, health consequences and infectious diseases among minority populations. The study is a collaboration among four Nodes: Pacific NW, Southwest, Oregon/Hawaii, and Ohio Valley.

Protocol CTN 0034, Developing Research Capacity and Culturally Appropriate Research Methods: Community-based Participatory Research Manual for Collaborative Research in Drug Abuse for American Indians and Alaska Natives. This study is in collaboration with the NIH National Center for Minority Health and Health Disparities and will be conducted in the Pacific Northwest Node.

Protocol CTN 0035, Access to HIV and Hepatitis Screening and Care among Ethnic Minority Drug Users In and Out of Drug Treatment. This study is in collaboration with the NIH National Center for Minority Health and Health Disparities and will be conducted in the CA-AZ Node.

Protocol CTN 0036, Epidemiology and Ethnographic Survey of "Cheese" Heroin Use among Hispanics in Dallas County. This study is in collaboration with the NIH National Center for Minority Health and Health Disparities and will be conducted in the Texas Node.

In addition to the primary CTN trials, there are currently three secondary analyses using data across several of the completed trials:

(1) Gender Differences in the Prevalence and Predictors of HIV Risk Behaviors, PI: Audrey Brooks (CA/AZ Node);

(2) Pattern of alcohol use and alcohol-related diagnoses among drug abusing/dependent participants, PIs: Dennis Donovan and Bryan Hartzler (Pacific Northwest Node);

(3) The relationships between demographic characteristics of patients and therapists, measures of therapeutic process and therapeutic alliance, and outcomes, PIs: Alyssa Forcehimes (Southwest Node) and Kathleen Burlew (Ohio Valley Node).

There are also 37 funded studies supported by independent grants that use CTN studies as a platform and 21 completed, ongoing, or planned studies funded as supplements to the clinical trials.

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

Abi-Dargham, Anissa -- New York State Psychiatric Institute
Imaging Dopamine Transmission in Comorbid Schizophrenia and Cannabis Dependence

Bannon, Michael J. -- Wayne State University
Cocaine-Binding Dopamine Transporter: Molecular Biology

Banta-Green, Caleb -- University of Washington
Quantitative Drug Surveillance System Development

Benowitz, Neal L. -- University of California, San Francisco
Pharmacokinetics and Pharmacodynamics of Nicotine

Benveniste, Helene -- State University New York, Stony Brook
Role of Astroglia in Cocaine-induced Neurotoxicity

Boudreaux, Edwin D. -- University of Medicine/Dentistry of New Jersey - Robert Wood Johnson Medical School
The Sentinel Events Model: A Dynamic Model of Substance Use Cessation

Brown, Edson S. -- University of Texas, Southwest Medical Center, Dallas
Citicoline for Bipolar Disorder and Cocaine Dependence

Bruijnzeel, Adriaan W. -- University of Florida
Nicotine Withdrawal and Relapse: Role of Neuroadaptations in Brain Stress Systems

Carlson, Robert G. -- Wright State University
Opioid Use Trajectories and HIV Risk among Young Adults in Ohio

Cheer, Joseph Francois Rene -- Albany Medical College
Endogenous Cannabinoid Control of Reward Substrates

Chen, Xinguang -- Wayne State University
Measuring Cigarette Smoking Behavior Progression with Cross-Sectional Data

Conklin, Cynthia A. -- University of Pittsburgh at Pittsburgh
Self-Report and Behavioral Reactivity to Combined Smoking Cues

Coop, Andrew -- University of Maryland, Baltimore
Opioids with Delta Antagonist and Mu Agonist Activity

Cooper, Donald C. -- University of Texas, Southwest Medical Center, Dallas
Plasticity of Excitability in Ventral Subiculum after High Cocaine Intake

Culverhouse, Robert C. -- Washington University
Genetic Interactions Contributing to Alcohol and Nicotine Dependence

Dani, John A. -- Baylor College of Medicine
Cellular and Synaptic Physiology during the Progression to Nicotine Abuse

Davis, W. Rees -- National Development and Research Institutes
Prescription Opioids among Street Drug Users: Medical Use, Misuse and Diversion

De Biasi, Mariella -- Baylor College of Medicine
Regulation of Proteasomal Function by Nicotine

Devi, Lakshmi A. -- Mount Sinai School of Medicine of NYU
Post-Translational Regulation of Opioid Receptors

Dickson-Gomez, Julia B. -- Medical College of Wisconsin
Drug Use, Housing Access, Stability and HIV Risk among Low-Income Urban Residents

Difranza, Joseph R. -- University of Massachusetts Medical School, Worcester
Imaging of Nicotine Sensitization in Humans: A Translational Application of fMRI

Dimaggio, Charles -- Columbia University Health Sciences
Changes in Substance Abuse Patterns Following the Terrorist Attacks of September 11th

Dong, Yan -- Washington State University
Cocaine-Induced Adaptation in NMDA Receptors in Nucleus Accumbens

Duclos, Richard I. -- Northeastern University
Inhibition of Endocannabinoid Biosynthesis via Diacylglycerol Lipase

Dunigan, Robert L. -- Brandeis University
Treatment Engagement and Time to Recidivism for African-American Male Offenders

Edwards, Jessica M. -- Pacific Institute for Research and Evaluation
Neighborhood Context, Drug Use, and Risky Sexual Behavior among U.S. Adolescents

Ehrlich, Michelle E. -- Mount Sinai School of Medicine of NYU
Post-Synaptic Striatal TrkB: Role in the Response to Cocaine

Eisch, Amelia J. -- University of Texas, Southwest Medical Center, Dallas
Cdk5 and Adult Hippocampal Neurogenesis

Elwyn, Laura J. -- State University of New York at Albany
Perception of Childhood Maltreatment: Implications for Early Adult Substance Abuse

Ensminger, Margaret E. -- Johns Hopkins University
Drug Abuse and Crime across the Life Course in an African-American Population

Fairbanks, Carolyn A. -- University of Minnesota, Twin Cities
Opioid Self-Administration in Chronic Pain

Fleckenstein, Annette -- University of Utah
Psychostimulants and Monoamine Transporters

Floyd, Leah -- Johns Hopkins University
HIV Disparities among Drug Users: Neighborhoods, Neurocognition and Sex Behavior

Frankle, William G. -- University of Pittsburgh at Pittsburgh
The Effects of Cannabis Use/Abuse on In Vivo Dopamine Function

Galloway, Gantt P. -- California Pacific Medical Center Research Institute
A Dose Ranging Study of Modafinil for Methamphetamine Dependence

Garvey, Arthur J. -- Harvard University Medical School
Duration of Behavioral Counseling Treatment Needed to Optimize Smoking Abstinence

Gerak, Lisa R. -- University of Texas Health Science Center, San Antonio
Discriminative Effects of Benzodiazepine Withdrawal

Gibbons, Frederick X. -- Iowa State University
Factors Influencing the Health Behavior of Young African-American Adults

Goldstein, Rita Z. -- Brookhaven National Laboratory
The Prefrontal Cortex in Reward Devaluation in Human Cocaine Addiction

Golub, Andrew L. -- National Development and Research Institutes
Transient Domesticity and Drugs: Ethnography Informs a Nationwide Analysis

Haggerty, Kevin P. -- University of Washington
Disparities of Drug Use in Emerging Adults

Havens, Jennifer R. -- University of Kentucky
Social Networks and HIV Risk among Rural Drug Users

Hayashida, Kenchiro -- Wake Forest University Health Sciences
Mechanism of Gabapentin Analgesia

Higgins, Stephen T. -- University of Vermont and State Agricultural College
Treating Cocaine Abuse: A Behavioral Approach

Huang, Li -- Duke University
Identification of Anti-HIV Agent(s) from Sophora Alkaloids

Hurd, Yasmin L. -- Mount Sinai School of Medicine of NYU
The Neuronal Basis of Cannabis-Induced Developmental Deficits in the CNS

Jacobsen, Leslie K. -- Yale University
Reward-Motivated Learning in Adolescent Cannabis Users

Kavanaugh, Michael P. -- University of Montana
Characterization and Use of Fluorescent Endocannabinoid Transporter Substrates

Kellar, Kenneth J. -- Georgetown University
Pharmacology and Regulation of Nicotinic Receptor Subtypes

Kipke, Michele D. -- Children's Hospital, Los Angeles
HIV Prevention for High Risk African-American Young Men

Kipke, Michele D. -- Children's Hospital, Los Angeles
African-American Young Men's Study

Ko, Mei-Chuan -- University of Michigan at Ann Arbor
Evaluation in Primates of Cocaine Esterase for the Treatment of Cocaine Toxicity

Koob, George F. -- Scripps Research Institute
Central Mechanisms of Nicotine Reinforcement and Dependence

Kurtz, Steven P. -- University of Delaware
Risk Reduction for Urban Substance Using MSM

Lavin, Antonieta -- Medical University of South Carolina
Effects of Repetitive Cocaine Administration in Activity of Cortical Interneurons

Law, Ping-Yee -- University of Minnesota, Twin Cities
Engineered Opioid Receptors as Therapeutic Agents for Pain Control

Li, Shi-Jiang W. -- Medical College of Wisconsin
Imaging Cocaine Valuations in the Human Brain by fMRI

Liu, Qing-Song -- Medical College of Wisconsin
Synaptic Plasticity in the Ventral Tegmental Area and Cocaine Addiction

Luthar, Suniya S. -- Columbia University Teachers College
Substance Abuse among Suburban Youth: A Prospective Study

Lynch, Wendy J. -- University of Virginia, Charlottesville
Dopaminergic and Glutamatergic Mechanisms of Cocaine Addiction: Sex Differences

Madden, Gregory J. -- University of Kansas, Lawrence
Impulsivity, Dopamine and the Behavioral Economics of Gambling

Manev, Hari -- University of Illinois at Chicago
A Role for 5-Lipoxyegenase in Cocaine's Actions

Marshall, John F. -- University of California, Irvine
Methamphetamine Abuse and Cortical Cell Injury

Mason, Walter A. -- University of Washington
Parent-Training Intervention to Prevent Adolescent Depression and Substance Use

Meisel, Robert L. -- Purdue University, West Lafayette
Dopamine Sensitization by Motivated Behaviors

Melikian, Haley E. -- University of Massachusetts Medical School, Worcester
Trafficking and Regulation of Monoamine Transporters

Mills, Edward M. -- University of Texas, Austin
Mechanisms of MDMA-Induced Hyperthermia

Morris, Marilyn E. -- State University of New York at Buffalo
Gamma-Hydroxybutyrate: Toxicokinetics, Toxicodynamics and Treatment Strategies

Mosberg, Henry I. -- University of Michigan at Ann Arbor
Conformation - Selectivity Relations of Opioid Peptides

Mustanski, Brian S. -- University of Illinois at Chicago
Gene-Environment Interaction Effects on HIV Risk

Nath, Avindra -- Johns Hopkins University
SSRI-Neuroprotection for HIV/Drug Abuse

Navarro, Hernan A. -- Research Triangle Institute
Ethnopharmacological Approach to Psychoactive Compounds

Nicosia, Nancy -- Rand Corporation
Role of Race in Criminal Justice Referrals to Treatment

Nyamathi, Adeline M. -- University of California, Los Angeles
An Arts Intervention for Drug-Using Homeless Youth

Ompad, Danielle C. -- New York Academy of Medicine
Methods for Evaluating the Physical and Social Environment of Urban Neighborhoods

Orlando, Maria -- Rand Corporation
Assessment of the Adolescent Therapeutic Community Treatment Process

Oser, Carrie B. -- University of Kentucky
African-American Female Drug Users: HIV, Health Disparities, and Criminality

Palmer, Abraham A. -- University of Chicago
Novel Methods to Map Stimulant QTLs in Advanced Intercross Lines

Pan, Ying-Xian -- Sloan-Kettering Institute for Cancer Research
Characterizing Exon 11 Promoter of the Mu Opioid Receptor Gene, OPRM

Pasternak, Gavril W. -- Sloan-Kettering Institute for Cancer Research
Synthesis and Pharmacology of Novel Opiates and Their Modulatory Systems

Pechnick, Robert N. -- Cedars-Sinai Medical Center
Viral-Mediated GDNF Expression and Cocaine Addiction

Pechnick, Robert N. -- Cedars-Sinai Medical Center
Nicotine Addiction: Influence of Prenatal and Adolescent Exposure

Pelham, William E. -- State University of New York at Buffalo
Development of Drug Use and Abuse in ADHD Adolescents

Peti, Wolfgang -- Brown University
Structural and Functional Analysis of the Sigma-1 Receptor

Picciotto, Marina R. -- Yale University
Anatomical Basis for Nicotine Addiction

Pierce, Robert Christopher -- Boston University Medical Campus
MPFC, N. Accumbens and Reinstatement of Cocaine Seeking

Popescu, Gabriela -- State University of New York at Buffalo
NMDA Receptors with Restricted Mobility of the Ligand Binding Domain

Porreca, Frank F. -- University of Arizona
NGF-Dependent Sensitization of Nociceptors by Opiates

Potter, Alexandra S. -- University of Vermont and State Agricultural College
The Functional Neuroanatomy of Acute Nicotinic Modulation of Impulsivity in Women

Potts, Geoffrey F. -- University of South Florida
Reward Sensitivity and Incentive Salience in Cigarette Smokers

Rajadhyaksha, Anjali M. -- Weill Medical College of Cornell University
RNAi Knockdown of Cav1.3 and Addiction

Redding, Colleen A. -- University of Rhode Island
Optimal TTM Tailoring for Population Cessation

Rowell, Tawandra Lashone -- University of Pennsylvania
The Impact of Drugs on the Sexual Behavior of African-American Male Inmates

Sanna, Pietro P. -- Scripps Research Institute
Gene Expression of Cocaine Dependence and Relapse

Self, David W. -- University of Texas, Southwest Medical Center, Dallas
Mechanisms of Altered Dopamine Signaling in Cocaine Addiction

Shadel, William G. -- Rand Corporation
Modeling the Effect of Cigarette Advertising on Adolescent Smoking

Stoops, William W. -- University of Kentucky
Human Lab Model of Behavioral/Pharmacological Treatment for Cocaine Dependence

Strathdee, Steffanie A. -- University of California, San Diego
Epidemiologic Study on Changing HIV Risks Among FSW-IDUs on the Mexico-US Border

Swann, William B. -- University of Texas, Austin
Interpersonal Processes, Identity and Smoking Cessation

Sweitzer, Sarah M. -- University of South Carolina at Columbia
Developmental Regulation of Endothelin Pain

Thomas, James B. -- Research Triangle Institute
Development of Levocabastine Analogues to Treat Methamphetamine Abuse

Tull, Matthew T. -- University of Maryland
PTSD and Predictors of Residential Drug Treatment Drop Out

Unger, Vinzenz M. -- Yale University
Structural Biology of Presynaptic Scaffolds

Vaidya, Jatin G. -- University of Iowa
An FMRI Study of Relative Reward Processing in Adolescents and Adults

Vallano, Mary L. -- Upstate Medical University
A Calcium/Calcineurin Signaling Cascade Regulates Neuronal Cannabinoid Receptors

Wagner, Karla D. -- University of Southern California
Gender Differences in Perceived Costs of Safer Injection among Injection Drug Use

Wang, Qiang -- University of Missouri, Kansas City
Metabotropic Glutamate Regulation of Amphetamine Action

Watkins, Linda R. -- University of Colorado at Boulder
Exploring the Potential of Glia for Regulating Clinically Relevant Opioid Actions

White, Mary Castle -- University of California, San Francisco
Methamphetamine Use in Inmates: Risk Behaviors, Health Status and Recidivism

Wolfe, Hannah -- St. Luke's-Roosevelt Institute for Health Sciences
Peer Intervention to Link HIV Positive Substance Abusers to Outpatient Care

Zhang, Heping -- Yale University
Analysis of Genomic Data for Complex Traits

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

Extramural Policy and Review Activities

Receipt, Referral, and Review

NIDA received 1098 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 813 applications.

OEA arranged and managed 26 grant review meetings in which 313 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 and contract proposal concept reviews.

NIDA's chartered committees consist of NIDA-E (Treatment Review Committee), NIDA-F (Health Services Review Committee), NIDA-L (Medications Development Committee), and NIDA-K (Training Committee). In addition to meetings of each of these committees, OEA staff held 22 Special Emphasis Panels for a variety of reasons:

Conflicts with the chartered committees
Center Grant Applications
Program Project Grant applications
Behavioral Science Track Award for Rapid Transition (B/START)
Imaging Science Track Awards for Research Transition (I/START)
Cutting-Edge Basic Research Awards (CEBRA) (R21)
Conference Grants (R13)
NIH Pathway To Independence (PI) Awards (K99/R00)
Minority Institutions' Drug Abuse Research Development Program (MIDARP)
Mechanism for Time-Sensitive Research Opportunities (R01)
Requests for Applications (RFAs)

OEA managed the following RFA reviews:

- DA08-002: Criminal Justice Drug Abuse Treatment Studies 2 (CJ-DATS 2)
- DA08-005: International Research Collaborations to Study HIV/AIDS and Drug Abuse

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

Concept Review

- N01DA-8-1137: International Research Training and Support

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Phase I SBIR Contract Reviews

- N43DA-8-4409: Topic 090 - Real Time fMRI Feedback System
- N43DA-8-2213: Topic 093 - Development of Website Training for Pain Specialists
- N43DA-8-2214: Topic 094 - Development of Website Training for Primary Care
- N43DA-8-5538: Topic 095 - Drug Abuse Screening Assessment
- N43DA-8-7764: Topic 097 - Nanoscience-based Design of Therapies

Phase II SBIR Contract Reviews

- N44DA-8-1131: International Substance Abuse Data Resource Center
- N44DA-8-2210: Development of Substance Abuse Training Methods
- N44DA-8-2212: Serious Game Technology
- N44DA-8-4405: Environment/Curb Teen Smoking
- N44DA-8-5535: A Market Technology Plan for Disseminating Workplace Drug Prevention Programs

R&D and non-R&D Contract Reviews

- N01DA-8-7763: Synthesis & Distribution of Drugs of Abuse and Related Compounds
- N01DA-8-8875: Analytical Services Center for MDP
- N01DA-8-8876: Assessment of Potential Cocaine Pharmacotherapies in Monkeys

Extramural Policy and Review Activities

Transfer of NIDA fellowship review to the CSR
NIDA fellowship applications that had previously been reviewed by NIDA's NIDA-K review committee (NRSA F30, F31, and F32), will now be reviewed at the Center for Scientific Review (CSR). This change became effective on the April 8, 2008 receipt date. CSR fellowship study sections can be viewed on the CSR website. For more information about this transfer, please see http://www.nida.nih.gov/ pdf/researchtraining/FellowshipFAQs.pdf.

Certificates of Confidentiality

Between December 13, 2007 and March 21, 2008 OEA processed 112 Certificate applications, including 23 for extension of expiration dates and 9 for amended protocols.

Staff Training and Development

The OEA Symposium Series, a forum for staff training and sharing of ideas and information, continued through Spring 2008. Activities included open forums for discussions and presentations that included the Privacy Act of 1974 and the E-Government Act of 2002 and utilization of e-applications for extramural program support.

Planned Meetings

Publications

Staff Highlights

Grantee Honors

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

Congressional Affairs (Prepared May 2, 2008)

Appropriations

On February 4, 2008, the President released his FY 2009 Budget. NIDA's proposed budget is $1,001,672,000, an increase of $972,000 over the FY 2008 enacted appropriation.

For NIH overall, the proposed budget is $29.465 billion - the same amount as was enacted for FY 2008.

Hearings, Briefings, and Events of Interest

U.S. Senate Hearing on Cocaine Sentencing Policy: On February 12, 2008, the Senate Judiciary Committee's Subcommittee on Crime and Drugs (Chairman: Joseph Biden (D-DE) held a hearing entitled "Federal Cocaine Sentencing Laws: Reforming the 100-to-1 Crack/Powder Disparity." The hearing followed a recent ruling by the U.S. Sentencing Commission to reduce the disparity in sentencing guidelines for those convicted of dealing two different forms of cocaine and, in certain cases, to make those reductions retroactive.

NIDA Director Dr. Nora Volkow appeared before the Subcommittee to discuss the basic psychopharmacology of the drug. Her testimony (http://www.drugabuse.gov/Testimony/2-12-08Testimony.html), which covered the epidemiology and medical consequences of crack and powder cocaine addiction, also made clear that differences in the subjective effects of alternate forms of cocaine are related to the route of administration (i.e., whether the drug is injected, smoked, or snorted). Dr. Volkow also discussed the important role of behavioral research, noting that no medication has yet proven effective in treating cocaine dependence, but that several behavioral therapies have. Further information and testimony of other witnesses are available at http://judiciary.senate.gov/hearings/hearing.cfm?id=3089.

U.S. Senate Hearing on Prescription Drug Abuse: On March 12, 2008, the Senate Judiciary Committee's Subcommittee on Crime and Drugs (Chairman: Joseph Biden (D-DE) and the Senate Caucus on International Narcotics Control (Co-Chairmen Joseph Biden and Charles Grassley (R-IA) held a hearing entitled "Generation Rx: The Abuse of Prescription and Over the Counter Drugs." The hearing was held to further investigate current prescription drug abuse issues, and to learn what we might do to ameliorate the problem.

NIDA Director Dr. Nora Volkow appeared before the Subcommittee and Caucus to discuss the science around this issue. Her testimony (http://www.drugabuse.gov/Testimony/3-12-08Testimony.html) covered the epidemiology, contributing factors, consequences, and NIDA research focused

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on addressing and alleviating prescription drug abuse and addiction. Further information and testimony of other witnesses are available at http://judiciary.senate.gov/hearings/hearing.cfm?id=3199.

Friends of NIDA Capitol Hill Briefing: On April 8, 2008, the Friends of NIDA, in conjunction with the Congressional Addiction, Treatment and Recovery Caucus, held its tenth in a series of briefings designed to educate members of Congress and their staff about substance abuse and addiction issues. This briefing focused on the genetics of drug abuse and addiction. Research has shown that the causes of drug abuse and addiction are complex, with genetic, environmental, and developmental factors all contributing. Genetics accounts for approximately half of an individual's vulnerability to addiction, including how genes interact with the environment and stage of development. Thanks to recent scientific advances, we are now poised to further untangle these factors and to use that knowledge to better tailor prevention and treatment strategies. In fact, NIDA is supporting research to define and measure aspects of the social environment to understand how genes may mitigate or amplify social influences, known to powerfully affect individual choices and behaviors related to substance abuse.

NIDA Director Dr. Nora Volkow began the briefing by summarizing the Institute's genetics research portfolio as it relates to addiction and drug abuse. Caryn Lerman, Ph.D., Mary W. Calkins, Professor and Director of the Transdisciplinary Tobacco Use Research Center at the University of Pennsylvania, then discussed emerging research on the role of genetic influences in smoking cessation and response to treatments for nicotine addiction. Finally, Alexandra Shields, Ph.D., Director of the Harvard/MGH Center on Genomics, Vulnerable Populations and Health Disparities at the Institute for Health Policy at Massachusetts General Hospital and Assistant Professor of Medicine at Harvard Medical School, addressed challenges translating emerging pharmacogenetic approaches to smoking cessation treatment to clinical practice. The event was cosponsored by 26 Friends of NIDA scientific and professional organizations and was well-attended by congressional and constituency group staff.

Bills of Interest

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

Potential Institute Name Change --H.R.1348/S. 1011 - On March 6, 2007, Representatives Patrick Kennedy (D-RI) and John Sullivan (R-OK) introduced H.R.1348, to redesignate the National Institute on Drug Abuse as the National Institute on Diseases of Addiction, and to redesignate the National Institute on Alcohol Abuse and Alcoholism as the National Institute on Alcohol Disorders and Health. Similarly, on March 28, 2008, Senators Joseph Biden (D-DE), Edward Kennedy (D-MA) and Michael Enzi (R-WY) introduced S. 1011, the Recognizing Addiction as a Disease Act of 2007, which would make the same changes. In a press release, Senator Biden said the intent of the legislation is to recognize addiction as a preventable and treatable neurobiological disease, and to better identify the roles and missions of our research institutes. "Addiction is a neurobiological disease - not a lifestyle choice - and it's about time we start treating it as such," said Sen. Biden. "We must lead by example and change the names of our Federal research institutes to accurately reflect this reality. By changing the way we talk about addiction, we change the way people think about addiction, both of which are critical steps in getting past the social stigma too often associated with the disease." The House bill was referred to the Health Subcommittee of the Energy and Commerce Committee; the Senate bill was marked up and passed by the Health, Education, Labor and Pensions Committee on June 27, 2007. The bill has been placed on the Senate calendar under General Orders. The bill is currently being "held" by Senator Jim

Planned Meetings

Publications

Staff Highlights

Grantee Honors

DeMint (R-SC). He must release his hold if the bill is to receive full consideration in the Senate.

Stem Cells - H.R. 3/S.5 - On January 5, 2007, Representative Diana DeGette (D-CO) introduced H.R. 3, the Stem Cell Research Enhancement Act of 2007. The Senate companion, S. 5, was introduced on January 4, 2007, by Senate Majority Leader Harry Reid (D-NV). The bills would require the Secretary of HHS to conduct and support research using human embryonic stem cells regardless of the date on which such cells were derived. Both the House and Senate passed their bills. The Senate bill was amended prior to floor consideration. As amended, the bill would also require the Secretary to conduct and support research involving methods of obtaining pluripotent stem cells that do not involve the use of human embryos. The House passed the amended Senate bill, thus sending the bill to the President. The President vetoed the bill. Concurrent with his veto, the President issued an Executive Order requiring the Secretary of HHS to enhance funding for research on alternative methods to derive pluripotent stem cells that do not involve human embryos.

Stem Cells - S. 30 - On April 11, 2007, the Senate passed S. 30, the Hope Offered Through Principled and Ethical Stem Cell Research Act, by a roll call vote of 70-28. The bill, introduced on March 29, 2007, by Representative Norm Coleman (R-MN) would require the Secretary to support research to develop pluripotent stem cells using methods that do not involve either the creation of, harm to, or destruction of human embryos. As mentioned above re: S.5, the President issued an Executive Order requiring the Secretary of HHS to enhance funding for research on alternative methods to derive pluripotent stem cells that do not involve human embryos.

Genetic Non-discrimination - H.R. 493/S. 358 - On January 16, 2007, Representative Louise Slaughter (D-NY) introduced H.R. 493, the Genetic Information Nondiscrimination Act of 2007. The Senate companion, S. 358, was introduced by Senator Olympia Snowe (R-ME) on January 22, 2007. These bills, which would prohibit discrimination in health insurance and employment on the basis of predictive genetic information, are identical to legislation passed by the Senate during the 109th Congress. The bills would prohibit health insurers in both the group and individual markets from (1) using genetic information to impose enrollment restrictions or to adjust premium or contribution amounts, (2) requesting genetic testing or results except as necessary for treatment, payment, or health care operations, or (3) requesting or requiring the use of genetic information for the purposes of underwriting. The bills define a genetic test as an analysis of human DNA, RNA, chromosomes, proteins, or metabolites that detects genotypes, mutations, or chromosomal changes. The House passed its original bill on April 25, 2007. On April 24, 2008, the Senate passed an amended version of the House bill; the House passed the final bill on May 1, 2008. The President has said he will sign the bill into law.

Insurance Parity for Mental Health and Substance Abuse - H.R. 1424/S.558 - On February 12, 2007, Senator Pete Domenici (R-NM) introduced the Mental Health Parity Act of 2007, a bill to provide parity between health insurance coverage of mental health benefits and benefits for medical and surgical services. On March 9, 2007, Representative Patrick Kennedy (D-RI) introduced the Paul Wellstone Mental Health and Addiction Equity Act of 2007, to amend section 712 of the Employee Retirement Income Security Act of 1974, section 2705 of the Public Health Service Act, and section 9812 of the Internal Revenue Code of 1986 to require equity in the provision of mental health and substance-related disorder benefits under group health plans. The Senate passed its bill in September of 2007; the House passed its bill on March 5, 2008. Negotiations continue in Congress in pursuit of a compromise bill.

Community Re-entry for Prisoners -- H.R. 1593/S. 1060 - On March 20,

2007, Representative Danny Davis (D-IL) introduced the Second Chance Act of 2007, to reauthorize the grant program for reentry of offenders into the community in the Omnibus Crime Control and Safe Streets Act of 1968, to improve reentry planning and implementation, and for other purposes. The Senate version of this bill was introduced by Senator Joe Biden (D-DE) on March 29, 2007. The bills include a strong focus on drug treatment in the criminal justice system, and consultation with NIDA is required in several bill sections. The House passed its bill in November, the Senate passed its bill in March of 2008, and the President signed it into law (P.L 110-199).

Tobacco -- H.R. 1108/S. 625 - On February 15, 2007, Representative Henry Waxman (D-CA) introduced H.R. 1108, the Family Smoking Prevention and Tobacco Control Act - a bill to protect public health by providing the Food and Drug Administration with certain authority to regulate tobacco products. Senator Edward Kennedy (D-MA) introduced an identical bill in the Senate. Both bills have been reported out by their respective Committees, and further action is pending.

Crack vs. Powder Cocaine - Several bills have been introduced to address the sentencing differences for those convicted of selling or possessing different forms of cocaine. Most attempt to equalize penalties. Representative Roscoe Bartlett (R-MD) introduced H.R. 79, the Powder-Crack Cocaine Penalty Equalization Act of 2007. Representative Charles Rangel (D-NY) introduced H.R. 460, the Crack-Cocaine Equitable Sentencing Act of 2007. Representative Bobby Scott (D-VA) introduced H.R. 5035, the Fairness in Cocaine Sentencing Act of 2008. Senator Jeff Sessions (R-AL) introduced S. 1383, the Drug Sentencing Reform Act of 2007. Senator Orrin Hatch (R-UT) introduced S. 1685, the Fairness in Drug Sentencing Act of 2007. Senator Joseph Biden introduced S. 1711, the Drug Sentencing Reform and Cocaine Kingpin Trafficking Act of 2007. All of these bills have been referred to their appropriate committees and further action is pending.

Freedom of Information - Several bills designed to broaden accessibility to government information were introduced last year (H.R. 1309, H.R. 1326, S. 849, S. 2427). Senator Patrick Leahy introduced S. 2488, the Open Government Act of 2007, to combine various proposals, which passed the House and Senate and became law in December, 2007. The law aims to promote accessibility, accountability and openness in government by strengthening Section 522 of Title 5, U.S. Code (the Freedom of Information Act).

H.R. 405 - On January 11, 2007, Representative Barbara Cubin (R-WY) introduced the Family-Based Meth Treatment Access Act of 2007, to amend the Public Health Service Act regarding residential treatment programs for pregnant and parenting women, a program to reduce substance abuse among nonviolent offenders, and for other purposes. The bill was referred to the Committee on Energy and Commerce. See. S. 884

H.R. 970 - On February 8, 2007, Representative Fred Upton (R-MI) introduced H.R. 970, the Dextromethorphan Distribution Act of 2007, to amend the Federal Food, Drug and Cosmetic Act with respect to the distribution of the drug dextromethorphan, and for other purposes. The bill was passed in October. See also S. 1378, S. 2274

H.R. 1155 - On February 16, 2007, Representative Eddie Bernice Johnson (D-TX) introduced H.R. 1155, a bill to amend Title XIX of the Social Security Act to remove the exclusion from medical assistance under the Medicaid Program of items and services for patients in an institution for mental diseases (the "IMD Exclusion"). The bill was referred to the Committee on Energy and Commerce.

H.R. 1170 - On February 16, 2007, former Representative Martin Meehan (D-MA) introduced H.R. 1170, the Comprehensive Awareness of Problem Gambling

Act of 2007. H.R. 1170 includes a research provision which would require the President to establish a national program of research on problem gambling. The bill would require the President to appoint an advisory commission to coordinate activities of Federal agencies relating to research on problem gambling including the activities of the NIH. The bill was referred to the Committee on Energy and Commerce.

H.R. 1199 - On February 27, 2007, Representative Dennis Cardoza (D-CA) introduced the Drug Endangered Children Act of 2007, to extend the grant program for drug-endangered children. The bill passed in September. See S. 1210.

H.R. 1200 - On February 27, 2007, Representative Jim McDermott (D-WA) introduced H.R. 1200, the American Health Security Act of 2007. The purpose of the bill is "to provide for health care for every American and to control the cost and enhance the quality of the health care system." Of interest to NIH is section 722, which would establish the Office of Primary Care and Prevention Research within the Office of the Director; require the establishment of a data system of information regarding primary care and prevention research that is conducted or supported by the ICs; require the establishment of a clearinghouse to provide information on research and prevention activities of the ICs that relate to primary care and prevention research; require a biennial report on primary care and prevention research; and authorize $150 million for FY 2008, $180 million for FY 2009, and $216 million for FY 2010. In addition, the legislation would amend the authorities of the NIH Director to require that sufficient resources are sufficiently allocated for projects on primary care and prevention research. H.R. 1200 was jointly referred to the House Committees on Energy and Commerce; Ways and Means; Oversight and Government Reform; and Armed Services.

H.R. 1663 - On March 23, 2007, Representative Pete Stark (D-CA) introduced HR 1663, The Medicare Mental Health Modernization Act of 2007, to amend title XVIII of the Social Security Act to expand and improve coverage of mental health services under the Medicare Program. The bill was referred to the Committee on Ways and Means, and the Committee on Energy and Commerce.

H.R. 1943 - On April 19, 2007, Representative Maxine Waters (D-CA) introduced the Stop AIDS in Prison Act of 2007, to provide for an effective HIV/AIDS program in Federal prisons. The bill passed the House in September, and was sent to the Senate, where it is pending before the Judiciary Committee.

H.R. 2073 - On April 30, 2007, Representative Patrick Kennedy (D-R.I.) introduced the Child Health Care Crisis Act of 2007, to help bring new professionals into the mental health services field. The bill creates educational incentives such as grants, scholarships and loan forgiveness programs to encourage more professionals to enter and remain in child and adolescent mental health. It would also support institutions of higher learning in their efforts to enhance and prioritize children's mental health issues in their curriculum and training opportunities. The bill was referred to the Committees on Energy and Commerce and Ways and Means. See S.1572.

H.R. 2223 - On May 8, 2007, Representative Jon Porter (R-NV) introduced this bill to direct the Director of the Office of National Drug Control Policy, in consultation with the Attorney General and the Secretary of Health and Human Services, to conduct a study on prescription drug take-back programs, and for other purposes. The bill was referred to the Committee on Energy and Commerce.

H.R. 2425 - On May 22, 2007, Representative John Boozman (R-AR) introduced the Stop Marketing Illegal Drugs to Minors Act, to amend the Controlled Substances Act to provide enhanced penalties for marketing

controlled substances to minors. The bill was referred to the Committees on the Judiciary and Energy and Commerce. See S. 1211.

H.R. 2552 - On May 24, 2007, Representative Edolphus Towns (D-NY) introduced the Hepatitis C Control and Prevention Act of 2007, to amend the Public Health Service Act to direct 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 was referred to the Committee on Energy and Commerce. See S. 1445.

H.R. 2645 - On June 11, 2007, Representative William Jefferson (D-LA) introduced the Judicial Initiative Mental Health and Substance Abuse Treatment Improvement Act of 2007, to amend the Juvenile Justice and Delinquency Prevention Act of 1974 to improve mental health and substance abuse treatment by providing grants for justice system personnel training, treatment programs and diversion programs, and for other purposes. The bill was referred to the Committees on Education and Labor and Judiciary.

H.R. 2647 - On June 11, 2007, Representative William Jefferson (D-LA) introduced the Mental Health and Substance Abuse Juvenile Services Improvement Act of 2007, to amend the Public Health Service Act to improve mental health and substance abuse services for juveniles. The bill was referred to the Committee on Energy and Commerce.

H.R. 2900 - On June 29, 2007, Congressman John Dingell (D-MI) introduced the FDA Amendments Act of 2007. The bill passed the House and was referred to the Senate in July. See S.1082.

H.R. 2994 - On July 11, 2007, Representative Lois Capps (D-CA) introduced the National Pain Care Policy Act of 2007, to amend the Public Health Service Act with respect to pain care. The bill was referred to the Committee on Energy and Commerce.

H.R. 3000 - On July 11, 2007, Representative Barbara Lee (D-CA) introduced the Josephine Butler United States Health Service Act. Of interest to NIH are provisions that would establish the United States Health Service and a National Health Board. Upon enactment, NIH, AHRQ, ATSDR, CDC, and SAMHSA would be transferred to the National Health Board. It would also establish the following new institutes: National Institute of Epidemiology; National Institute of Evaluative Clinical Research; the National Institute of Health Care Services; the National Institute of Pharmacy and Medical Supply; and the National Institute of Sociology of Health and Health Care. This bill has been reintroduced continually since the 105th Congress. The bill was referred to the House Committees on Energy and Commerce, Education and Workforce, and Ways and Means.

H.R. 3014 - On July 12, 2007, Representative Hilda Solis (D-CA) introduced the Health Equity and Accountability Act of 2007, to improve the health of minority individuals. Provisions of interest to NIH include a requirement that each Federal health agency develop and implement a national strategic action plan to eliminate disparities on the basis of race, ethnicity, and primary language and improve the health and health care of minority populations through programs relevant to the mission of the agency. NIH-related provisions would amend authorities of the National Center for Minority Health and Health Disparities (NCMHD) to require (1) the Director of the Center, in consultation with the respective Institute and Center (IC) directors or their designees, plan, coordinate, and evaluate research and other activities conducted or supported by the agencies of the NIH and carry out periodic re-evaluations of these activities; (2) annual review and revision of a comprehensive plan and budget for the conduct and support of relevant research; (3) systematic review of research activities, including establishment of mechanisms for tracking minority health and health disparities research conducted within the ICs, with

assessments of the appropriateness of such research within the overall goals and objectives of the Plan; and (4) early identification of applications and proposals for grants, contracts, and cooperative agreements supporting relevant extramural training, research, and development that are submitted to the ICs. In addition, provisions would require that the Director, NCMHD, expend all amounts appropriated under section 485E for minority health and health disparities research, in accordance with the section and applicable law and in collaboration with the Director, NIH, and the IC directors. The bill was referred to the House Committees on Energy and Commerce, Ways and Means, Education and Labor, Natural Resources, and Judiciary.

H.R. 3130 - On July 23, 2007, Representative Darlene Hooley (D-OR) introduced the Enhanced Methamphetamine Treatment Grants Assistance Act of 2007, to amend title V of the Public Health Service Act to provide for enhanced comprehensive methamphetamine treatment services. The bill was referred to the Committee on Energy and Commerce.

H.R. 3186 - On July 26, 2007, Representative Rick Larsen (D-WA) introduced the Meth Mouth Prevention and Community Recovery Act, to understand and comprehensively address the oral health problems associated with methamphetamine use. The bill was referred to the Committee on Energy and Commerce. See S. 1906.

H.R. 3187 - On July 26, 2007, Representative Brian Baird (D-WA) introduced the Meth Mouth Correctional Costs and Reentry Support Act, to amend title I of the Omnibus Crime Control and Safe Streets Act of 1968 to understand and comprehensively address the inmate oral health problems associated with methamphetamine use, and for other purposes. The bill was referred to the Committee on the Judiciary. See S. 1907.

H.R. 3409 - On August 3, 2007, Representative Ruben Hinojosa (D-TX) introduced H.R. 3409, the Place to Call Home Act, to create the conditions, structures, and supports needed to ensure permanency for the nation's unaccompanied youth, and for other purposes. The bill contains a number of provisions related to improving funding and coordination of drug and alcohol prevention and treatment services. The bill was referred to the Committees on Education and Labor, Ways and Means, Energy and Commerce, Financial Services, and Judiciary.

H.R. 3411 - On August 3, 2007, Representative Patrick Kennedy (D-RI) introduced H.R. 3411, the Juvenile Crime Reduction Act, to improve the treatment of young people in the juvenile justice system with mental health or substance use disorders. The legislation would establish a number of grant programs to increase training, technical assistance, and coordination of service providers, including those who provide addiction treatment services, to young people who are involved with the juvenile justice system. H.R. 3411 would establish a number of grant programs aimed at improving services for youth in the juvenile justice system with mental health or substance use disorders. The bill was referred to the House Committees on Education and Labor and Energy and Commerce.

H.R. 3433 - On August 3, 2007, Representative Steven Pearce (R-NM) introduced the Methamphetamine Treatment and Rehabilitation Best Practices Act of 2007, to direct the Secretary of Health and Human Services, acting through the Director of the National Institutes of Health, to conduct a survey of research available on methamphetamine addiction and treatment. The bill was referred to the Committee on Energy and Commerce.

H.R. 3434 - On August 3, 2007, Representative Steven Pearce (R-NM) introduced the Americans Saving Through Health Research Bonds Act of 2007. The bill would amend 31 USC 3105 to authorize the Secretary to designate one or more series of health research bonds or certificates (or any portion thereof)

to benefit each of the NIH institutes. The Secretary would be required to deduct and withhold ten percent of the amount of any interest payable under any such bond, which would be paid to the designated NIH institute to carry out research activities. It would also be required that the amount of any such payment would not be taken into account in making decisions regarding funds appropriated or otherwise provided to the NIH. The bill was referred to the Committee on Ways and Means.

H.R. 3561 - On September 18th, 2007, Representative Gene Green (D-TX) introduced H.R. 3561, the Community Coalitions for Access and Quality Improvement Act of 2007, legislation that would authorize a grant program aimed at better integrating health care delivery. Primarily concerned with expanding and coordinating the delivery of health services, H.R. 3561 seeks to increase access to health care for low-income and uninsured populations. In determining grant eligibility, priority would be given to applicants who seek to expand drug and alcohol addiction and mental health treatment services. The bill was referred to the House Energy and Commerce Committee.

H.R. 3656 - On September 26th, 2007, Representative Phil English (R-PA) introduced H.R. 3656, to require states to withhold assistance to applicants for, and recipients of, temporary assistance for needy families (TANF) with respect to whom there is substantial evidence of recent unlawful drug use. The legislation would require states to drug test TANF applicants and recipients suspected of using illicit drugs. The bill was referred to the Committee on Ways and Means.

H. R. 3749 - On October 4, 2007, Representative Darlene Hooley (D-OR) introduced H.R. 3749, the Methamphetamine Prevention Enhancement Act, to amend the Public Health Service Act to provide for the establishment of a Drug-Free Workplace Information Clearinghouse, to authorize programs to prevent and improve treatment of methamphetamine addiction, and for other purposes. The bill was referred to the Committee on Energy and Commerce.

H.R. 3992 - On October 30, 2007, Representative Bobby Scott (D-VA) introduced the Mentally Ill Offender Treatment and Crime Reduction Reauthorization and Improvement Act of 2007, to amend Title I of the Omnibus Crime Control and Safe Streets Act of 1968 to provide grants for the improved mental health treatment and services provided to offenders with mental illnesses, and for other purposes. The bill passed the House in January, 2008. See S. 2304.

H.R. 4053 - On November 1, 2007, Representative Shelley Berkley (D-NV) introduced the Mental Health Improvement Act of 2007, to improve the treatment and services provided by the Department of Veterans Affairs to veterans with post-traumatic stress disorder and substance use disorders, and for other purposes. The bill was referred to the Committee on Veterans Affairs, Subcommittee on Health. See S. 2162.

H.R. 4129 - On November 8, 2007, Representative Hilda Solis (D-CA) introduced the Homeless Access to Recovery through Treatment Act, to amend the Public Health Service Act to strengthen and expand substance abuse and mental health services to persons experiencing homelessness in the United States. The bill was referred to the Committee on Energy and Commerce.

H.R. 4232 - On November 15, 2007, Representative Patrick Kennedy (D-RI) introduced H.R. 4232, the Improving the Quality of Mental and Substance Use Health Care Act of 2007, to improve mental and substance use health care in the U.S. The bill was referred to the Committee on Energy and Commerce.

H.R. 4848 - On December 19, 2007, Representative Pete Stark (D-CA) introduced H.R. 4848 to extend parity in the application of certain limits to mental health benefits and for other purposes. The bill passed the House on

February 8, 2008.

H.R. 5176 - On January 29, 2008, Representative Gene Green (D-TX) introduced the Community Mental Health Services Improvement Act," to amend the Public Health Service Act with respect to mental health services. The Bill was referred to the Committee on Energy and Commerce, Subcommittee on Health. See S. 2182.

H.R. 5501 - On February 27, 2008, Representative Howard Berman (D-CA) introduced the Tom Lantos and Henry J. Hyde United States Global Leadership Against HIV/AIDS, Tuberculosis, and Malaria Reauthorization Act of 2008, to authorize appropriations for fiscal years 2009 through 2013 to provide assistance to foreign countries to combat HIV/AIDS, tuberculosis, and malaria, and for other purposes. The bill passed the House on April 2. Of particular interest to NIH are provisions that would (1) require the Secretary of HHS, acting through the CDC and NIH, to conduct appropriately programmatic relevant clinical and operational research to identify and evaluate new diagnostics, treatment regimens, and interventions to prevent and control malaria, (2) authorize the Secretary to participate with other countries in cooperative endeavors in biomedical research, health care services, health care research, or other related activities in furtherance of the activities, goals and objectives authorized under this act, (3) and require establishment, within the Department of State, of an interagency working group on HIV/AIDS, headed by the Global AIDS Coordinator and including representatives from HHS and the U.S. Agency for International Development, for the purposes of coordination of activities related to HIV/AIDS. See S. 2731.

H.R. 5554 - On March 6, 2008, Representative Michael Michaud (D-ME) introduced the Veterans Substance Use Disorders Prevention and Treatment Act of 2008, to amend Title 38, United States Code, to expand and improve health care services available to veterans from the Department of Veterans Affairs for substance use disorders, and for other purposes. The Committee on Veterans Affairs held subcommittee and committee hearings, and the bill was reported favorably (as the Justin Bailey Veterans Substance Use Disorder Prevention and Treatment Act of 2008 on April 30. If enacted into law, this bill would require that each VA medical center provide ready access to a full continuum of care for substance use disorders for veterans in need of such care. Under the legislation, this continuum of care is defined as including: Screenings for substance use disorder in all settings Detoxification and stabilization services Intensive outpatient care services Relapse prevention services Outpatient counseling services Residential substance use disorder treatment for veterans with severe recurring substance abuse or substance dependence Pharmacological treatment to reduce cravings, including opioid substitution therapy Coordination with groups providing peer to peer counseling Short-term, early interventions for substance use disorders Marital and family counseling The VA Secretary would also be required to reach out to veterans who served in Operation Enduring Freedom or Operation Iraqi Freedom to increase awareness of the availability of care, treatment and services from the VA for substance use disorders. The bill also authorizes a $1.5 million per year pilot program to test the feasibility of providing veterans who seek treatment for substance use disorders access to a computer-based self-assessment, education, and specified treatment program through a secure Internet website operated by the VA. Finally, the bill requires the Secretary of the VA to include a detailed report to Congress on the care, treatment and services provided by the VA during the most recently completed fiscal year. The report must include data from each VA medical facility, including information about the number of veterans who received substance use disorder screening; the number of veterans for whom a disorder was identified after a screening at a VA facility; the number of veterans who were referred by a VA facility for care, treatment or services; the number of veterans who actually received care, treatment or services; and the availability of the full continuum

of care.

H.R. 5613 - On March 3, 2008, Representative John Dingell introduced the Protecting the Medicaid Safety Net Act of 2008, to extend certain moratoria and impose additional moratoria on certain Medicaid regulations through April 1, 2009. The seven regulations targeted by this bill seek to limit certain types of services reimbursable under Medicaid provided by addiction treatment, mental health treatment and other healthcare providers. Reimbursement payments under Medicaid for targeted case management, rehabilitation, school-based transportation and outreach, hospital outpatient and other services provided through the health care system would be restricted under the proposed rules. The bill passed the House on April 23. See S. 2819.

H.R. 5619 - On March 13, 2008, Representative Rick Boucher (D-VA) introduced the Combat Methamphetamine Enhancement Act of 2008, to enhance the ability to combat methamphetamine. The bill was referred to the Committees on Energy and Commerce and Judiciary. See S. 2071.

H.R. 5819 - On April 17, 2008, Representative Nydia Velazquez introduced the SBIR/STTR Reauthorization Act, to amend the Small Business Act to improve the SBIR program and the STTR program, and for other purposes. The bill would reauthorize the programs until 2010 with allocation levels remaining at 2.5 percent for SBIR and 0.3 percent for STTR. The bill increases the award levels for SBIR and STTR Phase I at $300,000 and Phase II at $2,200,000. The measure would require the establishment of an advisory board at each participating agency to review quarterly reports and make necessary recommendations. Additionally, the bill would expand the eligibility criteria to allow small business concerns with multiple venture capital investment and ownership to apply for awards. Further, H.R. 5819 would provide flexibility to applicants for cross-over between the programs and to apply directly for Phase II awards. During committee markup, 15 amendments were adopted, some of which would provide for a preference in awarding grants to businesses owned by veterans, that are located in areas with high unemployment, working on rare-disease or nanotechnology-related research topics, or that have taken steps to increase energy efficiency and reduce carbon emissions. Finally, the bill would require rendering final decisions on applications within 90 days after closing of the solicitation, with some exceptions. The bill passed the House on April 23.

H.R. 5835 - On April 17, 2008, Representative Jan Schakowsky (D-IL) introduced the Health Promotion Funding Integrated Research, Synthesis, and Training Act, or the Health Promotion FIRST Act, to provide for increased planning and funding for health promotion programs of the Department of Health and Human Services. The bill would require OBSSR to develop, and periodically review and as appropriate revise, a plan on how to best develop the basic science of health promotion through the NIH agencies. The bill would also authorize $30 million for FY 2009 to conduct or support early research programs and research training regarding health promotion. The bill was referred to the Committee on Energy and Commerce.

H.R. 5842 - On April 17, Representative Barney Frank (D-MA) introduced the Medical Marijuana Patient Protection Act, to provide for the medical use of marijuana in accordance with the laws of the various States. The bill was referred to the Committee on Energy and Commerce.

H.R. 5843 - On April 17, Representative Barney Frank (D-MA) introduced the Act to Remove Federal Penalties for the Personal Use of Marijuana by Responsible Adults, to eliminate most Federal penalties for possession of marijuana for personal use, and for other purposes. The bill was referred to the Committees on Energy and Commerce, and Judiciary.

S. 884 - On March 14, 2007, Senator Richard Durbin (D-IL) introduced the

Family-Based Meth Treatment Access Act of 2007, to amend the Public Health Service Act regarding residential treatment programs for pregnant and parenting women, a program to reduce substance abuse among nonviolent offenders, and for other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions. See H.R. 405.

S. 980 - On March 23, 2007, Senator Dianne Feinstein (D-CA) introduced the Online Pharmacy Consumer Protection Act of 2007, to amend the Controlled Substances Act to address online pharmacies. The legislation seeks to impose registration and reporting requirements on pharmacies that deliver controlled substances via the Internet. In her comments on the bill's introduction, Senator Feinstein expressed particular concern with the growing problem of prescription drug abuse and addiction. As passed by the Senate, the measure would amend federal drug law to mandate that no controlled substance could be distributed via the Internet -- with some exceptions -- without a valid prescription by a health care practitioner who has physically examined the recipient at least once. The bill passed the Senate on April 1, and was referred to the House.

S. 1082 - On April 10, 2007, Senator Edward Kennedy (D-MA) introduced S. 1082, The Food and Drug Administration Revitalization Act. The bill is focused primarily on FDA and contains sections regarding user fees and drug safety monitoring procedures. As amended, the bill also contains several provisions of interest to NIH. First, the bill would expand the Clinicaltrials.gov registry to include mandatory reporting of certain drug and device clinical trials. The bill would also require that the ClinicalTrials.gov website provide corresponding linkages to peer-reviewed literature and certain publicly available FDA information regarding the results of those trials. Second, S. 1082 includes provisions to reauthorize the Best Pharmaceuticals for Children Act. Third, the bill contains provisions to expand research on pediatric devices. Finally, an amendment offered by Senator Barack Obama (D-IL) was added during floor debate, requiring the Secretary to contract with the Institute of Medicine to make recommendations regarding oversight and regulation of genetic tests. The Senate passed its bill in May.

S. 1210 - On April 25, 2007, Senator Diane Feinstein (D-CA) introduced S. 1210, the Drug Endangered Children Act of 2007, to extend the grant program for drug-endangered children. The bill was referred to the Committee on the Judiciary, where it is pending. See H.R. 1199.

S. 1211 - On April 25, 2007, Senator Diane Feinstein (D-CA) introduced the Saving Kids from Dangerous Drugs Act, to amend the Controlled Substances Act to provide enhanced penalties for marketing controlled substances to minors. The bill was referred to the Committee on the Judiciary. See H.R. 2425.

S. 1337 - On May 8, 2007, Senator John Kerry (D-MA) introduced the Children's Mental Health Parity Act, to amend title XXI of the Social Security Act to provide for equal coverage of mental health services under the State Children's Health Insurance Program. The bill was referred to the Committee on Finance.

S. 1367 - On May 10, 2007, Senator Tom Harkin (D-IA) introduced the Treatment and Prevention of Methamphetamine Abuse Act of 2007, to amend the Public Health Services Act to provide methamphetamine prevention and treatment services. The bill was referred to the Committee on Health, Education, Labor and Pensions.

S. 1378 - On May 14, 2007, Senator Patty Murray (D-WA) introduced S. 1378, the Dextromethorphan Distribution Act of 2007, to amend the Federal Food, Drug and Cosmetic Act with respect to the distribution of the drug dextromethorphan, and for other purposes. The bill was referred to the

Committee on Health, Education, Labor and Pensions, where it awaits action. See H.R. 970.

S. 1445 - On May 22, 2007, Senator Edward Kennedy (D-MA) introduced the Hepatitis C Epidemic Control Prevention Act of 2007. The bill directs 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. The bill was referred to the Committee on Health, Education, Labor, and Pensions. See H.R. 2552.

S. 1470 - On May 23, 2007, Senator Bill Nelson (D-FL) introduced the Drug Free Varsity Sports Act of 2007, to provide States with the resources needed to rid our schools of performance-enhancing drug use. The bill was referred to the Committee on Health, Education, Labor and Pensions.

S. 1572 - On June 7, 2007, Senator Jeff Bingaman (D-NM) introduced the Child Health Care Crisis Relief Act of 2007, 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. The bill was referred to the Committee on Health, Education, Labor and Pensions. See. H.R. 2073.

S. 1882 - On July 26th, 2007, Senator Chuck Hagel (R-NE) introduced S. 1882, the Public Health Preparedness Workforce Development Act of 2007. The bill would create scholarship, loan repayment, and grant programs to recruit and retain public health workers. Intended to increase the ratio of public health workers to the population, S. 1882 would bring doctors, nurses, researchers, technicians, and other medical workers, including those working in the behavioral sciences, into the public health field. The bill was referred to the Committee on Health, Education, Labor and Pensions.

S. 1906 - On July 31, 2007, Senator Max Baucus (D-MT) introduced the Meth Mouth Prevention and Community Recovery Act, to increase understanding and comprehensively address the oral health problems associated with methamphetamine use. The bill would require the Secretary of HHS to expand and intensify clinical research, health services research, and public health research on associations between substance use disorders, oral health, and the provision of dental care in collaboration with Federal and non-Federal entities. In addition, the bill would authorize funds to carry out this section as well as one that would require SAMHSA to support training of dental personnel to be aware of such findings. The bill was referred to the Committee on Health, Education, Labor, and Pensions. See H.R. 3186.

S. 1907 - On July 31, 2007, Senator Max Baucus (D-MT) introduced the Meth Mouth Correctional Costs and Reentry Support Act., to amend title I of the Omnibus Crime Control and Safe Streets Act of 1968 to understand and comprehensively address the inmate oral health problems associated with methamphetamine use, and for other purposes. The bill was referred to the Committee on the Judiciary. See H.R. 3187.

S. 2071 - On September 19, 2007, Senator Diane Feinstein introduced the Combat Methamphetamine Enhancement Act of 2007, to enhance the ability to combat methamphetamine. The bill passed the Senate on February 11, 2008, and was referred to the House. See H.R. 5619.

S. 2162 - On October 15, 2007, Senator Daniel Akaka (D-HI) introduced the Veterans Mental Health Improvements Act of 2007, to improve the treatment and services provided by the Department of Veterans Affairs to veterans with post-traumatic stress disorder and substance use disorders, and for other purposes. On April 8, 2008, the bill was reported out by the Committee on

Veterans Affairs and placed on the Senate legislative calendar. See H.R. 4053.

S 2182 - On October 17, 2007, Senator Jack Reed (D-RI) introduced the Community Mental Health Services Improvement Act, to amend the Public Health Service Act with respect to mental health services. The bill was referred to the Committee on Health, Education, Labor and Pensions. See H.R. 5176.

S. 2237 - On October 25, 2007, Senator Joseph Biden (D-DE) introduced the Crime Control and Prevention Act of 2007, an omnibus bill to fight crime. The legislation includes several drug-related programs. The bill was referred to the Committee on the Judiciary.

S. 2274 - On October 31, 2007, Senator Joseph Biden introduced the Dextromethorphan Abuse Reduction Act of 2007, to amend the Controlled Substances Act to prevent the abuse of dextromethorphan, and other purposes. The bill was referred to the Committee on the Judiciary.

S. 2304 - On November 5, 2007, Senator Pete Domenici (R-NM) introduced the Mentally Ill Offender Treatment and Crime Reduction Reauthorization and Improvement Act of 2007, to amend Title I of the Omnibus Crime Control and Safe Streets Act of 1968 to provide grants for the improved mental health treatment and services provided to offenders with mental illnesses, and for other purposes. On April 1, 2008, the bill was reported out by the Committee on the Judiciary and placed on the legislative calendar. See H.R. 3992.

S. 2731 - On March 7, 2008, Senator Joseph Biden (D-DE) introduced the Tom Lantos and Henry J. Hyde United States Global Leadership Against HIV/AIDS, Tuberculosis, and Malaria Reauthorization Act of 2008, to authorize appropriations for fiscal years 2009 through 2013 to provide assistance to foreign countries to combat HIV/AIDS, tuberculosis, and malaria, and for other purposes. On March 13, the Senate Committee on Foreign Relations (Senator Joseph Biden [D-DE], Chairman) marked up and ordered the bill reported. The bill was placed on the Senate legislative calendar. Of particular interest to NIH are provisions that would (1) require the Secretary of HHS, acting through the CDC and NIH, to conduct appropriately programmatic relevant clinical and operational research to identify and evaluate new diagnostics, treatment regimens, and interventions to prevent and control malaria, (2) authorize the Secretary to participate with other countries in cooperative endeavors in biomedical research, health care services, health care research, or other related activities in furtherance of the activities, goals and objectives authorized under this act, (3) and require establishment, within the Department of State, of an interagency working group on HIV/AIDS, headed by the Global AIDS Coordinator and including representatives from HHS and the U.S. Agency for International Development, for the purposes of coordination of activities related to HIV/AIDS.

S. 2819 - On April 3, 2008, Senator Jay Rockefeller (D-WV) introduced the Economic Recovery in Health Care Act of 2008, to preserve access to Medicaid and the State Children's Health Insurance Program during an economic downturn, and for other purposes. The bill was referred to the Committee on Finance. See H.R. 5613.

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

International Activities

Funding Initiatives

NIDA Funds Three International Tobacco Research Awards
Binational research teams in Argentina, Brazil, and Syria have been awarded NIDA R01 research project grants through the Fogarty International Center International Tobacco and Health Research and Capacity Building Program. The program supports transdisciplinary research and capacity-building projects that address the burden of tobacco consumption in low- and/or middle-income nations by funding U.S. researchers partnering with scientists and institutions in low- and/or middle-income nation(s), where tobacco consumption is currently (or anticipated to become) a public health priority. The major portion of the research must be conducted outside of the United States, and more than 60 percent of the direct costs requested must be used in the partner nation for either research and/or capacity strengthening of foreign institutions. The research teams include:

- Dr. Eliseo Perez-Stable, University of California San Francisco, will collaborate with Raul Mejia, Universidad de Buenos Aires, and Ethel Alderete, Universidad Nacional De Jujuy, to develop an intervention to prevent tobacco use among diverse youth in Northwest Argentina; to implement and evaluate a system-based smoking cessation intervention using a randomized trial design among physicians to promote smoking abstinence and quit attempts in their patients who smoke; and to develop policy interventions to promote smoke-free indoor space and regulation of tobacco products' advertising by continuing to analyze the tobacco industry documents on Argentina.
- Dr. Isabel Scarinci, University of Alabama at Birmingham, will collaborate with Brazilian scientists at the Pontificia Universidade Catolica do Parana to develop a Network for Tobacco Control among Women in Parana, Brazil, in order to establish community and institutional capacity to promote gender-relevant tobacco control efforts among Brazilian women through community-based participatory research and training. The goals of the network are to reduce tobacco use and exposure to environmental tobacco smoke among Brazilian women, and to develop a cadre of well-trained researchers in tobacco control.
- Dr. Wasim Maziak, University of Memphis and the Syrian Center for Tobacco Studies, will study adolescent tobacco use patterns and determinants: a school-based longitudinal study will examine trends in tobacco use in 4,000 Syrian youth; a laboratory study of 240 waterpipe users will investigate waterpipe toxicant exposure, dependence, and risk; and a randomized clinical trial will test a smoking cessation intervention in 250 smokers.

NIDA/CICAD Research Awards Announced

Planned Meetings

Publications

Staff Highlights

Grantee Honors

Through its Latin America Initiative, NIDA and the Inter-American Drug Abuse Control Commission (CICAD) cosponsor the Competitive Research Award Fund to support drug use research in the region. Awards support pre- or postdoctoral students conducting research in any area of the drug use field. Priority is given to projects involving secondary analysis of existing research databases, such as national drug use surveys. The national drug commissions in Organization of American States member countries review initial applications and forward appropriate projects to the CICAD Inter-American Observatory on Drugs for review by representatives from NIDA and CICAD. The call for applications for the second round of awards was issued in October 2007. The second-round awards include:

- **Argentina**
  - Ariel Gerardo Blanc - Analysis of risk and protection factors associated with the increase and decrease of psychoactive substance use among secondary school students in the Province of Entre Rios, 2001-2005.
  - Jorge Andres Bustos - Drug use and abuse: Study of the sociodemographic profiles, patterns of use, cognitive aspects, and beliefs regarding pharmacology.
- **Bolivia**
  - Erik Fernandez Revollo - Psychological risk and protective factors for drug use in the cities of La Paz and El Alto.
- **Brazil**
  - Marcelo Niel - The "coming out" process and its influence on mental health and the abuse or dependence on psychoactive substances among male homosexuals.
  - Monica Siqueira Malta - Ten years of free access and universal treatment for HIV/AIDS: Evaluating the impact of the Brazilian response to the AIDS epidemic among drug users.
  - Virginia Martins Carvalho - Study on crack use related to violent deaths in the state of Sao Paulo.
  - Nathalia Susin - Mapping the profile of psychoactive drug users in specialized clinics.
- **Chile**
  - Marcos Antonio Munoz Robles - Typology and sociodemographic characterization of drug users in Chile.
  - Marta Ester Belmar-Mellado - Relationship between the expectations related to tobacco use with body image: a comparative study among Spanish and Chilean adolescents.
- **Colombia**
  - Catalina López Quintero - Perceived harmfulness of drugs and its association with drug use onset and transition to an established pattern of drug use among adolescents in Bogotá, Colombia.
  - Marcela Correa Muñoz - Relationship and impact of psychoactive substance use on health in Colombia.
  - Luz Adriana Rivera Gonzalez - Life habits that include drug use prevalence in the student population of the Popular Catholic University of Risaralda.
  - Juan Sebastián Sabogal Carmona - Determining the composition of drugs of abuse seized in Bogota during the second semester of 2008.
- **Ecuador**
  - Clara Inés Jácome - Critical descriptive analysis of the application of the Psychosomatic Exam in the penal procedures of Ecuador and its legal consequences.

Mexico

- Marycarmen Noemí Bustos - Psychosocial factors associated with drug consumption among high school students in Jalisco.

- **Uruguay**
  - Carla Sacchi - Gender analysis of the development of illegal drug consumption among students at the school of Professional Technical Education of Montevideo (2001-2007).
  - Marcelo Rossal - Reciprocity and distribution of cocaine paste: An anthropological focus.
  - Soledad Brescia, Gabriela López, and Margarita Wschebor - Patients in the psychiatric hospital and comorbidity with psychoactive substance consumption.

Binational Agreements

NIH and India Agree To Cooperate on Research into Mental Health, Neurology, & Addiction
The National Institutes of Health (NIH) and the Department of Biotechnology of the Ministry of Science and Technology of the Republic of India (DBT) have signed a 5-year agreement to facilitate increased research collaboration related to mental health, neurology, and addictive disorders. NIDA, the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, and DBT will identify and conduct collaborative biomedical and behavioral research in areas such as (1) translational and clinical research for new therapeutics and biologicals; (2) genetic testing and mapping of brain disease and disorders; (3) animal models for collaborative research, including non-human primate models; (4) stem-cell biology research; (5) public repositories, such as genetic repositories; (6) advanced brain-imaging technologies, including magnetic resonance imaging; (7) computational neuroscience and neuroinformatics; and (8) data, tool, and resource sharing. Cooperative activities are likely to include workshops and meetings to identify priorities, share experiences, and discuss areas of scientific collaboration; direct links between institutions in both countries; and increased collaboration and exchanges among scientists in both countries to conduct research, research training, and product development. The agreement calls for both nations to identify appropriate funding sources for the reciprocal activities, which are to be assessed under the countries' normal review processes. The Fogarty International Center drafted the agreement, which was signed March 4, 2008, by NIH Director Elias A. Zerhouni, M.D., and Dr. Raj Bhan, Secretary of India's Department of Biotechnology. For more information about Indo-U.S. collaborations, e-mail Thomas C. Mampilly at the Fogarty International Center: mampillyt@mail.nih.gov. For more information about NIDA priorities for Indo-U.S. collaborations, e-mail International Program Director Steven W. Gust, Ph.D.: ipdirector@nida.nih.gov.

International Visitors

The Acting U.S. Surgeon General, Rear Admiral Steven K. Galson, M.D., M.P.H., joined staff from NIDA, NCI, NHLBI, NIMH, FIC, SAMHSA and CDC and Russian public health experts at NIDA on February 12, 2008 to discuss anti-smoking efforts. The meeting was organized by Allison Chausmer, Ph.D., DBNBR; IP Director Steven W. Gust, Ph.D., and IP Program Analyst Dale Weiss also participated. The Russian delegation expressed particular interest in conveying anti-smoking messages to health care providers, banning smoking in public places, and NIDA outreach materials.

Dr. Ali Dhansay, Vice President South African Medical Research Council (MRC) visited the Fogarty International Center on February 28, 2008. Dale Weiss, IP

met with Dr. Dhansay at FIC to apprise him of NIDA's activities in the Southern African region and to hear about the work the MRC is doing related to drug addiction.

Research Results

International Program-Supported Researchers Enhance Intravenous Self-Administration in Mice

Researchers supported by a NIDA Distinguished International Scientist Collaboration Award (DISCA) have developed a new catheter that improves the ability to conduct intravenous self-administration experiments in mice. Petri Hyytia, Ph.D., Finland National Public Health Institute, and his DISCA partner, Gregory P. Mark, Ph.D., Oregon Health & Science University, miniaturized the catheter used in rats and embedded the tubing in a nylon mesh catheter base implanted underneath a mouse's skin between the scapulae. The new design prevents mice from dislodging the catheter or chewing the external tubing, significantly improving patency times and minimizing the chewing problems reported in previous experiments with mice. The researchers used the new catheter to establish reliable methamphetamine (MA) self-administration in mice, generating a typical MA dose-response curve documenting the inverse relationship between unit doses and rates of self-administration: as doses decreased, responding increased. Drs. Hyytia and Mark report that the new catheter design will enhance pharmacological studies with various drugs acting on acetylcholine receptors, studies in which drug self-administration is combined with microdialysis, and experiments employing an increasing number of genetically engineered mouse lines to clarify the actions of MA in the brain and the neural basis of MA addiction.

DISCA Researchers Find Reducing Stress Hormones May Prevent Relapse to Cocaine Use

Preliminary data from experiments conducted by Meera Vaswani, Ph.D., All India Institute of Medical Sciences, and her NIDA Distinguished International Scientist Collaboration Award (DISCA) research partner, Nicholas Goeders, Ph.D., Louisiana State University, found that reducing stress hormones may prevent relapse to cocaine use. The researchers administered a combination of metyrapone and oxazepam, which reduced corticosterone compared to vehicle in rats, indicating a trend toward the effectiveness of the drug combination in preventing relapse to cocaine use. The two investigated the biological basis of stress and the subsequent activation of the hypothalamo-pituitary-adrenal (HPA) axis in cocaine reinforcement, documenting that the HPA axis is involved in relapse to cocaine seeking. Dr. Vaswani is awaiting approval to conduct clinical trials of the combination drug to treat heroin addiction in India.

Inhalant Abuse Working Group Formed in East and Southern Africa

Drug abuse professionals working in East and Southern Africa have formed an inhalant abuse working group to raise general awareness, develop education materials, train service providers, educate government officials, and promote scientific research on the topic. Meeting in conjunction with a November 2007 UNODC Regional Consultation in Mombasa, Kenya, 15 participants from 11 countries appointed two coordinators for the East and Southern Africa Inhalant Abuse Working Group: former NIDA Humphrey Fellow Dr. Peter Ndege, Kenyan National Agency for the Campaign against Drug Abuse Authority, and Mr. Rogers Kasirye, Uganda. The group intends to develop a listserv of interested groups to collect data for further analysis and provide training on inhalant abuse-related research, prevention, and treatment. Participants noted that little is known about inhalant abuse in Sub-Saharan Africa, although anecdotal evidence indicates that inhalant abuse is an issue in most cities among all groups, regardless of socioeconomic status, age, gender, or educational status. Members reported that glue, paint thinner, and gasoline are the most commonly abused substances, and that nongovernmental organizations are working with inhalant abusers despite the fact that they do not document this

work. Participants represented Botswana, Kenya, Malawi, Mauritius, Mozambique, Seychelles, Swaziland, Tanzania, Uganda, Zambia, and Zanzibar.

Fellowships

NIDA Selects Mexican Epidemiologist for DISCA Award
Octavio Campolo, Ph.D., University of Guadalajara, has been selected as a NIDA Distinguished International Scientist to collaborate with Fernando Wagner, Sc.D., Morgan State University. Drs. Campolo and Wagner will restructure data sets, complete data analysis, and prepare manuscripts for publication for two research projects: (1) risk factors for substance use in high school students in Jalisco, Mexico; and (2) HIV and hepatitis in drug addicts in West Mexico. The two also plan to prepare a grant proposal to further collaborate on projects investigating the prevalence and associated factors for substance use among youths in the Mexican state of Jalisco.

Chinese &Thai Researchers Named 2008 WHO/NIDA/CPDD International Traveling Fellows
Yu Liu, Ph.D., Chinese National Institute on Drug Dependence, Peking University, and Rasmon Kalayasiri, M.D., a psychiatrist and instructor at Chulalongkorn University, Thailand, have been selected as the 2008 WHO/NIDA/CPDD International Traveling Fellows. 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. Liu will work with Tom Kosten, M.D., Baylor College of Medicine, to advance their collaborative research on morphine vaccine development, which is supported jointly by NIDA and the Chinese government. An expert in animal models of neurobehavioral and neurochemical adaptations associated with substance use and abuse, Dr. Liu will be responsible for using various behavioral rodent models to screen and evaluate the candidate vaccines. Dr. Liu earned her doctoral degree from Wake Forest University and completed a postdoctoral fellowship in the behavioral animal laboratory there in 2007. Dr. Kalayasiri will work with Robert T. Malison, M.D., and Joel Gelernter, M.D., Yale University School of Medicine, to discuss research projects on gene by environment interaction studies of methamphetamine-induced psychosis (MIP), potential collaborations with psychiatric genetics laboratories in the United States to analyze Thai DNA samples, quality control of the interview data in an ongoing investigation into the genetics of opioid dependence in Northern Thailand, and the possibility of a new, case-control study of opioid dependence. Preliminary data from Dr. Kalayasiri's current work on MIP show that a history of marijuana use, conduct disorder, exposure to frightening traumatic events, and poor childhood relationship with caregivers predict risk for MIP in dependent individuals. Severity of methamphetamine use (i.e., dependence and greater use, and earlier onset of use) was correlated with MIP. In 2006, Dr. Kalayasiri completed a postdoctoral fellowship in the Yale Drug Dependence Genetics Research Training Program.

Former Humphrey Fellows Succeed upon Returning Home

- Rehana Kader, a 2006-2007 Hubert H. Humphrey Drug Abuse Research Fellow at Virginia Commonwealth University (VCU), has received a scholarship from the Medical Research Council of South Africa (MRC) to complete a Ph.D. while working in the MRC Alcohol and Drug Research Unit. As a doctoral candidate at the University of Stellenbosch, Ms. Kader will investigate the relationship between substance use, misuse, and sexual HIV risk behavior among patients attending HIV clinics, developing and evaluating an intervention to improve the way in which substance use or misuse is addressed within HIV and AIDS treatment facilities. Her Humphrey Fellowship mentor, Dr. J. Randy Koch, VCU, is also the cosupervisor for Ms. Kader's doctoral studies. At MRC, Ms. Kader is working on projects to: (1)

monitor the prevalence of methamphetamine-related presentations at psychiatric hospitals in Cape Town; (2) improve substance abuse treatment outcomes in South Africa by developing service quality metrics; and (3) develop an HIV Consumer Survey for South Africa.

- Dr. Peter Kenneth Ndege, 2006-2007 Humphrey Fellow at Virginia Commonwealth University, is now a Consultant Physician and Drug Abuse Prevention, Treatment, and Policy Specialist at the Kenyan National Agency for the Campaign against Drug Abuse Authority (NACADAA).
- Alamgir MD, 2006-2007 Humphrey Fellow at Johns Hopkins University, is Deputy Secretary in the Bangladeshi Ministry of Home Affairs.

NIDA Hosts Orientation for INVEST and Humphrey Fellows
A diverse group of 26 researchers, policymakers, and treatment providers from 22 nations visited NIDA to learn about the National Institutes of Health (NIH) and the public health perspective on drug abuse. Despite their diverse backgrounds and research interests, each individual was invited to a NIDA International Program orientation for Hubert H. Humphrey and NIDA INVEST Drug Abuse Research Fellows, which was held on January 24-25, 2008. Representatives from NIDA Divisions, Programs, and Centers discussed the Institute's international research activities and funding priorities, before meeting with the Fellows individually or in small groups to discuss structuring future research projects and identifying potential collaborators. The Fellows also toured the National Library of Medicine and the Fogarty International Center on the NIH campus. INVEST Fellows spend 12 months conducting postdoctoral research with a NIDA grantee at a U.S. institution. Humphrey Fellows spend 10 months in mentored academic study as part of the U.S. Department of State Fulbright program; NIDA cosponsors the Hubert H. Humphrey Fellowships in Drug Abuse Research at Virginia Commonwealth University. Interested Humphrey Fellows from programs at Johns Hopkins University and Emory University also participated in the orientation.

Dr. Wilson M. Compton, M.D., M.P.E., Director, DESPR, presented on Trends in Drug Abuse: Urgent Problems for Physicians as an invited lecturer for the 120th Anniversary Symposium, Majidol University, Bangkok, Thailand, March 19, 2008.

Dr. Frank Vocci, Director, DPMCDA, spoke at the First International Symposium on Addiction Medicine: Neurobiology of Addiction to Alcohol and Other Drugs, held in San Jose, Costa Rica on February 28-29, 2008. His presentations were on the NIDA medications development program and Pharmacotherapy for Addictions: Status Update (co-presented with Dr. Ahmed Elkashef).

Drs. Ivan Montoya and Jag Khalsa, DPMCDA, participated in a two-day workshop at the National School of Public Health in Medellin, Colombia on March 5-6, 2008. They discussed research opportunities and funding at NIDA and drug abuse treatment evaluation.

Drs. Ivan Montoya and Jag Khalsa participated in the annual meeting of the Colombian College of Neuropsychopharmacology, in Bogota, Colombia on March 7-9, 2008. They lectured on the advances in the treatment of opioid addiction and the medical consequences of drug abuse.

Dr. Ivan Montoya gave the closing lecture of the annual meeting of the Society of Drug and Alcohol of Spain, in La Coruna on April 12, 2008. Dr. Marilyn Huestis, Chief, Chemistry and Drug Metabolism, IRP, recently traveled to Beijing and Shanghai, China to present the impact of recent research findings on interpretations of drug test results in drug treatment, workplace and criminal justice programs. The Institute of Forensic Medicine of the Department of Internal Security in Beijing and the Institute of Forensic Sciences of the Department of Justice in Shanghai supported Dr. Huestis' travel. The importance of drug treatment, and toxicology research and analysis was

discussed at meetings with the Deputy Ministers of Internal Security and Justice and other scientists from The International Association of Forensic Toxicologists. Dr. Huestis also met with researchers, post-graduate fellows and doctoral students at both institutions to discuss analytical issues and research projects.

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

Meetings/Conferences

The **Blending Hand-Off Meeting** for the CTN Protocol that examined **Young Adult Buprenorphine Treatment** met in Bethesda, Maryland on February 28, 2008. Dr. Timothy P. Condon, Deputy Director, NIDA, chaired this meeting which was coordinated by Dr. Denise Pintello. The objective of the meeting was to discuss study results from three community treatment programs (CTPs) and determine if a new Blending Team product should be developed. Participants included ATTC directors, NIDA researchers, NIDA and SAMHSA staff and CTP members. It is anticipated that a Blending Team will be created to develop a new module to highlight these study results.

The National Institute on Drug Abuse (NIDA) organized a highly successful program at the **American Psychiatric Association (APA) Annual Meeting in Washington, D.C., May 3-8, 2008**. A number of NIDA staff and NIDA researchers participated in several symposia and workshops on a wide range of topics such as, *Drug Abuse, HIV, and the Brain; Gene-Environment-Development Interactions: Implications for Psychiatric and Substance Abuse Disorders; and Diagnosis and Treatment of Adolescents/Young Adults with Substance Use Disorders*. This program builds on previous tracks NIDA has conducted at the APA Annual meeting since 1998.

The **National CTN Steering Committee Meetings** were held February 25-28, 2008 in Rockville, Maryland. The following meetings/committees convened:
CTP and PI Caucuses
Exercise Concept Team
Members of the STAGE-12 (CTN 0031) study team
Special Groups: Pharmacotherapy, Exercise, and CTP Authorship
Executive Committee
Research Utilization Committee
Research Development Committee
Node Coordinator Workgroup
Steering Committee
Design & Analysis Workshop

The Special Populations Office, OD, NIDA convened a two-day **Special Populations Research Development Seminar workshop** on October 25-27, 2007, in Bethesda, MD. The seminar brought back new investigators, who attended an initial two-day workshop, to present draft research applications for review and discussion in a "mock review" session chaired by NIDA staff. In addition, participants met with NIDA-funded investigators and senior NIDA program staff to discuss research opportunities at NIH.

The Special Populations Office, OD, NIDA and the Substance Abuse Mental Health Services Administration (SAMHSA) hosted the **Substance Abuse, Criminal Justice, and HIV in African Americans: Technical Assistance workshop** on October 15-16, 2007 in Silver Spring, MD. The workshop

convened NIDA/SAMHSA staff and NIDA grantees to serve as speakers and mentors to early/new investigators who plan to prepare grant applications for NIDA program announcements related to substance abuse, criminal justice and HIV/AIDS.

The Special Populations Office, OD, NIDA, convened a meeting of **NIDA's Minority/Ethnic Researchers and Scholars Workgroups** on October 31 - November 1, 2007 at the Bethesda Marriott Conference Center in Bethesda, MD. The meeting was centered on discussion and plans for future activities geared towards increasing the number of underrepresented minorities and women in substance abuse research and training these respective populations. During the meeting, NIDA Director, Dr. Nora Volkow provided an overview of the Institute's mission and research priorities and NIDA's Division Directors discussed their particular division's priorities.

Dr. Timothy P. Condon, Deputy Director, NIDA, presented "Advances in Drug Abuse and Addiction Research: Implications for Treatment" at the Demand Reduction Conference: What Works to Reduce Drug Use, on January 24, 2008, in Budapest, Hungary.

Dr. Timothy P. Condon presented "Emerging Trends in Drug Abuse: Monitoring to Stay Ahead of the Curve" at the Community Anti-Drug Coalitions of America (CADCA) National Leadership Forum XVIII on February 14, 2008, in Washington, D.C.

Dr. Timothy P. Condon provided opening remarks and presented "Buprenorphine in the Treatment of Opioid Addiction: Balancing Medication Access with Quality Care" at the Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration/National Institute on Drug Abuse, National Institutes of Health 2008 Summit on Buprenorphine in the Treatment of Opioid Addiction: Balancing Medication Access with Quality Care on February 21, 2008, in Washington, D.C.

Dr. Timothy P. Condon presented the "NIDA Deputy Director's Report" at the CTN National Steering Committee Meeting on February 27, 2008, in Bethesda, Maryland.

Dr. Timothy P. Condon participated in the Federal Roundtable Discussion on the Future of Drug Courts sponsored by the Congress of State Drug Court Associations of the National Association of Drug Court Professionals on March 3, 2008, in Washington, D.C.

Dr. Timothy P. Condon presented "Addiction as a Brain Disease: Implications for Prevention and Treatment" at the New Jersey Prevention Network, Back to the Basics...With An Eye on the Future on March 7, 2008, in Atlantic City, New Jersey.

Dr. Timothy P. Condon presented "NIDA Progress, Priorities & Plans for the Future" to the leadership of the Association for Addiction Professionals and the National Association of Addiction Treatment Providers during the 21st annual Advocacy in Action conference on March 10, 2008, in Washington, D.C.

Dr. Timothy P. Condon highlighted the role of science and the research that NIDA is doing to understand and prevent inhalant abuse at a press briefing on inhalant use hosted by the National Inhalant Prevention Coalition, with sponsorship from the Substance Abuse and Mental Health Services Administration (SAMHSA), on March 13, 2008, in Washington, D.C.

Dr. Timothy P. Condon presented the opening remarks for the NIH Office of Research on Women's Health (ORWH) Seminar Series on Sex and Gender Research: Substance Abuse on March 27, 2008, in Bethesda, Maryland.

Planned Meetings

Publications

Staff Highlights

Grantee Honors

Dr. Timothy P. Condon presented "Advances in Drug Abuse and Addiction Research: Implications for Prevention, Treatment and Recovery" at the 31st Annual Governor's Conference on Substance Abuse on April 8, 2008, in Des Moines, Iowa.

Dr. Timothy P. Condon presented "It's a Brain Disease: Beyond a Reasonable Doubt - The Neuroscience of Addiction" at the California Association of Drug Court Professionals' 2008 Annual Collaborative Justice Conference on April 9, 2008, in Anaheim, California.

Dr. Cindy Miner, Deputy Director, OSPC, was invited to lead a discussion on drug abuse and addiction in response to the popularity of the drug abuse chat day for the students at Rockville High School, Rockville Maryland, on February 21, 2008.

Drs. Cindy Miner, Gaya Dowling and Ms. Carol Krause of OSPC led a panel discussion on NIDA's first ever web chat day entitled, "The Real Inside Scoop on What Teens Want to Know About Drug Abuse" at the 2008 Joint Meeting on Adolescent Treatment Effectiveness held in Washington D.C., on March 26, 2008.

Dr. Denise Pintello, Special Assistant to the Deputy Director, delivered the keynote address at George Mason University's Department of Social Work Conference on March 19, 2008, to faculty members, graduate and undergraduate students and provided an overview on social work career pathways and the importance of applying evidence-based research to practice.

Dr. Gayathri J. Dowling presented "It's a Brain Disease: Drug Addiction Best Practices and Effective Strategies for Treatment and How Judges Can Apply this Information" on behalf of Dr. Timothy P. Condon at the Michigan Association of Drug Court Professionals on February 12, 2008, in Lansing, Michigan.

Dr. Gayathri J. Dowling presented "The Science of Addiction" at the Third Annual Summit on Substance Abuse, Mental Health, and School Safety Best Practices for Working with Youth on March 12, 2008, in Pine Mountain, Georgia.

Dr. Ruben Baler, OSPC, presented a workshop on "Basic Neuroscience and the Science of Addiction" at the 31st annual PRIDE Conference, April 1-4, 2008 in Cincinnati, Ohio.

Dr. Lula Beatty, Chief, SPO, served as a reviewer for the 2008 Head Start conference.

Dr. Lula Beatty participated in the meeting of the Committee on Women in Psychology of the American Psychological Association in Washington, DC in September 2007.

Dr. Lula Beatty presented an overview of NIDA's involvement in HIV/AIDS research at the National African American Advisory Committee meeting of the National Association of State Alcohol and Drug Abuse Directors (NASADAD) in Washington, DC in October 2007.

Dr. Lula Beatty has been serving as NIDA's representative to the NCMHD Forum Planning Committee, a group to plan a 2008 conference on NIH health disparities research and programs.

Dr. Lula Beatty attended the National Leadership Workshop on Mentoring Women in Biomedical Careers sponsored by NIH's Office of Research on Women's Health in November 2007.

Dr. Lula Beatty served on the planning committee for the "Building Strong and Healthy Families: Connecting Marriage Research to Practice" conference supported by the Administration for Children and Families, DHSS, to be held June 17-19, 2008 at the University of North Carolina.

Dr. Lula Beatty attended the "Summit on Abuse and Violence in Relationships: Connecting Agendas and Forging New Directions" sponsored by the American Psychological Association on February 28-29, 2008 in Bethesda, Maryland.

Dr. Lula Beatty participated in the meeting of the Society of Women in Psychology, APA on March 1, 2008 in Bethesda, Maryland.

Dr. Lula Beatty participated in the meeting "Enhancing Diversity in Science" organized by the Consortium on Social Sciences Associations on February 28, 2008 in Washington, DC.

Dr. Lula Beatty attended a professional development program for early career scientists sponsored by NINDS and supported by the Special Populations Office on March 4, 2008 in Washington, DC.

Dr. Lula Beatty participated in the planning committee for the CSAT satellite conference at CPDD to be held June 14, 2008 in Puerto Rico.

Dr. Lula Beatty attended the meeting of the Committee on Women in Psychology, American Psychological Association, on March 28-29, 2008 in Washington, DC.

Ana Anders, Public Health Analyst, SPO, participated in the National Hispanic Science Network annual conference held in Miami Beach, FL on September 26-28, 2007.

Ana Anders, as a representative of NIDA, participated in the Latino Behavioral Health Institute annual conference in Los Angeles, CA on October 2-4, 2007.

Ana Anders, as 2007 president of the NIH Hispanic Employee Organization, along with the HEODC, chaired the committee that planned the observance of the Hispanic Heritage Month on October 11, 2007 where Dr. Nora Volkow was the keynote speaker.

Ana Anders is a member of the Virtual Program for Career Development and Capacity Building for Latin American and Caribbean Women Scientists workgroup, comprised of other NIH Institutes (NIDA has the lead through the NHSN), the WHO, PAHO, UNESCO, and FLACSO from Argentina.

Ana Anders gave a presentation on drug abuse prevention to an association of journalists, young scientists and the "drug czar" at the University of Cardenal Herrera on November 7- 8, 2007 in Valencia, Spain.

Ana Anders was a member of the NIH Diversity Council planning committee, which presented the NIH Art and Science Diversity Expo. on December 5, 2007.

Ana Anders participated in a National Hispanic Science Network on Drug Abuse Steering Committee meeting at the University of Louisiana in New Orleans, Louisiana on January 11-13, 2008.

Ana Anders gave a talk on Health Disparities at the Blue Cross Blue Shield Association in Maryland on January 30, 2008.

Ana Anders gave a presentation on Health Disparities at the University of Maryland School of Social Work, College Park, Maryland on February 26, 2008.

Drs. Cecelia Spitznas and Lisa Onken of DCNBR along with Drs. Thomas Brady, Richard Denisco and Wilson Compton of DESPR organized a meeting on Screening for Drug Abuse in Primary Care held May 12, 2008 at NIDA in Bethesda. The purpose of the meeting was to obtain expert feedback on Provider Guidelines for Screening for Drug Abuse.

Dr. David Shurtleff, Director, DBNBR, chaired the Early-Career Grant Writing

session and presented on "Research Funding Opportunities: Learning the NIH System" at the 14th Annual Conference of the Society on NeuroImmune Pharmacology (March 12-15, 2008).

Dr. David Shurtleff gave a presentation on "Basic Research at NIDA: An Overview" at the Rush University Center for Compulsive Behavior and Addiction on April 22, 2008.

Dr. Jerry Frankenheim organized two symposia panels for the Winter Conference on Brain Research, Snowbird Utah - "Neurological Emergencies with Methamphetamine & MDMA (Rodent Models)," January 29, 2008, and "What Are the Roles of Trace Amine-Associated Receptor 1 in Primates?," February 1, 2008.

Dr. Geraline Lin, DBNBR, organized and chaired a NIDA Neuroscience Consortium-sponsored Cutting Edge Seminar Series Mini Symposium entitled, "Groundbreaking Optical Technologies: Unprecedented Opportunities for Biomedical Research" on March 20, 2008. Speakers included: Drs. Karl Deisseroth, Mark Schnitzer and Guoping Feng.

Dr. Nancy Pilotte, DBNBR, was invited to participate and speak at Career Day activities at Purdue University on February 21, 2008. Dr. Pilotte gave a presentation entitled: "The Road From Application to Grant."

Dr. Christine Colvis, DBNBR, gave a presentation on existing proteomics programs and funding opportunities at NIDA to Human Proteome Organization World Congress representatives January 29, 2008, Bethesda, MD.

Dr. Christine Colvis co-organized the MLSCN (Molecular Libraries Screening Centers Network) Satellite meeting at the Society for Biomolecular Sciences conference April 6, 2008, St. Louis, MO.

Dr. Christine Colvis gave a presentation on funding opportunities at NIDA at the US Human Proteome Organization meeting March 18, 2008, Bethesda North Marriott, Bethesda, MD.

Dr. Joni Rutter, DBNBR, Genes, Environment, and Health Initiative: Translating Whole Genome Association Data into Clinical Practice: March 10-11, 2008, Bethesda, MD.

Dr. Christine Colvis served as a moderator at the annual all-hands meeting of the National Technology Centers for Networks and Pathways March 20-21, 2008, Pooks Hill Marriott, Bethesda, MD.

Drs. Jonathan D. Pollock and Joni Rutter with the Genetics Workgroup organized and chaired the NIDA Short Course on the Genetics and Epigenetics of Addiction, held at the North Bethesda Marriott Hotel, Bethesda, MD, March 31-April 4, 2008.

Dr. John Satterlee, DBNBR, a leader in the NIH epigentics roadmap project, attended the "Epigenetics and Behavior Meeting", sponsored by Nature Genetics and Nature Neuroscience, March 31, 2008 in Houston, TX.

Dr. John Satterlee attended the Keystone Meeting on the "Molecular Basis for Chromatin Modifications and Epigenetic Phenomena," April 7- April 12, 2008, Snowmass, CO.

Dr. Jonathan D. Pollock organized and chaired a symposium at the Society for Biological Psychiatry entitled, "Mapping Complex Traits for Addictive and Psychiatric Disorders in Mice," May 2, 2008, Washington, D.C. Presentations were given by Drs. David Threadgill, Timothy Wiltshire, Kari Buck, and Daniel Goldowitz on technical advances and recent discoveries in mapping gene variants for complex traits for addiction and psychiatric disorders.

Dr. Jonathan D. Pollock organized and chaired a symposium at the American Psychiatric association, entitled, "Gene-Environment-Development Interactions: Implications for Psychiatric and Addictive Disorders," May 7, 2008, Washington, D.C. Talks were given by Drs. Christopher Cowan, Frances Champagne, Julia Kim-Cohen, and Stephen Suomi.

Dr. Jonathan D. Pollock, a leader in the NIH Knockout Mouse Project, attended the International Knockout Consortium Meeting in Toronto, Ontario, May 13, 2008.

At the 14th Annual Conference of the Society on NeuroImmune Pharmacology (March 12-15, 2008), Diane Lawrence (DBNBR) and Linda Chang (Univ. Hawaii) co-chaired a session on "Oxidative Stress, AIDS and Drug Abuse." Bryan Yamamoto was a plenary speaker, discussing the role of oxidative stress in neuronal injury produced by amphetamine-related drugs of abuse. Other speakers included Norman Haughey, Annadora Bruce-Keller, Nuran Ercal, and Linda Chang. This symposium covered current findings in cell culture and animal models, human research, and CNS therapeutics approaches, and addressed the role of oxidative stress in mediating the consequences of drug abuse on HIV pathogenesis particularly in the brain.

Dr. Cora Lee Wetherington, DBNBR, made welcoming remarks on behalf of NIDA and served as a group facilitator at the American Psychological Association's Summit on Violence and Abuse in Relationships: Connecting Agendas and Forging New Directions, February 28-29, 2008. Hyatt Regency Hotel, Bethesda, MD. NIDA was a co-sponsor of the Summit.

Dr. Cora Lee Wetherington organized and chaired the symposium, "Issues in Drug Abuse Treatment of Women: Translation from the Lab to the Clinic," at the 3rd International Congress on Women's Mental Health, Melbourne, Australia, March 17-20, 2008. Speakers: Angela Waldrop (Medical University of South Carolina), Rajita Sinha (Yale University School of Medicine), Dace Svikis (Medical College of Virginia), and Sherry McKee (Yale University School of Medicine).

Dr. Cora Lee Wetherington organized and opened the NIH Office of Research on Women's Health (ORWH) seminar, "Sex & Gender Research: Substance Abuse," March 27, 1-3, Lipsett Auditiorium, NIH main campus. As part of ORWH's seminar series, this year they are featuring research on sex/gender differences supported by their Specialized Centers of Interdisciplinary Research (SCOR) on Sex and Gender Factors Affecting Women's Health (P50s) Program. NIDA administers three of the eleven SCORs in that program, and ORWH chose drug abuse as the first topic to feature in the SCOR seminar series. The speakers represented the three NIDA SCORs: Sari Izenwasser (Co-Investigator of the University of Miami SCOR; Emmalee Bandstra, PI), Rajita Sinha (PI of Yale University School of Medicine SCOR), and Himanshu Upadhyaya (Co-Investigator of the Medical University of South Carolina SCOR; Kathleen Brady, PI).

Dr. Cora Lee Wetherington was a planning committee member and session moderator for the meeting, Women and Smoking: Understanding Socioeconomic Influences, April 9-10, 2008 in Annapolis, MD. The meeting was sponsored by NIDA, NCI, NICHD, NIH Office of Research on Women's Health, DHHS Office of Women's Health, GlaxoSmith Kline, Inc, American Legacy Foundation, and Pfizer, Inc.

Dr. Cora Lee Wetherington gave an invited classroom lecture, "The Pervasiveness of Sex/Gender Difference in Drug Abuse," at American University for the psychology course, Women & Mental Health, April 14, 2008.

Dr. Samia Noursi, DBNBR, presented a talk on "Science to Services" at an Innovative Session: Roundtable Discussion at the Society for Research on

Adolescents, Chicago, IL, March 2008.

Dr. Samia Noursi moderated an Innovative Session: Roundtable Discussion titled "Innovative Methods for Teaching Adolescent and Emerging Adult Development: A Session for those who Teach" at the Society for Research on Adolescents, Chicago, IL, March 2008.

Dr. Samia Noursi is a lead participant on an ad hoc subcommittee formed by the Office of Research on Women's Health (ORWH) at the NIH Office of the Director to plan for the Office's Strategic Planning for the years 2009-2014.

Dr. Minda Lynch, DBNBR, presented "Do Drugs of Abuse Hijack the Brain?" at the Third Annual Brain Day, hosted by the VCU Department of Psychology in Richmond, VA on March 14, 2008. This event was part of Brain Awareness Week activities and approximately 350 local high school students attended.

Dr. Allison Chausmer was an invited presenter for "SRNT Global Network Committee meeting", at the annual meeting for the Society for Research on Nicotine and Tobacco, held in Portland, OR on February 28, 2008.

Dr. Allison Chausmer, DBNBR, co-organized a 2008 SRNT pre-conference workshop entitled "Global Tobacco Control Research Funding: Opportunities and Priorities", with William Riley (NIMH), Catherine Jo (ACS), Tom Glynn (ACS) and Scott Leischow (University of Arizona).

Dr. Joseph Frascella, Director, DCNBR, attended a meeting entitled "Forging Alliances among Funders in Obesity Prevention and Control" on February 20-21, 2008 in Bethesda, MD. This meeting was a collaborative effort between NIH, CDC, and the Robert Wood Johnson Foundation to initiate an effort to advance coordination and collaboration across research funding organizations to address research, translation/dissemination, and evaluate initiatives in the area of obesity prevention and control, with a focus on those affecting children and adolescents.

Drs. Harold Gordon and Steven Grant, both of DCNBR, together with the National Institute of Mental Health organized a workshop on Imaging Imagining, The Mirror System and Beyond: Neural Representation of the Self and Others which was held on February 20-21, 2008 at the Neuroscience Center, Rockville, MD. The meeting was sponsored by the Office of Science Policy and Communications (OSPC). A major purpose was to determine the latest research on an emerging technology of imaging of various aspects of thought processes including empathy, insight, goal-directed behavior, decision-making, etc. Another purpose was to determine how research in this field can be utilized to further the mission of our institutes.

Dr. Steven Grant represented NIDA at the annual meeting of the Cognitive Neuroscience Society in San Francisco, California on April 11- 16, 2008.

Dr. Steven Grant participated in the panel on Psychiatric Disorders that was part of the symposium on "Brain Pacemakers: A Promising Approach and a New Era of Hope for Neurological Disorders" co-sponsored by HHS and the Cleveland Clinic that was held at the Health and Human Services Hubert H. Humphrey Building in Washington, DC on May 6, 2008.

Dr. Steven Grant organized and chaired the symposium on "Brain Substrates of Impaired Error Detection, Moral Judgment, and Agency as Core Deficits in Substance Abuse" at the annual meeting of the American Psychiatric Association in Washington, DC on May 8, 2008. The speakers were Hugh Garavan (Trinity College), Kent Kiehl (Mind Institute), Janet Metcalfe (Columbia Univ), and Jordan Grafman (NINDS Intramural Research Program).

Drs. Laurence Stanford and Joseph Frascella, DCNBR, participated in a Roundtable entitled "Abuse, Addiction, and Pain Relief: Time for Change" in

Bethesda, MD on February 8, 2008.

Dr. Laurence Stanford participated in a NINDS Professional Development Workshop in Washington, DC on March 3-4, 2008.

Dr. Joseph Frascella attended a meeting entitled "Decision Making in Eating Behavior: Interacting Perspective from the Individual, Family, and Environment" in Bethesda, MD, April 14-15, 2008.

Dr. James Bjork of the Clinical Neuroscience Branch, DCNBR, gave a presentation on adolescent risk-taking entitled ''Teenage Decisions and How They Affect our Community" at Magruder High School in Rockville, Maryland on January 15, 2008. An account of the talk was published in the Wednesday, January 23, 2008 issue of the Montgomery County Gazette.

Dr. James Bjork gave a prevention-oriented talk on Jan 26th, 2008 about alcohol effects on the brain to an audience of female African-American teens by invitation of the Montgomery County Section of the National Council of Negro Women, Inc.

Debra Grossman, DCNBR and Dr. Cora Lee Wetherington, DBNBR, participated in an interagency meeting, "Tobacco and Young, Low-SES Women: Federal Collaboration to Make a Difference" on March 11-12, 2008. This ongoing federal partnership is focused on promoting activities to prevent and reduce tobacco use in young, low-SES women.

Dr. Lisa Onken, DCNBR, in collaboration with OBSSR, NIAAA, NCI, and AHRQ organized an NIH symposium series on Mechanisms of Behavior Change. For Part I of the symposium series, on February 27, 2008, Dr. Mathew Nock spoke on "Getting Back to Basics: Using Basic Behavioral Research to Study Mechanisms of Clinical Change," and Dr. Marsha Bates discussed, "Translation Science Framework: Using Basic Behavioral Research to Identify Clinically Significant Mechanisms of Behavioral Change." Part I can be viewed at: http://videocast.nih.gov/. For Part II of the symposium series, Dr. Warren Bickel presented, "Escaping the Tyranny of Small Decisions: A Conceptual Proposal," and Roy Baumeister spoke about, "Pathways to Self-Destruction: How and Why People Screw Themselves Up," on April 16, 2008. This symposium is available by videocast at http://videocast.nih.gov.

Dr. Lisa Onken, DCNBR, was on the planning committee for the 3rd International Conference on HIV Treatment Adherence. The meeting was a collaborative effort between NIMH, NIDA, and IAPAC, and took place on March 17-18, 2008.

Dr. Nicolette Borek, DCNBR, participated in a grant writing workshop and co-presented a talk on NIDA funding priorities at the 12th Biennial Meeting of the Society for Research on Adolescence, Chicago, IL, March 5-8th, 2008.

Dr. Bryan Fantie, DCNBR, presented Grand Rounds on "The Cranial Nerves and Cerebral Blood Circulation" for the Postdoctoral Pediatric Neuropsychology Program at Children's National Medical Center, Rockville, MD on March 12, 2008.

Dr. Bryan Fantie presented an invited lecture on "Emotion and the Brain" to the Postdoctoral Pediatric Neuropsychology Program at Children's National Medical Center, Rockville, MD on March 19, 2008.

Dr. Bryan Fantie attended "Epigenetics & Behavior," an Emergence & Convergence Mini-Symposium sponsored by Fondation IPSEN and the Nature Publishing Group, held in Houston, TX on March 31, 2008.

Dr. Bryan Fantie served as an Evaluator for the 2008 Intel Science Talent Search, America's oldest and most prestigious national science research

competition for high school seniors.

Dr. Frank Vocci, Director, DPMCDA, spoke at the Texas Physician's Retreat for Volunteers in Physician Health and Rehabilitation meeting on January 12, 2008 at South Padre Island, Texas on Hot Topics in Addiction.

Dr. Frank Vocci spoke at the Washington State Psychiatric Association meeting on March 15, 2008 in Seattle, Washington. His presentation was on new medications to treat stimulant dependence and cognitive remediation of stimulant users.

Dr. Ivan Montoya, DPMCDA, organized a two-day (February 28 and 29th, 2008) meeting of experts to discuss the progress in the development of medications for the treatment of cannabis-related disorders and define future directions in the field.

Drs. Ivan Montoya, Jag Khalsa and Frank Vocci organized and co-chaired a symposium at the American Society of Addiction Medicine annual meeting in Toronto (Canada) on April 11, 2008. The theme of the symposium is "Smoking Cessation in the Practice of Addiction Medicine".

Drs. David J. McCann and Nathan M. Appel, DPMCDA, participated as exhibitors at the Cambridge Healthtech Institute's 15th International Molecular Medicine Tri-Conference, representing the NIH RAID (Rapid Access to Interventional Development) Program. The program makes available, on a competitive basis, critical resources needed for the development of novel small molecules as therapeutic agents.

Dr. Jag Khalsa, DPMCDA, participated in the Annual Meeting of the American Society of Addiction Medicine (ASAM), April 10-13, 2008, Toronto, Canada, and presented three symposia: (i) Smoking Cessation in the Practice of Addiction Medicine, for Dr. Ivan Montoya, (ii) The Endocannabinoid System: Regulatory and Reinforcing Function in Health, and (iii) Collaborations Between the International Society of Addiction Medicine (ISAM) and ASAM: Addiction Medicine Practices. Dr. Khalsa also participated in the ASAM Scientific Program Committee where the next year's scientific agenda was planned.

Dr. Wilson M. Compton, M.D., M.P.E., Director, DESPR, presented "Uncertainty and Discovery in Linking Drug Abuse Public Health Research to Neuroscience" as the Eli Robins Lecture-Grand Rounds, Washington University. Saint Louis, Missouri, February 18, 2008.

Dr. Wilson M. Compton presented on "Drug Abuse and Addiction as Brain Diseases" at the National Workshop for Federal District Judges, Redondo Beach, California, March 11, 2008.

Dr. Wilson M. Compton Co-Chaired a panel on "Screening and Brief Interventions for Adolescents" as part of the Joint Meeting on Adolescent Treatment Effectiveness, Washington, DC, March 26, 2008.

Dr. Wilson M. Compton served as discussant on a panel on "Spotlight on U.S. Geography Linkages to Developing Regions", Association of American Geographers, Boston, Massachusetts, April 18, 2008.

Dr. Meyer Glantz, DESPR, presented a plenary paper on "The Fundamental Nature of Co-Occurring Mental Health and Substance Abuse Conditions" to the 2008 Annual Meeting of the NIMH Outreach Partnership Program Portland, Maine, April 1, 2008.

Dr. Elizabeth Robertson, DESPR, was the discussant for a presentation titled Mindfulness of Thought and Emotion at the Garrison Institute Symposium on Developmental Issues in Contemplative Education, April 4 to 6, 2008, in Garrison, NY.

Dr. Aria Crump, DESPR, chaired a symposium "HIV Prevention for Adolescents in Drug Abuse Treatment" at the 2008 Joint Meeting on Adolescent Treatment Effectiveness (JMATE) at the Grand Hyatt Washington in Washington, D.C., on March 25-27, 2008. The panel of presenters included Drs. Hyman Hops, Oregon Research Institute, Jacqueline Lloyd, Temple University, and S. Lisbeth Jarama, NOVA Research Company. Dr. Richard Jenkins, Prevention Research Branch, was the discussant for the symposium.

LeShawndra Price, DESPR, chaired an invited symposium entitled "Funding Priorities and Research Opportunities at the National Institutes of Health" at the 12th Biennial Meeting of the Society for Research on Adolescence in Chicago, IL on March 7, 2008. Participants included Aria Crump and Kathy Etz from DESPR and Nicolette Borek from DCNBR in addition to representatives from NIMH, NIAAA, and CSR.

Drs. David Liu, Jeng-Jong Pan and Paul Wakim, CCTN, attended the Second PROMIS Conference: Improving Measurement of Patient-Reported Outcomes - New Tools and the Science behind Them, March 2-5, 2008, in Bethesda, MD.

Dr. Paul Wakim attended the Spring Meeting of the International Biometric Society - Eastern North American Region (ENAR), Statistics in Practice: Creative Solutions to Bioscience Challenges, March 16-19, 2008, in Arlington, VA.

Dr. Harold Perl, CCTN, serves on the faculty for the two annual NIH Regional Seminars on Program Funding and Grants, sponsored by the NIH Office of Extramural Research (OER). These seminars are intended to help demystify the application and review process, clarify Federal regulations and policies, and highlight current areas of special interest or concern. The seminars serve the NIH mission of providing education and training for the next generation of biomedical and behavioral scientist. The faculty of NIH policy, grants management, review, and program staff provide a broad array of expertise and encourage personal interaction between themselves and seminar participants. The first 2008 seminar convened in San Antonio, Texas from March 25-27, 2008. The second 2008 seminar will take place in Chicago, IL on June 18 - 20, 2008.

Carmen Rosa, CCTN, co-chaired a symposium titled "Women and Substance Abuse Treatment: Exploring Women-Focused Treatments and Services" at the American Psychiatric Association (APA) Annual Meeting, held May 3-8 2008 in Washington, DC. Speakers included: Shelly Greenfield, M.D. (Harvard), Denise Hien, Ph.D. (Columbia), Susan Tross, Ph.D. (Columbia), Susan Gordon, Ph.D. (Seabrook House) and Kathleen Brady, M.D. (MUSC).

Dr. Petra Jacobs, CCTN, co-chaired a symposium titled "Diagnosis and Treatment of Adolescent/Young Adults with Substance Use Disorders" at the American Psychiatric Association (APA) Annual Meeting on May 5, 2008. Speakers included: George Woody, M.D. (Pennsylvania) Geetha Subramaniam, M.D. (Johns Hopkins), Oscar Bukstein, M.D., MPH, (Pittsburgh) Michael Robbins, Ph.D. (Miami), and Ramon Solhkhah, M.D. (Columbia).

Dr. Teri Levitin, Director, OEA, spoke at the University of Tennessee in Knoxville about the NIH review process and new policies and procedures at NIH.

Dr. Meena Hiremath, OEA, participated in "Leadership Skills for Non-Supervisors" in Shepardstown, WV from March 16-March 21, 2008.

Dr. Gerald McLaughlin, OEA, served as a judge for the Georgetown University Graduate Student Research Days in March, 2008.

Dr. Gerald McLaughlin co-founded and co-chaired the Scientific Program and Review Interest Group (SPRIG) whose theme in 2007-2008 is Springboards to

Science Leadership and Management, and he arranged several lecture-discussion sessions.

Dr. Gerald McLaughlin coordinated high school DC Area College Fairs in 2008 for the University of Iowa.

Dr. Eliane Lazar-Wesley, OEA, participated on the NIDA workgroup for the transition of NIDA's fellowship applications to CSR.

Dr. Jayanthi Subramaniam, IRP, gave a talk entitled Effects of Marijuana Abuse, at the Youth Science Fair held in Washington D.C. on March 19, 2008.

Dr. Natascha Wilson, IRP, gave a talk entitled Cerebrovascular Perfusion Correlates with Performance on a Neurobehavioral Test Battery: Gender Differences, at the Youth Science Fair held in Washington D.C. on March 19, 2008.

Dr. Jean Lud Cadet, IRP, gave a talk entitled Methamphetamine-induced apoptosis involves the FasL/Fas death pathway, at the University of Florida in Gainesville, FL on March 17, 2008.

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Media and Education Activities

Press Releases

January 22, 2008 -- **NIH Announces New Initiative in Epigenomics**. The National Institutes of Health (NIH) will invest more than $190 million over the next five years to accelerate an emerging field of biomedical research known as epigenomics. The NIH is making this a priority in its research portfolio, taking it on as an NIH Roadmap initiative. Grant applications are now being accepted for research on epigenome mapping centers, epigenomics data analysis and coordination, technology development in epigenetics, and discovery of novel epigenetic marks in mammalian cells.

January 29, 2008 -- **Does the Desire for Drugs Begin Outside Awareness? NIDA Research Reveals Subconscious Signals Can Trigger Drug Craving Circuits.** Using a brain imaging technology called functional magnetic resonance imaging (fMRI), scientists have discovered that cocaine-related images trigger the emotional centers of the brains of patients addicted to drugs -- even when the subjects are unaware they've seen anything. The study, published January 30 in the journal PLoS One, was funded by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health (NIH).

Articles of Interest

December 11, 2007, *Associated Press*—"Study: Overall Teen Drug Use Declining"--Mention of 2007 Monitoring the Future Survey.

January 3, 2008, *Newsweek, "The Anti-Drug Drugs"*—Interviews with Dr. Nora Volkow and NIDA grantee Dr. Thomas Kosten about vaccines to treat cocaine and nicotine addiction.

January 7, 2008, *WAMU/NPR Radio, "Kojo Nnamdi Show"*—Interviews with Dr. Frank Vocci and NIDA grantee Dr. Thomas Kosten about vaccine to treat cocaine addiction.

January 9, 2008, *Time, "A Drug to End Drug Addiction"*—Interviews with Dr. Frank Vocci and NIDA grantee Dr. Thomas Kosten about vaccine to treat cocaine addiction.

January/February, 2008, *Eating Well magazine, "Change the Way You Think About Food"*—Interview with Dr. Nora Volkow about the brain's response to food, and obesity/food addiction.

February 7, 2008, *Wall Street Journal, "When Mixing Medications Can Be Deadly"*—Interview with Dr. Nora Volkow about the potential serious consequences of combining prescription medications.

March 3, 2008, *Newsweek, "The Hunt for An Addiction Vaccine"*—Cover story on addiction that included interviews with Dr. Nora Volkow, Dr. Frank Vocci, and NIDA grantees Dr. Thomas Kosten and Dr. Tom McLellan.

March 17, 2008, *National Public Radio/Talk of the Nation, "Brain Enhancers: 'Professor's Little Helper'?"*—Interview with Dr. Nora Volkow about performance enhancing drugs. < p>April 9, 2008, *Des Moines Register, "Meth slips, medication abuse soars, expert says"*—interview with Dr. Timothy Condon about prescription drug abuse.

Dr. Frank Vocci, Director, DPMCDA, was interviewed by Deborah Shelton of the Chicago Tribune in late December 2007 on medications to assist quitting smoking.

Dr. Frank Vocci was interviewed by Neil Scott of the radio program Recovery Coast to Coast on office-based treatment of opiate addiction on February 1, 2008.

Dr. Frank Vocci was interviewed by Dr. Jill Adams on the NIDA medications development program for an article in the March 7, 2008 issue of Science.

Dr. Frank Vocci participated in a Buprenorphine Roundtable with the press on February 22, 2008.

Dr. Frank Vocci was interviewed by Julia Lyon of the Salt Lake Tribune on February 22, 2008 on methamphetamine addiction and pharmacotherapies.

Dr. Frank Vocci was interviewed by Alison Knopf of Alcoholism and Drug Abuse Weekly on February 25, 2008 as a follow up to the Buprenorphine Summit meeting.

Dr. Frank Vocci was interviewed by Jeneen Interlandi of Newsweek on multiple occasions for the cover story of February 26, 2008 on substance Abuse and the search for treatments.

Dr. Frank Vocci was interviewed by Maggie Koerth-Baker of MSNBC website on medications to treat addiction on March 3, 2008.

Dr. Joseph Frascella, Director, DCNBR, conducted an interview for the show "The Real Life Survival Guide", a show on WNPR, Connecticut Public Radio on the topic of addiction science, March 4, 2008.

Dr. Joseph Frascella conducted an interview for Dining Out Magazine on the issue of "food addiction" on March 5, 2008.

March 10, 2008. Alcoholism & Drug Abuse Weekly (Vol 20[10]) "Sex-Methamphetamine Fusion Issues Complicate Recovery If Not Addressed" Interview with Steven Grant, Chief of the Clinical Neuroscience Branch.

January 7, 2008. Steven Grant, Chief of the Clinical Neuroscience Branch, DCNBR was interviewed on the internet talk radio program "One Hour at a Time" on the VoiceAmerica Health & Wellness Channel. The topic was the biological and brain basis of addition and how they effect treatment.

January 31, 2008. Steven Grant, Chief of the Clinical Neuroscience Branch, DCNBR was interviewed by Gonzalo Moriera for a radio show on RTP (Radio and Television from Portugal) regarding Methamphetamine abuse.

January 31, 2008. Steven Grant, Chief of the Clinical Neuroscience Branch, DCNBR was interviewed by NIH Radio regarding the NIDA-supported publication by A.R. Childress and colleagues on "Limbic Activation by "Unseen" Drug and Sexual Cues" (PLOS One 3(1) e1506, 1-7, 2008)

David A. Gorelick, M.D., Ph.D., a senior investigator in the Office of the

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Scientific Director, IRP, was quoted on the use of anti-drug vaccines in a January 1, 2008 article in the Houston Chronicle newspaper.

Brain Awareness Week

On March 12 - 13, 2008, Dr. Roger Sorensen, DBNBR, participated in Brain Awareness Week at the National Museum of Health and Medicine, Walter Reed Army Medical Center. Middle school students were invited to the "Welcome To Roger's Party" exhibit booth for an interactive discussion on the physical and societal harms of alcohol and drug abuse. The students also played a "party game" during which they attempted to navigate an obstacle course while wearing Fatal Vision prism goggles that simulate the impaired visuomotor performance that can result from excessive alcohol or drug use.

Drs. Allison Chausmer and David Thomas (DBNBR, BCSRB) participated at Brain Awareness Week activities held at the National Museum of Health and Medicine, located at the Walter Reed Medical Center, Washington DC, March 12th-13th, 2008. A total of 750 school children from Maryland, District of Columbia and Virginia schools attended this event. NIDA staff played the educational computer game, Who Wants to be a NIDA Neuroscientist, with the children. David Thomas led the development of the computer-based version of this game. Drs. Jane Acri and Dave White, DPMCDA, also participated.

Upcoming Confernences/Exhibits

American Psychiatric Association 161st Annual Meeting Washington, DC	May 3-8, 2008
NIDA Blending Conference Cincinnati, OH	June 2-3, 2008
Joint Conference of the State Associations of Addiction Services (SAAS) and the Network for the Improvement of Addiction Treatment (NIATx) Orlando, FL	June 22-25, 2008
American Academy of Nurse Practitioners (AANP) 23rd National Conference National Harbor, MD	June 26-July 1, 2008

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Planned Meetings

A CCTN-DCNBR joint workshop is scheduled for May 20, 2008. The title of the workshop is **Pain, Stress and Healthier Life Choices with an Eastern Approach.** The presenters, Drs. Lixing Lao and Kevin Chen (University of Maryland School of Medicine) plan to discuss how acupuncture and/or meditation are useful in 1) coping with pain or stress; 2) a choice for healthier lifestyles; and 3) managing addiction. They plan to also discuss the concerns and challenges in experimental design and project implementation and how evidence-based studies can be carried out.

The next **National CTN Steering Committee Meeting** is planned for June 3-6, 2008 in Cincinnati, OH.

The National Institute on Drug Abuse (NIDA) will again sponsor the "Grant Writing Workshop" and the "Tutorials Workshop" at the **College on Problems of Drug Dependence (CPDD) Annual Scientific Meeting.** This year's conference will be held in **San Juan, Puerto Rico, on June 14-19, 2008.** The "Tutorials Workshop" provides junior investigators with fundamental information from a variety of scientific disciplines representing the breadth of drug abuse and addiction research. Speakers for this workshop are selected from amongst NIDA's T32 Training Directors to each give a presentation on a research topic within their field of expertise. The "Grant Writing Workshop" is designed to orient new research investigators to NIDA and the grant application process. NIDA will also be offering a limited number of travel awards to partially defray the cost of attending this conference.

Drs. James Bjork, DCNBR, and Minda Lynch, DBNBR, will co-chair the forthcoming symposium "Adults are from Mars, and Adolescents are from Venus" to be held at the annual meeting of the **College on Problems of Drug Dependence** on June 16, 2008 in San Juan, Puerto Rico. The speakers will be Janet Neisewander (Arizona State University), Sari Izenwasser (University of Miami), Nicole Schramm Sapyta (Duke University), and Yasmin Hurd (Mount Sinai School of Medicine).

A workshop titled: "Implementing Evidence-based Treatments: The CTN and TreatNet Models" is planned for NIDA's international forum on June 14th at the CPDD 2008 annual meeting in San Juan, Puerto Rico. The symposium is co-chaired by Dr. Betty Tai from NIDA and Dr. Juana Thomas Rossello from UNODC.

Drs. Ivan Montoya, DPMCDA, and Marya Hynes from the Organization of American States will co-chair a workshop on Drug Abuse Research Collaboration in Latin America, at the annual NIDA International Meeting in San Juan on June 13, 2008.

Dr. Ivan Montoya and Robert Walsh, DPMCDA, will co-chair a workshop during

CPDD in San Juan to discuss the FDA and NIH regulatory aspects of grants involving clinical trials.

Drs. Ivan Montoya and Joni Rutter, DCNBR, will co-chair a symposium on Pharmacogenetics of the Medications for the Treatment of Addictions at the CPDD meeting in San Juan.

NIDA will host its second **"Mentored K Awardees Meeting: Making the Transition to Independent Scientist"** in North Bethesda, Maryland on July 24-25, 2008. The meeting will offer a forum for mentored K awardees to:

- meet with NIDA program staff, Division Directors, and the NIDA Director and Deputy Director;
- learn strategies that will maximize their likelihood of successfully obtaining RO1 support ("grantsmanship");
- receive practical advice about transitioning to and succeeding in an independent research career;
- showcase their own current research and network with other awardees at similar points in their careers.

Second, third, and fourth year NIDA mentored K awardees are invited to attend.

The **American Psychological Association (APA)** is holding its annual convention in Boston, Massachusetts, from August 14-17, 2008. As in previous years, NIDA (in collaboration with NIAAA) and APA Divisions 50 (Addictions) and 28 (Psychopharmacology and Substance Abuse) are planning a Poster Session/Social Hour focusing on Early Career Investigators. The 2008 session will take place on August 14 from 4-6 pm. Drs. Teri Levitin and Harold Perl will be teaching their popular half-day course on grantsmanship ("Inside the Black Box at NIH (NIDA & NIAAA): Grant Writing Tips They Didn't Teach You in Graduate School"). This free course is open to all, regardless of career status. Dr. Harold Perl will present a talk entitled, "Implementation Science: Transforming Evidence Into Real-World Practice" as part of the seminar "Evidence Based Practice: Cutting Edge Issues", at the APA on Saturday August 16, 2008.

Dr. Steven Grant, DCNBR, will give a presentation titled "Clinical Neuroscience of Addiction: Advances and Prospects" in the symposium "What is the fundamental nature of addiction?" at the annual meeting of the **American Psychological Association** to be held in Boston, Mass on August 14-18, 2008. The symposium will be chaired by Meyer Glantz (DESPR) and the other speakers include Wilson Compton, (DESPR), Kevin Conway (DESPR) and Robert F. Krueger (University of Minnesota).

Drs. Steven Grant, DCNBR, and Minda Lynch, DBNBR, co-organized and will co-chair a symposium titled "Do Drugs of Abuse Produce Cognitive Rigidity?" at the annual meeting of the **American Psychological Association** to be held in Boston, Mass on August 14-18, 2008. The speakers will be Geoff Schoenbaum (University of Maryland), David Q Beversdorf (Ohio State University), Martin Paulus (UCSD), and Hans Breiter (Massachusetts General Hospital).

Drs. Eve Reider and Belinda Sims will co-chair a symposium at the 2008 annual convention of the **American Psychological Association**, entitled "Potential of Universal Childhood Prevention to Reduce Later Criminal Behavior" through Division 37 (Child and Family Policy and Practice) and the APA Mini-Convention on Interpersonal Violence.

Dr. James Bjork, DCNBR, organized and will chair the forthcoming symposium "Willpower: What really governs our choices?" to be held as part of NIDA's mini-convention **"Frontiers in Addiction Research"** on Friday November 14, 2008 in Washington, DC. The speakers will be Patrick Haggard (University

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College, London), Brian Knutson (Stanford University), Paul Glimcher (New York University), and Jonathan Cohen (Princeton University).

Dr. Steven Grant, DCNBR, and Dr. Rita Goldstein, Brookhaven National Laboratory, co-organized and will co-chair a symposium titled "Functional Neuroimaging Evidence for a Brain Network Underlying Impaired Insight (into illness) in Drug Addiction" at the annual meeting of the **Society for Neuroscience** to be held in Washington, DC on November 15-29, 2008. The speakers will be AD "Bud" Craig (Barrow Neurological Institute), Antoine Bechara (University of Southern California), Hugh Garavan (Trinity College), and Anna Rose Childress (University of Pennsylvania).

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NIDA Publications

Research Report Series: Comorbidity of Drug Abuse and Mental Illness
NIH Pub. No: 08-5771
When two disorders or illnesses occur simultaneously in the same person, they are called comorbid. This new research report addresses the comorbidity of drug abuse and addiction and other mental disorders. It explores the complex ways in which genetic, developmental and environmental factors appear to interact to predispose individuals to develop both diseases or to have a greater risk of the second disorder after the first appears. The report describes the prevalence of, as well as the diagnostic and treatment challenges posed by comorbid conditions that involve drug abuse, addiction and other mental disorders.

Addiction Science & Clinical Practice
Volume 4, Issue No. 1
NIH Pub. No. 08-6172
In this issue, Dr. Alan J. Budney and colleagues review recent research on marijuana dependence withdrawal, and treatment. Dr. Sharon Samet and colleagues discuss instruments used to diagnose psychiatric disorders and their utility in diagnosing abuse and addiction. Dr. Diana Sylvestre explains the disease process, screening methods, and treatment of hepatitis C in the context of addiction medicine. Finally, Drs. Michael Dennis and Christy Scott explore the discrepancy between acute-care models of addiction treatment and the compelling evidence that addiction is a chronic condition.

Monitoring the Future - National Results on Adolescent Drug Use, Overview of Key Findings: 2007
NIH Pub. No.: 08-6418
Provides a summary of drug use trends from a survey of 8th-, 10th-, and 12th grade students nationwide. Also includes perceived risk, personal disapproval, and perceived availability of each drug by this group.

Epidemiologic Trends in Drug Abuse - Community Epidemiology Work Group - June 2007
NIH Pub. No.: 08-6200A
This report is a synthesis of findings and highlights of data reported at the semiannual meeting of the CEWG.

Epidemiologic Trends in Drug Abuse - Community Epidemiology Work Group - Volume II - June 2007
NIH Pub. No. 08-6204A
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.

NIDA NOTES

NIDA NOTES, Vol. 21, No. 6
NIH 07-3478
The lead story explores a new therapy, Behavioral Treatment of Substance Abuse in Severe and Persistent Mental Illness, which boosted attendance at treatment sessions, reduced drug abuse, and improved quality of life for substance abusers whose mental illnesses greatly complicate their recovery. Also included are features on mice whose dopamine receptors have been genetically altered, rendering them insensitive to the rewarding effects of cocaine; the link between opioid use and immune system inhibition; the effects of the often-abused solvent toluene on the brain; and the relationship between a mother's cigarette smoking when pregnant and the early manifestation of behavioral problems and disorders in her child. The Director's Column reports on the NIH Blueprint for Neuroscience Research, a knowledge- and resource-sharing system for NIH-funded neuroscientists. This issue also includes a complete index to NIDA Notes Volume 21.

NIDA NOTES, Volume 22 Innovations Special Issue
NIH 07-3478
This special issue features recent groundbreaking discoveries in drug abuse research that connect to the work of scientists across many disciplines. The lead story describes findings about receptors on neurons and glial cells that offer promise for pain relief without the negative side effects of currently used opioids. The Director's Perspective looks at how NIDA fosters interdisciplinary, breakthrough work; it describes two innovative NIDA programs: Cutting-Edge Basic Research Awards (CEBRA) and the Translationally Oriented Approaches, Devices and Strategies (TOADS) Workgroup. Other research reports discuss optical technologies that expand research and therapeutic possibilities by revealing neural circuits in living animals; discoveries of an unexpected role for the immune system in eliminating extra synapses during brain development; and work in genetics that identifies dozens of genes that influence vulnerability to drug dependence and indicates parts of the brain beyond the dopamine reward system that may contribute to addiction risk.

Brain Power! NIDA Junior Scientists

NIDA is reprinting both Brain Power! NIDA Junior Scientists for grades 2-3 and Brain Power! NIDA Junior Scientists for grades 4-5. Both sets of materials were designed for use in the classroom and include about 5 days worth of lessons. The materials have been extremely popular among teachers.

CTN-Related Publications

Seven editions of the CTN Bulletin Board were distributed. The Bulletin Board is an electronic report on the progress of the protocols, committees, and node activity in the CTN. The Bulletin has wide readership within and outside the CTN and NIDA.

Data from eleven CTN trials are now available on the CTN Data Sharing Web Site. Another three data sets will be available by the end of June 2008. Currently more than 115 research scientists have downloaded one or more data sets. These data sets are in compliance with HIPAA and CDISC (Clinical Data Interchange Standards Consortium) standards in support of the interoperability required by the NIH Roadmap. Starting this summer, flat file postings of the current data sets will also be available on the CTN Data Sharing website.

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International Publications

New Look for International Program Web Site, E-News
The NIDA International Program launched a redesigned Web site in March, www.international.drugabuse.gov, improving the site's navigation and visual design.

NIDA International Program E-News Letter

January 2008 - This issue reported on the formation of an Inhalant Abuse Working Group in East and Southern Africa, a NIDA Director's Award presented to Dr. Ivan Montoya for his efforts to help implement the Institute's Latin American Initiative, and binational research teams in Argentina, Brazil, and Syria who have been awarded NIDA R01 research project grants through the Fogarty International Center International Tobacco and Health Research and Capacity Building Program. The issue also announced extended deadlines for abstract submission and links to the online registration site for the 2008 NIDA International Forum.

April 2008 - This issue announced the Indo-US binational agreement to cooperate on research into mental health, neurology, and addiction; the results of DISCA-supported research on intravenous self-administration studies in mice and the role of stress hormones in relapse to cocaine use; and a NIDA meeting on anti-smoking efforts that featured the U.S. Surgeon General and NIDA staff briefing Russian public health experts. The issue also reported on the selection of Octavio Campolo, Ph.D., University of Guadalajara, as a DISCA awardee; and the 2008 WHO/NIDA/CPDD International Traveling Fellows: Yu Liu, Ph.D., Chinese National Institute on Drug Dependence, Peking University; and Rasmon Kalayasiri, M.D., Chulalongkorn University, Thailand.

Other Publications

Acri, J.B., Chiang, N., McCann, D.J., Shih, M.L., and Vocci, F.J. Summary of NIDA Medications Workshop: New Opportunities for Chemists and Pharmacologists. Drug Alcohol Depend., 92, pp. 307-311, 2008.

Somoza, E., Somoza, P., Lewis, D., Li, S.H., Winhusen, T., Chiang, N., Vocci, F., Horn, P., and Elkashef, E. The SRPHK1 Outcome Measure for Cocaine Dependence Trials Combines Self- Report, Urine Benzoylecgonine Levels, and the Concordance between the Two to Determine a Cocaine-Use Status for each Study Day. Drug Alcohol Depend., 93, pp.132-140, 2008.

McCann, D.J. Potential of Buprenorphine/Naltrexone in Treating Polydrug Addiction and Co-occuring Psychiatric Disorders. Clinical Pharmacology and Therapeutics 83(4), pp. 627-630, 2008.

White, D.A., Michaels, C.C., and Holtzman, S.G. Periadolescent Male but not Female Rats have Higher Motor Activity in Response to Morphine Than Do Adult Rats. Pharmacology, Biochemistry and Behavior 89, pp. 188-199, 2008.

Khalsa, J.H. and Vocci, F. Clinical Management of Drug Addicts Infected with Human Immunodeficiency Virus and Hepatitis C Virus, J. Addictive Diseases, 27(2), pp. 1-10, 2008.

Bjork, J.M., Momenan, R., Smith, A.R., and Hommer, D.W. Reduced Posterior Mesofrontal Cortex Activation by Risky Rewards in Substance-Dependent Patients. Drug and Alcohol Dependence, 95, pp. 115-128, 2008.

Singh, H.H., Rapaka, R.S., and Shurtleff, D. NIDA Drug Supply and Analytical Services Program: Providing Research Resources and Tools to the Scientific Community. Drug and Alcohol Dependence 95, pp. 182-186, 2008.

Sharp C.W., Rosenberg N., and Beauvais, F. Substance Abuse: Inhalant-Related Disorders. Psychiatry, 3rd Edition. A. Tasman M. Maj, M.B. First, J. Kay, and J. A. Lieberman (Eds) Wiley: 2008.

Thomas, Y.F., and Compton, W.M. Rural Populations Are Not Protected from Drug Use and Abuse. The Journal of Rural Health, 23, pp. 1-3, 2007.

Bukoski, W.J., and Compton, W.M. Drug Abuse Research Collaboration in the 21st Century. In: Scheier, L.M. and Dewey, W.L. (Editors): The Complete Writing Guide to NIH Behavioral Science Grants. New York: Oxford University Press, 2008.

Dr. Redonna Chandler, Chief of the Services Research Branch of DESPR was a lead editor of a Special Edition of the Journal of Substance Abuse Treatment. Sacks, S., Chandler, R., and Gonzales, J. Responding to the Challenge of Co-Occurring Disorders: Suggestions for Future Research. Journal of Substance Abuse Treatment 24, pp. 139-146.

Graham, D.L., Noailles, P.A. and Cadet, J.L. Differential Neurochemical Consequences of an Escalating Dose-binge Regimen followed by Single-day Multiple-dose Methamphetamine Challenges. J. Neurochem., 2008. [Epub ahead of print]

Herning, R., Better, W. and Cadet, J.L. EEG of Chronic Marijuana Users During Abstinence: Relationship to Years of Marijuana Use, Cerebral Blood Flow and Thyroid Function. Clin. Neurophysiol. 119(2), pp. 321-331, 2008.

Krasnova, I.N., Li, S.M., Wood, W.H., McCoy, M.T., Prabhu, V.V., Becker, K.G., Katz, J.L. and Cadet, J.L. Transcriptional Responses to Reinforcing Effects of Cocaine in the Rat Hippocampus and Cortex. Genes Brain Behavior 7(2), pp. 193-202, 2008.

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Staff Highlights

Staff Honors and Awards

In recognition of visionary contributions in the establishment and continued development of the society, **Dr. Charles Sharp**, DBNBR, received the 2007 Society for Neuroimmune Pharmacology (SNIP) Herman Friedman Founder's Award, which was named in honor of Herman Friedman. Dr. Friedman was Professor and Chair of the Department of Medical Microbiology and Immunology from 1978 to 2003, and then became Emeritus Professor and Distinguished University Professor at USF. He was an effective leader for 25 years, building a successful, well-funded, and widely recognized faculty, whose NIDA-funded work on the effects of cannabinoids and other abused substances on immune function and infection established his department as one of the major groups in the field. Dr. Friedman had a long and distinguished career as a research scientist.

Dr. Marilyn Huestis, IRP, has recently been appointed to the World Anti-doping Agency's (WADA) Prohibited List Committee. The Prohibited List was first published in 1963 under the leadership of the International Olympic Committee. Since 2004, as mandated by the WADA Code, the list of prohibited substances and methods in elite sports, including the Olympics, is reviewed, revised as necessary and published each year by the Prohibited List Committee. The List is a cornerstone of the Code and a key component of harmonization.

Dr. Marilyn Huestis recently was selected for the American Association of Clinical Chemistry's Outstanding Contributions in a Selected Area of Research award for 2008. This award recognizes especially meritorious research contributions by an individual in a specific area of clinical chemistry. The clinical chemists who have received this award have achieved national and international status for their pioneering efforts in an area of research considered fundamental to the science and have been considered among the world's foremost experts in that specific discipline.

Dr. Lula Beatty, Director, SPO, received the Susan Rosenberg Zalk award for mentoring from the Society for the Psychology of Women, American Psychological Association, in September 2007.

Dr. Lula Beatty received the Public Service Award from the Science Directorate, American Psychological Association, in October 2007.

Staff Changes

Dr. Kristopher Bough joined the Medications Research Grants Branch of DPMCDA in February 2008. Dr. Bough came to NIDA from the FDA, where he

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was a primary drug reviewer for two years in the Office of Generic Drugs. Prior to joining the FDA, Dr. Bough was in academia where his work encompassed a wide breadth of behavioral, electrophysiological and genetic neuroscience research aimed at elucidating the mechanistic underpinnings of an alternative treatment for epilepsy. His published work includes 11 first-author papers, one invited manuscript, two reviews and three book chapters. As a Project Officer within the MRGB, Dr. Bough will be responsible for managing a portfolio of clinical research grants for drug abuse and dependence. Kristopher holds a B.S. degree in Biology from Gettysburg College and an M.S. and Ph.D. in Biology from Georgetown University.

Dr. Bethany Griffin Deeds joined DESPR's Epidemiology Research Branch in February 2008. Her program area is the social epidemiology of drug use including drug markets, violence and HIV. She received her B.A. in Biology at the University of Dayton and an M.A. in Biology at The College of William Mary before managing HIV prevention services and research in the Division of Adolescent Medicine at the University of Maryland Medical School for five years. She also holds a Ph.D. in Public Policy from the University of Maryland Graduate School with a research focus on adolescent violence and substance use. Prior to joining NIDA, she was an Assistant Professor in the Department of Pediatrics at the University of Maryland Medical School for four years where she directed Connect to Protect: Baltimore, one of 13 national sites investigating how community partnerships can reduce adolescent HIV incidence and prevalence by making structural changes to the environment.

Dr. LeShawndra Price joined DESPR's Epidemiology Research Branch in December 2007. Her program areas include childhood psychopathology, health disparities, and the impact of child abuse & neglect, living in poverty, and parental incarceration as precursors for drug use. Prior to joining NIDA, Dr. Price was Chief of both the Stress and Trauma Program and the Disruptive Behavior Program at the National Institute of Mental Health. Dr. Price's academic background includes a B.A. in Psychology from Wake Forest University and an M.A. and Ph.D. in Developmental Psychology from the University of North Carolina at Chapel Hill.

Dr. Jeff Schulden joined DESPR's Epidemiology Research Branch in February 2008. Prior to joining NIDA, Dr. Schulden served as a medical epidemiologist with the Behavioral and Clinical Surveillance Branch of the Division of HIV/AIDS Prevention, CDC. He worked on a range of projects to improve access to HIV testing and services among high-risk and hard-to-reach populations. From 2002-2004, he served as an Epidemic Intelligence Service (EIS) officer with CDC's Division of Violence Prevention. He received his B.A. from Duke University and his M.D. from Harvard Medical School. He completed residency training in psychiatry at New York Presbyterian Hospital, Cornell University.

The CCTN is pleased to welcome **Dr. Steven Sparenborg**. Dr. Sparenborg has extensive experience working in preclinical and clinical neuroscience/pharmacology areas in the U.S. Army, FDA, NIH, and private industry. Dr. Sparenborg has a degree in biological psychology and has worked in clinical research and clinical trials. From 1995-1999, he served as a Health Scientist Administrator (Commissioned Corp) at NIDA in the then Medications Development Division (now DPMC) and was appointed the Acting Chief, Regulatory Affairs Branch shortly before he left NIDA. During his tenure at MDD/NIDA, he was involved in programs and projects aimed at developing anti-cocaine addiction pharmacotherapies. In the past nine years, Dr. Sparenborg served as a managing consultant with Hoyle Consulting, Inc. in Maryland, where he advised and supported clinical trials research, development, and registration of FDA-regulated pharmaceuticals and biologics. Within the CCTN, he will be part of our Psycho-Pharmacology Team.

NIDA's Office of Extramural Affairs (OEA) is pleased to have new colleagues from DEAS joining us: Lisa Gerring, Sonya Freeman, and Grace Murgolo.

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John Fitzgerald's dissertation based on CTN 0008 data received Division 55 of the American Psychological Association Patrick DeLeon Prize for Outstanding Student Contribution to the Advancement of Pharmacotherapy at the 2007 APA Annual Meeting in August. John Fitzgerald conducted a secondary analysis of the Baseline workforce and treatment unit data for his dissertation in System Science: Social Psychology at Portland State University. The analysis used HLM to assess individual and organizational influences on staff attitudes toward naltrexone, methadone and buprenorphine. Patrick DeLeon invited him to prepare the analysis for publication and to submit it to the journal he edits: Psychological Services.

Dr. Erik Gunderson received the 2007 Ambulatory Medicine Teacher of the Year Award from the Department of Medicine at Columbia University. The award was based in part from his development of a curriculum on recognition of prescription opioid use disorders and for involvement of medical residents in his clinical research on buprenorphine treatment of opioid dependence in primary care.

Dr. Leonard Jason at DePaul University was recently recognized as the fourth most productive clinical psychology researcher during the five-year period spanning 2000 to 2004 in an article by P.K. Stewart, Y.P. Wu & M.C. Roberts entitled *Top producers of scholarly publications in clinical psychology PhD Programs* in the 2007 *Journal of Clinical Psychology*, 63(12), 1209-1215. During this period Dr. Jason published 87 articles.

Dr. Ellen Rose Meara of Harvard University has recently been named to the Institute of Medicine Committee on Smoking Cessation in Military and Veteran Populations'.

Dr. Kevin Oschsner, Columbia University, received the Young Investigator Award in Cognitive Neuroscience at the Annual Meeting of the Cognitive Neuroscience Society in San Francisco, CA, April 13, 2008.

The CTN Northern New England Node is pleased to announce that **Dr. Jennifer Sharpe Potter** has received a 5-year Career Development Award (K23) from the National Institute on Drug Abuse. Dr. Potter will focus on the important overlap between pain and addiction, with the ultimate goal of developing and studying a treatment approach for substance-dependent patients with chronic pain.

The Oregon/Hawaii Node is pleased to report that **Traci Rieckmann, Ph.D.**, has received a K23 award for a CTN platform study - Adoption of Evidence-Based Practices in Substance Abuse Treatment. The award supports four years of training and career development activities plus research on adoption of evidence-based treatments.

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José Szapocznik, Ph.D., has been named chairman of the Department of Epidemiology and Public Health at the Miller School of Medicine. Dr. Szapocznik also serves as associate dean for community development and director of the Center for Family Studies at the Miller School. He is considered a pioneer in the national effort to prevent and treat adolescent drug abuse and other behavior problems among Hispanic youth. Dr. Szapocznik's Brief Strategic Family Therapy(TM) has received national and international recognition for its success as a family-based intervention.

Dr. Patrick Tolan of the University of Illinois at Chicago received the 2007 Star of Science Award from the Children's Brain Research Foundation.

Dr. Patrick Tolan of the University of Illinois Chicago gave the Allen L. Edwards Lecture at the University of Washington in February 2007, entitled, "The Promise of Current Scientific Knowledge about Child and Adolescent Conduct Problems."

The **Center for Drug Free Living (CFDFL)**, a community treatment program in the Florida Node, has been awarded a $100,000 Blue Foundation grant. The funds will be used to establish and provide infrastructure support for a regional hepatitis care consortium (HepCaN).

The Robert Wood Johnson Foundation has named **Homeward Bound, Inc.**, a Texas not-for-profit substance abuse treatment agency in the CTN, as one of six awardees under its Advancing Recovery program.

Congratulations go to **Residence XII**, a women's treatment program in Kirkland, Washington, a CTP member of the Pacific Northwest Node. The agency has been selected to receive the James W. West, M.D., Quality Improvement Award from the National Association of Addiction Treatment Providers (NAATP). The award is given annually to one or more member programs to recognize their efforts in the area of quality improvement.

Planned Meetings

Publications

Staff Highlights

Grantee Honors