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Research Findings - Basic Neurosciences Research

Human White Blood Cells Synthesize Morphine

It has been reported that human plasma actually contains low concentrations of morphine. To date, however, the origin and biological substrates and pathways involved in the endogenous synthesis of morphine have been less clear. Now, researchers from the Neuroscience Research Institute at the State University of New York-College at Old Westbury have uncovered one such a pathway. This group, led by Dr. George Stefano, has shown that one likely source for plasma morphine is in the immune system's white blood cells (WBC). Specifically, Dr. Stefano and his colleagues recently reported that WBC express CYP2D6, an enzyme capable of synthesizing morphine from several substances including codeine. They further demonstrated that morphine can be synthesized from L-DOPA, the precursor for the neurotransmitter dopamine--an unexpected finding. The research team went on to show that WBC, in fact, can release morphine. These results demonstrate that the biosynthetic pathways for the neurotransmitter dopamine and morphine are linked. Furthermore, these results raise additional questions about the role of these two chemical messengers in modulating the immune system. Zhu, W., Cadet, P., Baggerman, G., Mantione, K.J., and Stefano,G. Human White Blood Cells Synthesize Morphine: CYP2D6 Modulation. Journal of Immunology, 175, pp. 7357-7362, 2005.

Endocannabinoids Act on Inhibitory Interneurons and Modulate an Intrinsic Population Rhythm of Hippocampal Neurons

Theta rhythms are behaviorally relevant electrical oscillations, intrinsic to neuronal populations, particularly the hippocampus. These hippocampal theta waves are controlled by endocannabinoids (eCB) that act on inhibitory neurons. When a so-called principal neuron discharges an action potential, its release of eCB sends a feedback signal to the inhibitory interneurons, which in turn affects the discharge pattern and intensity of the principal neurons that they innervate. This phenomenon is seen wherever endocannabinoids affect theta rhythm. Often, glutamatergic and/or cholinergic inputs, shaped by these inhibitory postsynaptic potentials (IPSPs) drive the intra-hippocampal theta oscillations. Dr. Alger's recent work shows that the IPSPs controlling theta rhythm appear to be controlled by eCBs. Specifically, Dr. Alger has shown that if all the glutamate receptors are blocked, the cholinergically-induced theta rhythm IPSPs in the hippocampus can be transiently interrupted by action potential-induced, eCB release. Because these actions are rapid, the intrinsic neuronal network may constitute the fundamental mechanism for temporal coding and decoding in the hippocampus. Disruption of theta rhythms might be one mechanism by which cannabinoid drugs may cause cognitive dysfunction. Reich, C.G., Karson, M.A., Karnup, S.V., Jones, L.M. and Alger, B.E. Regulation

of IPSP Theta Rhythm by Muscarinic Receptors and Endocannabinoids in Hippocampus. Journal of Neurophysiology, 94(6), pp. 4290-4299, 2005.

Staff Highlights

Grantee Honors

Pentapeptides and the Kappa Receptor

The rationale for the use of conformationally-restricted peptides has been that they reduce the number of multiple conformations available to flexible endogenous opioid peptides, such as dynorphin A, and allow a better understanding of those conformation(s) that may be contributing to the binding of a peptide to a receptor, and that may be involved in signal transduction or interruption of signal. Short cyclized peptides of four or five amino acids have been used with considerable success to better define the mu and delta receptor binding requirements; examples of these are the peptides prepared by Dr. Henry Mosberg and his associates: JOM-13 (delta receptor-specific), and JOM-6 (mu receptor-specific). Results previously obtained by Dr. Mosberg have suggested that pentapeptides cyclized by a 2,5 bridge produce enhanced kappa opioid receptor (KOR) affinity, and that a D-cysteine in the fifth position (rather than D-penicillamine), and a phenylalanine (Phe) in the third position was a requirement for kappa activity. These researchers have now prepared a series of pentapeptides with enhanced kappa receptor binding (Ki less than 5 nM), having a C-terminal cysteine, with a 2,5 cyclization consisting of disulfide, methylene, or ethylene dithioether linkage, and with a C-terminal amide structure. Modeling of the compound (Tyr-c[D-Cys-Phe-Phe-D-Cys]NH2) with the highest kappa affinity (Ki of 1.6 nM) bound to a model of the KOR, based on the rhodopsin crystal structure and previous modeling of the mu receptor, has indicated several important structural features, including hydrogen bonding between KOR anionic residues and the tyrosine nitrogen and phenolic oxygen in position one, interaction of Phe 3 with aromatic receptor residues in helix seven, accommodation of the disulfide bridge in a binding pocket between extracellular loop 2 and the extracellular ends of helices five and six. Phe 4 interacted with the side chains of residues in extracellular loop 2. Of considerable significance is the finding that this compound binds effectively at all three opioid receptor types, mu, delta, and kappa, with picomolar affinity at the mu receptor. The next step in this process will be to modify the Phe 3 side chain, such as introducing a basic substituent to interact with the neighboring negative charges of aspartate 204 and 206 in extracellular loop 2, in an effort to maximize or improve the kappa selectivity. The point of these findings is that cyclic pentapeptides can be designed, by careful amino acid selection and use of modeling, which can be accommodated by all three opioid receptor binding sites, and that they need not necessarily be longer peptides such as dynorphin A, in order to achieve reasonable kappa receptor binding. Further specific modifications of these pentapeptides may result in enhanced kappa receptor specificity. Przydzial, M.J., Pogozheva, I.D., Ho, J.C., Bosse, K.E., Sawyer, E., Traynor, J.R., and Mosberg, H.I. Design of High Affinity Cyclic Pentapeptide Ligands for _-opioid Receptors. The Journal of Peptide Research, 66(5), pp. 255- 262, 2005.

Parallel Synthesis and Biological Evaluation of Different Sizes of Bicyclo[2,3]-Leu-Enkephalin Analogues

Parallel synthesis of peptides and peptidomimetics has been an important approach to search for biologically active ligands. A novel systematic synthesis of different size bicyclic dipeptide mimetics was developed on solid-phase supports. By taking advantage of the enantioselective synthesis of unsaturated amino acids and their N-methylated derivatives, the hemiaminal problem was prevented in the pathway to thiazolidine formation. The bicyclic dipeptide was generated on the solid-phase support in three steps by an unconventional method. By inserting this bicyclic scaffold into the synthesis of a larger bioactive peptide, 11 different sizes of bicyclo[2,3]-Leu-enkephalin analogues were synthesized in a fast and efficient way. Modeling studies show that a

reversed turn structure at positions 2-3 was favored when an L- and L-bicyclic scaffold was used, and that an extended conformation at the N-terminal was favored when a D- and L-bicyclic scaffold was inserted. Binding affinities and bioassay studies show ligands with micromolar binding affinities and antagonist bioactivities for the [6,5]- and [7,5]-bicyclo-Leu-enkephalin analogues. Dr. Hruby and colleagues demonstrated that [6,5]-and [7,5]-bicyclic scaffold inserted peptide analogues can be generated in parallel synthesis on solid-phase support in 12 steps based on N-Fmoc chemistry using Wang resin. The amino acid precursors were synthesized from the previously developed methods followed by modification of their functional groups. It appears this is the first example of a parallel synthesis of [6,5]- and [7,5]-bicyclic dipeptide mimetics inserted into peptide analogues directly using -aldehyde amino acid derivatives and cysteine derivatives. Eleven analogues were synthesized, and their structure-biological activity relationship was examined. Some of the [6,5]- and [7,5]-bicyclo[2,3]-Leu-enkephalin analogues showed micromolar binding affinities and potent antagonist activities. The receptor selectivity decreased as the ring flexibility increased. Modeling studies indicated that the D- and L-bicyclic scaffold provided an extended backbone conformation similar to the DPDPE X-ray crystal structure at the corresponding positions. Interestingly, however, these analogues are antagonists whereas DPDPE is an agonist. Apparently the highly restricted bicyclic scaffold does not allow the ligand--receptor complex to form a bioactive agonist conformation. Gu, X., Ying , J., Min, B. , Cain, J.P., Davis, P., Willey, P., Navratilova , E., Yamamura , H.I., Porreca , F. and Hruby, V.J. Parallel Synthesis and Biological Evaluation of Different Sizes of bicyclo[2,3]-Leu-enkephalin Analogues. Peptide Science, 80(2-3), pp. 151-163, 2005.

Prenatal Cocaine Exposure and Brain Development

It has been demonstrated that exposure to cocaine increases cell death (i.e., apoptosis) in the fetal brain. To examine the molecular mechanisms of this effect, Dr. Michael Lidow and his group conducted studies in a mouse model of prenatal cocaine exposure. These studies demonstrate that maternal cocaine use is capable of interfering with a range of apoptosis-related genes in the cells of the fetal cerebral wall making these brain cells more sensitive to death-inducing signals. However, this increase in potential for apoptosis is likely to result in actual cell death only when and where the affected cells are subjected to a death-promoting local environment, with the distribution and harshness of such tissue environment depending not only on the cocaine exposure itself but also on fetal developmental stage, maternal health, nutritional status, etc. Consequently, the severity and scope of structural and functional impacts of the pro-apoptotic gene alterations in the offspring of cocaine-abusing mothers should be prone to significant variability due to idiosyncratic use of cocaine and a great diversity in the quality of prenatal care. Furthermore, apoptosis represents just one of several potentially negative influences of cocaine exposure on fetal corticogenesis, with proliferation, migration, and differentiation of cortical cells also being affected by this drug. Novikova, S.I., He, F., Bai, J., Badan, I., Lidow, I.A. and Lidow, M.S. Cocaine-induced Changes in the Expression of Apoptosis-related Genes in the Fetal Mouse Cerebral Wall. Neurotoxicology and Teratology, 27, pp. 3-14, 2005.

Potent Cannabinergic Indole Analogues as Brain Imaging Agents for the CB1 Cannabinoid Receptor and its X-Ray Crytallographic Structure

A series of novel aminoalkylindoles was synthesized in an effort to develop compounds that are potent agonists at the CB1 cannabinoid receptor and that are easily labeled with radioisotopes of iodine for biochemical and imaging studies. 2-Iodophenyl-[1-(1-methylpiperidin-2-ylmethyl)-1H-indol-3-yl]methanone (AM2233, 8) had a very high affinity for the rat CB1 receptor,

with most of the affinity residing with the (R)-enantiomer. Radioiodinated 8, (R)-8, and (S)-8 were prepared by radioiododestannylation of the tributyltin analogues in high yields, radiochemical purities, and specific radioactivities. In a mouse hippocampal membrane preparation with [131I](R)-8 as radioligand, racemic 8 exhibited a Ki value of 0.2 nM compared with 1.6 nM for WIN55212-2. In autoradiographic experiments with mouse brain sections, the distribution of radioiodinated 8 was consistent with that of brain CB1 receptors. Again, very little specific binding was seen with the (S)-enantiomer [131I](S)-8 and none occurred with the (R)-enantiomer [131I](R)-8 in sections from CB1 receptor knockout mice. Radioiodinated 8 thus appears to be a suitable radioligand for studies of CB1 cannabinoid receptors. In addtion, for further gaining insights into structure activity relationship, X-ray crystallographic structure was determined. At present, there are only limited number of such successful studies on cannabinoid ligands and this is one of the successful elucidation of the three dimensional structure. Results of the single-crystal X-ray study of 8 were also reported in this publication. The solid-state structure outlines some important conformational features of the molecule. First, the N-methylpiperidinyl group exists in a chair conformation, with the N-methyl group being equatorial and in close proximity to the iodo substituent of the benzoyl ring. The carbonyl group lies in the plane with indole in an anti conformation with respect to the indole C2-C3 bond. Conversely, the 2-iodophenyl ring is gauche with its plane forming a 73 angle with the plane of the indole. Deng, H., Gifford, A.N., Zvonok, A.M., Cui, G., Li, X., Fan, P., Deschamps, J.R., Flippen-Anderson, J.L., Gatley S.J. and Makriyannis, A. Potent Cannabinergic Indole Analogues as Radioiodinatable Brain Imaging Agents for the CB1 Cannabinoid Receptor. Journal of Medicinal Chemistry, 48 (20), pp. 6386-6392, 2005.

Adamantyl Cannabinoids: A Novel Class of Cannabinergic Ligands

Structure activity relationship studies have established that the aliphatic side chain plays a pivotal role in determining the cannabinergic potency of tricyclic classical cannabinoids. Dr. Makriyannis and his coworkers have now synthesized a series of analogs in which a variety of adamantyl substituents were introduced at the C3 postion of delta-8-THC. A lead compound from PI's laboratory, (-)-3-(1-adamantyl)-delta-8-tetrahydrocannabinol (AM411), was found to have robust affinity and selectivity for the CB1 receptor as well as high in vivo potency. The X-ray crystal structure of AM411 was determined. Exploration of the side chain conformational space using molecular modeling approaches has allowed the investigators to develop cannabinoid side pharmacophore models for the CB1 and CB2 receptors. The results suggest that although a bulky group at the C3 position of classical cannabinoids could be tolerated by both CB1 and CB2 binding sites, the relative orientation of that group with respect to the tricyclic component can lead to receptor subtype selectivity. Lu, D., Meng, Z., Thakur,G.A., Fan, P., Steed, J., Tartal, C.L., Hurst, S.P., Reggio, P.H., Deschamps, J.R., Parrish, D.A., George, C., Jarbe, T.U.C., Lamb, R.J. and Makriyannis, A. Adamantyl Cannabinoids: A Novel Class of Cannabinergic Ligands. Journal of Medicinal Chemistry, 48, pp. 4576-4585, 2005.

Cannabinoids Reverse Capsaicin-Evoked Sensitization of Spinal Pain Fibers

Dr. Donald Simone and colleagues induced excitation and sensitization of wide-dynamic-range (WDR) and high-threshold (HT) spinal nociceptive neurons by intraplantar injection of 0.1% capsaicin (10 µl) in rats. Low doses of the cannabinoid agonist, CP 55,940, applied intrathecally attenuated this capsaicin-evoked sensitization of WDR and HT spinal pain fibers. These same doses of capsaicin did not alter the responses of WDR and HT neurons in naïve rats. The effects of CP 55,940 on pain sensitization were blocked by pretreatment of the spinal cord with the CB1 receptor antagonist, SR141716A, indicating that the

effect was CB1 receptor mediated. These studies demonstrate that cannabinoid application to the spinal cord prevents capsaicin-evoked central sensitization. Johanek, L.J. and Simone, D.A. Cannabinoid Agonist, CP55, 940, Prevents Capsaicin-induced Sensitization of Spinal Cord Dorsal Horn. Journal of Neurophysiology, 93(2), pp. 989-997, 2005.

Ketamine Produces a Lasting Disruption in Mouse Auditory Evoked Potentials

In humans, ketamine, an NMDA glutamate receptor antagonist, appears to produce persisting cognitive disruptions. In the present studies, auditory evoked potentials (AEP) were measured in four mouse strains administered ketamine. The acute effects of ketamine on AEP varied among the strains. The C3H and FVB strains were selected for a chronic ketamine study, based on the difference in effects of acute ketamine on the amplitude of the N1 evoked potential component. Acute ketamine dose-dependently decreased N1 amplitude in the C3H mice and did not affect any AEP component of FVB mice. The N1 is a cortically-generated evoked potential component. Both strains exhibited similar acute ketamine metabolism. In the chronic study, immediately after the final daily injection of ketamine, neither strain displayed alterations in AEP measures, suggesting adaptation of the previously vulnerable C3H mice. A week after the last exposure to ketamine, there was a decrement of the N1 amplitude in both the C3H (acutely sensitive) and FVB (acutely insensitive) strains, indicating a lasting deficit in information processing, even, in the FVB mice, in the absence of acute changes. Since decreased N1 amplitude is a reliable characteristic of patients with schizophrenia, the present observations in mice are consistent with the idea that NMDA hypo-function may be involved in the cognitive deficits of schizophrenia, as well as those of ketamine abusers. Maxwell, C.R., Liang, Y., Ehrlichman, R.S., Trief, D.F., Majumdar, S., Kanes, S.J., Karp, J. and Siegel, S.J. Ketamine Produces Lasting Disruptions in Encoding of Sensory Stimuli. Journal of Pharmacology and Experimental Therapeutics (epub), 2005.

Methamphetamine Damage to Dopamine Nerve Endings May Be Due to Activation of Microglia

In the September 2005 NIDA Director's Report, several lines of evidence were reported from Donald M. Kuhn's lab indicating that microglia, activated by methamphetamine (METH), may contribute to METH's characteristic neurotoxicity to dopamine-containing neuron terminals. While microglia are the primary immune defense cells in the brain, usually safeguarding and supporting neuronal functions, excessive microglial activation can cause harm to neurons. Now, this group has supplied additional evidence in support of this hypothesis. Dizocilpine (MK-801) and dextromethorphan (DXM) were tested for the ability to block microglial activation in an in vivo (mouse) METH model of neurotoxicity. The METH-induced activation of striatal microglia was reduced significantly by doses of MK-801 and DXM that also protected against DA nerve terminal damage. The researchers also determined that MK-801 and DXM can directly block activation of mouse microglial cells in culture. Since the specific action or property of METH that leads to microglial activation in vivo is not yet known (they hypothesize that it may be mediated by dopamine quinone formation), lipopolysaccharide (LPS) and the neurotoxic HIV protein Tat72, which are prototypical microglial activators, and which cause dopamine neuronal toxicity after direct infusion into brain, were used as model compounds. Two independent measures of microglial activation were assessed - enhanced expression of cellular cyclooxygenase-2 and increased secretion of tumor necrosis factor-_. It was observed that MK-801 and DXM prevented both LPS- and Tat72-induced activation of microglia in a concentration-dependent manner. The present results indicate that the ability of MK-801 and DXM to protect against METH neurotoxicity is related to their common property as

blockers of microglial activation. Several associated lines of investigation indicate that microglia are active participants in METH neurotoxicity and are not solely responding to neuronal damage. Thomas, D.M. and Kuhn, D.M. MK-801 and Dextromethorphan Block Microglial Activation and Protect Against Methamphetamine-induced Neurotoxicity. Brain Research, 1050, pp. 190-198, 2005.

Inhibitors of MEK Block Reconsolidation of Cocaine-Associated Memory

Memory for drug-paired cues resists extinction and contributes to relapse; however, the molecular mechanisms underlying these associations are not understood. Now researchers have shown that cocaine-conditioned place preference (CPP) in rats activates extracellular signal-regulated kinase 1/2 (ERK), two downstream transcription factors, ets-like gene-1 (Elk-1) and cAMP response element binding protein (CREB), and Fos, in the nucleus accumbens core (AcbC) but not shell. Intra-AcbC infusions of U0126, an inhibitor of the ERK kinase mitogen-activated protein kinase (MEK), immediately after CPP retrieval, prevent both the activation of ERK, Elk-1, CREB, and Fos and preference for the cocaine-associated chamber. When tested again 24 hr or 14 days after intra-AcbC infusions of U0126 or another MEK inhibitor, PD98059, CPP retrieval and concomitant protein activation were significantly attenuated. Thus, inhibition of the ERK signaling pathway in the AcbC not only blocked rats' preference for a drug-paired environment (CPP retrieval), but when the inhibitor was infused just after the recall had occurred, the rats had impairments in memory for the drug-paired cues that lasted at least two weeks afterward (reconsolidation paradigm). Together, these findings indicate the necessity of the AcbC ERK signaling pathway for drug-paired contextual cue memories and suggest that these strong memories can become susceptible to disruption by therapeutic agents. This experiment has translational relevance because the MEK inhibitors were given after the rats had already learned the cocaine-place association; this is analogous to treatments in people given after, not before, they are abusing drugs. Miller, C.A. and Marshall, J.F. Molecular Substrates for Retrieval and Reconsolidation of Cocaine-associated Contextual Memory. Neuron, 47(6), pp. 873-884, 2005.

A Role for the Distal Carboxyl Tails in Generating the Novel Pharmacology and G Protein Activation Profile of mu and delta Opioid Receptor Hetero-oligomers

Opioid receptor pharmacology in vivo has predicted a greater number of receptor subtypes than is explained by the profiles of the three cloned opioid receptors, and the functional dependence of the receptors on each other shown in gene-deleted animal models remains unexplained. Dr. Susan George has shown that one potential mechanism for such findings is the generation of novel signaling complexes by receptor hetero-oligomerization. In the present study, they show that deltorphin-II is a fully functional agonist of the mu-delta heteromer, which induced desensitization and inhibited adenylyl cyclase through a pertussis toxin-insensitive G protein. Activation of the mu-delta receptor heteromer resulted in preferential activation of Galpha(z), illustrated by incorporation of GTPgamma(35)S, whereas activation of the individually expressed mu and delta receptors preferentially activated Galpha(i). The unique pharmacology of the mu-delta heteromer was dependent on the reciprocal involvement of the distal carboxyl tails of both receptors, so that truncation of the distal mu receptor carboxyl tail modified the delta-selective ligand-binding pocket, and truncation of the delta receptor distal carboxyl tail modified the mu-selective binding pocket. The distal carboxyl tails of both receptors also had a significant role in receptor interaction, as evidenced by the reduced ability to co-immunoprecipitate when the carboxyl tails were truncated. The interaction between mu and delta receptors occurred

constitutively when the receptors were co-expressed, but did not occur when receptor expression was temporally separated, indicating that the hetero-oligomers were generated by a co-translational mechanism. Fan, T., Varghese, G., Nguyen, T., Tse, R., O'Dowd, B.F. and George, S.R.. A Role for the Distal Carboxyl Tails in Generating the Novel Pharmacology and G Protein Activation Profile of mu and delta Opioid Receptor hetero-oligomers. Journal of Biological Chemistry, 280(46), pp. 38478-38488, 2005. [Epub 2005 Sep 13]

Dopamine Receptor Oligomerization Visualized in Living Cells

G protein-coupled receptors occur as dimers within arrays of oligomers. Dr. George and her group visualized ensembles of dopamine receptor oligomers in living cells and evaluated the contributions of receptor conformation to the dynamics of oligomer association and dissociation, using a strategy of trafficking a receptor from one cellular compartment to another. They incorporated a nuclear localization sequence into the D1 dopamine receptor, which translocated from the cell surface to the nucleus. Receptor inverse agonists blocked this translocation, retaining the modified receptor, D1-nuclear localization signal (NLS), at the cell surface. D1 co-translocated with D1-NLS to the nucleus, indicating formation of homooligomers. Administration of a dopamine antagonist retained both receptors at the cell surface, and removal of the drug allowed translocation of both receptors to the nucleus. They found that differences in receptor conformation disrupted the oligomer that ligand-binding pocket occupancy by the inverse agonist induced a conformational change. They demonstrated robust heterooligomerization between the D2 dopamine receptor and the D1 receptor. The heterooligomers could not be disrupted by inverse agonists targeting either one of the receptor constituents. In sum, they describe a novel method showing that a homogeneous receptor conformation maintains the structural integrity of oligomers, whereas conformational heterogeneity disrupts it. O'Dowd, B.F., Ji, X., Alijaniaram, M., Rajaram, R.D., Kong, M.M., Rashid, A., Nguyen, T. and George, S.R. Dopamine Receptor Oligomerization Visualized in Living Cells. Journal of Biological Chemistry, 280(44), pp. 37225-37235, 2005. [Epub 2005 Aug 22]

Brain Dopamine Fluctuates After Cocaine Administration In Behaving Rats

Cocaine is known to alter the extracellular concentrations of dopamine in dopamine-rich areas of the brain. Both rapid (phasic) and slower (tonic) changes in its extracellular concentration contribute to its complex actions. However, most of the data we have on these fluctuations come from studies of microdialysates, which cannot provide temporal resolution on a real-time scale. Cyclic voltammetry overcomes this limitation, and provides continuous resolution at the millisecond scale. Dr. Wightman and his group showed dose-dependent changes in extracellular dopamine after repeated intravenous infusions of the drug into behaving rats. He found that cocaine modified dopamine release in two ways: dopamine concentration transients increase in frequency and in magnitude immediately upon infusion, and there was a gradual increase in the steady-state concentration of dopamine which occurred over 90 seconds, and likely reflected the ability of cocaine to inhibit dopamine uptake. Heien, M.L., Khan, A.S., Ariensen, J.L., Cheer, J.F., Phillips, P.E.M., Wassum, K.M. and Wightman, R.M., Real-time Measurement of Dopamine Fluctuations after Cocaine in the Brain of Behaving Rats. Proceedings of the National Academy of Sciences, 102, pp. 10023-10028, 2005.

Moody: a Novel Conserved Gene Required for Cocaine and Nicotine Sensitivity

Drosophila has been invaluable in illuminating many aspects of basic biology

because of the power and rapidity of fruit fly genetics. Drosophila is particularly useful for identifying new and unexpected genes involved in a biological process, since no a priori assumptions are made about the identities of genes involved. This can be achieved for example when a chemical mutagen is used to disrupt the DNA of a large number of flies. The animals are then sorted or screened to identify the very rare animals that have a particularly interesting phenotype, in this case sensitivity to cocaine. The mutant gene is then mapped to smaller and smaller chromosomal regions until the single gene (in flies, 1 out of about 12,000) responsible for the mutant phenotype is identified. Alternatively, transposons, made of up of DNA can be made to hop into different genes, and in this manner disrupt the function of the normal genes. Each and every fly with a different gene disrupted by the transposon can be screened. The sequence of the transposon can be used to locate the disrupted gene that is associated with the altered phenotype. Many biological processes are evolutionarily conserved, so identification and characterization of genes involved in a phenomenon such as drug sensitivity in fruit flies may shed light on drug sensitivity in humans. Drs. Bainton, Heberlein, and co-workers used a genetic screen to identify Drosophila mutants with increased sensitivity to cocaine. Interestingly, the cocaine-sensitive "moody" mutant also had increased sensitivity to nicotine, but was resistant to the acute effects of alcohol. Molecular identification of "moody" revealed that it is an evolutionarily conserved G-protein coupled receptor (GPCR) of previously unknown function. Moody encodes two alternate splice forms: moody-alpha and moody-beta. Surprisingly, if either splice form is defective, the flies are more sensitive to cocaine. Antibody staining shows that moody protein is expressed in surface glial cells required for proper maintenance of the blood-brain barrier (BBB). Data are also presented that indicate that moody-alpha and moody-beta "are actively required to maintain the integrity of the blood-brain barrier in the adult fly." How does "moody" modulate sensitivity to cocaine? One possibility is that a minor BBB defect simply allows more drug to enter the CNS of the flies. Several lines of reasoning argue against this possibility, the most compelling of which is that "moody" mutants are sensitive to cocaine and nicotine, but resistant to alcohol which readily passes through the BBB. Another possibility is that minor defects in the BBB could increase permeability of the CNS to ions, hormones, or other small molecules and that these molecules in turn modify drug sensing CNS structures leading to increased sensitivity to particular drugs. The identification of a novel GPCR that mediates cocaine and nicotine sensitivity and also plays a role in blood-brain barrier maintenance suggests several new and previously unanticipated research avenues. Future research into the human version of "moody" and related genes may provide insight into why some people are more or less sensitive to particular drugs. Identification of pharmaceuticals that increase the levels of the human version of "moody" could potentially be of use in reducing the effects of cocaine and nicotine.
Bainton, R.J., Tsai, L.T., Schwabe, T., DeSalvo, M., Gaul U. and Heberlein, U. Moody Encodes Two GPCRs that Regulate Cocaine Behaviors and Blood-brain Barrier Permeability in Drosophila. Cell. Vol. 123, pp. 145-156, 2005. Schwabe, T., Bainton, R.J., Fetter R.D., Heberlein, U. and Gaul, U.. GPCR Signaling is Required for Blood-brain Barrier Formation in Drosophila. Cell, 123, pp. 133-144, 2005.

Chromatin Remodeling Mediates Neuronal and Behavioral Changes Induced By Cocaine

Epigenetics is the study of heritable and long-term changes in gene function that occur without a change in the DNA sequence. Chromatin structure and function, including regulation of gene expression, is heavily regulated through a series of enzyme-mediated covalent modifications that target genomic DNA, histones, and other molecules. Histone deacetylases (HDACs) and histone acetylases remodel chromatin, a complex of histone proteins and DNA, in the vicinity of a particular gene by removing or adding acetyl groups to histones,

respectively. Long term changes in gene expression are thought to underlie addiction. Researchers in the Nestler and Self laboratories investigated the role of histone modification near the promoters of genes that play a critical role in cocaine addiction. Acute, but not chronic cocaine exposure is known to induce expression of the cfos gene while chronic exposure leads to the induction of the delta Fos B gene. Using chromatin immunoprecipitation (ChIP) the Nestler and Self laboratories found that acute but not chronic cocaine exposure leads to increased acetylation of histone H4 at the cfos promoter, but had no significant effect on histone H3 acetylation. Conversely, this group found that chronic but not acute cocaine exposure leads to increased acetylation of histone H3 of the delta FosB promoter, but had no significant effect on histone H4 acetylation. In addition, chronic cocaine induces acetylation of histone H3 at the brain derived neurotrophic factor (BDNF) and cyclin-dependent kinase 5 (Cdk5) promoter. Using a ChIP assay, the Nestler and Self laboratories show directly that the deltaFosB protein directly regulates the expression of the Cdk5 gene and that BDNF is regulated by chronic cocaine through a different transcription factor. These data suggest that a histone code (acetylation of histones H4 or H3 near the promoters of particular genes) may in part specify which genes are modulated in response to acute or chronic cocaine administration. Taking these experiments one step further, the Nestler and Self laboratories showed that administration of the HDAC inhibitor trichostatin A, prior to cocaine administration enhances reward responses to cocaine by increasing H3 acetylation, while overexpression of the HDAC4 gene in the striatum decreases reward responses to cocaine by inhibiting H3 acetylation. Pharmaceuticals targeting histone modifying enzymes could therefore be potentially valuable therapeutic agents for treating addiction to cocaine or, possibly, other drugs of abuse. HDAC inhibitors are currently under investigation for the treatment of Huntington's Disease and other neurodegenerative diseases. Kumar, A., Choi, K.H., Renthal, W., Tsankova, N.M., Theobald, D.E., Truong, H.T., Russo, S.J., Laplant, Q., Sasaki, T.S., Whistler, K.N., Neve, R.L., Self, D.W. and Nestler, E.J. Chromatin Remodeling is a Key Mechanism Underlying Cocaine-induced Plasticity in Striatum. Neuron, 48, pp. 303-314, 2005.

Activity-Dependent Subcellular Localization of NAC1

NAC1 is a protein that is upregulated in the brain's nucleus accumbens following chronic self-administration of cocaine. Overexpressing NAC1 in the nucleus accumbens antagonizes the actions of cocaine suggesting that NAC1 acts as a homeostatic protein. This protein belongs to the BTB/POZ family of proteins. Because of its nuclear localization in the cell and its ability to suppress transcription in a yeast assay of transcription, Dr. Mackler and his colleagues have previously suggested that NAC1 acts as a transcription factor. In a report in the European Journal of Neuroscience, Dr. Mackler and his colleagues suggest that neuronal activity causes the translocation of NAC1 from the nucleus of a nerve cell into the cytoplasm. Blockade of electrical activity by tetrodotoxin in cortical nerve cells prevented translocation of NAC1 from the nucleus to the cytoplasm. Depolarization by high potassium of both undifferentiated PC12 cells, a pheochromocytoma cell line, and Neuro2A cells also caused translocation of NAC1 from the nucleus to the cytoplasm. Dr. Mackler and his colleagues subsequently show that the translocation of NAC1 from the nucleus to the cytoplasm is mediated by protein kinase C phosphorylation at serine residue 245 in NAC1. Dr. Mackler suggests that the exclusion of NAC1 from the nucleus by activity may function to remove repression of transcription of target genes. Because BTB/POZ proteins function to degrade proteins through ubiquitination in cullin-E3 ligase complexe in the proteosomes, and the preliminary observation that NAC1 binds cullin3, Dr. Mackler and his colleagues suggest that NAC1 may also function in the cytoplasm to degrade specific proteins. Korutla, L., Champtiaux, N., Shen, H.W., Klugmann, M., Kalivas, P.W. and Mackler, SA. Activity-dependent Subcellular Localization of NAC1. European Journal of Neuroscience, 22(2), pp.

397-403, 2005.

Extracellular Signal-Regulated Kinases (ERK) and DARPP-32 Modulation by Drugs of Abuse

Pharmacological blockade of ERK kinases have been shown to block cocaine reward while the knockout of ERK1 increases morphine reward. The differences may be attributed to upregulation of ERK2 activity in the ERK1 knockout. In a recent paper Valjent et al. show that ERK2 activation by amphetamine requires activation of D1 dopamine receptors and NMDA receptors. The activation of ERK by drugs of abuse such as amphetamine cocaine, nicotine, morphine, and 9-tetrahydrocannabinol is absent in mice lacking DARPP-32. A point mutation in DARPP-32 at Thr-34 residue specifically involved in protein phosphatase-1 inhibition prevented ERK activation by drugs of abuse in the striatum but not in the prefrontal cortex. Phosphorylation of DARPP-32 at Thr-34 inhibits the protein-phosphatase-1 leading to increased phosphorylation of striatal enriched tyrosine phosphatase (STEP). This in turns prevents dephosphorylation of ERK. Blocking either phosphorylation of DARPP-32 on Thr34 or reducing ERK phosphorylation by 80 percent, prevent cocaine sensitization. These results suggest that DARPP-32 acts as a coincidence detector of glutamatergic and dopaminergic signals. Thus converging inputs from the prefrontal cortex and striatum triggered by environmental stimuli and internal rewarding stimuli are integrated by DARPP-32 to activate ERK producing changes in a specific subset of striatal neurons. Valjent, E., Pascoli, V., Svenningsson, P., Paul, S., Enslen, H., Corvol, J.C., Stipanovich, A., Caboche, J., Lombroso, P.J., Nairn, A.C., Greengard, P., Herve, D. and Girault, J.A. Regulation of a Protein Phosphatase Cascade Allows Convergent Dopamine and Glutamate Signals to Activate ERK in the Striatum. Proceedings of the National Academy of Sciences, USA, 102(2), pp. 491-496, 2005.

Distinct Cell Process Regulation Observed in Neuronal Migration

During brain development, neuronal proliferation, neuronal migration and axonal pathfinding are three major events to lay down basic structures for neural circuit formation, followed by axonal termination and synapse formation to complete the initial stage of brain development. Alteration in the formation of neuronal circuits is hypothesized to contribute to addiction. Secreted guidance cues such as netrins, ephrins, semaphorins, Slits, and the chemokine SDF are thought to guide axons to their target neurons. A fundamental question is whether the same guidance cues are used by migrating neurons to locate their final position as those used by axons to find their target neurons. In axonal pathfinding, axons turn by retracting an area of growth cone in the direction being repelled and extend the growth cone towards the area that the axon is turning, resulting in a reorienting of the axonal shaft. To test whether migrating neurons use the same process to find their final location, Dr. Rao and his collaborators observed the migration of neurons from the subventricular zone to the olfactory bulb in post-natal rats. They found that the process of guiding migrating neurons is different from the one used by axons. Instead of a single growth cone bending toward or away from a guidance cue, migrating neurons extend processes and retract multiple processes until the appropriated direction is discovered. Dr. Rao and his colleagues show that neurons from the subventicular zone turn away from the chemorepellent, Slit protein, through repeated rounds of process extension and retraction, instead of choosing a direction and reorienting the movement of the cell body into a given area of the extended process. A close observation reveals that Slit causes the cell body to preferentially extend its processes on the side away from this chemorepellent; however, it takes rounds of repeated process extension and retraction before the cell body completes a turn. Dr. Rao and his colleagues suggest that the distinct cellular events in neuronal migration reflect different cell signal transduction in interpreting the cues and in sensing the gradient of

diffusing environmental cues. Ward, M.E., Jiang, H. and Rao Y. Regulated Formation and Selection of Neuronal Processes Underlie Directional Guidance of Neuronal Migration. Molecular and Cellular Neuroscience, 30(3), pp. 378-387, 2005.

Developmental Hypothalamus Affected by NMDA Receptor Mediated Changes of Gap Junctions between Differentiating Neurons

During brain development, the initial communications between neurons relies heavily on electric transmission through gap junctions. During the maturation of the brain, with onset of chemical transmission via chemical synaptic junctions, gap junctions between neurons are uncoupled, down regulated or mostly eliminated, except in some subset of neurons in specific areas, including at least glutaminergic neurons in the prefrontal cortex and nucleus accumbens. Using gap junction permeable dye, contrasted with un-permeable dye, an initial wave of gap junction coupling was observed at neonatal age in rat hypothalamus, and was found to decrease dramatically two weeks after birth. This decrease and uncoupling of gap junction was associated with the activation of NMDA receptor, whose activity is essential for memory, reward and addiction. The NMDA receptor initiates a signaling cascade that increases the phosphorylation of calcium-cyclic AMP response element binding protein (CREB) that eventually down regulates the expression of connexin 36, the component protein for neuronal gap junction. Inhibition of NMDA receptors with antagonists or suppressing CREB phosphorylation abolishes uncoupling of gap junction and downregulation of connexin 36. The researchers suggest that NMDA receptor activity contributes to the developmental uncoupling of gap junctions via CREB-dependant down regulation of connexin 36. This work may provide new insight on how developing brain can be altered as the consequence of being exposed to drugs of abuse, since both cocaine and amphetamine have recently been found to suppress connexin 36 expression in prefrontal cortex and nuceus accumbens. Arumugam, H., Liu, X., Colombo, P.J., Corriveau, R.A. and Belousov, A.B. NMDA Receptors Regulate Developmental Gap Junction Uncoupling Via CREB Signaling. Nature Neuroscience, 8(12), pp. 1720-1726, 2005.

Melanocortin-1 Receptor Gene Variants Affect Pain and m-Opioid Analgesia In Mice And Humans

Melanocortin-1 receptor (MCR1) was recently found to mediate k-opioid receptor analgesia, especially in female mice and human volunteers. This was an unexpected finding because MCR1 is thought to be primarily involved in skin/hair pigmentation and immunomodulation. Mogil and colleagues tested MCR1 mutant mice and humans of various hair color for sensitivity to pain and m-opioid analgesia. Mice were tested for their basal sensitivity on six different assays of acute and tonic nociception. Human volunteers were also tested for tolerance to acute pain. For both mice and humans, morphine and its derivative, morphine-6-glucuronide (M6G), were assessed for their effectiveness in reducing pain. In mice, mutants for MCR1 displayed reduced nociceptive responses to morphine and M6G and this effect was significant for both sexes. Studies in human volunteers with two or more variant alleles of the MCR1 gene in amino acids known to abolish MCR1 functionality, compared to volunteers with no or one variant, showed that baseline tolerance differed significantly between genotypes, with greater tolerance for pain in volunteers with the MCR1 variant. In addition, analgesic responses after M6G were greater in MCR1 variant subjects compared to controls. In contrast to the k-opioid receptor analgesia, the effect on the m-opioid receptor is not sex-dependent. This study eloquently demonstrates the power of direct mouse to human translation in genetic studies. Mogil and colleagues show a significant link between MCR1 gene variants, pain tolerance, and potential efficacy of

analgesics acting on the m-opioid receptor. Larger human studies are needed to validate these findings in this important area of pain research. Mogil, J.S., Ritchie, J., Smith S.B., Strasburg, K., Kaplan, L., Wallace, M.R., Romberg, R.R., Bijl, H., Sarton, E.Y., Fillingim, R.B. and Dahan, A. Melanocortin-1 Receptor Gene Variants Affect Pain and Mu-opioid Analgesia in Mice and Humans. Journal of Medical Genetics, 42, pp. 583-587, 2005.

Identification and Functional Characterization of Brainstem Cannabinoid CB2 Receptors

There are two known receptor targets for cannabis, cannabinoid receptors 1 and 2 (CB1 and CB2). It has long been believed that CB1 was present in the central nervous system, while CB2 was used primarily by cells of the immune system and not present in the nervous system. NIDA researchers have found that CB2 is present and functional in neurons of some select brain regions, particularly the brain stem. They found evidence of CB2 receptors in neurons of the dorsal motor nucleus of the vagus, the nucleus ambiguus and the spinal trigeminal nucleus. The blood vessels and glia in these regions did not appear to express CB2 receptors. The potential significance of finding CB2 receptors in the brainstem is that therapeutics could be developed to affect the CB2 receptor selectively without the psychoactive effects that act through the CB1 receptor. Such therapeutics, if localized to the brainstem might be used to alleviate emesis and nausea. Van Sickle, M.D., Duncan, M., Kingsley, P.J., Mouihate, A., Urbani, P., Mackie K., Stella, N., Makriyannis, A., Piomelli, D., Davison, J.S., Marnett, L.J., Di Marzo, V., Pittman, Q.J., Patel, K.D. and Sharkey, K.A. Identification and Functional Characterization of Brainstem Cannabinoid CB2 Receptors. Science, 310(5746), pp. 329-332, 2005.

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

Research Findings - Basic Behavioral Research

The Ventral Pallidum Has Multiple Roles In Encoding Reward Cues And Generating Responses To Natural Rewards

The ventral pallidum (VP), an output nucleus of the striatum, is a focal point for brain limbic circuits, receiving projections from, among other areas, the nucleus accumbens (NAS) and ventral tegmental dopamine neurons. VP is known to be an important substrate for natural and drug reward. Two studies from the laboratories of Kent Berridge and J. Wayne Aldridge have now further elucidated the function of VP neurons. One study asked how the VP contributes to the generation of hedonic impact of a natural reward and the motivation to eat. Using a novel microinjection and functional mapping procedure, the investigators neuroanatomically localized and neurochemically characterized substrates in the VP that mediate increases in eating behavior and enhancements in taste hedonic "liking" reactions, which are assessed in the rat by taste reactivity measures such as licking and orofacial reactions to droplets of sucrose. They tested the effects of locally altering _-opioid and GABAA transmission, because signals from NAS to VP are carried by these transmitters. Although opioids are generally associated with increased hedonic response and eating behavior, they found that the _-opioid agonist DAMGO caused increased "liking" reactions to sucrose only in the posterior VP and actually suppressed such reactions in the anterior and central VP. DAMGO similarly stimulated eating behavior in the posterior and central VP and suppressed eating in the anterior VP. In contrast, the GABAA antagonist bicuculline increased eating behavior at all VP sites, yet completely failed to enhance sucrose "liking" reactions at any site. These results reveal that the VP has dissociable functions in generating increased food reward and increased eating behavior, and also that hedonic enhancement and eating are systematically mapped within the VP. The second study used neurophysiological approaches to examine how reward is coded by VP neurons, and test the effects of amphetamine on this encoding. Rats learned that a Pavlovian conditioned stimulus (CS+1 tone) predicted a second conditioned stimulus (CS+2 feeder click) followed by an unconditioned stimulus (UCS sucrose reward). Some rats were sensitized to amphetamine after training. Electrophysiological activity of ventral pallidal neurons was later recorded under the influence of vehicle or acute amphetamine injection. Both sensitization and acute amphetamine increased VP firing at CS+2, but produced no changes at CS+1 and minimal changes to UCS. The investigators used a new computational approach called 'Profile Analysis' to gain more insight into the behavioral relevance of these alterations in firing patterns. The analysis showed that mesolimbic activation by prior sensitization or acute amphetamine incrementally shifted neuronal firing profiles away from prediction signal coding (maximal at CS+1) and toward incentive coding (maximal at CS+2), without changing hedonic impact coding (maximal at

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UCS). This pattern suggests that mesolimbic activation produces a transformation from predictive information into incentive salience coded in VP neuron firing patterns. These results support predictions from incentive-sensitization theories and suggest why cues temporally proximal to drug presentation may precipitate cue-triggered relapse in human addicts. Smith, K.S. and Berridge, K.C. The Ventral Pallidum and Hedonic Reward: Neurochemical Maps of Sucrose "Liking" and Food Intake. The Journal of Neuroscience, 25, pp. 8637- 8649, 2005. Tindell, A.J., Berridge, K.C., Zhang, J., Peci–a, S. and Aldridge, J.W. Ventral Pallidal Neurons Code Incentive Motivation: Amplification by Mesolimbic Sensitization and Amphetamine. European Journal of Neuroscience, 22, pp. 2617-2634, 2005.

The Orexin System May Be a Therapeutic Target for Treatment of Drug Addiction

The orexins (or hypocretins) are neuropeptides recently identified as neurotransmitters in lateral hypothalamic neurons. While the lateral hypothalamus has been historically implicated in reward and motivation, it has mostly been studied with respect to feeding behavior. Although orexins have been proposed to have a function in feeding, most studies have focused on their role in arousal and sleep. Anatomical studies, however, show that orexin neurons in the lateral hypothalamus project to reward-associated brain regions, including the nucleus accumbens and ventral tegmental area. This pattern of projections suggested to the investigators that orexin neurons may have a general role in reward and motivation, consistent with their proposed function in feeding. The study combined the use of a conditioned place-preference procedure to measure the rewarding properties of morphine, cocaine and food with immunohistochemical techniques to determine whether orexin neurons were activated when rats expressed a preference for environments associated with the rewards. The investigators found that activation of lateral hypothalamic orexin neurons is strongly linked to preferences for cues associated with both drug and food reward. They then tested the functional implications of this activation by chemically activating lateral hypothalamic orexin neurons. This activation reinstated drug-seeking behavior. They obtained further evidence for a direct role of orexin in reinstatement by showing that reinstatement was completely blocked by prior administration of an orexin A antagonist. Further, they discovered that administration of the orexin A peptide directly into the ventral tegmental area would reinstate drug seeking. These data reveal a new role for lateral hypothalamus orexin neurons in reward seeking, drug relapse, and addiction, and implicate these neurons in the circuitry that integrates environmental cues with consummatory rewards. These findings may have significant implications for development of treatments for drug addiction, because they extend the therapeutic potential for the orexin system, which has been studied intensively as a target for treatment of sleep and eating disorders. Harris, G.C., Wimmer, M. and Aston-Jones, G. A Role for Lateral Hypothalamic Orexin Neurons in Reward Seeking. Nature, 437, pp. 556-559, 2005.

New Behavioral Apparatus for Concurrent Measures of Feeding and Locomotion In Rats

Drug abuse researchers are increasingly interested in monitoring more than one behavior simultaneously, and in behavioral assessment conducted in more naturalistic settings. However, problems arise when one activity can interfere with another. For example, psychostimulants induce locomotion and stereotypy, and also suppress eating. Studies of the biobehavioral actions of psychostimulants commonly focus on locomotion and less commonly on feeding, and only rarely are these measures used concurrently in the same animal. Since hyperactivity induced by a psychostimulant may compete with other motor behaviors, including eating, it would be useful to concurrently

assess changes in eating and locomotion after psychostimulant treatment. To address this need, Dr. Paul Wellman and his colleagues modified an automated activity chamber in order to obtain minute-by-minute recordings of food consumption in parallel with an assessment of locomotion. In this apparatus, rats are offered a palatable mash diet suspended from an electronic balance positioned on the ceiling of the activity chamber. (The use of a palatable diet ensures that the rats will eat an adequate and consistent amount during a one hour test session, without the need for food deprivation). As a test of this system, they performed an experiment to characterize temporal changes in both locomotion and eating produced by administration of hypophagic doses of nicotine tartrate (0.28 mg/kg, i.p.) or cocaine hydrochloride (7.5 mg/kg, i.p.). At these doses, nicotine suppressed eating and locomotion, whereas cocaine suppressed eating, but facilitated forward locomotion. These outcomes support the viability of the apparatus and the concurrent method for dissociating drug effects on both feeding and locomotion. Dr. Wellman will be using this apparatus in his studies on the behavioral functions of _-1 adrenoreceptor subtypes with the goal of identifying new drugs that inhibit eating without activating brain reinforcement systems. Wellman, P.J., Ho, D.H. and Davis, K.W. Concurrent Measures of Feeding and Locomotion in Rats. Physiology & Behavior, 84, pp. 769-774, 2005.

Cocaine- and Amphetamine-Regulated Transcript (CART) Peptides Modulate the Locomotor and Motivational Properties of Psychostimulants

CART peptides were originally identified because their cDNA was up-regulated in the striatum, but not elsewhere in the brain, by acute cocaine and amphetamine administration. This finding led Dr. Pastor Couceyro and his colleagues to suspect that CART peptides might be important for the behavioral actions and addictive properties of psychostimulants. In their studies, the behavioral effects of cocaine and amphetamine were examined in CART knockout (KO) and wild-type (WT) mice. They found that acute amphetamine administration increased ambulatory locomotor activity in both WT and CART KO animals, but whereas the WT mice also exhibited greater vertical activity, stereotyped grooming, and head bobbing at the higher doses, the CART KO mice did not. Repeated amphetamine treatment produced robust locomotor sensitization in WT mice but only rarely did so in CART KO mice. Amphetamine elicited conditioned place preference in both genotypes, but its potency was reduced in the CART KO mice such that only the highest dose produced conditioning equal to that observed in the WT mice. Intravenous cocaine self-administration was also observed in both genotypes, but CART KO mice consumed less cocaine and responded less than did WT mice. Although the behavioral effects of psychostimulants were generally reduced in the CART KO mice relative to WT, open field activity and sucrose preference were not significantly different between the two groups. The attenuated effects of amphetamine and cocaine in CART KO mice suggest a positive neuromodulatory role for CART peptides in the locomotor and motivational properties of psychostimulants and implicate CART peptides in psychostimulant addiction. Couceyro, P.R., Evans, C., McKinzie, A., Mitchell, D., Dube, M., Hagshenas, L., White, F.J., Douglass, J., Richards, W.G., and Bannon, A.W. Cocaine- and amphetamine-regulated transcript (CART) Peptides Modulate the Locomotor and Motivational Properties of Psychostimulants. The Journal of Pharmacology and Experimental Therapeutics, 315, pp. 1091-1100, 2005.

Cocaine Exposure Makes Actions Insensitive To Outcomes But Not To Extinction

This study investigated the behavioral processes that are involved in persistent drug seeking despite adverse outcomes, which characterizes drug addiction. Such behavior might be explained by drug-induced modifications in learning

circuits, causing drug-seeking to become so habitual that it is impervious to outcome. Another possibility is that drug exposure reduces response inhibition. A third hypothesis, favored by Drs. Schoenbaum and Setlow from the results of this study, is that addictive behavior results from drug-induced alterations in the orbitofrontal cortex (OFC) resulting in decreased control of behavior by the value of expected outcomes. To test whether drug exposure can cause persistent behavior, and to distinguish between these accounts of such behavior, the investigators tested rats that had been exposed to 14 days of cocaine injections (and saline injected control animals) in a Pavlovian 'reinforcer devaluation' task, which provides independent assessments of the control of behavior by antecedent cues versus outcome representations. Twenty-one days after the cocaine (or saline control) treatment, rats were trained in the devaluation task: light cues (CS) were paired with food (UCS) for eight daily sessions and conditioning was assessed by response to the CS. After this conditioning, rats were assigned to either the 'devalued' or 'non-devalued' groups. The 'devalued' group received taste aversion training on days 1 and 3 by administration of LiCl immediately after free access to the same food used as the UCS. The 'non-devalued' group also received LiCl on days 1 and 3, but they received food pellets only on days 2 and 4. After training, probe tests consisted of presentation of the light CS in the absence of food delivery, and other tests were conducted to evaluate the conditioned taste aversion. The main result was that, during the probe tests, saline-treated devalued rats spent significantly less time in the food cups in response to the light CS compared to their non-devalued counterparts, whereas for cocaine-treated rats, there was no difference in responding between the devalued and non-devalued groups. Cocaine-treated animals did show extinction at the same rate as saline-treated animals during repeated exposure to CS alone, although their responses remained higher because they were elevated on the first day of extinction training. Thus, cocaine exposure caused persistent responding a month after the last drug treatment, and this deficit resulted from an inability to use representations of outcome value to guide behavior rather than from changes in stimulus-response learning or response inhibition. The results suggest that alterations in OFC, which is known to be involved in devaluation learning, may be extremely important for persistent drug-seeking behavior in the face of adverse outcomes. Schoenbaum, G. and Setlow, B. Cocaine Makes Actions Insensitive to Outcomes but not Extinction: Implications for Altered Orbitofrontal-Amygdalar Function. Cerebral Cortex, 15, pp. 1162-1169, 2005.

Sex and Estrous Cycle Phase Influence Conditioned Cue-Induced Reinstatement Of Cocaine-Seeking Behavior In Rats

Studies comparing cocaine self-administration in male and female rats have found that females exhibit greater sensitivity in a variety of outcomes; for example, they acquire self-administration more quickly, a greater percentage of females acquire self-administration, females exhibit greater disruption in the diurnal control over cocaine intake, and they exhibit greater motivation for cocaine. Additionally, females exhibit greater cocaine-primed reinstatement of cocaine-seeking behavior. Dr. Ron See and colleagues at the Medical University of South Carolina now report sex differences in reinstatement of cocaine seeking behavior using a conditioned-cue procedure. Separate groups of rats were trained to bar press for varying doses of i.v. cocaine (0.25, 0.4, 0.5, 0.6, and 1.0 mg/kg per infusion). Each infusion was paired with a compound conditioned stimulus (CS) consisting of a light and tone. Following the establishment of stable cocaine self-administration, cocaine responding was extinguished and during reinstatement, the ability of the CS alone (without cocaine) was assessed. During the extinction period, females exhibited more extinction responses (i.e., greater resistance to extinction) than males, perhaps reflecting greater cocaine motivation. During the reinstatement period in which bar-presses produced the CS, but not cocaine, both males and females in all the training dose groups exhibited increased bar-pressing relative to the

extinction responding. At intermediate training doses (0.4, 0.5, 0.6 mg/kg) there were no sex differences in reinstatement. Females trained at the lowest dose (0.25 mg/kg) and the highest dose (1.0mg/kg), however, exhibited less bar pressing for the CS than did males. Analysis of reinstatement by females tested during the estrous phase (versus non-estrous) indicated that those trained on the 0.25 mg/kg dose did not show reinstatement, although estrous status did not affect reinstatement at the other training doses. In summary, sex differences in reinstatement occurred at the highest and lowest training dose wherein reinstatement was greater in males than females and at the lowest training dose reinstatement was not observed in estrous females. Given that prior research has shown greater cocaine-primed reinstatement in females than males, the authors suggest that there are sex differences in the variables that control reinstatement. Specifically, females may be more vulnerable to pharmacologically induced reinstatement, whereas males may be more vulnerable to conditioned cue-induced reinstatement. Further research on these sex differences, including hormonal control, and their implications for relapse in humans is warranted. Fuchs, R.A., Evans, A., Mehta, R.H., Case, J. M. and See, R.E. Influence of Sex and Estrous Cyclicity on Conditioned Cue-induced Reinstatement of Cocaine-seeking Behavior in Rats. Psychopharmacology, 179, pp. 662-672, 2005.

Exogenous Progesterone Attenuates the Subjective Effects of Smoked Cocaine In Women, But Not In Men

Several preclinical studies have shown greater sensitivity to cocaine in females as compared to males. Further, many of these behavioral effects are modulated by the estrous cycle, and are eliminated by ovariectomy and subsequently restored by administration of estradiol, suggesting a role for estradiol in male-female differences in cocaine sensitivity. On the other hand, there is suggestive evidence from both preclinical and clinical studies that progesterone may also play a role in cocaine's subjective effects and may contribute to male-female differences in cocaine sensitivity. Drs. Suzette Evans and Richard Foltin of the New York State Psychiatric Institute and Columbia University pursued this possibility by comparing the subjective effects of exogenously administered progesterone in males and in females. In inpatient sessions, each female was studied in the mid-luteal phase (when both progesterone and estradiol were elevated), in the follicular phase (when progesterone was negligible and estradiol was elevated), and in a follicular phase in which progesterone was administered. A dose of 150 mg oral micronized progesterone was given so that the progesterone levels approximated those of the mid-luteal phase. Each male was studied under progesterone administration and under placebo. For each subject a full cocaine dose-response curve (0, 6, 12, and 25 mg cocaine) was obtained in each session. Replicating prior studies, cocaine's subjective effects were greater in the follicular phase than the luteal. Progesterone administration during the follicular phase resulted in an attenuation of the positive subjective effects, but did not alter the subjective effects in males. Drs. Evans and Foltin are now conducting a study to determine whether the administration of progesterone will attenuate cocaine self-administration. Evans, S.M. and Foltin, R.W. Exogenous Progesterone Attenuates the Subjective Effects of Smoked Cocaine in Women, But Not in Men. Neuropsychopharmacology (Online publication: 4 August 2005 at http://www.acnp.org/citations/Npp080405050186/default.pdf)

Cigarette Smoking Produces Dose-Dependent Effects On Subjective, Cardiovascular, and HPA Axis Measures In Men

This study investigated the acute effects of smoking a low- or high-nicotine cigarette on HPA hormones, subjective effects and cardiovascular measures in healthy, nicotine-dependent men. The high-nicotine cigarette was associated with higher peak plasma nicotine levels, and higher ratings on "high", "rush",

"liking", and reduced ratings of "craving". Plasma ACTH levels and epinephrine levels were significantly increased following the high-, but not low-, nicotine cigarette. Cortisol levels decreased significantly following the low-nicotine cigarette, and were significantly lower than following the high-nicotine cigarette. DHEA levels were significantly reduced following the low-nicotine cigarette, and significantly increased following the high-nicotine cigarette. Both cigarette types were associated with increased heart rate, with the high-nicotine cigarette producing a significantly higher elevation than the low-nicotine cigarette. The high-yield cigarette was also associated with increased blood pressure. Given that nicotine produced dose-related effects on HPA hormones, the authors conclude that activation of the HPA axis may contribute to the abuse-related effects of cigarette smoking. Mendelson, J.H., Sholar, M.B., Goletiani, N., Siegel, A.J. and Mello, N.K. Effects of Low- and High-nicotine Cigarette Smoking on Mood States and the HPA Axis in Men. Neuropsychopharmacology, 30, pp. 1751-1763, 2005.

The Smoking Consequences Questionnaire - Adult (SCQ-A) Test Is Effective When Evaluating Smokers With Psychiatric Conditions

This study examined the factor structure and psychometric characteristics of the SCQ-A in smokers with psychiatric conditions, including mood disorders, PTSD, and non-PTSD anxiety disorders, and psychotic disorders. A confirmatory factor analysis of the instrument indicated that the factor structure derived by the instrument's authors provided an adequate fit to the data. In addition, many of the 10 subscales of the SCQ-A demonstrated adequate internal consistency as assessed by Cronbach's alpha as well as adequate test-retest reliability over the course of 1 week. Based on the data derived from this sample, the SCQ-A has adequate psychometric properties for applications involving smokers with psychiatric conditions. Buckley, T.C., Kamholtz, B.W., Mozley, S.L., Gulliver, S.B., Holohan, D.R., Helstrom, A.W., Walsh, K., Morissette, S.B. and Kassel, J.D. A Psychometric Evaluation of the Smoking Consequences Questionnaire-Adult in Smokers with Psychiatric Conditions. Nicotine and Tobacco Research, 7, pp. 739-745, 2005.

Smoking Urge Affects Time Perception

Smokers were divided into high-urge and low-urge conditions, and were informed they would be allowed to smoke in 2.5 min. Measures of time perception were completed, with high-urge smokers reporting 45 s to pass significantly more slowly than did low-urge smokers. The high-urge smokers from the first experiment anticipated (but did not actually report) that their urges would climb steadily over the next 45 min if they were not permitted to smoke. Another group of high-urge smokers reported their urges over 45 min. These urge ratings did not show the steady rise anticipated by the first group. Results suggest that smoking urge may affect time perception and that craving smokers over-predict the duration and intensity of their own future smoking urges if they abstain. Sayette, M.A., Loewenstein, G., Kirchner, T.R. and Travis, T. Effects of Smoking Urge on Temporal Cognition. Psych Addictive Behavior, 19, pp. 88-93, 2005.

Nicotine Increases Impulsive Choice and May Decrease the Value of Delayed Reinforcers

Dr. Jesse Dallery and colleagues have been investigating the effects of acute and chronic nicotine (vehicle, 0.03, 0.1, 0.3 and 1.0 mg/kg nicotine) on impulsive choice behavior in the rat. In these studies, animals made choices between a one- and a three-pellet reinforcer in a discrete trials procedure, with an increasing delay in receiving the larger reinforcer until the pattern of choices reflected indifference between the two alternatives. The latency to make the

first response of the session increased under the acute 1.0 mg/kg dose, with no consistent differences in the effects of acute and chronic nicotine on response latency and lever pressing during the delays between choices. Acute injections of nicotine dose-dependently increased impulsive responding. After chronic injections, impulsive responding was increased equivalently regardless of dose, and it was increased even in the absence of nicotine. After drug injections were terminated, behavior remained impulsive for about 30 drug-free sessions, and then responding gradually returned to baseline levels. The results suggest that increases in impulsive choice were not due to anorectic effects, response biases or changes in conditioned reinforcement. Thus, nicotine appears to decrease the value of delayed reinforcers. Furthermore, although chronic nicotine exposure produced effects on impulsive choice behavior that were long-lasting, these effects reversed with the passage of time. Dallery, J. and Locey, M.L. Effects of Acute and Chronic Nicotine on Impulsive Choice in Rats. Behavioral Pharmacology, 16, pp.15-23, 2005.

Agonist Pharmacotherapy For Cocaine

N-[1-(2-benzo[b]thiophenyl)cyclohexyl]pi-peridine (BTCP), a potent dopamine reuptake inhibitor, substitutes for the reinforcing effects of cocaine and meets other criteria for possible agonist pharmacotherapeutic potential. Following the methadone model of agonist pharmacotherapy for opiate addiction, potential agonist pharmacotherapeutic agents for cocaine addiction should substitute for the subjective effects of cocaine, but with a slow onset and sustained duration of action. At the same time, such agents should lack priming effects that may induce craving and lead to relapse. A further desirable feature of such an agent would be the ability to prevent craving elicited by cocaine-related stimuli. The purpose of this study was to determine (1) whether BTCP modifies reinstatement of cocaine-seeking elicited by cocaine-related environmental stimuli and (2) whether BTCP itself produces priming effects. Male Wistar rats were trained to associate discriminative stimuli (DS) with cocaine availability (0.25 mg/infusion) versus non-reward and then were subjected to repeated extinction sessions during which cocaine and DS were withheld. Subsequent presentation of the cocaine associated DS produced recovery of cocaine-seeking (i.e., conditioned reinstatement). Most importantly, BTCP (2.5-30 mg/kg; i.p.) did not attenuate the conditioned reinstatement induced by the cocaine DS. Instead, BTCP potentiated this effect at 10 mg/kg. To test whether BTCP, by itself, exerts priming effects, different groups of rats were trained to self-administer cocaine (0.25 mg/infusion) for 2 weeks. After a 2-week extinction period, BTCP (5, 10 and 20 mg/kg, i.p.) was administered during a test session. Compared to vehicle injections, BTCP reinstated cocaine-seeking at all doses, showing that BTCP not only increases cocaine-seeking induced by cocaine-related stimuli but itself produces priming effects following abstinence. The results suggest that, in cocaine abstinent rats, BTCP produces cocaine-like effects. Its value as a pharmacotherapy, in the manner of methadone, is thereby questionable. Martin-Fardon, R., Lorentz, C.U., Stuempfig, N.D. and Weiss, F. Priming with BTCP, a Dopamine Reuptake Blocker, Reinstates Cocaine-seeking and Enhances Cocaine Cue-induced Reinstatement. Pharmacology, Biochemistry and Behavior, 82, pp. 46-54, 2005.

Brief Access To Sweets Protects Against Cocaine Relapse

Previous research has shown that drugs of abuse can lead to a devaluation of natural rewards, associated with decreases in the intake of sweets or food and, conversely, that the availability of natural rewards (e.g., food) can attenuate cocaine self-administration in animals and humans. The present study used rats to investigate whether brief access to a sweet, palatable solution would reduce both cocaine-seeking and drug-induced relapse following a 3-month period of withdrawal. In this experiment rats were taught to lick a tube to self-administer IV cocaine. After two weeks of training, rats were required to make

20 licks (FR20) on the tube for a single infusion (0.33 mg/0.2 ml of cocaine). Sixteen rats acquired stable cocaine self-administration. These rats were then returned to their home cages for a 3-month period of withdrawal. During the subsequent ten day extinction phase of the experiment, matched groups of 8 rats were given 5 min access to either distilled water or to a palatable solution of glucose and saccharin immediately prior to being placed in the test chambers for a 1 hr extinction session. During extinction, responses to the tube did not lead to cocaine infusions. The results indicated that the rats given 5 min access to the sweetened solution licked significantly less during the first four extinction sessions than those given access to distilled water. Thus, a mere 5 min access to a glucose-saccharin solution reduced cocaine seeking during extinction compared to water controls. Next, a reinstatement procedure was used to test for the effects of the palatable solution on relapse. Following extinction, therefore, both groups of rats were tested for tube licking following IP injections of saline and cocaine (5mg/kg) on separate days. Results showed that while cocaine-induced reinstatement was robust in the water group, it was fully prevented by prior access to the palatable solution. These results represent a first step in providing a scientific foundation for developing therapeutic interventions for cocaine seeking and relapse based on alternative rewards. Liu, C. and Grigson, P.S. Brief Access to Sweets Protect Against Relapse to Cocaine-seeking. Brain Research, 1049, pp. 128-131, 2005.

Extended Access To Cocaine May Not Increase the Motivation To Seek Drugs

Extended access to cocaine self-administration leads to increased drug intake and thus may mimic features of uncontrollable, escalated intake in human addiction. Escalated intake produces shifts in the dose response curve for cocaine self-administration, suggesting that sensitivity to reinforcing effects of the drug is enhanced following high intakes. In another behavioral paradigm, extended access in "binges" produces a dysregulated pattern of intake that may represent disrupted behavioral homeostasis. This disruption can be attenuated by manipulating periods of withdrawal and with non-contingent drug administration or stress. Dr. Dave Roberts and his colleagues recently tested animals that had self-administered cocaine on an extended access schedule, in a progressive ratio (PR) operant schedule for cocaine reinforcement. Break-points from these PR schedules, that is, the maximum number of operant responses an animal makes to receive cocaine, are believed to quantify the strength of motivation for drugs. They also tested the effect of varied periods of drug withdrawal on break points for cocaine. Two studies were conducted with rats trained to self-administer 1.5 or 0.75 mg/kg i.v. cocaine (per infusion) over 40 or 20 days under a fixed ratio schedule. Animals trained with the 1.5 dose were tested in a PR schedule after training and then underwent an escalation regimen with this dose for 6 hours per day over 14 days. Rats in the second study were not assessed in the PR schedule after training, but underwent the same escalation fixed ratio schedule for 14 days with 0.75 mg/kg cocaine. Following the escalation procedure in both studies, animals were withdrawn from drug for either one, or seven days. After this forced deprivation rats were tested for break points. Results revealed that even though all animals increased their cocaine intake during the escalation phase, break points for cocaine did not change after either one or seven days of withdrawal. Thus, there was a dissociation between the increased intake of drug and willingness to "work" to obtain it. While the latter is believed to reflect strength of the drug as a reinforcer, the 6 hour escalation paradigm may mimic increased drug consumption seen during addiction, but possibly not an increased motivation to obtain drug. Furthermore, differences between break point shifts assessed in this 6 hour escalation paradigm, and in a binge model of self-administration, indicates that the patterning of drug intake may be important in changes produced in motivation for the drug. Liu, Y., Roberts, D.C.S. and Morgan, D. Effects of Extended-access Self-administration and

Deprivation on Breakpoints Maintained by Cocaine in Rats. Psychopharmacology, 179, pp. 644-651, 2005.

Effects of Reinforcement Contingency On Cocaine-Induced Cognitive Deficits

Chronic cocaine has been associated with cognitive deficits on tasks of executive function that are mediated by the frontal cortex. Animal models have been used to study these deficits and relate the functional impairments to specific cortical regions, and other areas known to be important in working memory circuitry. Dr. Kathleen Kantak has been studying cocaine's effects on tasks mediated by different areas of prefrontal cortex such as the prelimbic subregion, the insular/orbital subregion, and associated regions in hippocampus, dorsal striatum and amygdala. Wistar rats in these studies were taught to self-administer a total of 14-18 mg/kg i.v. cocaine (or saline) over two hours per day, Monday through Friday, for 2 _ months prior to behavioral testing in a radial arm maze. Animals were grouped into triads and tested in the maze over 4 more months of 5 days/week cocaine self-administration. Each triad included one animal that actively self-administered cocaine, and two animals that received passive infusions yoked to the schedule of the self-administering rat -- one getting yoked cocaine, and the other, yoked saline. Behavioral tests were conducted in the following manner: Within 30 min after completion of self-administration, catheters were flushed and all rats were tested individually on three tasks: (1) A visuospatially guided delayed win-shift task that requires a functionally intact prelimbic prefrontal cortex; (2) An odor-guided delayed win-shift task that assesses more lateral aspects of the rodent prefrontal cortex and requires a functionally intact insular/orbital prefrontal region; and (3) A win-shift task, which lacks a delay and requires a functionally intact hippocampus. Results from the self-administration data suggest that cocaine was functioning as a reinforcer in animals responding to receive contingent drug infusions. Results from maze testing revealed no differences for contingency (active or passive infusion) or infusion solution (cocaine or saline) conditions on the visually-guided delayed win-shift task. On the (hippocampally mediated) win-shift task, both groups receiving cocaine - those self-administering and those that were yoked - had shorter session latencies at criterion, but speed or latency to acquire the task was not affected. However, on the odor-guided task, only cocaine animals contingently administering cocaine were impaired. These animals required more sessions to reach criterion on the task and made significantly more errors. These differences reveal that long-term daily exposure to cocaine produces a particular pattern of deficits across multiple memory systems. Similar patterns of cognitive impairment have been observed in human cocaine abusers, who perform poorly on tasks that depend upon the orbitofrontal cortex. Moreover, the new finding from the present study is that contingent exposure impairs the ability to learn a task that depends on prelimbic regions of the frontal cortex. Kantak, K.M., Udo, T., Ugalde, F., Luzzo, C., Di Pietro, N. and Eichenbaum, H.B. Influence of Cocaine Self-administration on Learning Related to Prefrontal Cortex or Hippocampus Functioning in Rats. Psychopharmacology, 181, pp. 227-236, 2005.

Marijuana Produces Changes In Sensitivity To Both Reinforcement and the Risk of Loss

Regular marijuana users score higher than non-users on measures of risky behaviors, include high-risk sexual behaviors. However, it is unknown whether risk taking precedes, or is induced, by marijuana use. Laboratory based investigations can assess risk when volunteers are given a choice between two or more options and one of the options has some probability greater than zero of producing either a reinforcing or an aversive consequences, and the probability of the aversive consequence is unknown at the time the risky option is chosen. This procedure has been used by Dr. Scott Lane and his colleagues

to assess marijuana associated risk behavior in volunteers who report occasional use of this drug (i.e., two to 12 times per month). The subjects of this study had an average of 7.4 uses in the previous 30 days. All participated in four experimental sessions during which they smoked NIDA supplied marijuana cigarettes and placebo cigarettes. Smoked marijuana doses were either one half of a 1.77% (w/w) delta-9-THC cigarette (plus _ placebo), both halves of a 1.77% cigarette, or both halves of a 3.89% cigarette and were administered by the subjects in a paced, cued smoking procedure. Subjects were trained in the computerized risk-taking task, which was a discrete-trial, two-choice procedure. An algorithm produced a constant probability of monetary reinforcement on any given response and selection of any given option required completion of a variable ratio 25 operant schedule to assess drug effects on motor function after which time the outcome was displayed (i.e., earnings or loss). Cardiovascular and subjective, self-report measures verified the well-known physiological and psychological effects of smoked marijuana. Marijuana did not alter response rates and there was no effect of placebo administration. Risky decisions were evaluated by comparing results on the computerized task prior to, and after, smoking each dose of marijuana. Results revealed that there was a significant difference in risk taking between placebo and the highest marijuana dose. Using first-order Markov transition probabilities, it was apparent that following the 3.89% dose of THC, subjects were more likely to persist on the risky option, whether they were winning or losing. Multiple regression analyses suggested that subjects with stronger and deeper inhalation topographies (i.e., greater CO boost, heart rate change, and number of inhalations) had the greatest increase of risk taking with this high dose. The authors suggest that this dose may affect cortical modulation of behavioral inhibition, and that this is the mechanism responsible for increased risk taking responses, but further investigations will be required to determine the biobehavioral substrates for this drug effect. Lane, S.D., Cherek, D. R., Tcheremissine, O.V., Lieving, L.M. and Pietras, C. J. Acute Marijuana Effects on Human Risk Taking. Neuropsychopharmacology, 30, pp. 800-809, 2005.

A Role For mGlu5 Receptors In Drug Reinforcement and Incentive Motivation

Metabatropic glutamate (Glu) receptors have been implicated in the rewarding properties of drugs of abuse such as psychostimulants and nicotine. For example, mice lacking the mGlu5 receptor do not self administer cocaine, and animals treated with a specific antagonist for this site show reduced intake of both cocaine and nicotine while operant responding for food is unaffected. While these findings provide evidence that central metabatropic Glu receptors are important for the reinforcing properties of these drugs, i.v. self-administration paradigms do not allow for examining motivation to consume the drug. Recently, NIDA supported investigators in the laboratory of Dr. Athina Markou have assessed the effects of the mGlu5 antagonist, MPEP, in rats responding to receive nicotine or cocaine under progressive ratio (PR) schedules of reinforcement. Rats were initially trained on fixed ratio schedules until stable self-administration rates were obtained over three weeks, and then switched to a PR schedule that required increasingly greater responses to receive drug infusions. After four days where stable break points were obtained (the response number where animals stop responding for drug), a single day of extinction testing was conducted during which time stimuli previously paired with operant responding for reward were present, but responses were not reinforced by drug infusions or food. Then, PR responding was re-established and animals were tested with 0 thru 9mg/kg MPEP pretreatment, in counterbalanced order. Results show that, as expected, break points decreased on the extinction test day. Break points for the drugs and for food were also significantly decreased by the mGlu5 antagonist, although comparisons at the highest MPEP dose reveal that break points were more disrupted for drug self-administration than for the non-drug reinforcer. These decreases resemble

those seen when animals were tested under extinction conditions without food or drug reinforcement. This outcome suggests that MPEP may be affecting both the motivation to consume drugs of abuse and food. In addition, when break points obtained under extinction conditions were compared to those after the highest dose of MPEP, results suggest that blockade of Glu5 receptors also decreased the motivational properties of secondary reinforcers. While prior studies examining MPEP effects on drug self-administration with fixed ratio schedules suggest that this drug may have pharmacotherapeutic potential for blocking drug reinforcement, the present observations suggest that the Glu5 site may be involved in more general processes of motivation to seek rewards, including behaviors under the control of learned, incentive motivational stimuli. Paterson N.E. and Markou A. The Metabotropic Glutamate Receptor 5 Antagonist MPEP Decreased Break Points for Nicotine, Cocaine and Food in Rats. Psychopharmacology, 179, pp. 255-261, 2005.

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

Research Findings - Behavioral and Brain Development Research

Maternal Cocaine Use During Pregnancy and Physiological Regulation in 4- to 8-Week-Old Infants

In their report on associations between maternal cocaine use during pregnancy and physiological regulation in infants at 4 to 8 weeks of age, Drs. Schuetze and Eiden provided data for 141 mother-infant dyads (77 cocaine-exposed and 64 nonexposed) recruited at birth. Physiological measures of regulation included heart rate (HR) and respiratory sinus arrhythmia (RSA), assessed during a 15-minute period of sleep. Results indicated a dose-dependent relationship between prenatal exposure to cocaine and RSA. The analyses found no evidence that fetal growth or other prenatal exposure to substances mediated this association or that fetal growth or maternal age moderated this association. Analyses did indicate that birth weight (BW), but not birth length (BL), head circumference (HC) or other substance use mediated the association between prenatal exposure to cocaine and HR. In their conclusions, the researchers note that the findings highlight the importance of considering level of exposure when assessing infant outcomes. Schuetze, P. and Eiden, R.D. The Association Between Maternal Cocaine Use During Pregnancy and Physiological Regulation in 4- to 8-Week-Old Infants: An Examination of Possible Mediators and Moderators. Journal of Pediatric Psychology, 31, 2006 (Epub ahead of print, 2005).

Prenatal Drug Exposure and Mother-Infant Interaction

Based on data from the Maternal Lifestyle Study, a multi-site investigation of development following prenatal drug exposure, this report provides findings for mother-infant interactions observed at 4 months infant age. Specifically, the face-to-face still-face (FFSF) paradigm was used, a standardized procedure in which infants engage in face-to-face interaction with the caregiver, and also have to deal with a stressful interaction during which the caregiver becomes poker-faced as well as vocally and gesturally unresponsive. The sample involved 236 cocaine-exposed and 459 non-cocaine-exposed infants (49 were opiate-exposed and 646 non-opiate-exposed). No opiate exposure effects were observed. Mothers of cocaine-exposed infants showed more negative engagement than other mothers. The cocaine-exposed dyads also showed higher overall levels of mismatched engagement states than other dyads, including more maternal negative engagement when the infants were in states of neutral engagement. Infants exposed to heavier levels of cocaine showed more passive-withdrawn negative engagement and engaged in more negative affective matching with their mothers than other infants. The study authors conclude that although effect sizes were small, cocaine exposure, especially heavy cocaine exposure, was associated with subtly negative interchanges,

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which may have a cumulative impact on infants' later development and their relationships with their mothers. Tronick, E.Z., Messinger, D.S., Weinberg, M.K., et al. Cocaine Exposure is Associated with Subtle Compromises of Infants' and Mothers' Social-Emotional Behavior and Dyadic Features of Their Interaction in the Face-to-Face Still-Face Paradigm. Developmental Psychology, 41, pp. 711-722, 2005.

Staff Highlights

Grantee Honors

Prenatal Cocaine/Polydrug Use and Maternal-Infant Feeding Interactions During the First Year of Life

In research conducted at Case Western Reserve University, relationships between prenatal cocaine use and quality of maternal-infant interactions were examined. The Nursing Child Assessment Feeding Scale (NCAFS) was used with a sample of 341 mothers (155 with prenatal cocaine use and 186 without prenatal cocaine use) and their infants at 6.5 and 12 months infant age. Analyses included a number of sociodemographic and maternal covariates, including postnatal substance use. Women who used cocaine during pregnancy were found to be less sensitive to infant cues at 6.5 and 12 months than were non-cocaine-using women. At 6.5 months, heavier prenatal cocaine use was related to less maternal responsiveness to infants. In infants, prenatal cocaine exposure was related to poorer clarity of cues. The investigators found no significant cocaine effects on maternal social-emotional growth fostering, cognitive growth fostering, or infant responsiveness to mother. The study authors note implications of the findings for clinicians and intervention programs. Minnes, S., Singer, L.T., Arendt, R. and Satayathum, S. Effects of Prenatal Cocaine/Polydrug Use on Maternal-Infant Feeding Interactions During the First Year of Life. Developmental and Behavioral Pediatrics, 26, pp. 194-200, 2005.

Cocaine Use During Pregnancy and Preschool Development at 3 Years of Age

In this University of Florida longitudinal cohort study, 154 pregnant cocaine users were recruited and were matched on race, parity, socioeconomic status, and perinatal risk with 154 noncocaine users. The study protocol involves examining development of the children at multiple ages. This report presents findings for the children at 3 years of age based on two measures, the Bayley Scales of Infant Development, and the Vineland Adaptive Behavior Scales (the latter involving caregiver report). A preschool development variable was created, using the Bayley Mental and Psychomotor Development Indices, and the Communication and Motor Skills subscales of the Vineland. Based on structural equation modeling analyses, the researchers concluded that environmental factors accounted for most of the variance in the preschool development variable, and that prenatal cocaine exposure exerted an indirect effect on preschool development through its effect on birth head circumference. Behnke, M., Eyler, F.D., Warner, T.D., et al. Outcome from a Prospective, Longitudinal Study of Prenatal Cocaine Use: Preschool Development at 3 Years of Age. Journal of Pediatric Psychology, 31, 2006 (Epub ahead of print, 2005).

Aggression at Age 5 Years Relative to Prenatal Cocaine Exposure, Gender, and Environmental Risk

In a project conducted by researchers from Robert Wood Johnson Medical School, childhood aggression at age 5 years was examined using a multiple risk model that included prenatal cocaine exposure, environmental risk, and gender as predictors. Aggression was assessed in 206 children using multiple methods, including teacher report, parent report, child's response to hypothetical provocations, and child's observed behavior. Also examined was a composite score that reflected high aggression across contexts. Multiple aspects of the

environment were assessed and quantified using a cumulative environmental risk score. Analyses indicated that a significant amount of variance in each of the aggression measures and the composite was explained by the predictors. The factors that were independently related differed depending on the outcome. Prenatal cocaine exposure, gender, and environmental risk were all related to the composite aggression score. The investigators concluded that prenatal cocaine exposure, being male, and living in a high-risk environment were all predictive of aggressive behavior at 5 years. They also suggested that it is this group of exposed boys at high environmental risk that is most likely to show continued aggression over time. Bendersky, M., Bennett, D. and Lewis, M. Aggression at Age 5 as a Function of Prenatal Exposure to Cocaine, Gender, and Environmental Risk. Journal of Pediatric Psychology, 31, 2006 (Epub ahead of print, 2005).

Mental Health Outcomes of Cocaine-Exposed Children at 6 Years of Age

Case Western Reserve University investigators assessed mental health outcomes for 6-year-old children who were either cocaine-exposed (CE) or not-cocaine-exposed (NCE) during the prenatal period. The sample of 322 children (169 CE and 153 NCE) were enrolled in this longitudinal study since birth. The children were assessed for mental health symptoms (not diagnoses) using the Dominic Interactive (DI), a child self-report measure, and the Child Behavior Checklist (CBCL), reflecting caregiver report of behavioral problems. Results indicated that CE children were more likely to self-report symptoms in the probable clinical range for oppositional defiant disorder (ODD) and attention deficit hyperactivity disorder (ADHD). In contrast, prenatal cocaine exposure was not related to child behavior based on the CBCL. When data were analyzed relative to type of caregiving environment, CE children in adoptive or foster care were rated as having more problems with aggression, externalizing behaviors, and total behavioral problems than NCE children and CE children in maternal or relative care. Also, CE children in adoptive or foster care self-reported more externalizing symptoms than CE children in maternal or relative care and NCE children. Findings could not be attributed to caregiver intelligence or depressive symptoms, or to the quality of the home environment. The investigators noted that although further studies are needed to understand the basis for the more negative ratings by adoptive or foster caregivers of their CE children, the self-report of symptoms by CE children indicates a need for psychological interventions. Linares, T.J., Singer, L.T., Kirchner, H.L., et al. Mental Health Outcomes of Cocaine-Exposed Children at 6 Years of Age. Journal of Pediatric Psychology, 31, 2006 (Epub ahead of print, 2005).

Prenatal Cocaine Exposure and Language Functioning at 6 and 9.5 Years: Moderating Effects of Child Age, Birthweight, and Gender

In this report from an ongoing longitudinal cohort study of development following prenatal drug exposure, results are presented for language functioning at 6 and 9.5 years relative to prenatal cocaine exposure (PCE) and other individual and environmental variables. Analyses involved data for 160 low-income, urban children who completed a standardized language assessment. Based on multivariate longitudinal analyses using generalized estimating equations (GEE), the authors concluded that age, birthweight, and gender moderated the relation between PCE and school-aged children's language. For example, children with PCE had lower receptive language than unexposed children at 6 but not at 9.5 years, lower expressive language if they had lower birthweight, and lower expressive and total language if they were female. Other risk (e.g., violence exposure) and protective factors (e.g., preschool experience) were related to language outcomes regardless of PCE status. Beeghly, M., Martin, B., Rose-Jacobs, R., et al. Prenatal Cocaine Exposure and Children's Language Functioning at 6 and 9.5 Years: Moderating

Effects of Child Age, Birthweight, and Gender. Journal of Pediatric Psychology, 31, 2006 (Epub ahead of print, 2005).

Somatic Complaints in Children and Community Violence Exposure

Dr. Delaney-Black and her colleagues examined the relationship between witnessing or being a victim of community violence and somatic complaints (appetite, sleep, stomachache, and headache) in a sample of 6- and 7- year old urban African-American children recruited before birth. Participants (N= 268) were neighborhood controls from a larger longitudinal study on prenatal substance exposure and school age outcomes and were included in these analyses if they had no prenatal exposure to hard illicit drugs and resided with their biological mothers. Community violence exposure (Things I Have Seen and Heard), stress symptomatology (Levonn), and somatic complaints (teacher- and self-report items) were assessed. Community violence witnessing and victimization were associated with stress symptoms ($r = .26$ and .25, respectively, $p < .001$); violence victimization was related to decreased appetite ($r = .16$, $p. < .01$), difficulty sleeping ($r = .21$, $p< .001$), and stomachache complaints ($r = .13$, $p < .05$); witnessed violence was associated with difficulty sleeping ($r = .13$, $p < .05$), and headaches ($r = .12$, $p < .05$). All associations remained significant after controlling for confounding variables (SES, prenatal alcohol exposure, maternal: current alcohol use, age, marital status, education, psychopathology, life stress; child: gender, number of people living in child's home, history of child abuse, presence of a chronic medical condition, anxiety and depression). Community violence exposure accounted for 10% of the variance in child stress symptoms, and children who had experienced community violence victimization had a 28% increased risk of appetite problems, a 94% increased risk of sleeping problems, a 57% increased risk of headaches, and a 174% increased risk of stomachaches. Results suggest clinicians treating these physical symptoms in children take into consideration exposure to community violence. Bailey, B.N., Delaney-Black, V., Hannigan, J.H., Ager, J., Sokol, R.J., and Covington, C.Y., J Dev Behav Pediatrics, 26(5), pp. 341-348, 2005.

The Effects of Hepatitis C, HIV, and Methamphetamine Dependence on Neuropsycho-logical Performance

Dr. Scott Letendre and his colleagues at the San Diego HIV Neurobehavioral Research Center examined the important question of the effects of hepatitis C virus (HCV) infection on neuropsychological (NP) performance while taking into consideration HIV serostatus and methamphetamine dependence. The researchers performed a cross-sectional analysis of a prospectively enrolled cohort of 239 HIV-seropositive and 287 HIV-seronegative subjects. In this study HCV-seropositive subjects performed worse on neuropsychological testing and were almost twice as likely to be diagnosed as globally impaired, compared with those who were HCV seronegative. Notably, in a multivariate analysis, HCV, HIV, and methamphetamine dependence were independently associated with worse performance, even after adjusting for Centers for Disease Control stage and antiretroviral use. HCV-RNA levels in plasma were higher in those with memory, but not global, impairment. In cerebrospinal fluid, HCV RNA was below 100 copies/ml in all specimens. In HIV-infected subjects, HCV was associated with higher levels of HIV RNA in CSF, but not in plasma. HCV was also associated with higher levels of monocyte chemotactic protein 1, TNF-alpha, and soluble TNF receptor II. HCV-seropositive subjects did not appear to have advanced liver disease. The authors conclude that HIV, HCV, and methamphetamine independently injure the central nervous system, leading to global neuropsychological impairment. HCV may injure the brain by viral or immune-mediated mechanisms. HCV-associated brain injury may be preventable or reversible because HCV infection is potentially curable. Letendre, S.L., Cherner, M., Ellis, R.J., Marquie-Beck, J., Gragg, B., Marcotte,

T., Heaton, R.K., McCutchan, J.A., and Grant, I., AIDS, Suppl 3, pp. S72-78, 2005.

Risk-Taking Propensity Across Adolescent Ever- and Never-Smokers

Dr. Carl Lejuez and his colleagues at the University of Maryland developed a computerized behavioral test to measure propensity for risk-taking called the Balloon Analogue Risk Task (BART). Recent research with the BART examined the relationship between risk propensity (measured by BART) and smoking status (ever-smoking (i.e., even one puff) versus never-smoking) in a sample of 125 predominantly African American high-school adolescents (M = 15.1, SD = 1.5). Results indicated that ever-smokers and never-smokers differed on risk-taking propensity; further risk-taking propensity was related to smoking status above and beyond both demographic variables (age and gender) and a measure of self-reported impulsive sensation seeking. Results point to the potential utility of a multimethod assessment approach (i.e., self-report measures and behavioral tasks) to identify adolescents' risk-taking susceptibilities and engagement in smoking and other risk-taking behaviors. Lejuez, C.W., Aklin, W., Bornovalova, M. and Moolchan, E.T., Nicotine Tobacco Research, 7(1), pp. 71-79, 2005.

Modeling Behavior in a Clinically Diagnostic Sequential Risk-Taking Task

As part of on-going research on the validity and clinical utility of the Balloon Analogue Risk Task (BART), researchers at the University of Maryland conducted analyses to model the cognitive processes underlying learning and sequential choice on this risk-taking task. These analyses were conducted to understand how these cognitive processes occur in a moderately complex environment and how these behaviors relate to self-reported real-world risk taking. The best stochastic model assumes that participants incorrectly treat outcome probabilities as stationary, update probabilities in a Bayesian fashion, evaluate choice policies prior to rather than during responding, and maintain constant response sensitivity. The model parameter associated with subjective value of gains correlates well with external risk taking. Both the overall approach, which can be expanded as the basic paradigm is varied, and the specific results provide direction for theories of risky choice and for understanding risk taking as a public health problem. Wallsten, T.S., Pleskac, T.J., and Lejuez, C.W., Psychological Review, 112(4), pp. 862-880, 2005.

fMRI Reveals Alterations in Spatial Working Memory Networks Across Adolescence

Dr. Susan Tapert and her colleagues at the University of California - San Diego have used functional neuroimaging to characterize the development of spatial working memory in adolescents. Their findings show that the frontal and parietal networks that are involved in working memory change over the course of adolescence, with activation of the left prefrontal and bilateral inferior posterior parietal regions increasing with age and activation of bilateral superior parietal cortex decreasing. Their data also demonstrate gender differences, with males showing greater activation of the anterior cingulate cortex and frontopolar cortex than females. Over the age range tested, there were no differences in performance on the working memory task, suggesting that the alterations in activation patterns with age represent the evolution of the strategies used in the task. Schweinsburg, A.D., Nagel, B.J. and Tapert, S.F. J. Int. Neuropsych. Soc. 11, pp. 631-644, 2005.

Event-related Potentials in Cocaine-Exposed Children During a

Stroop Task

Dr. Linda Mayes and her colleagues used high-density event related potential (ERP) recording to compare the performance of 8 year old children exposed in utero to cocaine to non-drug exposed children on a task that measures frontal lobe function and inhibitory control. Their findings showed that children that had been exposed to cocaine during gestation committed more errors on the task and responded more slowly during the task than children that had not been exposed. The pattern of the evoked responses also differed in the 2 groups of 8 year olds, with the children that had been exposed to cocaine activating different brain areas, and having more extensive activation, than the non-exposed children. Dr. Mayes and her colleagues hypothesize that early cocaine exposure may alter the process of regional brain specialization leading to slower task processing, the involvement of more cortical areas in accomplishing a task, and more time to complete the task. Mayes, L.C., Molfese, D.L., Key, A.P.F. and Hunter, N.C. Neurotoxicology and Teratology. 27, pp. 797-813, 2005.

Axial Asymmetry of Water Diffusion in Brain White Matter

Dr. Andrew Alexander and colleagues at the University of Wisconsin-Madison have analyzed the directions of water diffusion in the white matter tracts of the human brain that are oriented orthogonal to the major diffusivity direction. Their analysis shows that differences in diffusion patterns of the minor diffusivity directions may be a function of the fine structure of the white matter tracts, such as merging or diverging or crossing fibers. These patterns may be useful in detecting subtle changes in white matter structure as a result of injury or disease. These authors have also shown that the methods developed are sensitive to changes in the structural organization caused by infiltrative disease. Lazar, M., Lee, J.H., and Alexander, A.L., Magnetic Resonance in Medicine. 54, pp. 860-867, 2005.

Contributions of the Hippocampus and the Striatum to Simple Association and Frequency-based Learning

Dr. B.J. Casey and colleagues used fMRI to investigate the regions of the brain that are involved in learning simple associations and frequency-based learning. Their data suggest that the caudate nucleus activates to signal that an unexpected (i.e., infrequent) stimulus has occurred, supporting the hypothesis that the caudate nucleus is tuned to detect the occurrence of an unexpected event. The hippocampus was activated preferentially when an unexpected stimulus pairing, or association, occurred and its activation diminished as the stimulus pairings became more frequent. Thus both structures are involved in learning but they activate in response to different learning contexts. Amso, D., Davidson, M.C., Johnson, S.P., Glover, G., and Casey, B.J. Neuroimage. 27, pp. 291-298, 2005.

Mapping Cerebellar Vermal Morphology and Cognitive Correlates in Prenatal Alcohol Exposure

A number of previous studies have documented alterations in cerebral morphology in individuals exposed prenatally to alcohol and related these alterations to cognitive deficits. In this study, Dr. Elizabeth Sowell and colleagues used sophisticated surface-based morphometric techniques and neuropsychological measures to characterize the cerebellar vermis in prenatally-exposed children and adolescents. Alcohol-exposed study participants had significant reductions in the anterior and posterior cerebellar vermis and the alterations in anterior vermal morphology were correlated with a reduction in performance in verbal learning and memory tasks. O'Hare, E.D.,

Kan, E., Yoshii, J., Mattson, S.N., Riley, E.P., Thompson, P.M., Toga, A.W. and Sowell, E.R. Neuroreport. 16, pp. 1285-1290, 2005.

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

Research Findings - Clinical Neuroscience Research

Cue-Induced Stress Increases Craving and HPA Responses in More Frequent Users of Cocaine and Alcohol Relative to Less Frequent Users

Rajita Sinha and colleagues provided stressful or drug-related (and neutral) scripts of personal relevance to treatment-seeking cocaine dependent patients followed by self-report assessment of craving and anxiety as well as physiological measures including those associated with the HPA axis (e.g., heart rate, blood pressure, cortisol, ACTH). Results demonstrated that the more frequent users had enhanced drug craving and subjective anxiety plus a hypersensitivity to the HPA axis measured by increases in ACTH, cortisol, and prolactin (compared to a neutral condition). These findings suggest a facilitation of neuroendocrine response and may indicate an increased vulnerability whereby induced stress may enhance drug-taking in the first place and hasten relapse in those seeking treatment. Fox, H.C., Talih, M., Malison, R., Anderson, G.M., Kreek, M.J. and Sinha, R. Psychoneuroendocrinology, 30, pp. 880-891, 2005.

Treatment-Engaged Cocaine Patients Different in Brain Areas Activated in a Cue-Induced Stress Paradigm

Sinha and colleagues used fMRI BOLD to assess activation in cocaine patients in treatment while they listened to a personalized script description of a stressful event in their lives. Compared to controls, there was less activation in the anterior cingulate region, left hippocampal/parahippocampal region right fusiform gyrus, and the right postcentral gyrus. The patients had increased activity in the caudate and dorsal striatum; these activations were significantly associated with stress-induced craving ratings. The results are interpreted as patients having reduced control of emotion and distress during stress but increased reward circuitry which may be related to craving. Sinha, R., Lacadie, C., Skudlarski, P., Fulbright, R.K., Rounsaville, B.J., Koston, T.R., and Wexler, B.E. Psychopharmacology, Online: DOI 10.1007/s00213-005-0147-8, September 15, 2005.

Evidence for a Molecular Genetic Basis for Comorbidity between Dependence Vulnerability and Antisocial Behavior

Stallings and colleagues in Crowley's group used symptom counts in a Quantitative Trait Locus analysis in clinic-referred adolescents to search for a common gene or genes underlying both dependence vulnerability and conduct disorder symptoms. In single and multiple point analysis, the strongest peak was observed on chromosome 9q34 (near markers D9S1826 and D9S1838)

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with a LOD score of 2.65. Another peak for comorbidity was found on chromosome 3 though the larger contribution came from dependence vulnerability alone. A third peak for conduct disorder symptoms was found on chromosome 17. These data demonstrate a possible underlying etiology for these comorbid conditions. Stallings, M.C., Corley, R.P., Dennehey, B., Hewitt, J.K., Krauter, K.S., Lessem J.M., Mikulich-Gilbertson, S.K., Rhee, S.H., Smolen, A., Young, S.E., and Crowley, T.J. Archives of General Psychiatry, 62, pp. 1042-1051, 2005.

ADH4 Gene Variation is Associated With Alcohol and Drug Dependence

In a follow-up study Gelernter and associates confirmed a previously reported association between alcohol and drug dependence and the ADH4 gene after controlling for population stratification and admixture effects. In addition, seven SNPs at the ADH4 locus were genotyped; those at SNP2 (rs1042363) were significantly associated with drug (mainly cocaine) dependence as well as alcohol dependence. Also, one seven-variant haplotype and one diplotype were significantly associated with alcohol dependence and other seven-variant diplotypes were significantly associated with drug dependence-both opiate and cocaine. It is concluded that variation at ADH4 predisposes to alcohol and drug dependence. Luo, X., Kranzler, H.R., Lingjun, Z., Yan, B., Lappalainen, J. and Gelernter, J. Pharmacogenetics and Genomics, 15, pp. 755-768, 2005.

Sleep Quality Deteriorates During Abstinence From Binge Cocaine

In a collaboration between J. Allan Hobson of Harvard and the late Marian Fischman of Columbia, several aspects of sleep and sleep architecture were investigated in a 3-week, inpatient protocol where chronic cocaine users were given binge doses of cocaine followed by 2 weeks abstinence. Sleep monitors demonstrated deterioration in several aspects of sleep including, total sleep time, sleep efficiency, and sleep onset time. However, in spite of these objective measures of deteriorating sleep, the subjects did not report them subjectively. This was true even though some of the measures fell within the range of insomnia patients. Also shortened REM latency was in the range reported for patients with major depression. These data cannot distinguish whether these sleep disturbances preceded chronic cocaine use or were consequences of it. However, since similar neurotransmitter systems are involved (e.g., the dopamine system), further studies are encouraged of sleep disturbances in relation to drug-taking. Pace-Schott, E.F., Stickgold, R., Muzur, A., Wigren, P.E., Ward, A.S., Hart, C.L., Clarke, D., Morgan, A. and Hobson, J.A. Psychopharmacology, 179, pp. 873-883, 2005.

Further Evidence Where Brain Activation in Cannabis Abusers is Adversely Affected

Sinha and colleagues assessed cerebral activation using BOLD during a script-guided stress-inducing script in cocaine dependent individuals. When the group was divided into those who also were or were not concurrent cannabis abusers, it was demonstrated that the cannabis users had hypo-activation in frontal areas in the perigenual anterior cingulate during increased emotional stress. These results were found despite similar changes in physiological and behavioral anxiety measures during the script-induced emotional stress imagery. It is concluded that cannabis has a specific effect when taken together with cocaine in cocaine abusers. Li, C-s., R. Milivojenic, V., Constable, R.T. and Sinha, R. Psychiatry Research: Neuroimaging, 140, pp. 271-280, 2005.

fMRI-Acoustic Noise Alters Brain Activation During Working

Staff Highlights

Grantee Honors

Memory Tasks

Chang and colleagues at University of Hawaii studied the effects of scanner noise during functional magnetic resonance imaging (fMRI) to determine level of interference with brain function and change blood oxygenation level dependent (BOLD) signals. The effect of increased acoustic noise on fMRI during verbal working memory (WM) processing was studied with the sound pressure level of scanner noise increasing from ''Quiet'' to ''Loud'' echo planar imaging (EPI) scans. A WM paradigm with graded levels of task difficulty was used to further access WM load. Increased scanner noise produced increased BOLD responses (percent signal change) bilaterally in the cerebellum, inferior (IFG), medial (medFG), and superior (SFG) frontal, fusiform (FusG), and the lingual (LG) gyri, and decreased BOLD responses bilaterally in the anterior cingulate gyrus (ACG) and the putamen. This finding suggests greater recruitment of attention resources in these brain regions, probably to compensate for interference due to louder scanner noise. Increased working memory load increased the BOLD signals in IFG and the cerebellum, but decreased the BOLD signals in the putamen and the LG. These findings also support the idea that brain function requires additional attention resources under noisier conditions. Load- and acoustic-noise-related changes in BOLD responses correlated negatively in the WM network. This study demonstrates that MR noise affects brain activation pattern. Future comparisons between studies performed under different acoustic conditions (due to differing magnetic field strengths, pulse sequences, or scanner manufacturers) might require knowledge of the sound pressure level of acoustic noise during fMRI. Tomasi, D., Carperelli, E.C., Chang, L., Ernst, T. Neuroimage, 27, pp. 377-386, 2005.

Cerebral Metabolic Dysfunction and Impaired Vigilance in Recently Abstinent Methamphetamine Abusers

London and colleagues at UCLA assessed cerebral glucose metabolism (rCMRglc) with [F-18]fluorodeoxyglucose positron emission tomography in 17 abstinent (4 to 7 days) methamphetamine (MA) users and 16 control subjects performing an auditory vigilance task and obtained structural magnetic resonance brain scans. Error rates on the task were related to rCMRglc and hippocampal morphology. MA abusers had higher error rates than control subjects on the vigilance task. The groups showed different relationships between error rates and relative activity in the anterior and middle cingulate gyrus and the insula. Whereas the MA user group showed negative correlations involving these regions, the control group showed positive correlations involving the cingulate cortex. Across groups, hippocampal metabolic and structural measures were negatively correlated with error rates. Dysfunction in the cingulate and insular cortices of recently abstinent MA abusers contribute to impaired vigilance and other cognitive functions requiring sustained attention. Hippocampal integrity predicts task performance in methamphetamine users as well as control subjects. London, E.D., Berman, S.M., Voytek, B., Simon, S., Mandelkern, M.A., Monterrosa, J., Thompson, P.M.., Brody, A.L., Geagas, J.A., Hong, M.S., Hayashi, K.M., Rawson, R.A., Ling, W. Biological Psychiatry, 58(10), pp. 770-778, 2005.

Neurocognitive Features of HCV Infection in Drug Users: Potential Challenges and Lessons Learned

Gonzalez and colleagues at the University of Illinois, Chicago, conducted a review of the literature on similarities between human immunodeficiency virus (HIV) and HCV infection in their neurocognitive features. Injection drug users are at high risk of acquiring HCV infection, and the majority of HCV-infected persons are substance dependent. Examining neurocognitive functions among

HCV positive substance-dependent persons is a challenging, but by no means impossible, endeavor. Experiences from investigations of HIV infection and neurocognition, which have a relatively long scientific history, may help in providing direction for future investigations of HCV infection. They discuss challenges associated with research among drug users, advocate that the HIV literature can usefully inform studies of HCV, and review their own findings on neurocognition among substance users with HIV and/or HCV infection. Gonzalez, R., Jacobus, J., Martin. E.M. Clinical Infectious Disease; 41 Suppl. 1, pp. S45-S49, 2005.

Association Between Smoking and ADHD in Young Adults

Scott and colleagues at Duke University evaluated the relation between smoking-related variables and the number of retrospectively reported ADHD inattentive and hyperactive/ impulsive symptoms in a sample of young adults. The study population consists of 15,197 eligible participants from wave III of the National Longitudinal Study of Adolescent Health, a nationally representative sample of adolescents followed from 1995 to 2002. Logistic regression was used to examine the relation between self-reported ADHD symptoms and the lifetime likelihood of being a regular smoker, defined by having smoked at least 1 cigarette a day for 30 days. For individuals reporting regular smoking, the extent to which ADHD symptoms predicted age at onset of regular smoking was related to the number of cigarettes smoked: A linear relation was identified between the number of self-reported inattentive and hyperactive/impulsive symptoms and smoking outcome measures. Controlling for demographic and conduct disorder symptoms, each reported inattention and hyperactivity/impulsivity symptom significantly increased the likelihood of regular smoking. For those reporting lifetime regular smoking, reported symptoms decreased the estimated age at onset and increased the number of cigarettes smoked: Self-reported ADHD symptoms were found to be associated with adult smoking outcome variables in this nationally representative sample, providing further evidence of a likely link between ADHD symptoms and risk for tobacco use. Scott H., Kollins, S.H., McClernon, F.J. and Fuemmeler, B.F. Archives General Psychiatry. 62, pp. 1142-1147, 2005.

Frontal Glucose Hypometabolism in Abstinent Methamphetamine Users

Renshaw and colleagues at McLean Hospital and in Korea examined changes in relative regional cerebral glucose metabolism (rCMRglc) and potential gender differences in abstinent methamphetamine (METH) users. Relative rCMRglc was measured by 18F-fluorodeoxyglucose PET. Frontal executive functions, as assessed by Wisconsin card sorting test (WCST), were compared between 35 abstinent METH users and 21 healthy comparison subjects. In addition, male and female METH users and their gender-matched comparison subjects were compared to investigate potential gender differences. METH users had lower rCMRglc levels in the right superior frontal white matter and more perseveration and nonperseveration errors in the WCST, relative to healthy comparison subjects. Relative rCMRglc in the frontal white matter correlated with number of errors in the WCST in METH users. In the subanalysis for gender differences, lower rCMRglc in the frontal white matter and more errors in the WCST were found only in male METH users, not in female METH users, relative to their gender-matched comparison subjects. The current findings suggest that METH use causes persistent hypometabolism in the frontal white matter and impairment in frontal executive function. These findings also suggest that the neurotoxic effect of METH on frontal lobes of the brain might be more prominent in men than in women. Kim, S.J., Lyoo, I.K, Hwang, J., Young, H.S., Lee, H.L, Lee, D.S., Jeong, D. and Renshaw P. Neuropsychopharmacology, 30, pp. 1383-1391, 2005.

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

Streeter and colleagues at McLean Hospital measured changes in GABA levels in cocaine dependent (CD) subjects at baseline and after 8 weeks of treatment with pramipexole, venlafaxine, or placebo using proton (1H) magnetic resonance spectroscopy (MRS). CD subjects enrolled in a treatment trial for cocaine dependence were recruited for this study. GABA levels in the prefrontal lobe were measured before and after treatment. Mean percentage changes in GABA levels were as follows: Pramipexole +17.0±28.0%, venlafaxine +13.0±11.0%, and placebo _2.1±19.5%. Pramipexole-treated subjects had significantly increased brain GABA levels compared to placebo ($p=0.031$). Venlafaxine treatment was not significantly associated with increased GABA levels compared to placebo. The overall effect of drug treatment vs. placebo on brain GABA levels, including adjustment for baseline levels, was highly significant. Despite significant changes in GABA levels, there were no significant differences in the number of urine samples positive for cocaine metabolites. This study demonstrates that 1H MRS can measure changes in GABA levels following pharmacologic treatment. The increase in GABA levels, although significant, is modest compared to other MRS studies of depression or epilepsy associated with clinical improvements. The failure to see larger increases in GABA levels and an associated reduction in cocaine consumption may reflect the relatively low doses of medication used. Streeter, C.C., Hennen, J., Ke. Y., Jensen, J.E., Sarid-Segal O., Nassar, L.E., Knapp, C., Meyer, A.A., Twak, T., Renshaw, P. and Ciraulo, D.A. Psychopharmacology, 182, pp. 516-526, 2005.

Increased White Matter Hyperintensities in Male Methamphetamine Abusers

Renshaw and colleagues at McLean Hospital and in Korea used structural MRI to compare the prevalence, severity, and location of white matter signal hyperintensities (WMH) in methamphetamine (METH) abusers. Thirty-three METH abusers and 32 age- and gender-matched healthy comparison subjects were studied. Axial T-2 weighted images and fluid attenuated inversion recovery axial images were obtained using a 3.0 T MR scanner. The severity of WMH was assessed separately for deep and periventricular WMH. Ordinal logistic regression models were used to assess the odds ratio for WMH. The METH abusers had greater severity of WMH than the healthy comparison subjects (odds ratio: 7.06, 8.46, and 4.56 for all, deep, and periventricular WMH, respectively). Severity of deep WMH correlated with total cumulative dose of METH. Male METH abusers had greater severity of WMH than female METH abusers. Although male METH abusers had greater severity of WMH than male comparison subjects, there was no significant difference in WMH severity between female METH abusers and female comparison subjects. The current study reports increased WMH in METH abusers, which may be related to METH-induced cerebral perfusion deficits. In addition, female METH abusers had less severe WMH than male METH abusers, possibly due to estrogen's protective effect against ischemic or neurotoxic effects of METH. Bae, C.S, Lyoo, I.K., Sung, Y.H., Yoo, J., Yoon, C.S.J., Kimd, D-J., Hwang, D.W., Kime, S.J. and Renshaw, P. Drug and Alcohol Dependence, 81, pp. 83-88, 2006.

Functional Neuroanatomical Substrates of Altered Reward Processing in Major Depressive Disorder

Trembly and colleagues at the University of Toronto used fMRI to determine the brain mechanisms of anhedonia in major depressions. The hypothesis that a hypersensitive response to increased dopaminergic function in major depression involves the prefrontal cortex and the striatum was tested by

administration of dextroamphetamine sulfate. FMRI scans were acquired in a single session while the subject performed a simple attention task before and after single-blind administration of a 30-mg dose of oral dextroamphetamine. Twelve depressed subjects (mean age, 34.8 years, male-female ratio, 6), who met criteria for major depressive disorder (MDD) according to the DSM-IV, were not taking antidepressants, and had no comorbid Axis I disorders were compared to twelve healthy control subjects (mean age, 29.3 years, male-female ratio, 5). Dextroamphetamine-induced subjective effects were assessed using the Addiction Research Center Inventory. Subjects with major depression had a 2 fold larger subjective rewarding effects of dextroamphetamine compared to controls. Depressed subjects also had altered brain activation in response to amphetamine in the ventrolateral prefrontal cortex and the orbitofrontal cortex and the caudate and putamen. Theses results demonstrate that dopamine-related neuroanatomical substrates are involved in altered reward processing in MDD, suggesting that self-medication efforts may drive stimulant abuse in subjects with depression. Tremblay, L.K., Naranjo, C.A., Graham, S.J., Herrmann, N., Mayberg, H.S., Hevenor, S. and Busto, U.E. Arch Gen Psychiatry 62(11), pp. 1228-1236, 2005.

The Airway Sensory Impact of Nicotine Contributes to the Conditioned Reinforcing Effects of Individual Puffs from Cigarettes

Naqvi and Bechara at the University of Iowa examined the extent to which reward from cigarette smoking can be derived from the airway sensory effect of nicotine, in the absence of a direct central nervous system effect of nicotine. They measured self-reported increases in reward in response to individual puffs from nicotinized, denicotinized and unlit cigarettes within 7 s of inhalation, which is before nicotine had an opportunity to reach the brain. In addition, self-reported strength of airway sensations elicited by the puffs were obtained. Nicotinized puffs were rated as both stronger and more rewarding than denicotinized and unlit puffs, and the extent to which nicotine elicited reward was directly correlated with the extent to which nicotine elicited airway sensations. These results indicate that the airway sensory effects of nicotine contribute to the reward from puffs, above and beyond the reward derived from the airway sensory effects of non-nicotine constituents. These findings have implications for the interpretation of studies that use puffs as experimental units to examine nicotine reward. They also have implications for the use of denicotinized and low nicotine cigarettes as aids to smoking cessation. Naqvi, N.H. and Bechara, A. Pharmacology Biochemistry and Behavior, 81(4), pp. 821-829, 2005.

Smoking Expectancy Modulates Cue-Elicited Neural Activity

Wilson and colleagues at the University of Pittsburgh used fMRI to identify how brain activity during cue-induced drug craving is modulated by expectations regarding the opportunity to use a drug.. Male cigarette smokers deprived of nicotine for 8 hr were scanned during exposure to neutral (e.g., roll of tape) and smoking-related (a cigarette) stimuli after being instructed that they would or would not be able to smoke after the scans. As predicted, several brain regions (e.g., the anterior cingulate cortex) exhibited differential activation during cigarette versus neutral cue exposure. Moreover, they found that subregions of the prefrontal cortex (i.e., ventromedial, ventrolateral, and dorsolateral prefrontal cortices) showed cue-elicited activation that was modulated by smoking expectancy. These results highlight the importance of perceived drug use opportunity in the neurobiological response to drug cues. Wilson, S.J., Sayette, M.A., Delgado, M.R. and Fiez, J.A. Nicotine Tob Res., 7(4), pp. 637-645, 2005.

Abstinence-Induced Changes In Self-Report Craving Correlate With Event-Related fMRI Responses to Smoking Cues

McClernon and colleagues at Duke University used event-related fMRI to evaluate the stability of event-related responses to visual drug cues following smoking-as-usual and following overnight abstinence. In addition, self-reported craving measures were obtained before, during, and after scanning. Thirteen regions of interest were selected for analysis in a cohort of 13 dependent smokers. Responses to smoking cues were larger than to control cues in ventral anterior cingulate gyrus (vACG) and superior frontal gyrus. Responses to smoking cues in these and all other regions revealed no effects of abstinence/satiety, thus supporting the notion that cue-elicited brain responses are relatively stable. However, while the abstinence manipulation did not alter group-level responses to smoking cues, at the individual level, abstinence-induced changes in craving (abstinence minus satiety) were positively correlated with changes in fMRI response amplitude to smoking cues in frontal regions including left inferior frontal gyrus, left vACG, and bilateral middle frontal gyrus. These results suggest that brain responses to smoking cues, while relatively stable at the group level following short-term abstinence, may be modulated by individual differences in craving in response to abstinence-particularly in regions subserving attention and motivation. McClernon, F.J., Hiott, F.B., Huettel, S.A. and Rose, J.E. Neuropsychopharmacology, 30(10), pp. 1940-1947, 2005.

Decision Making, Impulse Control and Loss of Willpower to Resist Drugs: A Neurocognitive Perspective

Based on a review of the literature, Bechara at the University of Iowa concludes that that addicted people become unable to make drug-use choices on the basis of long-term outcome, and proposes a neural framework that explains this myopia for future consequences. He suggests that addiction is the product of an imbalance between two separate, but interacting, neural systems that control decision making, i.e., an impulsive, amygdala system for signaling pain or pleasure of immediate prospects, and a reflective, prefrontal cortex system for signaling pain or pleasure of future prospects. After an individual learns social rules, the reflective system controls the impulsive system via several mechanisms. However, this control is not absolute, because hyperactivity within the impulsive system can override the reflective system. He proposes that drugs can trigger bottom-up, involuntary signals originating from the amygdala that modulate, bias or even hijack the goal-driven cognitive resources that are needed for the normal operation of the reflective system and for exercising the willpower to resist drugs. Bechara, A. Nature Neuroscience 8(11), pp. 1458-1463, 2005.

Modulation of Prefrontal Cortex Activity by Information Toward a Decision Rule

Huettel and Misiurek at the Duke University used fMRI to investigate how the information content of a stimulus influences activity in brain systems that support decision making in healthy subjects. Subjects learned decision rules based upon the color, shape, or fill pattern of a series of stimuli. Each stimulus was classified by its information content, defined formally by the decision rules it excluded. While activity in dorsolateral prefrontal cortex (DLPFC) increased with increasing stimulus information, activity in the striatum did not. In contrast, within both the striatum and DLPFC, stimuli consistent with the rule evoked greater activity than stimuli inconsistent with the rule. This dissociation indicates that DLPFC supports modification of sets of stimulus-response contingencies while the striatum supports stimulus-specific learning. These results provide a foundation to examine how impaired frontal function may

alter specific aspects of decision-making in substance abusers. Huettel S.A. and Misiurek, J. Neuroreport, 15(12), pp. 1883-1886, 2004.

Selective Activation of the Nucleus Accumbens during Risk-Taking Decision Making

Paulus and colleagues at the University of California, San Diego used fMRI to probe the brain circuitry involved in risk-taking decision-making in 12 healthy control subjects. Deliberation prior to selection of safe relative to risky responses generated greater activation in the inferior frontal cortex, superior temporal gyrus, and middle temporal gyrus. In contrast, deliberation prior to selection of risky relative to safe responses generated greater activation in medial frontal cortex, occipital cortex, nucleus accumbens and caudate. Additionally, nucleus accumbens activation correlated positively with the harm avoidance subscale of the Temperament and Character Inventory (TCI) 125. These findings may provide target neural systems to study in substance abusing subjects who exhibit problematic risk-taking behaviors. Matthews S.C, Simmons A.N., Lane, S.D., Paulus, M.P. Neuroreport, 15(13), pp. 2123-2127, 2004.

Reward Sensitivity in Impulsivity

Potts and Martin at Rice University used even-related potentials to investigate the neural basis of impulsivity as expressed as choosing immediate small over delayed larger rewards. The anterior P2a event-related potential component was used as an index of reward-related orbitofrontal activity. In subjects higher on self-reported impulsiveness, the P2a was largest to non-predicted rewards and smallest in the absence of predicted rewards, consistent with the hypothesis of reward hypersensitivity in impulsivity. Martin L.E. and Potts, G.F. Neuroreport ,15(9), pp. 1519-1522, 2004.

MDMA Affects Both Error-Rate Dependent and Independent Aspects of Decision-Making in a Two-Choice Prediction Task

Paulus and colleagues examined whether MDMA alters decision-making in a way that depends on the manipulations of error rate, i.e., the degree of success and outcome. Forty-two normal, healthy volunteers were given placebo or 1.5 mg/kg p.o. MDMA in a randomized crossover design. Subjects completed the two-choice prediction task 120 min after administration of the drug. Decision-making characteristics were obtained at 20% error rate, 50% error rate or 80% error rate. MDMA did not significantly alter basic response characteristics such as response latency or switching. Rather, MDMA effects on decision-making were dependent on the error rate. MDMA increased the degree to which the previous stimulus influenced the selection of the current response at 20%, 50% or 80% error rate. At low error rates (i.e., high success rates), administration of MDMA increased the degree to which the previous response predicted the current response and the average response sequence predictability. Self-assessment of the psychological state induced by MDMA did not predict the MDMA induced decision-making patterns. These results support the hypothesis that acute administration of MDMA affects success-related response selection during decision-making. These results suggest that MDMA abuse may increase the likelihood of engaging in risky behavior mainly under conditions of initial success. Vollenweider, F.X., Liechti, M.E. and Paulus, M.P. Journal of Psychopharmacology, 19(4), pp. 366-374, 2005.

Probing Reward Function in Post-Traumatic Stress Disorder with Beautiful Facial Images

Elman and colleagues at McLean Hospital investigated dysfunction of reward

processing in post-traumatic stress disorder (PTSD). Male heterosexual Vietnam veterans with (n = 12) or without (n = 11) current PTSD were administered two tasks: (a) key pressing to change the viewing time of average or beautiful female or male facial images, and (b) rating the attractiveness of these images. There were no significant group differences in the attractiveness ratings. However, PTSD patients expended less effort to extend the viewing time of the beautiful female faces. These findings suggest a reward deficit in PTSD, and may contribute to the high incidence of substance abuse in patients with PTSD. Elman, I., Ariely, D., Mazar, N., Aharon, I., Lasko, N.B., Macklin, M., Orr, S.P., Lukas, S.E. and Pitman, R.K. Psychiatry Research, 135(3), pp. 179-183, 2005.

Quantitative PET Studies of the Serotonin Transporter in MDMA Users and Controls Using [C-11]Mcn5652 and [C-11]DASB

McCann and colleagues at Johns Hopkins Medical School used a novel PET ligand to follow-up on their initial report of loss of serotonergic makers in humans MDMA abusers. In the present study, 23 abstinent MDMA users and 19 non-MDMA controls underwent quantitative positron emission tomography (PET) studies using [C-11]McN5652 and [C-11]DASB, first- and second-generation serotonin transporter (SERT) ligands previously validated in baboons for detecting MDMA-induced brain serotonin neurotoxicity. Global and regional distribution volumes and two additional SERT-binding parameters were compared in the two subject populations using parametric statistical analyses. Strong correlations existed between the various binding parameters of [C-11] McN5652 and [C-11]DASB, both in individual brain regions and individual subjects. Global SERT reductions were found in MDMA users with both PET ligands, using all three of the above-mentioned SERT-binding parameters. Preplanned comparisons in 15 regions of interest demonstrated reductions in selected cortical and subcortical structures. Exploratory correlational analyses suggested that SERT measures recover with time, and that loss of the SERT is directly associated with MDMA use intensity. These quantitative PET data, obtained using validated first- and second-generation SERT PET ligands, provide strong evidence of reduced SERT density in some recreational MDMA users. McCann, U.D., Szabo, Z., Seckin, E., Rosenblatt, P., Mathews, W.B., Ravert, H.T., Dannals, R.F. and Ricaurte G.A. Neuropsychopharmacology, 30(9), pp. 1741-1750, 2005.

Regional Activation in the Striatum Is Related to Successful Learning in an Implicit Cognitive Task

Paulus and colleagues at the University of California, San Diego used fMRI to test whether striatal involvement in implicit learning depends on successful learning. Fifteen healthy normal subjects performed an implicit learning task, i.e., a task where subjects acquire a behavior without being necessarily aware of the rules governing the behavior. Dorsal and ventral striatum activation was observed in the eight participants who demonstrated implicit learning. Ventral striatum activations occurred to a greater extent in implicit learning versus non-implicit learning participants, and were correlated with the degree of reaction time advantage in implicit learning participants, even after controlling for general decreases in reaction time over time. These findings strengthen the specificity of the striatum in implicit learning and are suggestive of a dissociation of striatal regions relative to elements of implicit learning performance. These results provide a foundation for testing for the cognitive consequences of striatal dysfunction in substance abusers. Reiss J.P., Campbell, D.W., Leslie, W.D., Paulus, M.P., Stroman, P.W., Polimeni J.O., Malcolmson K.A. and Sareen, J. Neuroreport, 16(12), pp. 1291-1295, 2005.

Mapping Dopamine D2/D3 Receptor Function Using

Pharmacological Magnetic Resonance Imaging

Jenkins and colleagues at Massacheusetts General Hospital used pharmacological magnetic resonance imaging (phMRI) to determine whether regulation of dopamine release and. synthesis occurs via pre-synaptic dopamine (DA) D2/D3 autoreceptors (DARs). They hypothesized that relative cerebral blood volume (rCBV) changes induced by amphetamine could be modulated by DA D2 receptor antagonists and agonists in a manner consistent with modulation of DAR function. The MRI results were then compared to microdialysis under similar conditions. Iron oxide contrast agents were used to map changes in rCBV or dopamine release using microdialysis in response to an amphetamine challenge, pre-treatment and post-treatment with varying doses of the D2 antagonist eticlopride and the D2 agonist quinpirole. Antagonism of D2 receptors with eticlopride potentiated rCBV changes induced by amphetamine in the nucleus accumbens and caudate putamen in a dose-dependent manner. The amphetamine-induced increase in rCBV in the accumbens in animals pre-treated with eticlopride was paralleled by a similar percentage increase in DA release measured by means of microdialysis. Conversely, agonism of D2 receptors using quinpirole reduced amphetamine-induced rCBV changes in the caudate putamen and nucleus accumbens. The effects of both quinpirole and eticlopride on amphetamine-induced rCBV changes were largest in the nucleus accumbens. These results suggest that phMRI may potentially prove useful to map DA receptor function noninvasively in multiple brain regions simultaneously. Chen, Y.C.I., Choi, J.K., Andersen, S.L., Rosen, B.R. and Jenkins, B.G. Psychopharmacology, 180(4), pp. 705-715, 2005.

Startle Modulation during Conscious Emotion Regulation is Arousal-Dependent

LaBar and colleagues at Duke University examined whether conscious regulation of negative emotion affects human eyeblink startle responses through modulation of arousal- or valence-based processes. Healthy, normal control subjects were presented with negative, neutral, and positive pictures and directed to enhance, maintain, and suppress emotional responses. On emotional picture trials, startle responses decreased as a function of cue in the following order, enhance > maintain > suppress. Analysis of negative and positive picture trials separately revealed similar patterns of startle modulation by emotion regulation. There were no effects of emotion regulation on neutral trials. Results indicate that arousal, not valence, may be critical to startle modulation via conscious emotion regulation. These results have implications for understanding the neuronal basis of substance abuse therapies that employ emotional reappraisal approaches, such as cognitive behavioral therapy. Dillon, D.G. and LaBar, K.S. Behavioral Neuroscience, 119(4), pp. 1118-1124, 2005.

Influences of Emotion on Context Memory while Viewing Film Clips

Shimamura and Anderson at the University of California, Berkeley asked healthy normal controls to listen to words while viewing film clips (audio off). Film clips were classified as neutral, positively valenced, negatively valenced, and arousing. Memory was assessed in three ways: 1) recall of film content, 2) recall of words, and 3) context recognition. In the context recognition test, participants were presented a word and determined which film clip was showing when the word was originally presented. In two experiments, context memory performance was disrupted when words were presented during negatively valenced film clips, whereas it was enhanced when words were presented during arousing film clips. Free recall of words presented during the negatively valenced films was also disrupted. These findings suggest multiple

influences of emotion on memory performance. Anderson, L. and Shimamura, A.P. American Journal of Psychology, 118(3), pp. 323-337, 2005.

Impulsivity and Decision Making

Bechara and colleagues at the University of Iowa examined the links among the four facets of impulsivity (urgency, lack of premeditation, lack of perseverance, and sensation seeking) proposed by Whiteside and Lynam (2001) and decision-making processes. Thirty undergraduate students completed a self-report questionnaire evaluating impulsivity as well as a task measuring decision-making processes, the Iowa Gambling Task. Zero-order correlations and multilevel analysis revealed that only lack of premeditation was specifically linked to disadvantageous decisions on the Gambling Task. This suggests that premeditation is related to decision making involving assessment of long term outcomes and consequences. Zermatten, A., Van der Linden, M., d'Acremont, M., Jermann, F. and Bechara, A. Journal Of Nervous And Mental Disease, 193(10), pp. 647-650, 2005.

Concurrent CBF and CMRglc Changes During Human Brain Activation By Combined fMRI-PET Scanning

Detre and colleagues at University of Pennsylvania used a novel approach for concurrent measurement of regional cerebral blood flow (CBF) by MRI and regional cerebral metabolic rate for glucose consumption (rCMRglc) with positron emission tomographic (PET) in humans in normal subjects. F-18-labeled fluorodeoxyglucose was administered during the measurement of CBF by continuous arterial spin labeled magnetic resonance imaging (MRI) while subjects viewed a simple visual stimulus. Subsequent PET scanning demonstrated the distribution of labeled deoxyglucose during the MRI acquisition. An excellent concordance between regional CBF and regional fCMRglc during visual stimulation was found, consistent with previously published PET findings. Although initially validated using a brief, non-quantitative protocol, this approach can provide quantitative CBF and rCMRglc, with a broad range of potential applications in functional physiology and pathophysiology. Newberg, A.B., Wang, J.J., Rao, H.Y., Swanson, RL., Wintering, N., Karp JS., Alavi A., Greenberg, J.H. and Detre, J.A Neuroimage, 28(2), pp. 500-506, 2005.

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

Research Findings - Epidemiology and Etiology Research

Heritability Estimates Unchanged by Changes in Drug Prevalence

Researchers used data from a genetically informed sample to study whether changes in prevalence of drug use has an impact on rates of heritability. The lifetime history of use of tobacco, cannabis, cocaine, sedatives, and stimulants were assessed in 4826 twins from male-male and female-female pairs born in Virginia from 1934 to 1974. Using empirical methods based on prevalence by birth year, these twins were divided into three cohorts for each substance (e.g. for cannabis 1934-1953,1954-1968, and 1969-1974). Structural equation modeling was performed using the Mx software package. Prevalence rates for psychoactive substance use were found to differ substantially across cohorts, most markedly for cocaine, sedatives and stimulants, which were highest in the 1958-1963 cohort. However, for all substances, the best-fit model constrained estimates of the etiological role of genetic and environmental risk factors to be equal across both sex and cohort. That is, there was no evidence in this sample for any systematic relationship between heritability and prevalence of psychoactive substance use. These results suggest that the heritability of substance use may be a relatively stable characteristic of human populations and not highly variable as a result of changing patterns of drug accessibility and consumption. Kendler, K., Gardner, C., Jacobson, K., Neale, M. and Prescott, C. Genetic and Environmental Influences on Illicit Drug Use and Tobacco Use Across Birth Cohorts. Psychol Med, 35(9), pp. 1349-1356, 2005.

Differentiating Risk Factors for Drug Use and Drug Abuse/Dependence

This study asked whether there are risk factors that associate specifically with illicit drug use or illicit drug abuse/dependence, and whether the magnitude of the association is the same for use and abuse/dependence, across different categories of drugs. Data from 1943 female adult twins in a population-based Virginia sample were used to assess the association of 26 putative risk factors with use and abuse/dependence of six illicit psychoactive drugs. These factors, which include socio-demographic variables, religiosity, personality measures, childhood factors, and psychiatric diagnoses, were each examined in relation to drug use, abuse/dependence, or both. Several findings are notable: First, factors associate in similar patterns with different drug categories; second, there is a stronger association of significant socio-demographic factors with drug use, while the psychiatric diagnoses are more strongly associated with progression to abuse/dependence. Third, childhood sexual abuse was associated with drug use and with progression to abuse/dependence. This suggests complex, interacting pathways that determine drug habits in individuals. These results are hypothesis generating. Future studies of causal relationships may draw from the outcomes presented in these analyses.

Agrawal, A., Gardner, C., Prescott, C. and Kendler, K. The Differential Impact of Risk Factors on Illicit Drug Involvement in Females. Soc Psychiatry Psychiatr Epidemiol, 40(6), pp. 454-466, 2005.

P300 Amplitude Does Not Mediate Association Between Parental SUD and Offspring Neurobehavioral Disinhibition

This study investigated whether the P300 amplitude of the event-related potential mediates the association between parental substance use disorder (SUD) and child's neurobehavioral disinhibition, a known risk factor for SUD. The P300 amplitude was recorded using an oddball task in sons of fathers having either lifetime SUD (n = 105) or no psychiatric disorder (n = 160). Neurobehavioral disinhibition was assessed using measures of affect regulation, behavior control, and executive cognitive function. Parental SUD and child's P300 amplitude accounted for, respectively, 16.6% and 16.8% of neurobehavioral disinhibition variance. Controlling for parental and child psychopathology, an association between parental SUD and child's P300 amplitude was not observed. It was concluded that the P300 amplitude does not mediate the association between parental SUD and child's neurobehavioral disinhibition. Habeych, M., Sclabassi, R., Charles, P., Kirisci, L. and Tarter, R. Association Among Parental Substance Use Disorder, p300 Amplitude, and Neurobehavioral Disinhibition in Preteen Boys at High Risk for Substance Use Disorder. Psychol Addict Behav, 19(2), pp. 123-130, 2005.

Childhood Risk Categories Predict Adolescent Substance Involvement

Childhood risks for adolescent substance involvement include parental substance use disorders (SUDs), psychological dysregulation and early tobacco and alcohol experimentation. This study was designed to identify childhood risk categories predicting accelerated adolescent substance involvement across drug types and stages. The index subjects were 560 children recruited from high risk (n = 266) or low risk (n = 294) families based on fathers' SUDs. Assessments were conducted at approximately ages 11 (baseline), 13, 16, and 19 years. Childhood predictors included parent SUDs, early tobacco or alcohol use (i.e., substance use), and neurobehavior disinhibition (ND) as determined by indicators of cognitive, affective and behavioral disinhibition. A cluster analysis defined five risk categories based on baseline characteristics as follows: (1) High (n = 31; 100% had both parents with SUDs, 100% had early substance use, and the mean ND score = 58.9); (2) Intermediate-High (n = 76; 45% had one parent with SUD, 100% early substance use and ND = 51.9); (3) Intermediate (n = 76; 100% both parents with SUDs, 0% early substance use and ND = 51.4); (4) Intermediate-Low (n = 161; 100% with one SUD parent; 0% early substance use and ND = 49.9) and; (5) Low (n = 216; no parental SUD, no early substance use and ND = 47.5). Compared with all other groups, children in the High-risk group had significantly accelerated substance involvement across all substance types and stages. The ordering of risk categories from low to high was also consistent for all substance involvement outcomes. The findings indicate that these five risk categories constitute general liability classes for adolescent substance involvement, and may identify homogeneous groups of children requiring distinct preventive interventions. Clark, D., Cornelius, J., Kirisci, L. and Tarter, R. Childhood Risk Categories for Adolescent Substance Involvement: A General Liability Typology. Drug Alcohol Depend, 77(1), pp. 13-21, 2005.

Neurobehavior Disinhibition in Adolescence Predicts Drug Abuse in Adulthood

This study extends prior research by determining whether variation in the

Staff Highlights

Grantee Honors

developmental trajectories of liability to substance use disorder (SUD) is contributed by neurobehavioral disinhibition, parental substance use involvement, and demographic variables. The sample, participants in a long-term prospective investigation, consisted of 351 boys, evaluated at ages 10-12, 12-14, 16, 19, and 22, whose parents either had SUD or no adult psychiatric disorder. Neurobehavioral disinhibition in childhood, in conjunction with parental lifetime substance use/SUD, place the child at very high risk for SUD by age 22 if psychosocial maladjustment progresses in severity in early adolescence. These results indicate that monitoring social adjustment during the transition from childhood to mid-adolescence is important for identifying youth at very high risk for succumbing to SUD by young adulthood. Kirisci, L., Vanyukov, M. and Tarter, R. Detection of Youth at High Risk for Substance Use Disorders: A Longitudinal Study. Psychol Addict Behav, 19(3), pp. 243-252, 2005.

Comorbidity in Adults with ADHD and SUD

The objective of the study was to investigate the characteristics of adults with Attention Deficit Hyperactivity Disorder (ADHD) or substance use disorder (SUD), especially in the context of comorbid psychiatric disorders. Subjects were adults (n = 78) participating in a controlled family study of ADHD and SUD. Four groups were identified based on a diagnosis of ADHD or SUD: ADHD, SUD, ADHD + SUD, and neither ADHD nor SUD. All diagnoses were determined by structured clinical interview for DSM IV. Rates of psychiatric comorbidity were lowest in the controls, intermediate in the ADHD and SUD groups, and highest in the ADHD + SUD group. Relative to controls, the ADHD, SUD, and ADHD + SUD groups had higher rates of major depression, conduct disorder, antisocial personality disorder, agoraphobia and social phobia. Higher rates of psychiatric comorbidity, especially mood and anxiety disorders, exist in subjects with SUD + ADHD relative to subjects with SUD, ADHD, or controls. Clinicians need to be attentive to other psychiatric disorders that may occur in the large group of adults with ADHD + SUD. Wilens, T., Kwon, A., Tanguay, S., Chase, R., Moore, H., Faraone, S. and Biederman, J. Characteristics of Adults With Attention Deficit Hyperactivity Disorder Plus Substance Use Disorder: the Role of Psychiatric Comorbidity. Am J Addict, 14(4), pp. 319-327, 2005.

Risk of Becoming Cocaine Dependent 24 Months After First Use

This study explores estimates for the risk of becoming cocaine dependent within 24 months after first use of the drug, and study subgroup variation in this risk. The study estimates are based on the National Household Survey on Drug Abuse conducted during 2000-2001, with a representative sample of US residents aged 12 years and older (n=114 241). A total of 1081 respondents were found to have used cocaine for the first time within 24 months prior to assessment. Between 5 and 6% of these recent-onset users had become cocaine dependent since onset of use. Less [corrected] risk of recent cocaine dependence soon after onset of cocaine use was found for female subjects, young adults aged 21-25 years, and non-Hispanic Black/African-Americans. Use of crack-cocaine and taking cocaine by injection were associated with having become cocaine dependent soon after onset of use. These epidemiologic findings help to quantify the continuing public health burden associated with new onsets of cocaine use in the 21st century. O 'Brien, M., and Anthony, J. Risk of Becoming Cocaine Dependent: Epidemiological Estimates for the United States, 2000-2001. Neuropsychopharmacology, 30(5), pp. 1006-1018, 2005.

Experimental, Late and Continuous Smoking and Problem Behaviors During Adolescence, Late Adolescence and Early Adulthood

In this study, the authors assessed the relationship between adolescent tobacco smoking and measures of inner control, deviant behavior, and associating with deviant peers, which are indicators of problem behavior. African American (N = 333) and Puerto Rican (N = 329) early adolescents completed questionnaires in their classrooms in 1990 at Time 1 (T1) and were individually interviewed thereafter when they were late adolescents in 1995 at Time 2 (T2) and as young adults in 2000 at Time 3 (T3). The authors used ordinary least squares regression analysis to assess the comparative association of adolescent smoking patterns at T1 and T2 and the young adult outcomes at T3; they controlled for demographic variables, level of the outcome measure at T2, and marijuana use at T2. The analyses suggested that experimental tobacco smokers demonstrated more problem behaviors than did nonsmokers, and late and continuous smokers demonstrated more problem behaviors as young adults than did experimental smokers and nonusers. These findings may provide a useful guide to a next step that involves translational research. Brook, J., Balka, E., Rosen, Z., Brook, D. and Adams, R. Tobacco Use in Adolescence: Longitudinal Links to Later Problem Behavior Among African American and Puerto Rican Urban Young Adults. J Genet Psychol, 166(2), pp. 133-151, 2005.

Community-Based Study of HBV Immunization among Young Adults

A community-based study of the prevalence and correlates of hepatitis B virus (HBV) infection and immunization was conducted among young adults in a "drug supermarket" neighborhood in New York City. Four hundred eighty-nine young adults ages 18-24 years were recruited from Bushwick, Brooklyn through multistage household probability sampling (n = 332) and targeted sampling (n = 157), interviewed, and tested for three hepatitis B markers (HBsAg, anti-HBc, and anti-HBs). Serological evidence of HBV infection was found in 8.0% (6.0% in the household sample and 12.1% in the targeted sample) and of hepatitis B immunization in 19.6% (22.6% in the household sample and 13.4% in the targeted sample). HBV infection was higher among young adults who either used crack or injected drugs and among those who traded sex for money or drugs. Having Medicaid was significantly associated with lower odds of infection in the household sample and higher odds of immunization in the targeted sample. Although adolescent hepatitis B immunization has been a public health priority in the United States since 1995, nearly three-quarters of young adults in this community did not have serological evidence of being either exposed or immunized. Whereas subsequent younger generations benefited from universal childhood hepatitis B immunization, this particular cohort of young adults who live in communities like Bushwick presents a unique group for prevention intervention. Kottiri, B., Friedman, S., Euler, G., Flom, P., Sandoval, M., Neaigus, A., Des Jarlais, D. and Zenilman, J. A Community-Based Study of Hepatitis B Infection and Immunization Among Young Adults in a High-Drug-Use Neighborhood in New York City. J Urban Health, 82(3), pp. 479-487, 2005.

Receptive Syringe Sharing among IDUs during ESAP

Effective January 1, 2001, New York State enacted the Expanded Syringe Access Demonstration Program (ESAP), which allows syringes to be sold in pharmacies without a prescription or dispensed through doctors, hospitals, and clinics to persons 18 years of age or older and permits the possession of those syringes for the purposes of injecting drugs. In this study, researchers assessed changes in receptive syringe sharing since the inception of the ESAP. Sociodemographic characteristics and syringe use data regarding the last injection episode were combined from 3 projects (n = 1181) recruiting injection drug users in ongoing studies in Harlem and the Bronx in New York City from January 2001 through June 2003. These data were analyzed as serial cross

sections by calendar quarter. Findings showed that receptive sharing decreased significantly over time, from 13.4% in the first quarter to 3.6% in the last quarter. Obtaining the last injection syringe from an ESAP source (mostly pharmacies) increased significantly over time, from 7.5% in the first quarter to 25.0% in the last quarter. In multiple logistic regression analysis, variables that were significantly associated with less receptive sharing were syringe exchange and ESAP syringe source as well as time since ESAP inception. Female gender and white race/ethnicity were significantly associated with greater receptive sharing. These data show that the increase in the use of pharmacies and other ESAP syringe sources in this sample has been accompanied by a decline in receptive sharing. Pouget, E., Deren, S., Fuller, C., Blaney, S., McMahon, J., Kang, S., Tortu, S., Andia, J., Des Jarlais, D. and Vlahov, D. Receptive Syringe Sharing Among Injection Drug Users in Harlem and the Bronx During the New York State Expanded Syringe Access Demonstration Program. J Acquir Immune Defic Syndr, 39(4), pp. 471-477, 2005.

Adolescent Rebellion and Academic Failure among High and Low Income Youth

This study addressed whether upper class, suburban teenagers (144 females, 120 males) can engage in various problem behaviors and still maintain adequate academic grades, because of environmental safety nets, unlike their low-income, inner-city counterparts (123 females, 101 males). Three problem behavior dimensions were assessed among tenth graders that is, substance use, delinquency, and low school engagement. Academic achievement was assessed in terms of grades across four major subjects. Variable-based analyses indicated unique links with grades for self-reported delinquency and school disengagement in high- and low-income samples, but for substance use only among the former. Person-based analyses showed that in both schools, grades were clearly compromised among youth with disturbances in all three-problem domains. In addition, in the suburban school only, grades were low in the cluster characterized chiefly by high substance use. Results are discussed in terms of stereotypes regarding risks (or lack thereof) stemming from families' socioeconomic status; implications for theory and interventions are discussed. Luthar, S. and Ansary, N. Dimensions of Adolescent Rebellion: Risks for Academic Failure Among High and Low-Income Youth. Dev Psychopathol, 17(1), pp. 231-250, 2005.

Urban Built Environment and Depression: A Multi-level Analysis

Researchers assessed the relations between characteristics of the neighborhood internal and external built environment and past six month and lifetime depression. Depression and sociodemographic information were assessed in a cross sectional survey of residents of New York City (NYC). All respondents were geocoded to neighborhood of residence. Data on the quality of the built environment in 59 NYC neighborhoods were collected from the United Status census, the New York City housing and vacancy survey, and the fiscal 2002 New York City mayor's management report. Among 1355 respondents, residence in neighborhoods characterized by a poor quality built environment was associated with greater individual likelihood of past six month and lifetime depression in multilevel models adjusting for individual age, race/ethnicity, sex, and income and for neighborhood level income. In adjusted models, persons living in neighborhoods characterized by poorer features of the built environment were 29%-58% more likely to report past six-month depression and 36%-64% more likely to report lifetime depression than respondents living in neighborhoods characterized by better features of the built environment. These findings suggest that living in neighborhoods characterized by a poor quality built environment is associated with a greater likelihood of depression. Future prospective work designed to assess potential

mechanisms underlying these associations may guide public health and urban planning efforts aimed at improving population mental health. Galea, S., Ahern, J., Rudenstine, S., Wallace, Z. and Vlahov, D. Urban Built Environment and Depression: A Multilevel Analysis. J Epidemiol Community Health, 59(10), pp. 822-827, 2005.

Drug Use, Misuse, and the Urban Environment

Urbanization is probably the single most important demographic shift worldwide in the the past and new centuries. It represents a sentinel change from how most of the world's population has lived over the past several thousand years. As urban living becomes the predominant social context for the majority of the world's population, the very ubiquity of urban living promises to shape health directly and to indirectly affect what we typically consider risk factors or determinants of population health. Although a growing body of research is exploring how characteristics of the urban environment may be associated with health (e.g. depression) and risk behaviors (e.g. exercise patterns), relatively little research has systematically assessed how the urban environment may affect drug use and misuse. In this paper, the authors propose a conceptual framework for considering how different characteristics of the urban environment (e.g. collective efficacy, the built environment) may be associated with drug use and misuse, summarize the existing empiric literature that substantiates elements of this framework, and identify potential directions for future research. Galea, S., Rudenstine, S. and Vlahov, D. Drug Use, Misuse, and the Urban Environment. Drug Alcohol Rev, 24(2), pp. 127-136, 2005.

Neighborhood Factors and Crime

This study provides reliability information for a brief observational measure of physical disorder and determines its relation with neighborhood level crime and health variables after controlling for census based measures of concentrated poverty and minority concentration. Results come from psychometric analysis of block observation data comprising a brief measure of neighborhood physical disorder, and cross sectional analysis of neighborhood physical disorder, neighborhood crime and birth statistics, and neighborhood level poverty and minority concentration. The study was conducted in Pittsburgh, Pennsylvania, US (2000 population=334,563). Participants were selected from Pittsburgh neighborhoods (n=82) and their residents (as reflected in neighborhood level statistics). Results indicated that the physical disorder index showed adequate reliability and validity and was associated significantly with rates of crime, firearm injuries and homicides, and teen births, while controlling for concentrated poverty and minority population. In conclusion, this brief measure of neighborhood physical disorder may help increase our understanding of how community level factors reflect health and crime outcomes. Wei, E., Hipwell, A., Pardini, D., Beyers, J. and Loeber, R. Block Observations of Neighborhood Physical Disorder are Associated with Neighborhood Crime, Firearm Injuries and Deaths, and Teen Births. J Epidemiol Community Health, 59(10), pp. 904-908, 2005.

Heroin and HIV Risk in Tanzania

HIV risk through needle sharing is now an emerging phenomenon in Africa. This article describes the practices that heroin users are producing as they establish the rules and organization surrounding their drug use. Their practices and interactions reveal the ways that they become initiated into its use, how they progress to injecting, and the important role of local neighborhood hangouts in facilitating this process. Their practices, interactions and narratives also provide insights into what may be the most appropriate HIV-prevention

interventions. Semi-structured interviews were conducted during the months of February and July 2003 with 51 male and female injectors residing in 8 neighborhoods in the Dar es Salaam, Tanzania. Interviews were content coded and codes were collapsed into emergent themes around hangout places, initiation of heroin use, and progression to injecting. Interviews reveal that Dar es Salaam injectors begin smoking heroin in hangout areas with their friends, either because of peer pressure, desire, or trickery. One hangout place in particular, referred to as the ''geto '' (ghetto) is the main place where the organization and rules governing heroin use are produced. Three main types of heroin ''ghettoes '' are operating in Dar es Salaam. As users build a tolerance for the drug they move along a continuum of practices until they begin to inject. Injecting heroin is a comparatively recent practice in Africa and coincides with: (1) Tanzania transitioning to becoming a heroin consuming community; (2) the growing importance of youth culture; (3) the technical innovation of injecting practices and the introduction and ease of use of white heroin; and (4) heroin smokers, sniffers, and inhalers perceived need to escalate their use through a more effective and satisfying form of heroin ingestion. McCurdy, S., Williams, M., Kilonzo, G., Ross, M. and Leshabari, M. Heroin and HIV Risk in Dar es Salaam, Tanzania: Youth Hangouts, Mageto and Injecting Practices. AIDS Care, 17(1), pp. S65-S76, 2005.

Offending Trajectories Predict Drug Use

This longitudinal study examines the validity of differing offending pathways and the prediction from the pathways to substance use and depressive symptoms for 204 young men. Findings from this study indicated good external validity of the offending trajectories. Further, substance use and depressive symptoms in young adulthood (i.e., ages 23-24 through 25-26 years) varied depending on different trajectories of offending from early adolescence to young adulthood (i.e., ages 12-13 through 23-24 years), even after controlling for antisocial propensity, parental criminality, demographic factors, and prior levels of each outcome. Specifically, chronic high-level offenders had higher levels of depressive symptoms and engaged more often in drug use compared with very rare, decreasing low-level, and decreasing high-level offenders. Chronic low-level offenders, in contrast, displayed fewer systematic differences compared with the two decreasing offender groups and the chronic high-level offenders. The findings supported the contention that varying courses of offending may have plausible causal effects on young adult outcomes beyond the effects of an underlying propensity for crime. Capaldi, D. M., Wiesner, M., and Kim, H. K. Developmental Trajectories of Offending: Validation and Prediction to Young Adult Alcohol Use, Drug Use, and Depressive Symptoms. Developmental Psychopathology, 17 pp. 251-270, 2005.

Circumstances of Witnessed Drug Overdose in New York City: Implications for Intervention

Drug users frequently witness the nonfatal and fatal drug overdoses of their peers, but often fail to intervene effectively to reduce morbidity and mortality. Researchers assessed the circumstances of witnessed heroin-related overdoses in New York City (NYC) among a predominantly minority population of drug users. Among 1184 heroin, crack, and cocaine users interviewed between November 2001 and February 2004, 672 (56.8%) had witnessed at least one nonfatal or fatal heroin-related overdose. Of those, 444 (67.7%) reported that they or someone else present called for medical help for the overdose victim at the last witnessed overdose. In multivariable models, the respondent never having had an overdose her/himself and the witnessed overdose occurring in a public place were associated with the likelihood of calling for medical help. Fear of police response was the most commonly cited reason for not calling or delaying before calling for help (52.2%). Attempts to revive the overdose victim through physical stimulation (e.g., applying ice, causing pain) were

reported by 59.7% of respondents, while first aid measures were attempted in only 11.9% of events. Efforts to equip drug users to manage overdoses effectively, including training in first aid and the provision of naloxone, and the reduction of police involvement at overdose events may have a substantial impact on overdose-related morbidity and mortality. Tracy, M., Piper, T., Ompad, D., Bucciarelli, A., Coffin, P., Vlahov, D. and Galea, S. Circumstances of Witnessed Drug Overdose in New York City: Implications for Intervention. Drug Alcohol Depend, 79(8), pp. 181-190, 2005.

Ethnic Differences in Nicotine Dependence among Adolescents Explained by Level of Consumption

Researchers sought to compare nicotine-dependent smokers identified by the modified Fagerstršm Tolerance Questionnaire (mFTQ) and a scale based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), in a multiethnic adolescent sample. A school survey was conducted on 6th- to 10th-grade students (N=15,007) in a large urban public school system. The two scales formed two distinct factors. Concordance between the two classifications of nicotine dependence was low. The DSM identified a much larger number of nicotine-dependent smokers than the mFTQ, mostly because smokers met dependence criteria at much lower levels of cigarettes consumed, especially when they were depressed. Rates of dependence were higher among whites than minority-group members, especially African Americans. Control for level of cigarette consumption attenuated or eliminated ethnic differences. This investigation provides some understanding of youths defined as dependent by each scale but cannot by itself indicate which scale better measures dependence. Differences in dependence rates among ethnic groups are accounted for mostly by quantity of cigarettes smoked. Kandel, D., Schaffran, C., Griesler, P., Samuolis, J., Davies, M. and Galanti, R. On the Measurement of Nicotine Dependence in Adolescence: Comparisons of the mFTQ and a DSM-IV-Based Scale. J Pediatr Psychol, 30(4), pp. 319-332, 2005.

An Emerging HIV Risk Environment: A Profile of an MSM POZ Party in New York City

This study sought to develop a preliminary epidemiological description of a men who have sex with men (MSM) "POZ Party," an emerging risk environment for HIV+ MSM. As part of a pilot study in New York City in 2003, data were collected using a brief, behavioral intercept survey at entry to POZ Party events. Domains included demographic characteristics, history of HIV infection, motivations for attending POZ parties, lifetime and recent exposure to drugs (including use during POZ Party events), and recent sexual practices (both within both POZ Party venues as well as in non-POZ Party venues). Predominantly white and over the age of 30, subjects in the sample included a broad range of years living with HIV infection. Motivations for using a POZ Party venue for sexual partnering included relief from burdens for serostatus disclosure, an interest in not infecting others, and opportunities for unprotected sexual exchange. High rates of unprotected sex with multiple partners were prevalent in the venue. Although the sample evidenced high rates of lifetime exposure to illicit drugs, relatively little drug use was reported in these sexual environments. These reports are consistent with evidence from direct observation at the venues themselves, in which no drug use was apparent. Findings suggest that serosorting among HIV+ MSM may reduce new HIV infections, a stated interest of both POZ Party organizers and participants alike. However, high rates of unprotected sex in these venues signal continued risk for STIs. Additionally, unprotected sexual contact with HIV partners and status unknown partners outside POZ Party venues heightens concern for diffusion of HIV super infection. Clatts, M., Goldsamt, L. and Yi, H. An Emerging HIV Risk Environment: A Preliminary Epidemiological Profile of an MSM POZ Party in New York City. Sex Transm Infect, 81(5), pp. 373-376, 2005.

A Longitudinal Study of Developmental Patterns and Family Influences on Daily Smoking Initiation

This study sought to examine developmental patterns and family influences on the risk of daily smoking initiation from adolescence to young adulthood. A gender-balanced, ethnically diverse urban sample of 808 children aged 10-11 years was surveyed in 1985 and followed prospectively to age 21 in 1996. Discrete-time survival analysis was used to assess the hazard of initiation of daily smoking during this time period, as well as the effects of family factors on the risk of daily smoking initiation. Less parental smoking, more strict family monitoring and rules, and stronger family bonding predicted a significantly lower risk of daily smoking initiation, controlling for socio-demographic background. The decline in the impact of family bonding over time was marginally significant; however, none of the interactions between family factors and time were significant, indicating generally consistent family influences on daily smoking from age 10 to 21. These findings indicate that parent smoking contributes to the onset of daily smoking in their teenagers even if parents practice good family management, hold norms against teen tobacco use, and do not involve their children in their own tobacco use. Smoking prevention programs should include components focused on parents of adolescents. To reduce risks for daily smoking among adolescents, it is important to encourage parents to stop or reduce their own smoking. In addition, these data indicate that parents can reduce their children's risk of daily smoking initiation by reducing family conflict, by maintaining strong bonds with their children, by setting clear rules, and by closely monitoring their children's behaviors. Hill, K., Hawkins, J., Catalano, R., Abbott, R. and Guo, J. Family Influences on the Risk of Daily Smoking Initiation. J Adolesc Health, 37(3), pp. 202-210, 2005.

Perceptions of Parenting and Preadolescent Adjustment in Low and High Income Families

This study focused on contextual variations in parenting dimensions salient for preadolescent adjustment. The sample consisted of 614 sixth graders from two communities, one low and the other high income. Parenting dimensions included those known to be significant in each socioeconomic context: isolation from parents (emotional and physical), and parental emphasis on achievements (overall expectations and emphasis on integrity over success). Adjustment outcomes included subjective well being as well as school competence. Results showed that, on average, affluent children can perceive their parents as emotionally and physically unavailable to the same degree that impoverished youth do. Ramifications on adjustment also seem to be similar: Closeness to parents was beneficial for all, just as criticism was deleterious. Even after considering the quality of parent-child relationships, parents' physical absence (e.g., at dinner) connoted vulnerability for distress and for poor school performance in both groups. A few parenting dimensions varied by context and gender and are discussed within the overall implications of the findings for future research and practice. Luthar, S. and Latendresse, S. Comparable "Risks" at the Socioeconomic Status Extremes: Preadolescents' Perceptions of Parenting. Dev Psychopathol, 17(1), pp. 207-230, 2005.

Adolescent Panic Attacks and Personality Disorders During Young Adulthood

The goal of this study was to determine the association between panic attacks in adolescence and the risk of personality disorders during young adulthood. Data were drawn from the Children in the Community Study, a longitudinal epidemiological study of psychopathology across the life-course in 717 individuals in the community. Multiple logistic regression analyses were used to

determine the association between panic attacks during adolescence in 1983 and the risk of personality disorders during young adulthood in 1993, adjusting for differences in sociodemographic characteristics, adolescent personality disorders, and co-morbid depressive and substance use disorders. Panic attacks during adolescence (in 1983) were associated with an increased risk of any DSM-IV personality disorder (in 1993) during young adulthood, which persisted after adjusting for differences in sociodemographic characteristics, adolescent personality disorders, and co-morbid depressive and substance use disorders. Panic attacks were associated with a statistically significantly increased risk of Cluster A, B, and C personality disorders. These data provide initial evidence that panic attacks early in life are a marker or risk factor for the development of personality disorders in young adulthood. Replication of these findings is needed, as is more in-depth investigation into the mechanism of this link. If replicated in future research, these results may reveal a novel potential pathway for identifying youth at high risk for personality disorders. Goodwin, R., Brook, J., and Cohen, P. Panic Attacks and the Risk of Personality Disorder. Psychol Med, 35(2), pp. 227-235, 2005.

Predictors of Offspring Smoking

This study examined the interrelation of parental occupational status (blue- versus white-collar), parental education, parental smoking, parent-child relations, late adolescent tobacco use, and adult offspring smoking. A longitudinal data set was employed, composed of 603 participants who were first studied in childhood and then followed to mean age 27 years. Structural Equation Modeling (SEM) showed that the distal factors of parental blue-collar status, low parental educational achievement, and parental smoking were related to adult offspring smoking. Specifically, parental blue-collar status and parental smoking were mediated by the latent construct of the parent-child relationship, which in turn was mediated by smoking in late adolescence with respect to adult offspring smoking. Parental educational level was partially mediated by the parent-adolescent relationship but also had a direct path to adult offspring smoking. The most powerful predictor of offspring smoking in adulthood was smoking in late adolescence. Findings imply areas that may be targeted by intervention programs to decrease offspring tobacco use. Fagan, P., Brook, J., Rubenstone, E. and Zhang, C. Parental Occupation, Education, and Smoking as Predictors of Offspring Tobacco Use in Adulthood: A Longitudinal Study. Addict Behav, 30(3), pp. 517-529, 2005.

High Rates of ADHD in Offspring of Parents with ADHD and SUD

The authors used data from a study of the children of parents with and without substance use disorders (SUD)to evaluate the influence of parental SUD and ADHD on the risk for ADHD in offspring. Using structured psychiatric interviews, 96 families (183 youth; mean age 11.6 years) were assessed. The offspring were stratified into four groups based on parental status: children of parents with neither ADHD nor SUD, children of parents with SUD only, children of parents with ADHD only, and children of parents with both ADHD and SUD, and parental SUD and ADHD were used to predict ADHD in the offspring. The following rates of children with ADHD were reported: among children of parents with neither disorder (3%), children of parents with SUD (13%), children of parents with ADHD (25%), and children of parents with both ADHD and SUD (50%) ($p = .001$). Children of parents with ADHD or ADHD plus SUD were more likely to have ADHD in comparison with children of parents with neither diagnosis ($p < 0.05$). Children of parents with ADHD plus SUD were at greater risk of ADHD in comparison to children of parents with SUD only ($p = 0.01$). The results of this study seem to suggest that the offspring of SUD or ADHD parents are at elevated risk for ADHD compared to controls. The offspring of parents with both ADHD and SUD appear to be at the highest risk for ADHD, highlighting the need for careful screening of this group of youth for

ADHD. As noted by the authors, these findings merit replication in larger samples and with alternative ascertainment methods. Wilens, T., Hahesy, A., Biederman, J., Bredin, E., Tanguay, S., Kwon, A. and Faraone, S. Influence of Parental SUD and ADHD on ADHD in Their Offspring: Preliminary Results From a Pilot-Controlled Family Study. Am J Addict, 14(2), pp. 179-187, 2005.

Ecstasy Use Among Hispanic and Black Substance Users in New York City

Surveillance data suggest that use of ecstasy in the U.S. is predominantly among white adolescent and young adults. To investigate ecstasy use among substance users in New York City, researchers added questions to ongoing efforts to recruit heroin and cocaine users. Of 715 participants recruited, 58.3% were IDUs. The median age was 32 (range 17-64), 76.4% were male, 49.0% were currently homeless, 62.4% were Hispanic, 27.3% were black, and 34.5% were born outside the United States. Overall, 23.4% used ecstasy in their lifetime and 11.9% had used in the last-6 months. In multivariate logistic regression, correlates of lifetime ecstasy use included younger age, being born in the U.S., and current homelessness. A significant interaction was found between injection drug use and race where, compared to black non-IDUs, Hispanic non-IDUs, white IDUs were significantly more likely to have a history of lifetime ecstasy use and black IDUs were significantly less likely. These findings are limited to persons who use other drugs, but suggest that further investigation of ecstasy use in minority populations is warranted. Ompad, D., Galea, S., Fuller, C., Edwards, V. and Vlahov, D. Ecstasy Use Among Hispanic and Black Substance Users in New York City. Subst Use Misuse, 40(9-10), pp. 1399-1407, 2005.

HIV Transmission Behaviors in Jail/Prison Among Puerto Rican Drug Injectors in New York and Puerto Rico

This study examined HIV risk behavior in jail/prison among Puerto Rican drug injectors in New York (NY, n = 300) and Puerto Rico (PR, n = 200), and its relationship with later drug and sex risk behaviors. During 3 years prior to interview, 66% of NY and 43% of PR samples were incarcerated at least once. While incarcerated, 5% of NY and 53% of PR injected drugs. Few reported engaging in sex inside jail/prison (5% in both sites). Of those who engaged in risk behaviors in jail/prison, almost all reported having unprotected sex and sharing injection equipment. The impact of jail/prison risk behaviors on risk behaviors after release differed between the two sites: they were more related to subsequent sex risk behaviors in NY, and subsequent injection risk behaviors in PR. The findings indicate a need for effective drug treatment programs inside jail/prisons to reduce HIV-related risk behaviors among drug injectors during incarceration and after release. Kang, S.Y, Deren, S., Andia, J., Col—n, H.M., Robles, R. and Oliver-Velez, D. HIV Transmission Behaviors in Jail/Prison Among Puerto Rican Drug Injectors in New York and Puerto Rico. AIDS Behav, 9(3), pp. 377-386, September 2005.

Association of Sex, Hygiene and Drug Equipment Sharing with Hepatitis C Infection Among Non-IDUs in New York City

Hepatitis C virus (HCV) rates are higher in non-injecting drug users (NIDUs) than general population estimates. Whether this elevated HCV rate is due to drug use or other putative risk behaviors remains unclear. In this study, recent NIDUs of heroin, crack and/or cocaine were street-recruited from 2000 to 2003 and underwent an interview and venipuncture for HCV antibody assays. Multiple logistic regression analyses were used to assess correlates for HCV infection. Of 740 enrollees, 3.9% were HCV positive. The median age (intraquartile range) was 30 (35-24) years, 70% were male and 90% were

Black or Hispanic. After adjustment, HCV seropositives were significantly more likely than seronegatives to be older than 30 [adjusted odds ratio (AOR)=5.71], tattooed by a friend/relative/acquaintance [AOR=3.61], and know someone with HCV [AOR=4.29], but were less likely to have shared nail or hair clippers, razors or a toothbrush [AOR=0.32]. These findings suggest that non-commercial tattooing may be a mode of HCV transmission among NIDUs and education on the potential risk in using non-sterile tattooing equipment should be targeted toward this population. While no evidence was found for HCV transmission through NIDU equipment sharing or sexual risk behavior, further research is still warranted. Howe, C., Fuller, C., Ompad, D., Galea, S., Koblin, B., Thomas, D. and Vlahov, D. Association of Sex, Hygiene and Drug Equipment Sharing with Hepatitis C Virus Infection Among Non-Injecting Drug Users in New York City. Drug Alcohol Depend, 79(3), pp. 389-395, 2005.

Anti-Tobacco Advertising and Youth Beliefs and Behaviors

Recent state budget crises have dramatically reduced funding for state-sponsored antitobacco media campaigns. If campaigns are associated with reduced smoking, such cuts could result in long-term increases in state health care costs. Commercial ratings data on mean audience exposure to antitobacco advertising that appeared on network and cable television across the largest 75 media markets in the United States for 1999 through 2000 were combined with nationally representative survey data from school-based samples of youth in the contiguous 48 states. Multivariate regression models were used to analyze associations between mean exposure to state anti-tobacco advertising and youth smoking-related beliefs and behaviors, controlling for individual and environmental factors usually associated with youth smoking and other televised tobacco-related advertising. Mean exposure to at least 1 state-sponsored anti-tobacco advertisement in the past 4 months was associated with lower perceived rates of friends' smoking (odds ratio [OR], 0.72; 95% confidence interval [CI], 0.58-0.88), greater perceived harm of smoking (OR, 1.25; 95% CI, 1.11-1.42), stronger intentions not to smoke in the future (OR, 1.43; 95% CI, 1.17-1.74), and lower odds of being a smoker (OR, 0.74; 95% CI, 0.63-0.88). The investigators assert that this study is the first to explore the potential impact of state-sponsored anti-tobacco media campaigns while controlling for other tobacco-related advertising and other tobacco control policies, and conclude that state-sponsored anti-tobacco advertising is associated with desired outcomes of greater anti-tobacco sentiment and reduced smoking among youth. The investigators caution that recent cuts in these campaigns may have future negative health and budgetary consequences. Emery, S., Wakefield, M., Terry-McElrath, Y., Saffer, H., Szczypka, G., O 'Malley, P., Johnston, L., Chaloupka, F. and Flay, B. Televised State-Sponsored Anti-Tobacco Advertising and Youth Smoking Beliefs and Behavior in the United States, 1999-2000. Arch Pediatr Adolesc Med, 159(7), pp. 639-645, 2005.

Cocaine Use Related to Panic Attacks

This study uses the case-crossover method to estimate the magnitude of excess occurrence of panic attacks during months of cocaine use vs. months of no cocaine use, motivated by a prior estimate that cocaine users have three-fold excess risk of panic attack. The self-report data on cocaine and panic are from assessments of a nationally representative sample of 1071 recent panic cases age 18 years or older identified as part of the National Household Surveys on Drug Abuse conducted in the United States during 1994-1997. Based on case-crossover estimates, cocaine use is associated with a three-to-four-fold excess occurrence of panic attack (estimated relative risk (RR) = 3.3, p = 0.049; 95% confidence interval: 1.0, 13.7). Year-by-year, the RR estimates from four independent yearly replicates (1994-1997) are 5.0, 2.0,

3.0, and 3.0. While there are several important limitations, this study adds new evidence about a previously reported suspected causal association linking cocaine use to occurrence of panic attacks, and illustrates advantages of the epidemiologic case-crossover approach and new directions in research on hazards of illegal drug use. O 'Brien, M., Wu, L. and Anthony, J. Cocaine Use and the Occurrence of Panic Attacks in the Community: A Case-Crossover Approach. Subst Use Misuse, 40(3), pp. 285-297, 2005.

Influences of Early Attachment, Depression, Illicit Drug Use, and Perceived Support on Drug-dependent Mothers' Parenting

In this study, the authors used an attachment framework to examine how drug-dependent mothers' early bonding experience, depression, illicit drug use, and perceived support work together to influence the family environment. The authors hypothesized that (a) depression and drug use function as proxies for a stronger risk factor, the perceived absence of support available in everyday life, and (b) associations between mothers' early bonding experience and family environment are mediated by perceptions of support and nurture available in everyday life. The authors used a "building block" analytic approach and data collected from 125 mothers enrolled in methadone maintenance to test hypotheses. They expected that associations between mothers' early bonding experience and their perceptions of relationships with their children would be mediated by their perceptions of support and nurture available in their everyday life. Each of these hypotheses was supported for the first outcome, mothers' perceptions of family adaptability. Few psychosocial factors were associated with the second outcome, mothers' perceptions of family cohesion, and a majority of mothers (87.2%) in the sample reported no cohesion in their relationships with their children. Although preliminary, the findings suggest that perceptions of relationships in everyday life play a critical role in the etiology of drug-dependent mothers' parenting. Suchman, N., McMahon, T., Slade, A. and Luthar, S. How Early Bonding, Depression, Illicit Drug Use, and Perceived Support Work Together to Influence Drug-Dependent Mothers' Care Giving. Am J Orthopsychiatry, 75(3), pp. 431-445, 2005.

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

Research Findings - Prevention Ressearch

Raising Healthy Children Intervention Decreases Drug Use Frequency

Raising Healthy Children (RHC) is a preventive intervention designed to promote positive youth development by targeting developmentally appropriate risk and protective factors. In this study, the authors tested the efficacy of the RHC intervention on reducing adolescent alcohol, marijuana, and cigarette use. Ten public schools with 959 1st- and 2nd-grade students (54% male students, 18% minority, 28% low socioeconomic status), were matched and assigned randomly to either intervention or control conditions. A 2-part latent growth modeling strategy was used to examine change in both use versus nonuse and frequency of use outcomes when students were in Grades 6-10. Results indicated significant ($p < .05$) intervention effects in growth trajectories for frequency of alcohol and marijuana use but not for use versus nonuse. These findings provide support for preventive interventions that take a social development perspective in targeting empirically supported risk and protective factors and demonstrate the use of 2-part models in adolescent substance use research. Brown, E., Catalano, R., Fleming, C., Haggerty, K. and Abbott, R. Adolescent Substance Use Outcomes in the Raising Healthy Children Project: A Two-Part Latent Growth Curve Analysis. J Consult Clin Psychol, 73(74), pp. 699-710, 2005.

The Public Costs of Early Conduct Problems

This study explored the economic implications of conduct disorder (CD) among adolescents in 4 poor communities in the United States, participating in the Fast Track prevention project. The investigators examined a range of expenditures related to conduct disorder across multiple public sectors, including mental health, general health, school, and juvenile justice. Fast Track is a randomized controlled trial examining the efficacy of a multi-level, multi-year intervention to prevent conduct problems. Families with children identified as high risk for aggression were recruited during the child's kindergarten year and randomized to either the intervention or the comparison group, and a low risk control group was enrolled (n=1191; 50% African American, 47% Caucasian; 3% other). Fast Track families have been followed annually through 12th grade. This study focuses on 664 youth in the high risk comparison and low risk control groups, and used self- and parental-report data to estimate expenditures during a 7-year period in late adolescence (grades 6 through 12). Expenditures were contrasted for youths with CD and youths with oppositional defiant disorder, elevated symptoms (no CD diagnosis), and all others. Diagnosis was determined with a structured assessment. Additional public costs per child related to CD exceeded $70,000 over a 7-year period. The authors concluded that public expenditures on youths with CD are substantially larger

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than for youths with closely related conditions, reflecting the importance of prevention and early treatment for the disorder. Foster, E., Jones, D. and Jones, D.T. The High Costs of Aggression: Public Expenditures Resulting from Conduct Disorder. Am J Public Health, 95(10), pp. 1767-1772, 2005.

Community Coalitions and Adoption of Drug Prevention Programs

The study examined the relationship between six characteristics of community coalitions (size of region covered, structure, professional representation, resource sharing, size, and breadth of prevention stakeholder representation) and community organizational progress in adopting drug prevention programs. The study utilized baseline data from community leaders (n = 533) in 24 cities from Step Towards Effective Prevention (STEP), a multi-state, multi-city randomized trial that is evaluating the effects of a television-based prevention training intervention on adoption of evidence-based drug prevention programs. Confirmatory factor analysis yielded a measurement model with a good fit to the data on four of the characteristics. Structural equation modeling showed that these characteristics had significant positive relationships to organizational progress, with the exception of size of the region covered. Results suggest that coalitions which have a clear structure, professional focus, resource sharing, and a smaller service region are likely to show the most progress in adopting evidence-based drug prevention programs. Jasuja, G.K., Chou, C., Bernstein, K., Wang, E., McClure, M. and Pentz, M. Using Structural Characteristics of Community Coalitions to Predict Progress in Adopting Evidence-based Prevention Programs. Evaluation and Program Planning, 28(2), pp. 173-184, 2005.

Patterns of HIV Prevalence Among Injection Drug Users in Cross-Border Areas of Vietnam and China

This study assessed patterns of injecting drug use and HIV prevalence among injecting drug users (IDUs) in an international border area along a major heroin trans-shipment route. It included cross-sectional surveys of IDUs in 5 sites in Lang Son Province, Vietnam (n = 348) and 3 sites in Ning Ming County, Guangxi Province, China (n = 308). Respondents were recruited through peer referral ("snowball") methods in both countries, and also from officially recorded lists of IDUs in Vietnam. A risk behavior questionnaire was administered and HIV counseling and testing conducted. Participants in both countries were largely male, in their 20s, and unmarried. A majority of subjects in both countries were members of ethnic minority groups. There were strong geographic gradients for length of drug injecting and for HIV seroprevalence. Both mean years injecting and HIV seroprevalence declined from the Vietnamese site farthest from the border to the Chinese site farthest from the border. 10.6% of participants in China and 24.5% of participants in Vietnam reported crossing the international border in the 6 months prior to interview. Crossing the border by IDUs was associated with (1) distance from the border, (2) being a member of an ethnic minority group, and (3) being HIV seropositive among Chinese participants. It was concluded that reducing the international spread of HIV among IDUs will require programs at the global, regional, national, and "local cross border" levels. Des Jarlais, D., Johnston, P., Friedmann, P., Kling, R., Liu, W., Ngu, D., Chen, Y., Hoang, T., Donghua, M., Van, L., Tung, N., Binh, K. and Hammett, T. Patterns of HIV Prevalence Among Injecting Drug Users in the Cross-border Area of Lang Son Province, Vietnam, and Ning Ming County, Guangxi Province, China. BMC Public Health, 5, pp. 89-96, 2005.

Normative Beliefs and Substance Initiation

The current study investigated the effects of baseline levels of academic

achievement and longitudinal trends in normative beliefs on adolescent substance initiation across a 42-month time period. Participants were 272 rural adolescents who were an average of 12.3 years old at the baseline assessment. Academic achievement positively predicted the intercept and negatively predicted the growth-trajectory of normative beliefs regarding peer substance behavior. Further, baseline academic achievement negatively predicted initial levels, as well as the growth-trajectory, of substance initiation. The discussion addresses the influence of academic achievement and normative beliefs on substance initiation and the utility of latent growth curve modeling in studying longitudinal change. In addition, implications for prevention programming are discussed. Lillehoj, C.J., Trudeau, L. and Spoth, R. Longitudinal Modeling of Adolescent Normative Beliefs and Substance Initiation. Journal of Alcohol and Drug Education, 49(2), pp. 7-41, 2005.

Assertiveness and Alcohol Use in Rural Adolescents

There is evidence of higher prevalence rates for alcohol use among rural adolescents relative to urban adolescents. Strategies aimed at preventing adolescent alcohol use typically include the development of social skills to resist peer pressure; among the social skills frequently targeted is assertiveness. Self-report data were collected from a sample of rural adolescents (N-470) participating in a longitudinal preventive intervention study. Five hypothesized dimensions of assertiveness were validated with confirmatory factor analysis: specific substance refusal, individual rights, transaction, justice and social approach. Using gender as a between-subject factor, plus time and assertiveness as within-subject factors to predict an alcohol use composite index, repeated measures analysis revealed a number of significant findings. Several assertiveness dimensions were found to have significant effects on the alcohol use index (specific substance refusal, individual rights, and justices associate lower alcohol involvement; social assertiveness was associated with higher involvement). Moreover, there were significant two and three way interaction effects with time and gender. Goldberg-Lillehoj, C.J., Spoth, R. and Trudeau, L. Assertiveness Among Young Rural Adolescents: Relationship to Alcohol Abuse. J. Child and Adol Sub Abuse, 14(3), pp. 39-67, 2005.

Religiosity and Drug Use Among Mexican and Mexican American Youth

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

Effects of Culturally Adapted Parent Management Training

A randomized experimental test of the implementation feasibility and the efficacy of a culturally adapted Parent Management Training intervention was conducted with a sample of 73 Spanish-speaking Latino parents with middle-school-aged youth at risk for problem behaviors. Intervention feasibility was evaluated through weekly parent satisfaction ratings, intervention participation and attendance, and overall program satisfaction. Intervention effects were

evaluated by examining changes in parenting and youth adjustment for the intervention and control groups between baseline and intervention termination approximately 5 months later. Findings provided strong evidence for the feasibility of delivering the intervention in a larger community context. The intervention produced benefits in both parenting outcomes (i.e., general parenting, skill encouragement, overall effective parenting) and youth outcomes (i.e., aggression, externalizing, likelihood of smoking and use of alcohol, marijuana, and other drugs). Differential effects of the intervention were found related to youth nativity status such that parents of U.S.-born youth benefited more from participation in the intervention than parents of foreign-born youth. Martinez, C., and Eddy, J. Effects of Culturally Adapted Parent Management Training on Latino Youth Behavioral Health Outcomes. J Consult Clin Psychol, 73(5), pp. 841-851, 2005.

Rural Youth Attitudes Towards Substance Use and Violence

To determine the effectiveness of multi-component prevention campaigns (media and other community wide interventions) the authors conducted 15 focus groups with 169 male and female 6th-, 7th-, and 8th- graders. Participants were recruited from small to mid-size communities across the US. The focus groups examined youth attitudes towards their own use and their peers'' use of alcohol, tobacco, drugs, and violence. Several key findings emerged that may be utilized in future multi-component campaigns. First, youth value spending unstructured time with their friends. In terms of tobacco use, both boys and girls are worried about getting caught by their parents; but girls are more concerned about the physical effects of smoking in terms of their attractiveness to members of the opposite sex. In terms of alcohol use, girls were concerned about the dangers of drinking and driving (especially girls in 8th grade) and the pressure to have sex if a date is inebriated. Hispanic youth were more concerned about being a good role model for younger siblings than Caucasian youth. In terms of violence, girls were more likely to spread rumors while boys were more likely to engage in verbal and or physical violence. Finally, both boys and girls preferred prevention and intervention campaigns that were based on real situations and experiences, reflected their culture, were positive, and stress the capabilities of an individual to take action. Kelly, K.J., Comelle, M.G. and Edwards, R.W. Attitudes of Rural Middle-School Youth Toward Alcohol, Tobacco, Drugs, and Violence. The Rural Educator, 25(3), pp. 19-24, 2004.

Which Comes First in Adolescence - Sex and Drugs or Depression

The notion that adolescents self-medicate for depression with substance use and sexual behaviors is widespread, but the temporal ordering of depression and these risk behaviors is not clear. This study tests whether gender-specific patterns of substance use and sexual behavior precede and predict depression or vice versa. Data from the National Longitudinal Study of Adolescent Health were weighted to produce population estimates. The sample includes 13,491 youth, grades 7 to 11, interviewed in 1995 and again one year later. Multivariate logistic regression analyses, conducted in 2004, tested temporal ordering, controlling for covariates. The main outcome measures were depression, as measured by a modified Center for Epidemiological Studies-Depression Scale (CES-D), and three behavior patterns: (1) abstaining from sexual intercourse and drug use, (2) experimental behavior patterns, and (3) high-risk behavior patterns. Results showed that overall, sex and drug behaviors predicted an increased likelihood of depression, but depression did not predict sex and drug behaviors. Among girls, both experimental and high-risk behavior patterns predicted depression. Among boys, only high-risk behavior patterns increased the odds of later depression. Depression did not predict behavior in boys, or experimental behavior in girls; but it decreased the odds of high-risk behavior among abstaining girls (RRR=0.14) and increased

the odds of high-risk behavior (RRR=2.68) among girls already experimenting with substance use. Engaging in sex and drug behaviors placed adolescents, especially girls, at risk for future depression. Mechanisms of these relationships are yet to be determined. Hallfors, D.D., Waller, M.W., Bauer, D. and Ford, C.A. Which Comes First in Adolescence - Sex and Drugs or Depression? Am J Prev Med, 29(3), pp. 163-170, 2005.

Attitudes Toward HIV Prevention in China and Vietnam

Success of HIV prevention projects for injection drug users (IDUs) depends on the support of the community in which they are implemented. This article presents data from cross-sectional community surveys of HIV knowledge and attitudes toward peer-based HIV prevention interventions for IDUs in a border area of Lang Son Province, Vietnam and Ning Ming County, Guangxi Province, China. Analysis of these surveys at baseline and 18 months reveal generally high or improving levels of HIV knowledge and positive attitudes toward the interventions in both countries. Levels and knowledge tended to be higher in Vietnam than in China. Interviews with staff and peer educators suggest that the project's community education program efforts have increased support for the interventions and contributed to their smooth implementation. However, the community surveys also reveal some continuing deficits in HIV knowledge and understanding of the interventions, including perceptions that provision of new syringes will result in increased drug use. Additional education, including dissemination of countervailing project data, is needed to address these deficits and further increase community support for the interventions. Hammett, T., Norton, G., Kling, R., Liu, W., Chen, Y., Binh, K., Dong, H. and DesJarlais, D. Community Attitudes Toward HIV Prevention for Injection Drug Users: Findings from a Cross-border Project in Southern China and Northern Vietnam. J Urban Health, 82(4), pp. iv34-iv42, 2005.

Consistent Predictors of Substance Use in Emerging Adulthood are Male Gender and Previous Use

This 5-year longitudinal study followed a group of 848 adolescents attending an alternative high school in the emerging adulthood years and measured their adult role taking and substance use. Psychological factors at baseline, and adult role taking at the follow-up were examined as correlates of substance use during emerging adulthood. At this stage of life 74% of subjects were employed, 30% were married or engaged, and 53% had at least one child. One third of subjects were daily cigarette smokers, and 24% had used marijuana in the past 30 days. Forty-seven percent had experienced negative consequences of alcohol or drug use in the last year. The most consistent positive predictors of substance use in emerging adulthood were male gender and previous drug use. Addiction concern was a consistent negative predictor. After controlling for baseline psychosocial variables, attending school and being married at the five-year follow-up were negative correlates of both personal consequences and problems related to alcohol or drug use. Pentz, M.A., Mares, D., Schinke, S. and Rohrbach, L.A. Tobacco, Alcohol, and Other Drug Use Among High-risk Young People: A Five-year Longitudinal Study From Adolescence to Emerging Adulthood. Journal of Drug Issues, 35(2), pp. 333-356, 2005.

Implicit, Associative Memory Processes Influence Drug Use Motivation

This study evaluated the mediating role of implicit cognitive processes in the prediction of alcohol and marijuana use and examined the relationships between dissociative experiences, implicit processes, and sensation seeking in models of drug use and problem experiences. Participants were 467 diverse at-risk adolescents in California. Results from latent variable models revealed that

implicit cognition independently predicted alcohol and marijuana use and mediated the predictive effects of sensation seeking on drug use. Dissociative experiences did not predict implicit cognition or drug use in this sample, though this factor was a significant predictor of problem experiences and was positively correlated with sensation seeking. This research provides evidence suggesting that implicit, associative memory processes are influential in drug-use motivation. Ames, S.L., Sussman, S.Y., Dent, C.W., and Stacy, A.W. Implicit Cognition and Dissocative Experiences as Predictors of Adolescent Substance Use. American Journal of Drug and Alcohol Abuse, 31(1), pp. 129-162, 2005.

Coping Strategies and Mental Health Services

This study examined the relationship among trauma, coping, depression, and mental health service seeking in a probability sample of sheltered homeless and low-income housed women. Results highlight the diversity of trauma. In a longitudinal analysis, women who lived in shelters or experienced major violence had a twofold increase in their risk of depression over the 6-month follow-up. In a cross-sectional analysis, childhood sexual abuse, living in a shelter, physical violence, childhood physical abuse, and death or injury of a friend or relative predicted avoidant coping and symptoms of depression. Active coping and depression predicted mental health service seeking among traumatized women. Modifying coping strategies may ameliorate some of the negative impact of trauma and potentially enhance mental health service use among at-risk women. Rayburn, N.R., Wenzel, S.L., Elliott, M.N., Hambarsoomians, K., Marshall, G.N. and Tucker, J.S. Trauma, Depression, Coping, and Mental Health Service Seeking Among Impoverished Women. J Consult Clin Psychol, 73(4), pp. 667-677, 2005.

American Indian Girls Exceed American Indian Boys, White Girls and White Boys in Cigarette, Marijuana, Alcohol and Inhalant Use

This article documents the prevalence of self-reported substance use among White and American Indian adolescents enrolled in 7th grade in 1997 in a Northern Plains state. Data were collected by self-administered questionnaire preceding adolescents' participation in a randomized field trial of Project Alert (a 7th and 8th grade prevention curriculum). Rates of lifetime and past-month use of cigarettes and marijuana were higher among American Indians than among Whites of the same gender. American Indian girls exceeded American Indian boys as well as White girls and White boys on lifetime and past-month use of cigarettes, marijuana, alcohol and inhalants; differences in cigarette and inhalant use reached statistical significance. These findings add to the sparse literature on substance use among adolescents as young as 12 through 13 years old and underscore the importance of examining gender-specific substance use patterns early in adolescence. Spear, S., Longshore, D. and McCaffrey, D. Prevalence of Substance Use Among White and American Indian Young Adolescents in a Northern Plains State. Journal of Psychoactive Drugs, 37(1), pp. 1-16, 2005.

Drug Use and Violence: Psychopharmacological Influences

This study examined relationships between illegal and legal drug use and violence perpetration and victimization as well as possible mediators of these relationships. Subjects were continuation high school students followed prospectively over 5 years. Results indicated that illegal drug use predicted violence and victimization 5 years later and that earlier victimization was also associated with later illegal drug use. A measure intending to tap a psychopharmacological effects system was found to mediate the relationships between illegal drug use and victimization and violence. Results suggest that

violence and victimization prevention efforts may benefit by addressing the psychopharmacological effects of adolescent illegal drug use. Weiner, M.D., Sussman, S., Sun, P. and Dent, C. Explaining the Link Between Violence Perpetration, Victimization and Drug Use. Addict Behav, 30(6), pp. 1261-1266, 2005.

Adolescent Risk and Protection for Exposure to Community Violence

Community violence is recognized as a significant public health problem. However, a paucity of research has examined risk factors for community violence exposure across domains relevant to adolescents or using longitudinal data. This study examined youth aggressive behavior in relation to community violence exposure among a community epidemiologically defined longitudinal sample of 582 (45% female; 86% African American) urban middle school students (10-13 years of age). The participants were initially assessed in the fall of first grade as part of an evaluation of two school-based preventive interventions conducted by the Johns Hopkins University. In this article, internalizing behaviors, deviant peer affiliation, and parental monitoring were examined as moderators of the association between aggressive behavior and exposure to community violence over time. For males with aggressive behavior problems and deviant peer affiliation or low parental monitoring, co-occurring anxiety symptoms protected against subsequent witnessing community violence. In contrast, males with aggressive behavior problems and co-occurring depressive symptoms were at increased risk for witnessing community violence. These findings suggest that aggressive behavior, depressive symptoms, and deviant peer affiliation are potential risks for exposure to community violence. Also, increasing youth vigilance of surroundings or awareness of danger may be a possible means of reducing risk. Lambert, S., Ialongo, N., Boyd, R. and Cooley, M. Risk Factors for Community Violence Exposure in Adolescence. Am J Community Psychol, 36(1-2), pp. 29-48, 2005.

Changing Face of HIV/AIDS Among Native Populations

Despite progress in addressing the HIV/AIDS crisis in some populations, major challenges in the prevention of HIV/AIDS in Native American communities remain. This article details information about the biological, social, economic, and behavioral cofactors related to the rise in HIV/AIDS in Native American communities and follows with issues related to special populations and consideration of the unique prevention needs prevention in these subpopulations. The need for increased HIV testing is discussed as is the need for Native-specific programs and interventions. Finally, changes in the recognition of the culturally specific needs of Native American people are discussed and new resources are presented. Vernon, I. and Jumper-Thurman, P. The Changing Face of HIV/AIDS Among Native Populations. Journal of Psychoactive Drugs, 37(3), pp. 247-255, 2005.

Optimizing and Evaluating Behavioral Interventions

Although the optimization of behavioral interventions offers the potential of both public health and research benefits, currently there is no widely agreed-upon principled procedure for accomplishing this. This article suggests a multiphase optimization strategy (MOST) for achieving the dual goals of program optimization and program evaluation in the behavioral intervention field. MOST consists of the following three phases: (a) screening, in which randomized experimentation closely guided by theory is used to assess an array of program and/or delivery components and select the components that merit further investigation; (b) refining, in which interactions among the

identified set of components and their interrelationships with covariates are investigated in detail, again via randomized experiments, and optimal dosage levels and combinations of components are identified; and (c) confirming, in which the resulting optimized intervention is evaluated by means of a standard randomized intervention trial. To make the best use of available resources, MOST relies on design and analysis tools that help maximize efficiency, such as fractional factorials. A slightly modified version of an actual application of MOST to develop a smoking cessation intervention is used to develop and present the ideas. MOST has the potential to husband program development resources while increasing our understanding of the individual program and delivery components that make up interventions. Considerations, challenges, open questions, and other potential benefits are discussed. Collins, L., Murphy, S., Nair, V. and Strecher, V. A Strategy for Optimizing and Evaluating Behavioral Interventions. Ann Behav Med, 30(1), pp. 65-73, 2005.

Cross-Cultural Assessment of Perceived Competence in Rural South-African and Rural African-American Families

This study explored psychometric differences in baseline data from rural African-American and rural South-African adolescents to establish the cross-cultural validity of the Harter Perceived Competence Scale. This scale consists of three sub-scales measuring cognitive, social, and physical competencies. The goals of the study were to examine the psychometric properties of a Sepedi (Northern Soto) translated scale with a sample of rural Black South African 12-year-olds; and to compare the mean scores for the rural SA adolescents to a comparable sample of rural African American 12-year-olds. Two hundred twenty-three African American families and 157 South African families participated in the study. Results revealed that the internal consistency reliability was stronger for the African American sample (Cronbach''s alpha= .79 vs. .52). The African American sample also scored higher on the cognitive and social competency sub-scales. Principle components analysis revealed a three-factor solution (Perceived Cognitive Competency, Perceived Social Competency, and Perceived Lack of Competency) for both samples. The three factors accounted for 55% of the observed variance in the African American sample and 53% of the observed variance in the South African sample. Harrison, M.G., Malaka, D., Amoateng , A.Y. and Toldson, I. Perceived Competence of Rural South African and Rural African-American Families: A Cross-Cultural Assessment of Structural Validity. Ethnicity and Disease, 15(Summer 2005), pp. 379-386, 2005.

Focus Group Qualitative Data as Basis for Prevention Program in India

Findings of Focus Group Discussions (FGDs) were used as a formative assessment for Project MYTRI (Mobilizing Youth for Tobacco Related Initiatives in India), a randomized, multi-component, school-based trial to prevent and control tobacco use among youth in India. Forty-eight FGDs were conducted with students (N = 435) in sixth and eighth grades in six schools in Delhi, India. Key findings include: (a) students in government schools reported as "consumers" of tobacco, whereas students in private schools reported as "commentators"; (b) parents and peers have a strong influence on youth tobacco use; (c) chewing gutkha (a type of chewing tobacco) is considered less harmful and more accessible than smoking cigarettes; (d) schools are not promoting tobacco control activities; and (e) students were enthusiastic about the role government should play in tobacco control. Mishra, A., Arora, M., Stigler, M.H., Komro, K.A., Lytle, L.A., Reddy, K.S., and Perry, C.L. Indian Youth Speak About Tobacco: Results of Focus Group Discussions With School Students. Health Education and Behavior, 32, pp. 363-379, 2005.

Acculturative Stress and Resilience in Mexican American Youth

This article describes how Mexican-American youth utilize their energy, creativity, and resilience in order to cope with cultural tensions that arise from acculturative processes, role conflicts, family and peer interactions, school challenges, and identity formation processes. In order to examine how Mexican-American adolescents cope with stressors and traumas, focus groups and interviews were conducted. Participants consisted of 30 Mexican-American students and dropouts ranging in age from 13 to 18 years. The youth came from an urban setting with low socioeconomic status and consisted of both students and dropouts. This ethnographic study suggests that many Mexican-American adolescents navigate stressors and traumas in such a way that transforms the potentially distressing events into life-affirming rites of passage. Holleran, L. K. and Jung, S. Acculturative Stress, Violence, and Resilience in the Lives of Mexican-American Youth. Stress, Trauma, and Crisis, 8, pp. 107-130, 2005.

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

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

Cocaine Using Parents With and Without Custody Have Different Problems Upon Treatment Entry

Nancy Petry and colleagues at University of Connecticut School of Medicine examined demographic variables, Addiction Severity Index Scores, and Brief Symptoms Inventory scores of cocaine-using parents entering treatment. The 93 parents with custody showed more severe cocaine and alcohol problems than the 125 without custody. Parents without custody showed more psychiatric distress, employment and legal problems and a greater history of alcohol problems. The results suggest treatment needs for parents and their families may differ according to parental custody. Lewis, M.W. and Petry, N.M. American Journal of Addiction, pp. 403-415, October 2005.

Gamblers with Antisocial Personality Disorder (ASPD) Exhibit More Drug Problems

Nancy Petry and colleagues at University of Connecticut School of Medicine examined problems of 237 compulsive gamblers entering a treatment program and found that approximately 16.5% of participants met diagnostic criteria for ASPD. Male gender, history of illicit substance use, Addiction Severity Index Medical composite score, and the number of criteria for compulsive gambling diagnosis all were positive predictors of Antisocial Personality Disorder. These individuals were more likely to have had a history of substance abuse treatment and to have used a wider variety of substances at higher lifetime rates. The results add to the body of literature supporting a subtype of gambler characterized by high levels of other risk taking and illegal behavior such as substance abuse. Pietrzak R.H. and Petry N.M. Addiction, pp. 1183-1193, August 2005.

Therapist Skillfulness Predicts Patient Involvement in Motivational Interviewing

William Miller and colleagues at the University of New Mexico examined whether therapist skillfulness at conveying egalitarianism, empathy, genuineness, and warmth, all components of the philosophy or spirit of Motivational Interviewing (MI), were as important as engaging in specific MI counseling techniques such as asking open ended questions, for predicting client engagement and cooperation. Tapes of 103 sessions of motivational interviewing provided by trained therapists were coded and rated for both skillfulness and conformance to MI technique. Results showed that skillfulness rather than adherence to technique was more important. Additionally,

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therapists were able to engage in behaviors that are typically considered incompatible with MI, such as advice giving, provided they exhibited high levels of skillfulness with regards to conveying the MI spirit. This study suggests MI training programs should emphasize and therapist skills for conveying MI spirit before teaching MI techniques. It also suggests that a broader array of techniques may be able to be incorporated into this treatment approach provided they convey genuineness, empathy and other indicators of a warm collaboration. This work is significant because it underscores a potential reason why some clinicians might not produce good outcomes in motivational interviewing sessions and suggests further ways to improve therapist training. Moyers, T.B., Miller, W.R. and Hendrickson, S.M. Journal of Consulting and Clinical Psychology, pp. 590-598, August 2005.

After 30 Days of Abstinence, Cocaine Users Still Prefer Quicker Rewards

Steve Higgins and colleagues at the University of Vermont examined the phenomenon of delay discounting, which is the tendency of people to prefer smaller rewards available more quickly to larger rewards available farther in the future. High rates of discounting are thought to represent an impulsive behavioral style. Twenty-one cocaine users in treatment reporting no cocaine use in the previous 30 days, 21 cocaine users reporting at least one day of use in the past thirty days and 21 non-drug using controls were enrolled. Each participant was asked to equate $1000.00 at seven different future times to ranging amounts of money given immediately and the slope of these choices were plotted on a discounting curve. Controls consistently discounted the value of money given sooner less than both groups of cocaine users. This suggests that cocaine users have higher rates of impulsivity than non-users. Additionally, whereas studies of opioid users have shown that abstinence impacts discounting rates, this study did not show a difference between cocaine users with recent use and cocaine users with over a month of abstinence. The failure to find a change in discounting results associated with abstinence may indicate that cocaine users unlike opioid users retain an impulsive style with regards to monetary choices even after abstinence has been established. Heil, S.H., Johnson, M.W., Higgins, S.T. and Bickel, W.K. Addictive Behaviors, pp. (Epub), October 2005.

Subjective and Physiological Responses to Smoking Cues in Smokers with Schizophrenia

Dr. Tidey and colleagues at Brown Medical School conducted a study to test the effects of smoking cues on the urge to smoke and on negative affect among people with schizophrenia. They tested 25 outpatients' reactions to both neutral and smoking-related objects, just after smoking and after 2 hours of abstaining, and found that exposure to smoking cues consistently increased smoking urge levels, despite differences in medications and symptoms. Abstaining from smoking did not appear to alter these effects. The findings suggest that their model could be used to screen interventions that might be used to decrease reactions or exposure to smoking stimuli. The model might also be useful in investigating the neurobiological underpinnings of smoking urges among those with schizophrenia. Tidey, J.W., Rohsenow, D.J., Kaplan, G.B. and Swift, R.M. Nicotine and Tobacco, 7, pp. 421-429, 2005.

Preliminary Evidence of the Association between the History of Childhood Attention-Deficit/Hyperactivity Disorder and Smoking Treatment Failure

Dr. Humfleet and colleagues at the University of California, San Francisco, conducted a study to examine abstinence rates among 428 adult smokers

participating in two randomized controlled trials. Participants were treated with nicotine replacement, antidepressants, and psychological counseling. Childhood ADHD was assessed retrospectively by diagnostic interview. A history of childhood ADHD was diagnosed in 11% of the smokers. More smokers with a diagnosis of childhood ADHD relapsed than those with no such history, and they relapsed sooner. Only 1 of 47 smokers with childhood ADHD was still abstinent by week 52, compared with 18% of those without. Additionally, those with childhood ADHD relapsed after an average of 159 days, compared with 294 days for others. These results highlight the need to further evaluate smoking treatments for this high-risk group. Humfleet, G.L., Prochaska, J.J., Mengis, M., Cullen , J., Munoz, R., Reus, V. and Hall, S. Nicotine Tob Res., 7(3), pp. 453-460, 2005.

Smoking Cessation Research via the Internet: A Feasibility Study

This study demonstrated the feasibility of conducting a brief, self-help smoking cessation intervention over the Internet, using a one-group, pre-post design. The website was constructed to recruit participants, obtain informed consent, collect assessment data, provide a brief educational intervention and obtain 1-month follow-up data, all without human contact. Of the 538 participants who signed the consent form, 230 returned to complete the 1-month follow up assessment. Among these individuals, 92 made a serious attempt to quit smoking and 19 reported 7-day abstinence. Intention to quit smoking increased by 67% from baseline while 75% reported that they found the site helpful to quitting goals. The findings suggest that the web is a practical environment for delivering and evaluating smoking cessation interventions. More research is needed on Internet interventions, particularly on procedures to retain users for treatment and follow-up assessment. Internet interventions have the ability to treat large segments of the smoking population in a cost-effective manner. Stoddard, J.L., Delucchi, K.L., Munoz, R.F., Collins, N.M., Perez Stable, E.J., Auguston, E. and Lenert, L.L. Journal of Health Communication, 10, pp. 27-41, 2005.

Acute Nicotine Withdrawal Symptoms and Anxious Responding to Bodily Sensations

Dr. Zvolensky and colleagues from the University of Vermont conducted this study to determine whether acute nicotine withdrawal symptoms predict anxious responding to a biological challenge, relative to other established factors, like negative affectivity, anxiety sensitivity, and nicotine dependence. The sample consisted of 90 regular smokers who were in a state of relatively acute nicotine deprivation (approximately 120 min). Subjects were assessed for panic attack symptoms and self-reported anxiety before and after a 3-min voluntary hyperventilation challenge. Findings showed that acute nicotine withdrawal symptoms assessed pre-challenge predicted the post-challenge intensity of panic sensations. Moreover, the effect cannot be attributed to other theoretically relevant factors. This study is important because although previous work has found associations between panic and smoking, little research has investigated potential mechanisms by which smoking may contribute to panic problems. Zvolensky, M.J., Feldner, M.T., Leen-Feldner, E.W., Gibson, L.E., Abrams, K. and Gregor, K. Behaviour Research and Therapy, 43, pp. 1683-1700, 2005.

Cuban American Juvenile Offenders who Abuse Drugs Report Higher Rates of Some HIV Risk Behaviors than do Comparable African American Teens

Drs. Jessy Devieux and colleagues at Florida International University conducted a detailed assessment of HIV risk behaviors in a sub-sample of adolescents

participating in an HIV risk reduction intervention. Of the 137 participants in the interview assessment, 81 were African American teens and 57 were Cuban American teens, both with an average age of about 15.5 years old. Cuban American teens reported more unprotected sex acts and more anal sex acts in the 6 months prior to the interview than did African American teens. The groups were similar on the total number of sexual partners and sex acts reported. Regarding drug use, a greater proportion of Cuban American teens reported using drugs in the six months prior than did African American teens, and Cuban American teens reported engaging in unprotected sex while using drugs than did African American teens. The authors speculate that higher acculturation of Cuban American teens, and accompanying family conflict, may account for the relatively more risky behavior among Cuban American teens. More research is needed to clarify the processes leading teens of different backgrounds to initiate and maintain risky behaviors, and to identify the most effective ways to intervene to reduce risk. Devieux, J. G., Malow, R. M., Ergon-Perez, E., Samuels, D., Rojas, P., Kushal, S. R., Jean-Gilles, M. JSWPA, pp. 69-83, 2005.

Efficacy of Dose and Contingency Management Procedures in LAAM Maintained Cocaine-Dependent Patients

Dr. Oliveto and colleagues at Yale University randomly assigned opioid and cocaine dependent patients (n=140) to one of the following in a 12 week clinical trial: 1) LAAM (30,30,39mg/MWF) with contingency management; 2) LAAM (30,30,39mg/MWF) without contingency management; 3) LAAM (100, 100, 130mg/MWF) with contingency management; and 4) LAAM (100,100,130mg/MWF) without contingency management. Urine samples were collected 3 times per week. In contingency management, each urine negative for both opioids and cocaine resulted in a voucher worth a certain monetary value that increased for consecutively drug free urines. Vouchers were exchanged for mutually agreed upon goods and services. The groups did not differ on retention and baseline characteristics. Abstinence from both opioids and cocaine was greatest in the high dose LAAM plus contingency management group. However, contingency management procedures were not as effective in reducing cocaine use at the lower doses of LAAM. The results suggest than an efficacious maintenance dose may be necessary for contingencies to be effective in facilitating both opioid and cocaine abstinence in this dually dependent population. Oliveto, A., Poling, J., Sevarino, K.A., Gonsai, K.R., McCance-Katz, E.F., Stine, S.M., Kosten, T.R. Drug and Alcohol Dependence, 79(2), pp. 157-165, 2005.

Moderators of Effects of Motivational Enhancements to Cognitive Behavioral Therapy

Dr. Rosenblum and colleagues at the Institute for Treatment and Services Research, National Development and Research Institutes, Inc, in New York, conducted a study in which patient treatment matching hypotheses were tested for substance users randomly assigned to a group cognitive behavioral therapy (CBT; n=114) or a group motivational intervention (GMI; n=116). Treatment was scheduled twice weekly for 10 weeks. Using a patient attribute by treatment interaction design with a 15 week follow up, the study predicted that alexithymia, antisocial personality disorder, and network support for alcohol and drug use would be associated with less substance use for CBT subjects, and that hostility and lower motivation would be associated with less substance use for GMI subjects. Three of the hypothesized moderators were empirically supported: alexithymia, network support for alcohol, and antisocial personality disorder. The results indicate the use of assessing specific patient attributes to better inform treatment recommendations. Rosenblum, A., Cleland, C., Magura, S., Mahmood, D., Kosanke, N. and Foote, J. American J. Drug and Alcohol Abuse. 31(1), pp. 35-38, 2005.

Methadone versus Buprenorphine with Contingency Management or Performance Feedback for Cocaine and Opioid Dependence

Dr. Schottenfeld and colleagues at Yale University evaluated the efficacy of methadone vs. buprenorphine with contingency management or performance feedback for patients dependent on opioids and cocaine. One hundred and sixty -two subjects were provided manual guided counseling and randomly assigned in a double blind design to receive daily sublingual buprenorphine (12-16mg) or methadone (65-85mg, p.o.) and to contingency management or performance feedback. Contingency management subjects received monetary vouchers for opioid and cocaine negative urine tests; voucher value escalated during the first 12 weeks for consecutive drug free tests and was reduced to a nominal value in weeks 12-24. Performance feedback subjects received slips of paper indicating the urine test results. Primary outcome measures were the maximum number of consecutive weeks abstinent from illicit opioids and cocaine and the proportion of drug free tests. The findings indicate that the methadone treatment subjects remained in treatment significantly longer and achieved significantly longer periods of sustained abstinence and a greater proportion of drug free urine tests, compared with subjects who received buprenorphine. Subjects receiving contingency management achieved significantly longer periods of abstinence and a greater proportion of drug free tests during the period of escalating voucher value, compared with those who received performance feedback, but there were no significant difference between groups in these variables during the entire 24 -week study. The results suggest that methadone may be superior to buprenorphine for maintenance treatment of patients with co-occurring opioid and cocaine dependence. Combining methadone or buprenorphine with contingency management improved treatment outcome. Schottenfeld, R.S., Chawarski, M.C., Pakes, J.R., Pantalon, M.V., Carroll, K.M. and Kosten, T.R. American J. Psychiatry; 162(2), pp. 340-349, 2005.

Computer-based Brief Motivational Intervention for Perinatal Drug Use in Primary Care

Computer based brief motivational interventions may be able to reach a high proportion of at risk-individuals and thus have potential for significant population impact. Dr. Ondersma and colleagues at Wayne State University conducted a series of studies to determine the feasibility of delivering a computer-based brief motivational intervention, the Motivation Enhancement System (MES) for perinatal drug use. Overall, the women rated the MES as highly acceptable and easy to use and reported significant increases in state motivation at post-intervention and at one month follow up. These preliminary results suggest the feasibility of this approach. Ondersma, S.J., Chase, S.K., Svikis, D.S. and Schuster, C.R. Journal of Substance Abuse Treatment 28, pp. 304-312, 2005.

Cocaine Dependence and PTSD: A Pilot Study of Symptom Interplay and Treatment Preferences

Cocaine dependence and posttraumatic stress disorder (PTSD) frequently co-occur; however, little is known about patients' perceptions of symptom connectedness and preferences for treatment. Dr. Sudie Back and colleagues at the Medical University of South Carolina, conducted a preliminary investigation of patients' perceptions of symptom interplay and their preferences regarding concurrent or sequential models of psychotherapy, therapy format, and treatment modalities. Participants were 23 individuals with comorbid cocaine dependence and PTSD. The majority (95.5%) reported a functional relationship between cocaine use and PTSD symptoms. Improvement in PTSD symptoms

was typically (63.3%) associated with a decrease in cocaine use, and a worsening of PTSD symptoms was typically (86.4%) associated with an increase in cocaine use. In contrast, improvement/deterioration in cocaine use was not significantly related to subsequent improvement/deterioration in PTSD symptoms. This finding suggests that changes in PTSD symptoms may be an important risk factor to consider among individuals with cocaine dependence and PTSD. Approximately 41% preferred a concurrent model of therapy in which cocaine use and PTSD were treated simultaneously in therapy. The findings highlight the functional relationship between these two disorders and have direct implications for treatment interventions. Back, S.E., Brady, K.T., Jaanimagi, U. and Jackson, J.L. Addict Behavior, June 9, 2005 [Epub ahead of print].

Anxiety Disorders among Patients with Co-occurring Bipolar and Substance Use Disorders

Dr. Kolodziej and colleagues at Harvard and Boston University examined the prevalence and nature of anxiety disorder among treatment seeking patients diagnosed with current bipolar and substance use disorders, and investigated the association between anxiety disorders and substance use. Among 90 participants diagnosed with bipolar disorder I (n=75, 78%) or II (n=15, 22%), 43 (48%) had a lifetime anxiety disorder, with posttraumatic stress disorder (PTSD) occurring most frequently (n=21, 23%). They found that those with PTSD, but not with the other anxiety disorders assessed, began using drugs at an earlier age and had more lifetime substance use disorders, particularly cocaine and amphetamine use disorders, than those without PTSD. Most participants with PTSD were women, sexual abuse was the most frequently reported index trauma, and the mean age of the earliest index trauma occurred before the mean age of initiation of drug use. These findings highlight the heterogeneity of dually diagnosed patients, and the importance of further investigating the ramifications of a trauma history among those who are diagnosed with bipolar and substance use disorders. Kolodziej, M.E., Griffin, M.L., Najavits, L.M., Otto, M.W., Greenfield, S.F. and Weiss, R.D. Drug and Alcohol Dependence, 80(2), pp. 251-257, 2005.

Behavioral Treatment Approaches for Methamphetamine Dependence and HIV-Related Sexual Risk Behaviors Among Urban Gay and Bisexual Men

Dr. Shoptaw and colleagues evaluated the efficacy of four behavioral drug abuse treatments for reducing methamphetamine use and sexual risk behaviors in methamphetamine-dependent gay and bisexual men. Participants (N=162) were assigned to 16 weeks of one of four behavioral treatments: standard cognitive behavioral therapy (CBT), contingency management (CM), combined cognitive behavioral therapy and contingency management (CBT+CM) and a culturally tailored cognitive behavioral therapy (GCBT). CM and CBT+CM conditions were statistically better than CBT during treatment in retention, in longest period of consecutive urine samples negative for methamphetamine metabolites, and in the Treatment Effectiveness Score. GCBT significantly reduced unprotected receptive anal intercourse during the first four weeks of treatment. Between-group differences found during treatment, disappeared at follow-up with overall reductions in outcomes sustained to one-year. The authors conclude that among high-risk methamphetamine-dependent GBM, drug abuse treatments produced significant reductions in methamphetamine use and sexual risk behaviors. Drug abuse treatments merit consideration as a primary HIV prevention strategy for this population. Shoptaw, S., Reback C.J., Peck, J.A., Yang, X., Rotheram-Fuller, E., Larkins, S., Veniegas, R.C. Freese, T.E. and Hucks-Ortiz, C. Drug and Alcohol Dependence, 78(2), pp. 125-134, 2005.

Brief Motivational Intervention for Adolescent Smokers in Medical Settings

Investigators from Brown University conducted a study designed to determine the efficacy of two brief behavioral interventions for smoking cessation in adolescents treated in a hospital outpatient clinic or Emergency Department. Patients aged 14-19 years (N=85) were randomly assigned to receive either one session of motivational interviewing (MI) or standardized brief advice (BA) to quit smoking. Patients were proactively screened and recruited and not seeking treatment for smoking. Follow-up assessments were conducted at 1, 3, and 6 months post-intervention. Adolescents in both conditions reported smoking reductions at all three follow-ups. Those in the MI group also showed reduced cotinine levels at 3 months, unlike those in BA, and both groups showed reduced cotinine levels at 6 months. Overall, abstinence rates were low and did not differ between groups at 1 or 3 months. At 6 months, self-report data indicated that abstinence rates were significantly higher for the MI group than the BA group, but this difference was not confirmed biochemically. Groups did not differ in biochemically confirmed abstinence at any follow-up. The low rates of abstinence found are consistent with findings from other adolescent smoking cessation trials, which have generally effected only minimal change even among treatment-seeking adolescents. Colby, S.M., Monti, P.M., O'Leary Tevyaw, T. Barnett, N.P., Spirito, A., Rohsenow, D.J., Riggs, S. and Lewander, W. Addictive Behaviors, 30, pp. 865-874, 2005.

Smoking Stage of Change and Interest in an Emergency Department-based Intervention

This study sought to assess the prevalence and predictors of smoking stage of change and interest in an ED-initiated smoking intervention. Patients in an emergency department were interviewed immediately before discharge from the ED or transfer to an inpatient floor. Among those interviewed, 581 (40%) were current smokers, 117 (21%) were in precontemplation stage, 241 (43%) were in contemplation stage, and 197 (36%) were in preparation stage. Sixty-two percent endorsed at least "somewhat" agreement that smoking counseling should be provided in the ED, while nearly one half (49%) agreed to stay 15 extra minutes to do so. Fifty-nine percent of treating physicians/nurses screened patients for smoking status, however only 8% of patients reported receiving information about quitting. The findings indicate that most smokers have at least some desire to change and appear interested in ED smoking cessation counseling. Due to limited efforts in the ED, efforts may be better spent on counseling patients who are receptive and ready to change. Boudreaux, E.D., Baumann, B.M., Friedman, K. and Ziedonis, D.M. Acad Emerg Med, 12, pp. 211-218, 2005.

Intentions to Quit Smoking Change over Short Periods of Time

This study intended to assess the stability of intention to quit smoking over a 30-day period. One-hundred and fifteen US and Swedish smokers were randomized to complete Stage of Change (SOC) or ladder scales of intentions to quit at either 0, 7, 14, and 30 days or at 0 and 30 days in the absence of intervention. The results indicate that measures of intention to quit are often unstable over short periods of time. The results also indicate the four-assessment group had more progression in intention to quit than the two-assessment group, indicating that repeated measurement can influence intention outcomes. Hughes, J.R., Keely, J.P., Fagerstrom, K.O. and Callas, P.W. Addictive Behaviors, 30, pp. 653-662, 2005.

Distress Tolerance and Early Smoking Lapse

This paper discusses the theoretical and clinical implications of distress tolerance in smoking cessation. Whereas past work on smoking relapse has largely addressed the role of withdrawal symptoms and negative affect, the model presented by Brown et al. emphasizes that how one reacts to the discomfort of nicotine withdrawal is a more promising avenue of investigation. Development of a specialized and novel behavioral distress tolerance treatment for early smoking lapsers is proposed. Brown, R.A., Lejuez, C.W., Kahler, C.W., Strong, D.R., and Zvolensky, M.J. Clin Psychol Rev, 6, pp. 713-733, 2005.

The Effects of a Prison Smoking Ban on Smoking Behavior and Withdrawal Symptoms

This study investigated symptoms of distress and nicotine dependence as predictors of nicotine withdrawal symptoms among 188 incarcerated male smokers during a mandated smoking ban. Participants were assessed at three time periods: baseline, 4 days after the smoking ban, and 1 month after the smoking ban. Most smokers (76%) continued to smoke following the smoking ban. Smokers after the ban were more nicotine dependent and reported more withdrawal symptoms than participants that quit. An interaction was found such that distressed smokers had the highest level of nicotine withdrawal. The authors surmise that the low compliance with the smoking ban was due to low motivation to enforce the ban on the part of prison employees, since they were affected by the ban as well. These results have implications for how smoking bans are instituted in prison settings. Cropsey, K.L. and Kristeller, J.L. Addictive Behaviors, 30, pp. 589-594, 2005.

Acceptance of Nicotine Dependence Treatment Among Currently Depressed Smokers

Dr. Haug and colleagues at the University of California, San Francisco conducted this study to examine specific characteristics of psychiatric outpatients with depressive disorders who either accepted or refused available smoking cessation treatment. The sample (N=154) participated in a repeated contact experimental condition where they received a stage-based expert system program to facilitate treatment acceptance and were then offered smoking treatment, consisting of behavioral counseling, nicotine patch, and bupropion. Acceptors (N=53) were defined as those accepting behavioral counseling and pharmacological treatment at some point during the 18-month study, whereas refusers (n=101) received only the expert system. The number of days to treatment acceptance was significantly predicted by stage of change, with those in preparation entering treatment more quickly than contemplators or precontemplators. The variables most strongly associated with accepting treatment were current use of psychiatric medication and perceived success for quitting. Severity of depressive symptoms, duration of depression history, and history of recurrent depression were not related to treatment acceptance. The authors suggest that the findings have implications for the psychiatric assessment and treatment of smokers in clinical settings. Psychiatric medication may play a significant role in smoking cessation treatment acceptance by currently depressed smokers. Haug, N.A., Hall, S.M., Prochaska, J.J., Rosen, A.B., Tsoh, J.Y., Humfleet, G., Delucchi, K., Rossi, J.S., Redding, C.A. and Eisendrath, S. Nicotine and Tobacco Research, 7, pp. 217-224, 2005.

Contingency Management and Cognitive-Behavioral Treatment for Adolescent Marijuana Abuse Shows Promise

Investigators at the University of Vermont published data on an initial sample of 19 adolescents participating in a Stage-I treatment-development study targeting marijuana abuse and associated behavior problems. Adolescents participated in a 14-week treatment consisting of incentives for adolescent

abstinence, parent involvement in delivering contingencies, clinic-delivered incentives to parents for participation in treatment, and individual cognitive-behavioral treatment for adolescents. The results suggest that families had high levels of participation in treatment, and that abstinence from marijuana increased significantly from treatment entry to completion (improving from 37% abstinence to 74% abstinence). This study reports on a unique combination of two behavioral interventions found to be beneficial in treating drug abuse-contingency management and family involvement-and demonstrates that the two can be efficacious in treating adolescent marijuana abuse. Kamon, J., Budney, A. and Stanger, C. Journal of the American Academy of Child and Adolescent Psychiatry, 44, pp 513-521, 2005.

Researchers Should Evaluate Costs of Treatment in Addition to Efficacy and Effectiveness

Recognizing the role of cost in the availability and dissemination of treatments for drug abuse and related co-morbidities, Dr. William Fals-Stewart of the Research Triangle Institute and colleagues published guidelines to assist clinical researchers in including cost evaluations in their studies. Using marriage and family treatments as a model, the authors outline user-friendly guidelines to identify and define key constructs (i.e., cost, benefit, effectiveness), and offer recommendations of how to assess and analyze these constructs. This paper serves as a valuable tool in equipping researchers to design comprehensive studies of drug abuse treatment. Fals-Stewart, W., Yates, B.T. and Klosterman, K. Journal of Family Psychology, 19, pp. 28-39, 2005.

Ecologically-Based Family Therapy Reduces Drug Abuse among Substance Abusing Runaway Adolescents

Dr. Natasha Slesnick, recently joining the faculty at Ohio State University, and colleague Jillian L. Prestopnik, report on the efficacy of a family-based behavioral treatment for substance abuse among runaway teens. Substance-abusing teens were recruited at a homeless shelter, and 124 were randomly assigned to receive Ecologically-Based Family Therapy (EBFT) or to receive services as usual (SAU). Teens receiving EBFT had significantly greater reductions in substance use than did teens receiving SAU, with those reporting a history of physical or sexual victimization achieving even better outcomes in EBFT. Other areas of functioning (psychiatric diagnoses, delinquent behaviors, family functioning, knowledge of HIV risk, etc.) improved significantly for teens receiving either EBFT or SAU. These results suggest that a family-based behavioral treatment has potential to improve substance abuse among a high-risk population of runaway teens, and that there may be several avenues to intervening in other areas of functioning. Slesnick, N. and Prestopnik, J. L. Journal of Adolescence, 28, pp. 277-298, 2005.

Gender Differences among HIV-Positive Methadone Maintenance Patients Enrolled in a Medication Adherence Trial

Dr. Haug and colleagues at UCSF examined gender differences among HIV + methadone maintained patients on antiretroviral medications. Participants were enrolled in a larger clinical trial, which included a 4 week observation period using electronic monitors to track medication adherence. Contrary to previous literature, no significant differences were detected between men (n=42) and women (n=36) on medication adherence or depression. Both groups showed poor adherence during baseline (M=56% of doses taken on time), high overall prevalence of depression (47%) and illicit cocaine use (47%). Women reported significantly more medication side effects (M=21.4 vs.14.9), higher severity of ASI psychiatric problems (M=0.50 vs. 0.40), and lower SF-36 health related quality of life in physical (M=42.1 vs. 63.3) and emotional functioning (M=26.9

vs. 58.9) than men. Women tested positive for opioids at higher rates than men (53% vs. 29%, respectively, whereas men were more likely to be positive for benzodiazepines than women (26% vs. 6%, respectively). The findings suggest that gender differences between male and female methadone maintenance patients have relevance to treatment providers. Comprehensive assessment, specialized medical care and mental health services may be necessary in the treatment of HIV positive female drug abusers. Haug, N.A., Sorensen, J.L., Lollo, N.D., Gruber, C.A., Delucchi, K.L. and Hall, S.M. AIDS Care, 17(8), pp. 1022-1029, 2005.

Variations in Patterns of Highly Active Antiretroviral Therapy (HAART) Adherence

Strict adherence to HAART is necessary for successful suppression of HIV replication. A large number of individuals are non-adherent, however, and the reasons for non-adherence are varied and complex. Dr. Levine, Hinkin and colleagues at UCSF utilized cluster analyses to identify subgroups of adherers in a sample of 222 HIV positive individuals whose HAART use was electronically monitored. Five distinct subgroups were identified, with characteristic variations across the week and over the course of the 4-week study. Additional comparisons of demographic and behavioral variables found the poorer adherers to have higher rates of substance abuse, and that a group with higher rates of cognitive impairment had a consistent drop in adherence during the weekends. In addition, the group with the best adherence had more individuals over 50 years of age. The results suggest that interventions designed to improve adherence should be designed to accommodate this variability in adherence behavior. Levine, A.J., Hinkin, C.H., Castellon, S.A., Mason, K.L., Lam, M.N., Perkins, A., Robinet, M., Longshore, D., Newton, T., Myers, H., Durvasula, R.S. and Hardy, D.J. AIDS Behavior, 9(3), pp. 355-362, 2005.

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

Research Findings - Research on Pharmacotherapies for Drug Abuse

Effects of the Novel Kappa Opioid Receptor Antagonist, JDTic, on Reinstatement and Antidepressant Measures in Rats

The selective kappa opioid receptor antagonist, JDTic, was evaluated in two behavioral models relevant to the development of medications for the prevention of relapse to cocaine abuse. Both stress and depression have been linked to relapse to cocaine abuse in humans, so compounds with anxiolytic and antidepressant effects in animal models may have utility as treatments. JDTic administered orally at doses of 3, 10, and 30 mg/kg was found to dose-dependently block the effects of a footshock stressor to reinstate previously extinguished cocaine self-administration in Long-Evans rats. In contrast, JDTic did not block the effects of a priming injection of cocaine on reinstatement, suggesting that JDTic did not simply interfere with lever-pressing or have sedative effects. In the forced-swim test, JDTic reduced immobility and increased swimming in rats placed in a cylinder of water, which are effects similar to those produced by marketed SSRI antidepressants. It should be noted that JDTic has a long duration of action and was administered at least 23 hours prior to both tests. Kappa opioid receptor antagonism was verified by measuring blockade of kappa opioid receptor agonist-induced diuresis immediately after reinstatement testing; this ensured that relevant pharmacological activity was present at the time of testing. Taken together, the results suggest that JDTic has both anti-stress and antidepressant behavioral activity, which appears to be attributable to long-acting kappa opioid receptor antagonism. These effects may be desirable in a cocaine-relapse prevention treatment medication, and this compound is a promising lead that warrants further evaluation for safety and efficacy. Beardsley P.M., Howard, J.L., Shelton, K.L., and Carroll, F.I. Psychopharmacology 183, pp. 118-126, 2005.

A Randomized Placebo-controlled Trial of Gabapentin for Cocaine Dependence

In laboratory animals, augmentation of GABA neurotransmission results in inhibition of cocaine self-administration and inhibition of reinstatement to cocaine-seeking behaviors. If parallel effects were observed in humans, GABA-ergic medication should be effective both in the abstinence-induction as well as in the relapse-prevention phase of cocaine dependence treatment. Gabapentin is an anticonvulsant medication that increases human brain GABA levels. The safety and efficacy of gabapentin combined with relapse-prevention therapy in the treatment of cocaine-dependent individuals was evaluated. The study involved 129 individuals with cocaine dependence. Of the 99 participants who were randomized into a double-blind trial, 88% were males, 66% were minorities and with an average age of 39 years (range 22-58 years). After 2

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weeks of placebo lead-in, participants were randomized to receive either gabapentin 3200mg (1600mg bid) or placebo for 12 weeks, followed by 2 weeks of placebo lead-out. Prior to randomization, participants were stratified into four groups based on the principal route of cocaine use (smokers versus intranasal users) and the level of cocaine use during the 2 weeks of lead-in (high level versus low level). Throughout the 16 week study, participants received weekly individual relapse-prevention therapy. The outcome measures included: days of cocaine use and a binary indicator of abstinence based on urine toxicology test, self-reported cocaine craving and retention in treatment. Forty-nine percent of randomized patients completed 12 weeks of the trial. Retention did not differ by treatment group but cocaine-smokers dropped out of treatment at a significantly faster rate than intranasal users. For the entire sample, odds of cocaine use over the course of the study did not differ between gabapentin- and placebo-treated individuals. There was a significant difference in the odds of cocaine use between high and low-use groups, with the odds in high-use groups decreasing over time and odds in the low-use groups gradually increasing over the course of the study, such that by the end of the study low and high users were similarly likely to use cocaine. In the low-use group, there was a non-significant trend suggesting that gabapentin-treated subjects had more favorable outcome compared to placebo-treated individuals. There was no treatment effect on abstinence rates, craving or other substance use. Gabapentin at 3200mg/day was very well tolerated in this group of cocaine-dependent participants. When combined with weekly individual relapse-prevention therapy, gabapentin 1600mg bid was no more effective than placebo in the treatment of cocaine dependence. When reviewed in conjunction with other published studies, gabapentin and other GABA enhancing anticonvulsant medications may deserve further study as relapse-preventive agents in cocaine-dependent individuals who achieve abstinence early in treatment. Bisaga, A., Aharonovich, E., Garawi, F., Levin, F. R., Rubin, E., Raby, W. N. et al. Drug Alcohol Depend.,E- publication, 2005; A multisite double blind placebo controlled trial of 140 cocaine dependent patients was recently completed (data presented at CPDD 2005 by Eugene Somoza in a symposium entitled "Pharmacotherpy for Cocaine Addiction: An Update From NIDA/DPMC" which showed no effect for gabapentin over placebo in reducing cocaine use.

Anesthesia-Assisted vs Buprenorphine- or Clonidine-assisted Heroin Detoxification and Naltrexone Induction: A Randomized Trial

Rapid opioid detoxification with opioid antagonist induction using general anesthesia has emerged as an expensive, potentially dangerous, unproven approach to treat opioid dependence. To determine how anesthesia-assisted detoxification with rapid antagonist induction for heroin dependence compared with 2 alternative detoxification and antagonist induction methods. A total of 106 treatment-seeking heroin-dependent patients, aged 21 through 50 years, were randomly assigned to 1 of 3 inpatient withdrawal treatments over 72 hours followed by 12 weeks of outpatient naltrexone maintenance with relapse prevention psychotherapy. This randomized trial was conducted between 2000 and 2003 at Columbia University Medical Center's Clinical Research Center. Outpatient treatment occurred at the Columbia University research service for substance use disorders. Patients were included if they had an American Society of Anesthesiologists physical status of I or II, were without major comorbid psychiatric illness, and were not dependent on other drugs or alcohol. Anesthesia-assisted rapid opioid detoxification with naltrexone induction, buprenorphine-assisted rapid opioid detoxification with naltrexone induction, and clonidine-assisted opioid detoxification with delayed naltrexone induction. Withdrawal severity scores on objective and subjective scales; proportions of patients receiving naltrexone, completing inpatient detoxification, and retained in treatment; proportion of opioid-positive urine specimens. Mean withdrawal

severities were comparable across the 3 treatments. Compared with clonidine-assisted detoxification, the anesthesia- and buprenorphine-assisted detoxification interventions had significantly greater rates of naltrexone induction (94% anesthesia, 97% buprenorphine, and 21% clonidine), but the groups did not differ in rates of completion of inpatient detoxification. Treatment retention over 12 weeks was not significantly different among groups with 7 of 35 (20%) retained in the anesthesia-assisted group, 9 of 37 (24%) in the buprenorphine-assisted group, and 3 of 34 (9%) in the clonidine-assisted group. Induction with 50 mg of naltrexone significantly reduced the risk of dropping out (odds ratio, 0.28; 95% confidence interval, 0.15-0.51). There were no significant group differences in proportions of opioid-positive urine specimens. The anesthesia procedure was associated with 3 potentially life-threatening adverse events. These data do not support the use of general anesthesia for heroin detoxification and rapid opioid antagonist induction. Collins, E. D., Kleber, H.D., Whittington, R.A. and Heitler, N.E. JAMA, 294, pp. 903-913, 2005.

Response to Cocaine, Alone and in Combination with Methylphenidate, in Cocaine Abusers With ADHD

Attention deficit hyperactivity disorder (ADHD) is prevalent in adult cocaine abusers. Yet, it remains to be determined how the response to cocaine differs in cocaine abusers with ADHD compared to cocaine abusers without ADHD. Further, since ADHD is commonly treated with stimulants, such as methylphenidate (MPH), it is important to examine whether MPH maintenance alters the response to cocaine in cocaine abusers with ADHD. Thus, the first phase of this study compared the response to cocaine in adult cocaine abusers with ADHD to those without ADHD. The second phase assessed the effects of oral sustained-release methylphenidate (MPH-SR) maintenance (40 and 60mg) on the response to cocaine only in those with ADHD. Cocaine abusers with ADHD (N=7) and without ADHD (N=7) who were not seeking treatment remained inpatient initially for 1 week, when the effects of cocaine alone were tested (Phase 1). Cocaine abusers with ADHD remained inpatient for an additional 3 weeks, during which the effects of cocaine during oral MPH-SR maintenance were tested (Phase 2). During cocaine fixed dosing sessions, participants received four injections of i.v. cocaine (0, 16 or 48mg/70kg), spaced 14min apart. During cocaine choice sessions, participants had a choice between receiving i.v. cocaine (16 or 48mg/70kg) or two tokens, each exchangeable for US $2. Subjective effects related to ADHD symptoms (e.g. ratings of "Able to Concentrate") were significantly lower in cocaine abusers with ADHD compared to those without ADHD when placebo cocaine was administered. Active cocaine produced similar increases in cardiovascular and positive subjective effects in both groups and there was no difference in cocaine choice between the two groups. These data suggest that the response to cocaine is not different between cocaine abusers with ADHD compared to those without ADHD. When the cocaine abusers with ADHD were maintained on MPH-SR, cardiovascular effects were increased, however, this did not warrant termination of any test session. Maintenance on MPH-SR decreased some of the positive subjective effects of cocaine. Further, maintenance on a high dose of MPH-SR decreased cocaine choice. Thus, oral MPH-SR is safe in combination with repeated cocaine doses and decreases some of the positive and reinforcing effects of cocaine in cocaine abusers with ADHD. Collins, S.L., Levin, F.R., Foltin, R.W., Kleber, H.D. and Evans, S.M. Drug Alcohol Depend. (e-publication ahead of print) October 2005.

Buprenorphine Versus Methadone in the Treatment of Pregnant Opioid-dependent Patients: Effects on the Neonatal Abstinence Syndrome

Buprenorphine may be shown to be an alternate medication to methadone in

pregnant women. The purpose of this study was to compare the neonatal abstinence syndrome (NAS) in neonates of methadone and buprenorphine maintained pregnant opioid-dependent women and provide preliminary safety and efficacy data for a larger multi-center trial. In this randomized, double-blind, double-dummy, flexible dosing, parallel-group controlled trial, treatment involved daily administration of either sublingual buprenorphine or oral methadone using flexible dosing of 4-24 mg or 20-100 mg, respectively, Primary outcome measures were number of neonates treated for NAS; amount of opioid agonist medication used to treat NAS; length of neonatal hospitalization; and peak NAS score. Two of 10 buprenorphine-exposed and 5 of 11 methadone-exposed neonates were treated for NAS. Total amount of opioid-agonist medication administered to treat NAS in methadone-exposed neonates was three times greater than for buprenorphine-exposed neonates. Length of hospitalization was shorter for buprenorphine-exposed than for methadone-exposed neonates. Peak NAS total scores did not significantly differ between groups. Results suggest that buprenorphine is not inferior to methadone on outcome measures assessing NAS and maternal and neonatal safety when administered starting in the second trimester of pregnancy. Jones, H.E., Johnson, R.E., Jasinski, D.R., O'Grady, K.E., Chisholm, C.A., Choo, R.E., Crocetti, M., Dudas, R., Harrow, C., Huestis, M.A., Jansson, L.M., Lantz, M., Lester, B.M. and Milio, L. Drug Alcohol Depend. 79(1), pp. 1-10, July 2005.

Fetal Response to Maternal Methadone Administration

This study investigated the effect of methadone on fetal neurobehavioral functions and maternal physiologic indicators. Forty women were evaluated at peak and trough methadone levels. At peak methadone, fetal heart rate was slower, less variable, and displayed fewer accelerations. Fetuses displayed less motor activity and the integration between heart rate and motor activity was attenuated. Maternal heart rate and skin conductance were unchanged, but methadone administration was associated with lower respiratory rate. The conclusions were that maternal methadone administration has significant effects on fetal behavioral functions that are independent of maternal effects. Jansson, L.M., DiPietro, J. and Elko, A. Am. J. Obstetrics and Gynecology 193(3) pp. 611-617, September 2005.

Males and Females Differ in Response to Opioid Agonist Medications

Few clinical trials include sex as a factor. This analysis explored within-sex differences in response to opioid agonist medications. Males and females randomly assigned to buprenorphine, LAAM, or methadone were compared on opioid use and retention in treatment. Females receiving buprenorphine had less objective drug use than females receiving methadone, while males receiving LAAM had less objective drug use than males receiving buprenorphine. Retention in treatment was longer for both sexes receiving methadone versus LAAM. Within-subject change results indicate that all three medications benefit both sexes. Clinical trials should be designed to examine the impact of sex on outcomes. Jones, H.E., Fitzgerald, H.and Johnson, R.E. Am. J. Addict. 14(3) pp. 223-233, May-June 2005.

Isradipine Decreases the Hemodynamic Response of Cocaine and Methamphetamine: Results From Two Human Laboratory Studies

Massive hypertensive crises relating to cerebrovascular accidents such as strokes or ruptured aneurysms, or cardiovascular dysfunction and toxicity, are an important cause of morbidity and mortality associated with cocaine or methamphetamine use. Experimentally administered, pharmacologically effective doses of cocaine and methamphetamine may serve as a model for

studying the effects of these drugs on hemodynamic response and for examining the potential utility of the antihypertensive and dihydropyridine-class calcium channel antagonist isradipine to block these effects. This group examined, in two separate experiments of similar design conducted contemporaneously, the hemodynamic effects of cocaine or methamphetamine in the presence and absence of isradipine. In both experiments (total N = 31), isradipine pretreatment was provided to cocaine- or methamphetamine-dependent male and female subjects before intravenous administration of low and high doses of cocaine (0.325 or 0.650 mg/kg) or methamphetamine (15 or 30 mg), respectively, on separate test days. The results showed that both cocaine and methamphetamine administration produced predicted elevations in blood pressure (with peak response between 1 and 3 min after infusion). Apart from tachycardia, no arrhythmias were reported. Isradipine significantly reduced stimulant-associated increases in all measures of blood pressure except pulse pressure, but tended to enhance the effects of these drugs on heart rate. The conclusions were that clinical studies are needed to determine whether isradipine is therapeutically efficacious in preventing hypertensive crises and the associated cerebrovascular and cardiovascular sequelae in cocaine- or methamphetamine-dependent individuals. As there is no established pharmacotherapy for treating cocaine or methamphetamine dependence, identification of a medication that reduces the harmful medical consequences of these drugs would be scientifically and clinically important. Johnson, B.A., Wells, L.T., Roache, J.D., Wallace, C., Ait-Daoud, N. and Wang, Y. Am. J. Hypertens. 18(6), pp. 813-822, June 2005.

Comparison of Pharmacological Treatments for Opioid-dependent Adolescents: A Randomized Controlled Trial

The prevalence of heroin and other opioid use has markedly increased among adolescents in the last decade; however, virtually no research has been conducted to identify effective treatments for this population. The objective of this study was to evaluate the relative efficacy of two pharmacotherapies, buprenorphine hydrochloride and clonidine hydrochloride, in the detoxification of opioid-dependent adolescents. A double-blind, double-dummy, parallel-groups randomized controlled trial was conducted in a university-based research clinic from October 2001 to December 2003. Patients were a volunteer sample of 36 adolescents who met DSM-IV criteria for opioid dependence (ages 13-18 years eligible). Participants were randomly assigned to a 28-day, outpatient, medication-assisted withdrawal treatment with either buprenorphine or clonidine. Both medications were provided along with thrice weekly behavioral counseling and incentives contingent on opiate abstinence. Postdetoxification, all participants were offered the opportunity for continued treatment with the opiate antagonist, naltrexone hydrochloride. The main outcome measures were treatment retention, opiate abstinence, and human immunodeficiency virus risk behavior, along with measures of withdrawal and medication effects. The results of the study showed that a significantly greater percentage of adolescents who received buprenorphine were retained in treatment (72%) relative to those who received clonidine (39%) ($P<.05$). For those in the buprenorphine group, a significantly higher percentage of scheduled urine test results were opiate negative (64% vs 32%; $P = .01$). Participants in both groups reported relief of withdrawal symptoms and drug-related human immunodeficiency virus risk behavior. Those in the buprenorphine condition generally reported more positive effects of the medication. No evidence of opioid intoxication or psychomotor impairment was observed. Sixty-one percent of participants in the buprenorphine condition and 5% of those in the clonidine group initiated treatment with naltrexone. This study suggests that combining buprenorphine with behavioral interventions is significantly more efficacious in the treatment of opioid-dependent adolescents relative to combining clonidine and behavioral interventions. Marsch, L.A., Bickel, W.K., Badger, G.J., Stothart, M.E., Quesnel, K.J., Stanger, C. and

Brooklyn, J. Arch. Gen. Psychiatry, 62(10), pp. 1157-1164, October 2005.

Gender Effects Following Repeated Administration of Cocaine and Alcohol in Humans

Use of cocaine, alcohol, and the two drugs simultaneously is common and the risk of morbidity and mortality associated with these drugs is widely reported. This group carried out a double-blind, placebo-controlled, randomized study examining gender differences in response to administration of these drugs alone and in combination. Current users of cocaine and alcohol (n = 17) who met diagnostic criteria (DSM-IV) for cocaine dependence and alcohol abuse or dependence (not physiologically dependent on alcohol) and who were not seeking treatment for substance use disorders gave voluntary, written, informed consent to participate in three drug administration sessions:1) four doses of intranasal cocaine (1 mg/kg every 30 min) with oral alcohol (1 g/kg following the initial cocaine dose and a second drink at +60 min (120 mg/kg) calculated to maintain a plasma alcohol concentration of approximately 100 mg/dL; 2)four doses of cocaine and alcohol placebo; 3) cocaine placebo and alcohol. Pharmacokinetics were obtained by serial blood sampling, physiological measurements (heart rate and blood pressure) were obtained with automated equipment, and subjective effects were assessed using visual analog scales over 480 min. The results showed that responses to cocaine, alcohol, and cocaine-alcohol were equivalent by gender for most measurements. Women had higher heart rates following alcohol administration ($p = .02$). Women consistently reported higher ratings for "Feel Good", a measure of overall mental/physical well-being, for all study conditions, reaching statistical significance for cocaine ($p = .05$) and approaching significance for alcohol administration ($p = .1$). Women showed equivalent responses to drug administration with the exception of perception of well-being, which was significantly increased for women. These findings may have implications for differential risk for acute and chronic toxicity in women. McCance-Katz, E.F., Hart, C.L., Boyarsky, B., Kosten, T. and Jatlow, P. Subst. Use Misuse 40(4), pp. 511-528, 2005.

Safety and Immunogenicity of a Nicotine Conjugate Vaccine in Current Smokers

Immunotherapy is a novel potential treatment for nicotine addiction. The aim of this study was to assess the safety and immunogenicity of a nicotine conjugate vaccine, NicVAX, and its effects on smoking behavior. Smokers (n = 68) were recruited for a noncessation treatment study and assigned to 1 of 3 doses of the nicotine vaccine (50, 100, or 200 microg) or placebo. They were injected on days 0, 28, 56, and 182 and monitored for a period of 38 weeks. Results showed that the nicotine vaccine was safe and well tolerated. Vaccine immunogenicity was dose-related ($P < .001$), with the highest dose eliciting antibody concentrations within the anticipated range of efficacy. There was no evidence of compensatory smoking or precipitation of nicotine withdrawal with the nicotine vaccine. The 30-day abstinence rate was significantly different across the 4 doses ($P = .02$), with the highest rate of abstinence occurring in the 200 microgram group. The nicotine vaccine appears to be a promising medication for tobacco dependence. Hatsukami, D.K., Rennard, S., Jorenby, D., Fiore, M., Koopmeiners, J., de Vos, A. et al. Clin.Pharmacol.Ther., 78, pp. 456-467, 2005.

Effects of Cigarette Reduction on Cardiovascular Risk Factors and Subjective Measures

This study, conducted at the University of Minnesota, randomized smokers interested in significantly reducing cigarette use but not quitting to either start

12 weeks of smoking reduction immediately (n = 102), assisted by nicotine replacement therapy, or to a 6-week wait list (n = 49). Those starting smoking reduction were required to reduce smoking by 25% for 2 weeks, 50% for 2 weeks, and 75% during the final 2 weeks. After 6 weeks, the subjects were asked to maintain a 50% reduction or quit. Nicotine gum and, if necessary, nicotine patch were used to achieve reduction goals. The wait list group (n = 49) smoked ad libitum for 6 weeks and then reduced smoking as previously described. Cardiovascular biomarkers (eg, WBC count, cholesterol concentrations, BP, heart rate) were assessed at several time points after enrollment. During ad libitum smoking, cardiovascular biomarkers remained relatively stable with correlation coefficients across the various time measurements, ranging from 0.44 to 1.00 ($p < 0.01$ for all measures). Among successful nonabstinent reducers (64 of 151 subjects), significant improvements were found in many biomarkers (eg, hemoglobin, hematocrit, RBC and WBC counts, lipids, BP, heart rate, respiratory symptoms, all $p < 0.0167$). These results show the availability of reliable and dose-sensitive biomarkers and that reduction in smoking can lead to significant but only modest changes in cardiovascular risk factors in healthy smokers. It is not known whether the reductions in cardiovascular risk factors observed after smoking reduction are also associated with reduced disease risk. Additional research is necessary to address this issue. Hatsukami, D.K., Kotlyar, M., Allen, S., Jensen, J., Li, S., Le, C. et al. Chest, 128, pp. 2528-2537, 2005.

Treatment of Methadone-maintained Patients With Adult ADHD: Double-blind Comparison of Methylphenidate, Bupropion and Placebo

The purpose of this double-blind, three-arm, 12-week trial was to compare the efficacy of sustained-release methylphenidate or sustained-release bupropion to placebo in treating adult attention deficit hyperactivity disorder (ADHD) symptoms. The randomized sample consisted of 98 methadone-maintained patients who were predominately male (57%) and 40% Caucasian, 40% Hispanic and 20% African American. All participants met DSM-IV criteria for adult ADHD, with 53% meeting DSM-IV criteria for cocaine dependence/abuse. In addition to medication and treatment as usual at a methadone program, individuals received weekly individual cognitive behavioral treatment. Other than current employment status, there were no significant demographic differences across the three treatment groups. Seventy percent completed the 12-week trial. There were no differences in retention rate based on treatment group. A reduction in ADHD symptoms using the adult ADHD rating scale was observed in all three groups, but there were no significant differences in outcome between treatments. The placebo response rate was high, with 46% of the placebo group self-reporting substantial improvement in their ADHD symptoms (>30% reduction in adult ADHD rating scale). Using other ADHD outcome measures, the placebo response and medication response rates were substantially lower. There was no evidence of misuse of medication or worsening of cocaine use among those randomized to methylphenidate. Taken together, sustained-release methylphenidate or sustained-release bupropion did not provide a clear advantage over placebo in reducing ADHD symptoms or additional cocaine use in methadone-maintained patients. Levin, F.R., Evans, S.M., Brooks, D.J., Kalbag, A.S., Garawi, F. and Nunes, E.V. Drug Alcohol Depend (E-publication ahead of print) 2005.

What Came First, Major Depression or Substance Use Disorder? Clinical Characteristics and Substance Use Comparing Teens in a Treatment Cohort

This study utilized data on a treatment cohort from a randomized clinical trial that recruited adolescents with co-occurring major depression and substance

use disorder (N=126). The purpose of this study was to compare adolescents for whom the onset of depression was first versus those for whom the onset of substance use disorder was first or in the same year as depression. Intake clinical evaluations were abstracted to yield common stressors that included childhood abuse, early loss or death, exposure to violence, and attachment problems. Tobacco, alcohol, and cannabis initiation and dependence were compared for the depression first and substance use disorder first groups, and within those groups by gender. Among the substances studied, only cannabis dependence was significantly more prevalent among those with depression first. Comparisons suggest some differences in the developmental path toward comorbid depression and substance use disorders, but remarkable similarity in measures of dependence and severity. Although small samples limited statistical significance, observed differences suggest possible avenues for prevention or intervention. Libby, A M., Orton, H.D., Stover, S.K. and Riggs, P.D. Addict Behav, 30, pp. 1649-1662, 2005.

Smoking Policies in U.S. Outpatient Drug Treatment Facilities

Most drug treatment patients smoke cigarettes, and some facilities are beginning to help patients quit. Facility smoking policies can help or hinder this effort. The present study describes smoking policies in outpatient drug treatment. It is a secondary analysis of a survey on smoking cessation treatment in outpatient methadone maintenance facilities in the United States. One clinic leader (a medical director, head nurse, or clinic director) from each of the 697 U.S. facilities was invited to participate in the study. Main outcome measures included whether clinics had a written smoking policy as well as the types of indoor and outdoor policies in place for patients and staff. A total of 408 (59%) of U.S. clinics responded. Most clinics (73%) had a written smoking policy for patients, and more (82%) had written policies for staff. Over 90% banned indoor smoking by staff and patients. Few totally banned outdoor smoking. Approximately half in some way restricted where patients (48%) and staff (55%) smoke outdoors. Compared with clinics that did not treat nicotine dependence, significantly more clinics that treated nicotine dependence had written policies on smoking and restricted outdoor smoking for patients and staff. Likewise, many public clinics and those affiliated with hospitals had outdoor smoking restrictions for patients and staff. Drug treatment facilities routinely ban alcohol use and drug dealing on their grounds. Only 1 in 10 ban smoking. Outpatient facilities should restrict or ban outdoor tobacco use in order to remain consistent with their mission and avoid sabotaging clinic efforts to treat, and patient and staff efforts to stop, smoking. Richter, K.P., Choi, W.S. and Alford, D.P. Nicotine Tob Res, 7, pp. 475-480, 2005.

Cigarette Smoking Among Marijuana Users in the United States

The vast majority of drug users smoke cigarettes. Most use marijuana and no other illicit drug. Adult responses to the 1997 NHSDA (n = 16,661) were analyzed to explore relationships between marijuana use and cigarette smoking. Multivariate analyses controlled for other illicit drug use and other potential covariates. Nearly three-quarters of current marijuana users (74%) smoked cigarettes. Compared to nonusers, the adjusted odds of being a smoker were 5.43 for current marijuana users, 3.58 for past year marijuana users, and 2.02 for former marijuana users. Odds for cigarette smoking among current poly-drug users, compared to nonusers, were 2.3 to 1. Level of cigarette smoking was directly associated with frequency of marijuana use. Nationwide, an estimated 7 million adults smoke both substances and are at increased risk for respiratory illnesses and mortality. Cigarette smoking is a major co-morbidity of marijuana use and smoking cessation should be addressed among marijuana users in addition to their other illicit drug involvement. Richter, K. P., Kaur, H., Resnicow, K., Nazir, N., Mosier, M. C. and Ahluwalia, J.S. Subst Abuse, 25, pp. 35-43, 2005.

Effects of Tiagabine in Combination With Intravenous Nicotine in Overnight Abstinent Smokers

Preclinical studies suggest that medications enhancing the brain gamma amino butyric acid (GABA) system attenuate the rewarding effects of stimulants including nicotine. These preclinical studies have not been followed up in systematic human studies. This study was conducted to examine the effects of a GABAergic medication, tiagabine, on acute physiological and subjective effects of intravenous (i.v.) nicotine and on tobacco withdrawal symptoms in overnight abstinent smokers. The proposed mechanism of action for tiagabine is selective inhibition of GABA transporter type I, which leads to increases in synaptic GABA levels. Eight male and four female smokers participated in a double-blind, placebo-controlled, crossover study. In each of three experimental sessions, participants were treated orally with a single 4- or 8-mg dose of tiagabine or placebo. Two hours following the medication treatment, participants received i.v. saline, followed 30 min later by 1.5 mg/70 kg i.v. nicotine. Tiagabine treatment did not affect the heart rate or blood pressure changes induced by nicotine. There was a significant treatment effect for the subjective responses to nicotine, such that tiagabine, compared to placebo, attenuated the ratings of "good effects" and "drug liking." Tiagabine treatment at 8 mg attenuated the craving for cigarettes and enhanced the cognitive performance in the Classical Stroop Tests, compared to placebo or 4 mg tiagabine condition. These results suggest that the GABA enhancing medication tiagabine may reduce the rewarding effects of nicotine and improve cognitive performance in abstinent smokers. The utility of GABA medications for smoking cessation needs to be examined further in controlled clinical trials. Sofuoglu, M., Mouratidis, M., Yoo, S., Culligan, K. and Kosten, T. Psychopharmacology (Berl), 181, pp. 504-510, 2005.

Tiagabine Affects the Subjective Responses to Cocaine in Humans

In preclinical studies, medications which increase the synaptic GABA levels have been shown to block cocaine reinforcement. In this study, the interaction between a GABA enhancing medication, tiagabine, and cocaine in cocaine users was examined. A total of 7 subjects, 5 male and 2 female cocaine users had 2 experimental sessions. Before each session, subjects received either two oral doses of 4 mg of tiagabine or placebo. Starting 2 h after the second dose of medication treatment, subjects received an injection of saline followed by 2 escalating cocaine doses (0.15 and 0.3 mg/kg) intravenously. Tiagabine treatment did not affect the cocaine-induced blood pressure and heart rate changes but attenuated the subjective ratings of "stimulated" and "crave cocaine" in response to cocaine administration. These results suggest that tiagabine treatment attenuates some of the subjective effects of cocaine without affecting its cardiovascular effects. GABA medications, including tiagabine, are currently being evaluated in controlled clinical trials for the treatment of cocaine dependence. Sofuoglu, M., Poling, J., Mitchell, E. and Kosten, T. R. Pharmacol. Biochem. Behav., (e-publication ahead of print) December 2005.

Applicability of the Fagerstrom Test for Nicotine Dependence in Smokers With Schizophrenia

Up to 90% of individuals with schizophrenia smoke cigarettes, and many show signs of heavy dependence. Although the severity of nicotine dependence is often measured by the six-item Fagerstrom Test for Nicotine Dependence (FTND), this measure, in its current form, may not be as appropriate in this population--or in others whose smoking is regulated by others--as in the general population due to differences in smoking patterns, living arrangements,

and daily routines. These factors may produce an underestimate of nicotine dependence, which may have clinical implications for successful medical detoxification if the FTND scores are used to guide the dosage of nicotine replacement medication. Data indicate poor internal consistency reliability (alpha=.4581) and a factor pattern lacking simple structure (i.e., two nonmeaningful factors/components with substantial cross loadings) when administered to smokers with schizophrenia. Specific examples of problematic items and how these may contribute to an underestimate of tobacco dependence severity are discussed, as well as ways to modify the FTND to be more appropriate for this population. Steinberg, M.L., Williams, J.M., Steinberg, H.R., Krejci, J.A. and Ziedonis, D.M. Addict.Behav., 30, pp. 49-59, 2005.

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

Research Findings - Research on Medical Consequences of Drug Abuse and Infections: AIDA/HIV/HEP C Co-Infection

Management and Treatment of Injection Drug Users with Hepatitis C Virus (HCV) Infection and HCV/Human Immunodeficiency Virus Coinfection

Injection drug use is the major mode of hepatitis C virus (HCV) transmission in developed countries. Despite this, relatively few current and recovering injection drug users (IDUs) have received HCV treatment. Studies among individuals with a recent history of injection drug use or those receiving drug dependency treatment have provided evidence that these groups can be successfully treated for chronic HCV infection. These studies have provided the impetus to change guidelines for treatment of current and recovering IDUs, with a move toward individualized HCV treatment assessment and the removal of defined periods of illicit drug use abstinence. Strategies to improve access to HCV treatment for current and recovering IDUs include drug dependency treatment education and training for hepatologists and other HCV treatment physicians, HCV treatment education and training for addiction medicine physicians, development of multidisciplinary clinics, and peer-based education and support for individuals considering and receiving HCV treatment. Dore, G.J. and Thomas D.L.M., Semin Liver Dis. 25(1), pp. 18-32, February 2005.

Treating Hepatitis C Virus Infection in Active Substance Users

Although injection drug users represent the majority of new and existing cases of infection with hepatitis C virus (HCV), many lack access to treatment because of concerns about adherence, effectiveness, and re-infection. On the basis of a small but increasing body of evidence showing that injection drug users can undergo treatment for HCV infection successfully, the 2002 National Institutes of Health Consensus Statement on Hepatitis C has recommended that substance users be treated for HCV infection on a case-by-case basis. However, the criteria on which these treatment decisions should be made are unclear. The duration of pretreatment abstinence, concurrent psychiatric illness, intervening drug use, and the potential for injected interferon to cause relapse of drug use may all influence results of treatment for HCV infection. This overview presents preliminary data on the impact of these potential barriers on outcomes of treatment for HCV infection. Sylvestre, D.L. Clin Infect Dis, 40 Suppl 5:S321-4, April 15, 2005.

Prospective Evaluation of Community-acquired Acute-phase Hepatitis C Virus Infection

More than two-thirds of hepatitis C virus (HCV) infections in Western countries

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are caused by injection drug use, but prospective clinical data regarding the most common mode of HCV acquisition are rare, in part because acute-phase HCV infection is usually asymptomatic. To characterize acute-phase HCV infection, 179 HCV antibody-negative injection drug users were prospectively evaluated; 62 (34%) of these patients had seroconverted. Twenty of the participants who seroconverted had long-term follow-up with consistent monthly sampling before and after seroconversion, allowing detailed study. The first indication of HCV infection was the presence of HCV RNA in serum, which preceded elevation of alanine transaminase levels and total bilirubin levels to equal or greater than 2 times baseline in 45% and 77% of patients, respectively. No subjects had jaundice. The median time from initial viremia to seroconversion was 36 days (range, 32-46 days). In one instance, viremia was detected 434 days before seroconversion. However, in no other case was HCV RNA detected >63 days before seroconversion. In subjects with viral persistence, a stable level of HCV RNA in the blood was noted in some subjects within 60 days after the initial detection of viremia, but in others, it was not apparent until >1 year later. In subjects with long-term viral clearance, HCV became persistently undetectable as early as 94 and as late as 620 days after initial viremia. These data underscore the importance of nucleic acid screening of blood donations to prevent HCV transmission and of long-term follow-up to ascertain whether there is viral persistence, at least among injection drug users. Cox, A.L., Netski, D.M., Mosbruger, T., Sherman, S.G., Strathdee, S., Ompad, D., Vlahov, D., Chien, D., Shyamala, V., Ray, S.C. and Thomas, D.L. Clin Infect Dis. 40(7), pp. 951-958, April 1, 2005.

Epidemiology and Natural History of Hepatitis C Virus Infection in Injection Drug Users: Implications for Treatment

Effective methods to diminish the burden of hepatitis C virus (HCV) infection among injection drug users (IDUs) require consideration of the epidemiology and natural history of both hepatitis C and drug use. Most HCV infections are due to injection drug use, and most IDUs have HCV infection. In addition, HCV infection often occurs with other medical problems, such as human immunodeficiency virus infection and depression, which may complicate its recognition and management. Infection with HCV can be fatal, but usually not until years later, and persons may be unaware of the infection, allowing an individual to infect many others. Effective treatment is available for HCV infection; however, the therapy is prolonged, involving both weekly injections and daily oral medication, and is typically associated with significant adverse effects, such as fatigue, depression, and, rarely, life-threatening complications. Although clearly some IDUs want their HCV infection to be treated, many are unwilling or unable to initiate or sustain treatment with currently available therapies, and IDUs who are treated require considerable, multidimensional support. Solutions to the problem of HCV infection among IDUs must account for these facts. Sulkowski, M.S. and Thomas, D.L. Clin Infect Dis. 40 Suppl 5:S263-269, April 15, 2005.

The Hepatitis C Virus Alternate Reading Frame (ARF) and its Family of Novel Products: The Alternate Reading Frame Protein/F-protein, the Double-frameshift Protein, and Others

The hepatitis C virus (HCV) has an alternate reading frame (ARF) that overlaps the core protein gene. The overlapping reading frame distinguishes HCV from all of its known viral relatives, with the possible exception of GB virus B (GBV-B). The ARF is expressed during natural HCV infections and stimulates specific immune responses. Like several essential genes in other viruses (e.g., the human immunodeficiency virus polymerase) the ARF lacks an in-frame AUG start codon, suggesting that its expression involves unusual translation-level events. In vitro studies indicate that ribosomal frameshifting may be one of several processes that can lead to translation of the ARF. Frameshifting yields

chimeric proteins that have segments encoded in the core gene covalently attached to amino acids encoded in the ARF. A consistent nomenclature for the ARF's protein products has yet to be established. The authors propose that all proteins that contain amino acids encoded in the + 1 ARF be called alternate reading frame proteins (ARFPs) and that specific ARFPs, such as the ARFP/F-protein, the double-frameshift protein, and the short form of core + 1, be designated as follows: ARFP/F (ARFP/F-protein), ARFP/DF (double-frameshift), and ARFP/S (short form of core + 1). The roles of ARFPs in the HCV life cycle are not yet known. There is a significant possibility that ARFPs may be responsible for some of the effects attributed to the core protein, given that most studies seeking to define the function of the core protein have employed materials likely to contain a combination of the core protein and ARFPs. The observed effects of the core protein include the induction of liver cancer, transformation of cells, and alterations of immune responses. This article reviews the discovery of ARF, describes the RNA structural elements involved in core/ARF gene expression, discusses possible functions of ARFPs, and considers the potential usefulness of ARFPs in vaccines. The HCV ARF is the focus of a new and rapidly expanding area of research, and the results of many ongoing studies are currently available in abstract form only. The preliminary nature of investigations that have not yet been reviewed by peers is noted in the text. Branch, A.D., Stump, D.D., Gutierrez, J.A., Eng, F. and Walewski, J.L. Semin Liver Dis. 25(1), pp. 105-117, February 2005.

A Framework for Understanding Factors that Affect Access and Utilization of Treatment for Hepatitis C Virus Infection among HCV-mono-infected and HIV/HCV-co-infected Injection Drug Users

Treatment for hepatitis C virus (HCV) is rarely received by injection drug users (IDU), particularly those co-infected with HIV. The authors propose a framework for understanding factors that affect utilization and adherence to HCV therapy among HCV mono-infected and HIV/HCV-co-infected IDU. Provision of treatment requires calculation of risks and benefits including evaluation of a number of time-varying factors that collectively determine a gradient of treatment eligibility, advisability and acceptability, the relative importance of which may differ in co-infected and mono-infected IDU. Treatment eligibility is determined by a number of non-modifiable and modifiable contraindications, the latter of which can change over time rendering patients who were once ineligible eligible. Among those eligible, treatment need can be assessed by liver biopsy and therapy may be deferred in those with no liver disease and started in those with significant liver disease. Among those with moderate disease, further consideration of treatment advisability (medical factors that affect treatment response) and acceptability (individual, provider and environmental barriers) is needed before treatment decisions are made. These factors are dynamic and thus should be continually evaluated even among those who may not initially appear to be ready for treatment. An evaluation of this framework is needed to determine applicability and feasibility. Until then, treatment decisions should be made on an individual basis after careful consideration of these issues by provider and patient and efforts to develop novel strategies for identifying IDU who need treatment most (alternatives to liver biopsy) and multidimensional approaches to deliver treatment for HCV while addressing other factors including HIV infection, depression and drug use should be continued. Mehta, S.H., Thomas, D.L., Sulkowski, M.S., Safaein, M., Vlahov, D. and Strathdee, S.A. AIDS. 19 Suppl 3:S179-S189, October 2005.

Liver Enzyme Values in Injection Drug Users with Chronic Hepatitis C

Liver enzymes fluctuate in chronic hepatitis C virus infection. However, the range that can be attributed to the course of hepatitis C virus (versus an intercurrent cause of hepatitis) is unknown. The aim of this study was to characterize the range of liver enzyme values as a function of the upper limit of normal (ULN) of the assay among persons chronically infected with hepatitis C virus. Patients comprised one thousand and fifty-nine hepatitis C virus chronically infected individuals with < or =5 semi-annual evaluations. Alanine aminotransferase and aspartate aminotransferase levels were prospectively obtained. Potential causes of elevations were examined using serologic testing. Among 1059 individuals, 11,463 enzyme measurements were obtained over 6.5 years, of which 63.5% were <1.25x ULN, 26.5% were 1.25-2.5x ULN, 8.3% were 2.5-5x ULN, and 1.6% were 5-10x ULN; only 0.2% were>10x ULN. Elevations >10x ULN were transient, the alanine aminotransferase/aspartate aminotransferase ratio tended to be different at the time of the elevation compared to before and after and 24% were associated with acute viral hepatitis. On the other hand, subjects with elevations 5-10x ULN tended to have elevated levels throughout follow-up and only 8% were associated with acute viral hepatitis. Authors concluded that liver enzymes fluctuate up to 5x ULN in most hepatitis C virus-infected persons; clinicians should seek alternate explanations for those with higher alanine aminotransferase or aspartate aminotransferase levels, especially among hepatitis C virus-infected persons with greater than 10-fold elevations. Mehta, S.H., Netski, D., Sulkowski, M.S., Strathdee, S.A., Vlahov, D. and Thomas, D.L. Liver Enzyme Values in Injection Drug Users with Chronic Hepatitis C. Dig Liver Dis. 37(9), pp. 674-680, September 2005.

The Effect of HIV Infection on Overdose Mortality

The objectives of this study were to quantify the association of HIV infection with overdose mortality and explore the potential mechanisms. This was a prospective cohort study in which a total of 1927 actively injecting drug users who were HIV seronegative at baseline, of whom 308 later HIV seroconverted, were followed semi-annually for death from 1988 to 2001. Survival analyses using marginal structural and standard Cox models were used to evaluate the effect of HIV infection on the risk of overdose mortality. Results indicated that overdose death rates were higher in HIV-seropositive than HIV-seronegative drug users: 13.9 and 5.6 per 1000 person-years, respectively (P< 0.01). The hazard ratio (HR) was 2.54 [95% confidence interval (CI) 1.47, 4.38] for the marginal structural model and 2.06 (95% CI 1.25, 3.38) for the standard Cox model, both adjusted for demographics, drug injection characteristics, alcohol abuse, substance abuse treatment, and sexual orientation. Adjusting for possible time-varying mediators (i.e. drug use, medical conditions and healthcare access) in extended marginal structural models reduced the effect of HIV on overdose mortality by 30% (HR 1.82, 95% CI 1.01, 3.30). Abnormal liver function was associated with a higher risk of overdose mortality (HR 2.00, 95% CI 1.05, 3.84); adjustment for this further reduced the effect of HIV on overdose mortality. The authors conclude that HIV infection was associated with a higher risk of overdose mortality. Drug use behavior, systematic disease and liver damage associated with HIV infection appeared to account for a substantial portion of this association. The data suggest a group to target with interventions to reduce overdose mortality rates. Wang, C., Vlahov, D., Galai, N., Cole, S.R., Bareta, J., Pollini, R., Mehta, S.H., Nelson, K.E. and Galea, S. AIDS. 19(9), pp. 935-942, June 10, 2005.

Non-fatal Overdose and Subsequent Drug Treatment Among Injection Drug Users

Overdose is a leading cause of death among illicit drug users. Nine hundred twenty-four injection drug users (IDUs) in Baltimore, Maryland, were interviewed to characterize overdose events and determine the circumstances

under which they lead to drug treatment. Overall, 366 (39.7%) reported at least one non-fatal drug overdose. Most (96.2%) used heroin on the day of their last overdose and almost half (42.6%) used heroin and alcohol but few (4.1%) used tranquilizers or benzodiazepines. Five percent were in drug treatment when the overdose occurred and 7.1% had been incarcerated 2 weeks prior. One in four IDUs (26.2%) sought drug treatment within 30 days after their last overdose of whom 75% enrolled. Speaking with someone about drug treatment after the overdose was associated with treatment seeking (AOR 5.22; 95% CI: 3.12, 8.71). Family members were the most commonly cited source of treatment information (53.7%) but only those who spoke with spouses, crisis counselors and hospital staff were more likely to seek treatment. Not being ready for treatment (69.6%) and not viewing drug use as a problem (30.7%) were the most common reasons for not seeking treatment and being placed on a waiting list was the most common reason for not subsequently enrolling in treatment (66.7%). Of the IDUs treated by emergency medical technicians, ER staff or hospital staff, only 17.3%, 26.2% and 43.2% reported getting drug treatment information from those sources, respectively. Interventions that provide drug treatment information and enhance motivation for treatment in the medical setting and policies that reduce barriers to treatment entry among motivated drug users are recommended. Pollini, R.A., McCall, L., Mehta, S.H., Vlahov, D. and Strathdee, S.A. Drug Alcohol Depend. November 22, 2005.

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

Research Findings - Services Research

Office-Based Buprenorphine Treatment of Opioid Dependence

The authors compared patients entering a clinical trial of buprenorphine in a Primary Care Clinic (PCC) and those entering a local Opioid Treatment Program (OTP). They also compared the clinical characteristics and treatment outcomes of PCC patients with no history of methadone treatment to those with prior methadone treatment. PCC subjects (N=96) were enrolled in a 26-week randomized clinical trial of office-based buprenorphine/naloxone provided in a PCC. OTP subjects (N=94) were enrolled in methadone maintenance during the same time period. PCC subjects compared with OTP subjects were more likely to be male, full-time employed, have no history of methadone treatment, have fewer years of opioid dependence, and lower rates of injection drug use (IDU). The new-to-treatment PCC subjects were younger, more likely to be white, had fewer years of opioid dependence, were less likely to have a history of IDU, and had lower rates of hepatitis C than subjects with prior methadone treatment. Abstinence and treatment retention were comparable in both groups. The results suggest that office-based treatment of opioid dependence is associated with new types of patients entering into treatment. Treatment outcomes with buprenorphine in a PCC do not vary based on history of prior methadone treatment. Sullivan, L., Chawarski, M., O 'Connor, P., Schottenfeld, R. and Fiellin, D. The Practice of Office-Based Buprenorphine Treatment of Opioid Dependence: Is it Associated with New Patients Entering Into Treatment? Drug Alcohol Depend, 79(1), pp. 113-116, 2005.

Medical Exams At Entry To Treatment For Drug Abuse May Initiate Care For Hepatitis C

The researchers found in a national data base that all the methadone programs (n=95) and 50% of the drug-free programs (80 of 161) required a medical examination that included screening for signs and symptoms of liver disease and liver function testing. Nearly all the methadone programs (97%) provided referral to medical care or support for patients with test results positive for antibody to hepatitis C virus (HCV), compared with 75% of drug-free programs (P<.01). Drug-free programs requiring medical examinations provided education about HCV and testing for HCV to a larger proportion of their patients (P<.05) than those not providing the HCV education. These early screening medical visits are an important opportunity for monitoring and providing care for HCV infection, especially given the high dropout rates in the early stages of treatment for drug addiction. Hagan, H., Strauss, S., Astone, J. and Des Jarlais, D. Medical Examinations at Entry to Treatment for Drug Abuse as an Opportunity to Initiate Care for Hepatitis C Virus Infection. Clin Infect Dis, 40(5), pp. s297-s303, 2005.

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Prison TC has a Positive Influence on Post-release Employment, Especially for Aftercare Participants

This study examined the effects of post-release transitional therapeutic community treatment on the drug use and employment rates of 1,319 male drug involved prisoners in the Delaware corrections system followed for up to 5 years after release. A comparison group received standard post-release supervision. Abstinence rates were 32.2% in the treatment group and 9.9% in the no-treatment group, and the treatment group had a higher overall proportion of time free of drug use. Time to relapse was a mean of 28.8 months in the treatment group versus 13.2 months in the no-treatment group. Relapse was defined as any use of any drug and was confirmed by urinalysis. Positive effects were seen even for those who did not complete treatment. The treatment group had a significantly higher rate of employment after leaving work release (54.6%) than did the no-treatment group (45.4%). Treatment during the transitional period between prison and community showed substantial and persistent benefits even for a cohort marked with extensive criminal history, low rates of marital bonds, and substantial unemployment. Butzin, C.A., Martin, S.S. and Inciardi, J.A. Treatment During Transition from Prison to Community and Subsequent Illicit Drug Use. J Subst Abuse Treat, 28(4), pp. 351-358, 2005.

Cost of HIV Medication Adherence Support Interventions

The objective of this study was to determine the direct cost of HIV adherence support programs participating in a cross-site evaluation in the US. Data on the frequency, type, and setting of adherence encounters; providers' professions; and adherence tools provided were collected for 1,122 patients enrolled in 13 interventions at 9 sites. The site staff estimated the average duration of each type of encounter and national wage rates were used for labour costs. The median (range) adherence encounters/year among interventions was 16.5 (4.3-104.6) per patient; encounters lasted 24.6 (8.9-40.9) minutes. Intervention direct cost was correlated with the average frequency of encounters (r = 0.57), but not with encounter duration or providers' professions. The median direct cost/month was 35 dollars (5 dollars-58 dollars) per patient, and included direct provider costs (66%); incentives (17%); reminders and other tools (8%); and direct administrative time, provider transportation, training, and home delivery (9%). The median direct cost/month from a societal perspective, which includes patient time and travel costs, was 47 dollars (24 dollars-114 dollars) per patient. Adherence interventions with moderate efficacy costing 100 dollars/month or less have been estimated to meet a cost-effectiveness threshold that is generally accepted in the US. Payers should consider enhanced reimbursement for adherence support services. Schackman, B.R., Finkelstein, R., Neukermans, C.P., Lewis, L. and Eldred, L. The Cost of HIV Medication Adherence Support Interventions: Results of a Cross-Site Evaluation. AIDS Care, 17(8), pp. 927-937, 2005.

Distress Tolerance and Early Smoking Relapse

A significant percentage of smokers attempting cessation relapse to smoking within a matter of days and very few of these individuals recover to achieve abstinence. Current models of relapse devote insufficient attention to this phenomenon of early smoking relapse. Furthermore, studies attempting to relate severity of nicotine withdrawal symptoms to short-term smoking cessation outcomes have yielded equivocal results. The authors argue that how one reacts to the discomfort of nicotine withdrawal is a more promising avenue of investigation than severity of withdrawal, and that inability to tolerate the distress of nicotine withdrawal and associated negative affect is a key factor in

early smoking lapse and subsequent relapse. Early smoking lapsers are a particularly high-risk group of smokers, and no specialized treatment program exists to address the specific needs of these smokers. The authors propose a program that includes components of a standard smoking cessation program, both behavioral and pharmacological, as well as components derived from exposure-based procedures for anxiety related disorders. Development of such a program would aid this significant subpopulation of smokers at greatest risk for difficulties quitting smoking, with resulting important clinical and public health benefits. Brown, R., Lejuez, C., Kahler, C., Strong, D. and Zvolensky, M. Distress Tolerance and Early Smoking Lapse. Clin Psychol Rev, 25(6), pp. 713-733, 2005.

Hospital And Outpatient Health Services Utilization Among HIV-Infected Adults In Care: 2000-2002

Rapid changes in HIV epidemiology and antiretroviral therapy may have resulted in recent changes in patterns of healthcare utilization. The objective of this study was to examine sociodemographic and clinical correlates of inpatient and outpatient HIV-related health service utilization in a multi-state sample of patients with HIV. Demographic, clinical, and resource utilization data were collected from medical records for 2000, 2001, and 2002. The study was conducted at 11 U.S. HIV primary and specialty care sites in different geographic regions. Chosen for inclusion, for each year, were HIV-positive patients with at least one CD4 count and any use of inpatient, outpatient, or emergency room services. Sample sizes were 13,392 in 2000, 15,211 in 2001, and 14,403 in 2002. Main outcome measures were the number of hospital admissions, total days in the hospital, and the number of outpatient clinic/office visits per year. Inpatient and outpatient costs were estimated by applying unit costs to numbers of inpatient days and outpatient visits. Findings show that mean numbers of admissions per person per year decreased from 2000 (0.40) to 2002 (0.35), but this difference was not significant in multivariate analyses. Hospitalization rates were significantly higher among patients with greater immunosuppression, women, blacks, patients who acquired HIV through drug use, those 50 years of age and over, and those with Medicaid or Medicare. The mean annual outpatient visits decreased significantly between 2000 and 2002, from 6.06 to 5.66 visits per person per year. Whites, Hispanics, those 30 years of age and over, those on highly active antiretroviral therapy (HAART), and those with Medicaid or Medicare had significantly higher outpatient utilization. Inpatient costs per patient per month (PPPM) were estimated to be 514 dollars in 2000, 472 dollars in 2001, and 424 dollars in 2002; outpatient costs PPPM were estimated at 108 dollars in 2000, 100 dollars in 2001, and 101 dollars in 2002. In conclusion, changes in utilization over this 3-year period, although statistically significant in some cases, were not substantial. Hospitalization rates remain relatively high among minority or disadvantaged groups, suggesting persistent disparities in care. Combined inpatient and outpatient costs for patients on HAART were not significantly lower than for patients not on HAART. Fleishman, J., Gebo, K., Reilly, E., Conviser, R., Christopher Mathews, W., Todd Korthuis, P., Hellinger, J., Rutstein, R., Keiser, P., Rubin, H. and Moore, R. Hospital and Outpatient Health Services Utilization Among HIV-Infected Adults in Care 2000-2002. Med Care, 43(9), pp. 40-52, 2005.

HIV Intervention For Indigent Substance Abusing Women In The USVI

As the HIV/AIDS epidemic continues to expand and penetrate new communities around the globe, risk reduction intervention initiatives must continue to evolve and adapt to new challenges and populations. This is especially true in the Caribbean Basin, where the feminization of the HIV epidemic is tied to a cultural milieu characterized by pervasive gender

inequality. HIV intervention programs in the Caribbean must treat women's risks as a function of the social context, standards, and meanings of sexual behaviors and practices in the local community. As such, this article describes an initiative to develop an HIV prevention-intervention protocol for the cultural context of substance abusing women in the US Virgin Islands. Through street-based survey research combined with focus groups and in-depth interviews with such "cultural insiders" as members of the substance-abusing target population, members of the local public health and social services system, and community leaders, a culturally sensitive HIV/AIDS protocol was developed which addresses the supports and barriers to risk reduction faced by substance abusing women in the Virgin Islands. Surratt, H.L. and Inciardi, J. A. Developing an HIV Intervention for Indigent Women Substance Abusers in the United States Virgin Islands. J Urban Health, 82(3-4), pp. iv74-iv83, 2005.

Condom Attitudes and Behaviors Among Injection Drug Users

This study examined condom attitudes, preferences, barriers, and use among a sample of 550-injection drug using clients of syringe exchange programs in California. In multivariate analyses, positive attitudes toward condoms were significantly associated with consistent condom use for vaginal, anal, and oral sex in the past six months, beyond the effects of confounding socio-demographic and HIV risk variables. Participants commonly cited partner-related barriers to condom use, such as reluctance to use condoms with steady partners (34%). Almost a quarter of the sample cited dislike of condoms (e.g., because of pleasure reduction). In addition, a third of respondents stated specific preferences regarding condom brands, sensitivity, sizes, and textures. Interventions that increase awareness about positive aspects of condom use and sexual risk from steady partners may be successful in increasing condom use among injection drug users. Bogart, L.M., Kral, A.H., Scott, A., Anderson, R., Flynn, N., Gilbert, M.L. and Bluthenthal, R.N. Condom Attitudes and Behaviors Among Injection Drug Users Participating in California Syringe Exchange Programs. AIDS Behav, pp. 1-10, 2005.

The Intersection of Violence with Culture and HIV Risk Among Sex Workers

The Republic of South Africa has become an epicentre of heterosexual HIV transmission among Black women, and the interface between violence against women, substance abuse, and HIV risk is becoming evident. This article describes the characteristics of Black South African women who engage in sex work in Pretoria and examines their intersecting experiences of high-risk sexual behaviour, substance abuse, and victimization. Ninety-three women were recruited into the study. Field staff collected biological measures of drug use and administered a structured, self-report interview. Findings indicate that young South African women who engage in sex work and use drugs rely on this activity as their main source of income and are supporting other family members. The majority of sample women reported experiencing some victimization at the hand of men, either clients or boyfriends, with many reporting childhood abuse histories; young women also report great fear of future victimization. Findings also suggest that as a result of their decreased likelihood of using protection, women who reported any sexual or physical victimization are at increased risk for HIV and other STIs. Results support the critical need for targeted, comprehensive interventions that address substance abuse, sexual risk, and violence as interrelated phenomena. Wechsberg, W.M., Luseno, W.M. and Lam, W.K. Violence Against Substance-Abusing South African Sex Workers: Intersection with Culture and HIV Risk. AIDS Care, 17, Supplement 1, pp. s55-s64, 2005.

The Incidence Of, Risk Factors For, and Sequelae Of Herpes Zoster

Among HIV Patients In The Highly Active Antiretroviral Therapy Era

Whereas the incidence, risk factors, and clinical sequelae of herpes zoster have been studied in the general population and in HIV patients in the era before highly active antiretroviral therapy (HAART), they have yet to be fully understood in the current era of HAART. The investigators conducted a retrospective cohort study of patients enrolled in an urban HIV clinic between January 1, 1997 and December 31, 2001. Patients with an episode of herpes zoster during this period were identified, and their charts were reviewed. A nested case-control analysis was used to assess factors associated with an initial episode of herpes zoster. Multivariate conditional logistic regression analyses were used to assess risk factors for zoster. Logistic regression was performed to assess factors associated with complicated zoster. Two hundred eighty-two episodes of herpes zoster were identified in 239 patients. Of these episodes, 158 were new occurrences of zoster and 124 were recurrent zoster events. The incidence of zoster during the study period was 3.2 per 100 person-years of follow-up. The incident cases reflected the clinic population, with most patients being male (63%) and African American (77%) and having injection drug use as their HIV risk factor (49%). The mean age of the patients was 41 years. Sixty-seven percent of patients had single dermatomal involvement, and the thorax was involved in 41%. In multivariate regression, being on HAART (odds ratio [OR] = 2.39, 95% confidence interval [CI]: 1.65 to 3.49) and a CD4 count of 50 to 200 cells/mm (OR = 2.69, 95% CI: 1.44 to 5.01) compared with a CD4 count less than 50 cells/mm were associated with an increased risk of zoster. Twenty-eight patients (18%) developed post-herpetic neuralgia (PHN), and 29 patients (18%) had other complications. Male-to-male sex as an HIV risk factor (P = 0.02) and being on HAART at a zoster episode (P = 0.03) were protective against complicated zoster. Results suggest that zoster infection rates have not changed in the current HAART era but that a significant percentage of patients develop complications, particularly PHN, which is quite remarkable considering the young age of the population. Gebo, K., Kalyani, R., Moore, R. and Polydefkis, M. The Incidence of, Risk Factors for, and Sequelae of Herpes Zoster Among HIV Patients in the Highly Active Antiretroviral Therapy Era. J Acquir Immune Defic Syndr, 40(2), pp. 169-174, 2005.

Respiratory Symptom Relief Related To Reduction In Cigarette Use

Many smokers reduce their cigarette consumption during failed attempts to quit. This study reports the impact of changes in consumption on smoking-related respiratory symptom severity (SRRSS). Between February 2002 and May 2004, 383 smokers were recruited from 5 methadone maintenance programs for a randomized trial of nicotine replacement plus behavioral treatment, versus nicotine replacement alone for smoking cessation. Cigarette use in the 28 days prior to the interview, and severity of SRRSS using a 7-item respiratory index, were assessed at baseline and at 3-month follow-up. The outcome measured was the baseline, minus 3-month assessment difference in SRRSS score. Follow-up of 319 participants (83.3%), mean age 40.4 years, 51.4% male, who smoked 26.4 cigarettes per day, demonstrated a mean reduction of 16.7 cigarettes per day. A reduction in cigarette use was positively and significantly ($b=0.29$, $t=5.16$, $P<.001$) associated with a reduction in smoking-related symptom severity after adjusting for age, gender, race, years of regular smoking, baseline nicotine dependence, and history of treatment for asthma or emphysema. A 1.0 standard deviation reduction in average daily smoking (about 14.1 cigarettes) was associated with a 0.28 standard deviation decrease in smoking-related symptom severity. A reduction in symptom severity increases as absolute reduction in daily smoking increases. This is the first study to demonstrate an association between subjective short-term health

changes and reduction in smoking. Stein, M., Weinstock, M., Herman, D. and Anderson, B. Respiratory Symptom Relief Related to Reduction in Cigarette Use. J Gen Intern Med, 20(10), pp. 89-94, 2005.

Persistence Of Antidepressant Treatment Effects In A Pharmacotherapy Plus Psychotherapy Trial For Active Injection Drug Users

The objective of this study was to determine if combined psychotherapy and pharmacotherapy reduces reported depressive symptoms compared to an assessment only condition for active drug injectors over nine months. Using a randomized controlled trial at an outpatient academic research office, the researchers applied psychotherapy (eight sessions of cognitive behavioral therapy) plus pharmacotherapy (citalopram) to active injection drug users with a DSM-IV diagnosis of major depression, dysthymia, substance-induced mood disorder with symptoms persisting for at least three months, or major depression plus dysthymia, and a Modified Hamilton Rating Scale for Depression (MHRSD) score greater than 13. The MHRSD scale scores were then assessed at the completion of three, six, and nine months. Participants (n = 109) were 64% male and 82% Caucasian, with a mean baseline MHRSD score of 20.7. Depression subtypes included major depression only (63%), substance-induced depression (17%), and double-depression (17%). Study retention at nine months was 89%. At the completion of three months of acute treatment, 26% of combined treatment patients (n = 53), compared to 12% of control patients (n = 56), were in remission ($p = .047$). At both six and nine months, the between-group differences in remission rates and mean MHRSD scores were insignificant, although the overall mean MHRSD score decreased from baseline ($p < .01$). At all follow-up assessments, depression remission was significantly associated with lower heroin use. Among active drug injectors diagnosed with depression, symptoms decline over time. Combined treatment is superior to an assessment-only condition in depression remission rates at the end-of-treatment, but this difference does not persist. Stein, M., Solomon, D., Anderson, B., Herman, D., Anthony, J., Brown, R., Ramsey, S. and Miller, I. Persistence of Antidepressant Treatment Effects in a Pharmacotherapy Plus Psychotherapy Trial for Active Injection Drug Users. Am J Addict, 14(4), pp. 346-357, 2005.

Screening For Depressive Symptoms Among Homeless Adults With Latent Tuberculosis

The purpose of this study was to examine predictors of screening results for depressive symptoms in a Los Angeles homeless population with latent tuberculosis (TB). Four hundred and fifteen homeless adults participating in a nurse case managed intervention were included in this analysis. Logistic regression results indicated that those who reported a physical health limitation, multiple sex partners, daily drug use, alcohol dependence, or not having completed high school were more likely to screen positive. Social support from non-drug users was protective. Given the importance of adherence to TB treatment regimens, the high prevalence of a positive screening for depressive symptoms in the homeless and the potential for depression to reduce adherence rates, routine screening and treatment for depression in high risk homeless adults being treated for TB may be warranted. Berg, J., Nyamathi, A., Christiani, A., Morisky, D. and Leake, B. Predictors of Screening Results for Depressive Symptoms Among Homeless Adults in Los Angeles with Latent Tuberculosis. Res Nurs Health, 28(3), pp. 220-229, 2005.

The Role of Judicial Status Hearings In Drug Court: Six and Twelve Month Outcomes

This article presents outcomes for a study seeking to isolate the effects of status hearings for drug abusers participating in drug court and builds on previously published work in this area. Subjects (n=200) were recruited from a misdemeanor drug court located in Wilmington, Delaware. Drug court participants were randomly assigned in equal proportions to attend either bi-weekly judicial status hearings, or hearings only as needed in response to poor performance in the program. Study results revealed no significant group effects, or group-by-time effects for drug use, alcohol intoxication, criminal activities, criminal charges, employment problems, psychiatric problems, or social/family functioning. Earlier analyses by investigators had revealed significantly better during-treatment outcomes for certain high-risk participants assigned to bi-weekly status hearings; however, this interaction effect did not extend beyond the active phase of drug court participation. This finding lead investigators to speculate that judges might be less able to influence high risk offenders as their discharge date from drug court approaches. Results from the study did reveal a significant pre-to-post improvement for drug court participants as a whole on self-reported substance use and criminal activity from intake to follow-up. Marlowe, D.B., Festinger, D.S., Dugosh, K.L. and Lee, P.A. Are Judicial Status Hearings a "Key Component" of Drug Court? Six and Twelve Month Outcomes. Drug Alcohol Depend, 79(2005), pp. 145-155, 2005.

Common Processes May Account For Relapse Across Addictions

This study investigated the relationship between the duration of the most recent attempt to abstain from drug or alcohol use and psychological distress tolerance, as indexed by persistence on a mental arithmetic task. Participants were 89 individuals (63% male, 90% African American) in an inner-city residential substance abuse treatment facility; their mean age was 39 years. Results indicated that the duration of the most recent period of abstinence related positively to persistence on the psychological stress test, beyond the influence of demographics, substance use level, and negative affect. That is, the greater the capacity to tolerate psychological distress, the longer the period of abstinence. These findings extend previous work reporting significant positive relations between persistence on laboratory challenge procedures and the duration of abstinence following a quit attempt in smokers. This suggests that common processes may account for relapse across addictions. Daughters, S.B., Lejuez, C.W., Kahler, C.W., Strong, D.R. and Brown, R.A. Psychological Distress Tolerance and Duration of Most Recent Abstinence Attempt Among Residential Treatment-Seeking Substance Abusers. Psychol Addict Behav, 19(2), pp. 208-211, 2005.

Association of Childhood Physical Abuse To Poor Adult Outcomes

In asserting that men' s childhood physical abuse experiences are understudied, the investigators set out to obtain descriptions about men's personal childhood physical abuse histories and estimate their association with adult outcomes via a population-based telephone survey in urban areas with high frequency of domestic violence against girls and women. Two hundred ninety-eight (298) men were recruited through random-digit dialing. Interviewers asked six (6) items from the validated Conflict Tactics Scale and psychiatric, sexual, and legal history questions. One hundred of 197 (51%) participants had a history of childhood physical abuse. Most (73%) participants were abused by a parent. Childhood physical abuse history was associated with depression symptoms ($P = 0.003$), post-traumatic stress disorder symptoms ($P < 0.001$), number of lifetime sexual partners ($P = 0.035$), legal troubles ($P = 0.002$), and incarceration ($P = 0.007$) in unadjusted analyses and with depression symptoms ($P = 0.015$) and post-traumatic stress disorder symptoms ($P = 0.003$) in adjusted analyses. Potential limitations of the study pertain to whether there may have been inaccurate recall of past events. The lack of exposure time data disallowed direct comparison of abuse perpetration

by mothers versus fathers, and other unmeasured variables related to childhood physical abuse might better explain poor adult outcomes. The high frequency of childhood physical abuse histories in this population-based male sample, coupled with the high proportion of parent perpetrators and the association between childhood physical abuse and adult outcomes that are often associated with perpetration of violence, argues for more study of, and clinical attentiveness to potential adult outcomes of men's own childhood physical abuse histories. Holmes, W. and Sammel, M. Brief Communication: Physical Abuse of Boys and Possible Associations with Poor Adult Outcomes. Ann Intern Med, 143(8), pp. 581-586, 2005.

Buprenorphine: Preventing HIV Transmission and Improving Care Of HIV+ Opioid Dependents

Buprenorphine is a new medication used to treat opioid dependence that shows promise for reducing the rate of HIV transmission and improving the care of opioid-dependent patients with HIV infection. Although buprenorphine faces fewer clinical and regulatory barriers than does methadone, the optimal strategy for integration of office-based treatment of opioid dependence and HIV disease is an area of on-going research. This review addresses the introduction of buprenorphine, in terms of public health, policy, and clinical implications for HIV-infected patients and for HIV care providers. Sullivan, L., Fiellin, D. and Lidz, V.M. Buprenorphine: Its Role in Preventing HIV Transmission and Improving the Care of HIV-Infected Patients with Opioid Dependence. Clin Infect Dis, 41(6), pp. 891-896, 2005.

Training Substance Abuse Treatment Staff to Care for Co-occurring Disorders

This article describes the design and implementation of an intervention to improve the quality of mental health care provided in outpatient substance abuse treatment programs without requiring new treatment staff. The intervention focuses on individuals with affective and anxiety disorders and consists of three components: training and supervising staff, educating and activating clients, and linking with community resources. The researchers evaluated three treatment programs (one intervention and two comparison) for the first component by having program staff complete both self-administered questionnaires and semi structured interviews. Staff knowledge and attitudes about co-occurring disorders, job satisfaction, and morale all indicated an improvement at the intervention relative to the comparison sites. Hunter, S., Watkins, K., Wenzel, S., Gilmore, J., Sheehe, J. and Griffin, B. Training Substance Abuse Treatment Staff to Care for Co-Occurring Disorders. J Subst Abuse Treat, 28(3), pp. 239-245, 2005.

Diversified Substance Abuse Service Options Enhances Organization Survival

Using a nationally representative sample of 450 substance abuse treatment centers, this research considers the extent to which specific types of service diversification reduce the likelihood of treatment center closure in the private sector. Based upon periodic interviews with senior management over a period ranging from 1995 to 2003, 26.4% of centers ceased to offer substance abuse treatment services. The number of treatment tracks tailored to specific demographic groups was negatively associated with the likelihood of closure. However, there was a positive association between closure and offering an inpatient psychiatric program. These findings suggest that there may be strategic benefits in expanding services to meet the needs of diverse clientele. Knudsen, H., Roman, P. and Ducharme, L. Does Service Diversification Enhance Organizational Survival?: Evidence from the Private Substance Abuse

Treatment System. J Behav Health Serv Res, 32(3), pp. 241-252, 2005.

Culturally Specific Substance Use Prevention for Latino Youth

This study examined whether language preference, as an indicator of acculturation, moderated the effects of a culturally grounded substance use prevention intervention for Mexican and Mexican American middle school students (N = 2,146). The majority of the sample was male (52%). At baseline, participants were in 7th grade and post-tests were conducted when participants were in the 8th grade. The main hypothesis was that levels of program effectiveness would vary based on the language preference of the students and the specific culturally grounded version of the intervention they were assigned. Findings show that matching language preference to particular versions of the intervention did not influence substance use related program outcomes, but that overall program effects (intervention vs. control) did vary by language preference. English-language dominant participants, the most at risk sub-group, responded more positively to the intervention, while Spanish language dominant participants, did not demonstrate significant differences between the intervention and control groups. Implications for school social work prevention interventions and prevention science in general, are discussed. Marsiglia, F.F., Kulis, S., Wagstaff, D.A., Elek, E. and Dran, D. Acculturation Status and Substance Use Prevention in Mexican and Mexican-American Youth. Journal of Social Work Practice in the Addictions, 5(1-2), pp. 85-111, 2005.

Homeless Chronicity Links to Quality of Life Among Adult Addicts

Using data from a 2-year cohort of addicted persons, Dr. Kertesz and colleagues tested whether changes in mental and physical health-related quality of life (HRQOL) differed according to homeless chronicity. Using self-reported homelessness, subjects were classified as chronically homeless (CH; n = 60), transitionally homeless (TRANS; n = 108), or as housed comparison subjects (HSD; n = 106). The Short Form-36 Health Survey, administered at baseline and 2 follow-ups over a period of 2 years, provided a Mental Component Summary (MCS) and a Physical Component Summary (PCS) for HRQOL. Mixed model linear regression was used to test the association between housing status, MCS, and PCS. Additional models assessed whether medical, psychiatric, addiction, and social support measures could account for HRQOL differences. All subjects had low MCS scores at study entry. Nevertheless, there was a significant housing status-by-time interaction (P = 0.01). At final follow-up, CH and TRANS subjects had lower adjusted MCS scores than HSD subjects for the 3 groups, respectively; all P < or = 0.01). By contrast, housing status and PCS were not significantly associated (P = 0.19). Medical, psychiatric, addiction, and social support variables had significant associations with MCS, and their inclusion in the regression reduced the apparent effect of housing status on MCS. Chronic homelessness was associated with especially poor mental but not physical HRQOL over time. These findings reinforce a new typology of homelessness and mitigate against the notion that substance abuse alone accounts for the mental health status of the chronically homeless. Kertesz, S., Larson, M., Horton, N., Winter, M., Saitz, R. and Samet, J. Homeless Chronicity and Health-Related Quality of Life Trajectories Among Adults with Addictions. Med Care, 43(6), pp. 574-585, 2005.

Reductions In HIV Risk Behaviors Among Depressed Drug Injectors

This study examines if, by reducing depressive symptoms by combined psychotherapy and pharmacotherapy, whether a reduction of HIV drug risk behavior occurs compared to an assessment-only condition for active drug

injectors over 9 months. Active injection drug users with a DSM-IV diagnosis of major depression, dysthymia, substance-induced mood disorder with depressive features persisting for at least 3 months, or major depression plus dysthymia. In addition, participants had a Hamilton Rating Scale for Depression (MHRSD) score greater than 13. The study was conducted as a randomized controlled trial, and performed in an outpatient academic research office. The treatment group received psychotherapy (8 sessions of cognitive behavioral therapy) plus antidepressant pharmacotherapy over 3 months. The control group received assessment only. The primary outcome measurement instrument is the HIV Risk Assessment Battery (RAB) drug scale scores, measured at three, six and nine months, and depression remission (MHRSD score less than or equal to 8). There were 109 participants, of which 64% were male, 82% Caucasian, with a mean baseline MHRSD score of 20.7. Depression subtypes included major depression only (63%), substance-induced depression (17%), and double-depression (17%). Overall, study retention at nine months was 89%. Reported HIV drug risk scores decreased sharply over the first 3 months and continued to decline throughout the follow-up period. The differences between group differences were not significant (in the intention-to-treat analysis). However, highly adherent participants did show significantly lower HIV drug risk scores at 3 months (p less than .05), but not at 6 and 9 months. Depression remission was significantly associated with lower HIV drug risk scores at follow-ups. This study did not show that combined psychotherapy and pharmacotherapy could produce a significant reduction in HIV drug risk beyond that seen in an assessment-only control group; although both groups did show declines in HIV risk behavior. However, declines in HIV drug risk were found in participants with high protocol adherence, and those with depression remission. Stein, M., Anderson, B., Solomon, D., Herman, D., Ramsey, S., Brown, R. and Miller, I. Reductions in HIV Risk Behaviors Among Depressed Drug Injectors. Am J Drug Alcohol Abuse, 31(3), pp. 17-32, 2005.

Integrating Hepatitis C Services into Existing HIV Services

Using data collected in a telephone survey with 89 drug treatment units throughout the United States, this paper examines the extent to which drug treatment units have expanded their HIV services to include those for HCV, and the extent to which this expansion was facilitated by having HIV services in place. Overall, a greater proportion of methadone maintenance than drug-free treatment units provided services for HIV and HCV. The majority of units in both modalities that provided HIV- and HCV-related services expanded their HIV service delivery to include similar HCV services, and one third expanded all of their HIV services. A large number of these units, however, indicated that having an HIV service infrastructure did not facilitate this expansion, often because the units wanted to emphasize differences in the two viral infections. Strauss, S., Astone, J., Des Jarlais, D.,and Hagan, H. Integrating Hepatitis C Services into Existing HIV Services: The Experiences of a Sample of U.S. Drug Treatment Units. AIDS Patient Care STDS, 19(2), pp. 78-88, 2005.

Provision Of Mental Health and Substance Abuse Services Challenges The Dually Diagnosed

This paper reports on a survey of administrators (n = 26) and staff (n = 248) in 10 mental health and 16 substance abuse programs in Los Angeles County providing services to individuals with co-occurring disorders. Although half or more of the administrators and staff reported that their programs had some degree of on-site service integration, there was a lack of agreement within most programs as to the extent of integration. A substantial number of dually diagnosed clients in these programs were concurrently receiving either mental health or substance abuse services from other treatment providers, indicating that many of their clients needed to negotiate two distinct service systems. There may be a lack of cohesion regarding treatment approach even within the

same program. Future research is needed regarding the divergent perceptions of administrators and staff and their relationship to treatment outcomes. Gil-Rivas, V. and Grella, C. Treatment Services and Service Delivery Models for Dually Diagnosed Clients: Variations Across Mental Health and Substance Abuse Providers. Community Ment Health J, 41(3), pp. 251-266, 2005.

Employment Behaviors Among Drug Using Welfare Recipients

This study examines how drug using welfare recipient's employment behaviors (i.e., expectations, employment commitment, job search self-efficacy, job-seeking support from friends, economic hardship and anxiety) affected employment-seeking behavior and impacted the welfare-to-work mandate. Regression analyses estimate the effect of the seven psychosocial domains on employment seeking behaviors and job search intensity on a sample of 222 welfare-to-work recipients in Houston. The results show that psychological domains affected drug users and non-drug users differently as they searched for employment. Specifically, self-efficacy and anxiety are negatively related to job seeking behavior. In addition, job expectations and economic hardship were both positively related to job-search intensity. Psychosocial domains such as motivation and job search efficacy are good predictors of employment seeking behaviors, but these factors are not as powerful among the drug using population. Thus, specific interventions must be developed for drug using welfare recipients if they are expected to exit welfare and integrate into the labor force successfully. Montoya, I. D. Employment Behaviors Among Drug Using Welfare Recipients. Journal of Addictions Nursing, 16 pp. 187-193, 2005.

People Who Feel Shame are More Likely to Have Substance Abuse Problems Whether or Not They Have Criminal Histories

Previous research has demonstrated that shame-proneness (the tendency to feel bad about the self) relates to a variety of life problems, whereas guilt-proneness (the tendency to feel bad about a specific behavior) is more likely to be adaptive. The current analyses sought to clarify the relations of shame-proneness and guilt-proneness to substance use problems in three samples with differing levels of alcohol and drug problem severity: college undergraduates (Study 1 N=235, Study 2 N=249) and jail inmates (Study 3 N=332). Across samples, shame-proneness was generally positively correlated with substance use problems, whereas guilt-proneness was inversely related (or unrelated) to substance use problems. Results suggest that shame and guilt should be considered separately in the prevention and treatment of substance misuse. Dearing, R.L., Stuewig, J. and Tangney, J.P. On the Importance of Distinguishing Shame from Guilt: Relations to Problematic Alcohol and Drug Use. Addict Behav, 30(7), pp. 1392-1404, 2005.

Women in Outpatient Treatment for Methamphetamine Improved Family Relationships and Their Medical Condition Relative to Men

This prospective longitudinal study examined treatment outcomes among 1,073 methamphetamine-abusing patients (567 women, 506 men) from 32 community-based outpatient and residential programs in 13 California counties. Data were collected at intake and at 3 months and 9 months after admission. With one exception, improvements from baseline to follow-up were observed in all areas measured by the Addiction Severity Index for both women and men in either modality. Compared to men, women demonstrated greater improvement in family relationships and medical problems, and similar improvement in all other areas, despite the fact that more women were unemployed, had childcare responsibilities, were living with someone who also used alcohol or drugs, had been physically or sexually abused, and reported more psychiatric symptoms. Implications for service improvement are

discussed. Hser, Y., Evans, E. and Huang, Y. Treatment Outcomes Among Women and Men Methamphetamine Abusers in California. J Subst Abuse Treat, 28(1), pp. 775-785, 2005.

An Improvement in Virologic Response to Highly Active Antiretroviral Therapy in Clinical Practice From 1996 Through 2002

Early studies of highly active antiretroviral therapy (HAART) use in clinical practice suggested sub optimal rates of viral suppression. HAART regimens and expertise in the use of HAART have since evolved, and the investigators sought to determine how virologic response to HAART has changed in clinical practice. They compared all patients (1,255) who started a first HAART regimen from 1996 through 2002 in a longitudinal cohort of HIV-infected patients in care in Baltimore. There were significant improvements in suppressing HIV RNA to < 400 copies/mL, ranging from 43.8% (1996) to 72.4% (2001-2002) by 6 months and from 60.1% (1996) to 79.9% (2001-2002) by 12 months (both $P < 0.01$ for trend). There were also significant improvements in CD4 cell response. Over time, there was a significant increase in the use of a nonnucleoside reverse transcriptase inhibitor (NNRTI) or boosted protease inhibitor (PI) regimen compared with a single PI as well as an increase in the number of patients who were antiretroviral (ARV) naive. There was also a significant temporal trend from 1996 through 2002 in achieving a suppressed HIV RNA level, adjusting for being ARV naive, specific HAART regimen, CD4 cell count, HIV-1 RNA level, and demographic factors. These observations suggests that improved virologic response may also be attributable to other factors such as a greater focus on medication adherence, improved ARV tolerability, and ease of dosing. Moore, R., Keruly, J., Gebo, K. and Lucas, G. An Improvement in Virologic Response to Highly Active Antiretroviral Therapy in Clinical Practice from 1996 through 2002. J Acquir Immune Defic Syndr, 39(2), pp. 195-198, 2005.

Length of Stay in Drug Abuse Treatment Impacted by Program Size

Admissions to 20 publicly funded alcohol and drug detoxification centers in Massachusetts were examined to identify program and patient variables that influenced length of stay. The last admission during fiscal year 1996 was abstracted for patients 18 years of age and older seeking alcohol, cocaine, or heroin detoxification (n=21,311; 29% women). A hierarchical generalized linear model examined the effects of patient and program characteristics on variation in length of stay and tested case-mix adjustments. Program size had the most influence on mean adjusted length of stay; stays were more than 40% longer in detoxification centers with 35 or more beds (7.69 days) than in centers with less than 35 beds (5.42 days). The study highlights the contribution of program size to treatment processes and suggests the need for more attention to program attributes in studies of patient outcomes and treatment processes. Jonkman, J., McCarty, D., Harwood, H., Normand, S. and Caspi, Y. Practice Variation and Length of Stay in Alcohol and Drug Detoxification Centers. J Subst Abuse Treat, 28(1), pp. 11-18, 2005.

Patterns Of Diagnoses In Hospital Admissions In A Multi-State Cohort of HIV-Positive Adults In 2001

Admissions for AIDS-related illnesses decreased soon after the introduction of highly active antiretroviral therapy (HAART), but it is unclear if the trends have continued in the current HAART era. The investigators examined the diagnoses for hospitalizations of patients with HIV in 2001. Demographic and healthcare data were collected for 8,376 patients from 6 U.S. HIV care sites. Diagnoses

were categorized into 18 disease groups and Poisson regression was used to analyze the number of admissions for each of the 4 most common groups. Investigators also compared patients with admissions for AIDS-defining illnesses (ADI) with patients admitted for other diagnoses. Findings revealed that twenty-one percent of patients had at least 1 hospitalization. Among patients hospitalized at least once, 28% were hospitalized for an ADI. Comparing diagnosis categories, the most common hospitalizations were AIDS-defining illnesses (21.6%), gastrointestinal (GI) diseases (9.5%), mental illnesses (9.0%), and circulatory diseases (7.4%). In multivariate analysis, women had higher hospitalization rates than men for ADI (incidence rate ratio [IRR], 1.50; 95% confidence interval [CI], 1.25-1.79) and GI diseases (IRR, 1.52; 95% CI, 1.15-2.00). Compared with whites, blacks had higher admission rates for mental illnesses (IRR, 1.70; 95% CI, 1.22-2.36), but not for ADI. As expected, CD4 count and viral load were associated with ADI admission rates; CD4 counts were also related to hospitalizations for GI and circulatory conditions. Thus, five years after the introduction of HAART, AIDS-defining illnesses continue to have the highest hospitalization rate among the diagnosis categories examined. This result emphasizes the importance of vaccination for pneumonia and influenza, as well as prophylaxis for Pneumocystis jiroveci pneumonia. The relatively large number of mental illness admissions highlights the need for co-management of psychiatric disease, substance abuse, and HIV. Overall, the majority of patients were hospitalized for reasons other than ADI, illustrating the importance of managing comorbid conditions in this population. Data from this cohort of patients with HIV may help guide the allocation of healthcare resources by enhancing our understanding of factors associated with variation in inpatient utilization rates. An understanding of healthcare utilization patterns is important for optimization of care and resource allocation. Betz, M., Gebo, K., Barber, E., Sklar, P., Fleishman, J., Reilly, E. and Christopher Mathews, W. Patterns of Diagnoses in Hospital Admissions in a Multistate Cohort of HIV-Positive Adults in 2001. Med Care, 43(9), pp. 3-14, 2005.

High Rates Of Primary Mycobacterium Avium Complex And Pneumocystis Jiroveci Prophylaxis In The U.S.

National data from the mid-1990s demonstrated that many eligible patients with HIV infection do not receive prophylaxis for opportunistic infections (OIs) and that racial and gender disparities existed in OI prophylaxis receipt. The investigative team examined whether demographic disparities in the use of OI prophylaxis persisted in 2001 and whether outpatient care was associated with OI prophylaxis utilization. Demographic, clinical, and pharmacy utilization data were collected from 10 U.S. HIV primary care sites in the HIV Research Network (HIVRN). This study consisted of adult patients (>or=18 years old) in longitudinal HIV primary care. Indications for Pneumocystis jiroveci pneumonia (PCP) or Mycobacterium avium complex (MAC) prophylaxis were 2 or more CD4 counts less than 200 or 50 cells/mm(3) during calendar year (CY) 2001, respectively. Using multivariate logistic regression, they examined demographic and clinical characteristics associated with receipt of PCP or MAC prophylaxis and the association of outpatient utilization with appropriate OI prophylaxis. As for findings, among eligible patients, 88.1% received PCP prophylaxis and 87.6% received MAC prophylaxis. Approximately 80% had 4 or more outpatient visits during CY 2001. Adjusting for care site, male gender (odds ratio [OR], 1.47), Medicare coverage (OR, 1.60), and having 4 or more outpatient visits in a year (OR, 2.34) were significantly associated with increased likelihood of PCP prophylaxis. Adjusting for care site, having 4 or more outpatient visits in a year (OR, 1.85) was associated with increased likelihood of receipt of MAC prophylaxis. There were no demographic or insurance characteristics associated with receipt of MAC prophylaxis. In conclusion, the overall prevalence of OI prophylaxis has increased since the mid-1990s, and previous racial and HIV risk factor disparities in receipt of OI

prophylaxis were found to have waned. Integration into the healthcare system is considered an important correlate to receiving OI prophylaxis. Gebo, K., Fleishman, J., Reilly, E., Moore, R. and Moore, R. High Rates of Primary Mycobacterium Avium Complex and Pneumocystis Jiroveci Prophylaxis in the United States. Med Care, 43(9), pp. 23-30, 2005.

Motivational Group Counseling For Substance Users In A Soup Kitchen

Soup kitchens tend to serve substance abusing homeless adults. 289 soup kitchen guests who reported drug or alcohol problems were randomly assigned to information and referral (I and R) plus peer advocacy (N=139) or to an experimental 12-session motivational group followed by a 36-session cognitive-behavioral group, plus I and R and peer advocacy. Experimental subjects were significantly more likely to have increased their participation in some type of substance abuse intervention during the follow-up period; and they were significantly more likely to have reduced both drinking and heavy drinking at follow-up than the comparison group. Experimental intervention was more effective for participants with higher rather than lower substance abuse severity at baseline. These results support the concept that motivationally enhanced group counseling, provided as a low-threshold outreach intervention, can help to increase participation in formal treatment and 12-step groups and to reduce substance abuse, particularly for those starting with high severity of use. Rosenblum, A., Magura, S., Kayman, D. and Fong, C. Motivationally Enhanced Group Counseling for Substance Users in a Soup Kitchen: A Randomized Clinical Trial. Drug Alcohol Depend, 80(1), pp. 91-103, 2005.

Physician Attitudes Regarding the Prescription of Medical Marijuana

Surveys of physicians' attitudes regarding the therapeutic value of marijuana are rare. Drawing on a national sample of 960 (adjusted response rate 66%) family physicians, general internists, obstetrician-gynecologists, psychiatrists, and addiction specialists, who offered opinions about the legal prescription of marijuana as medical therapy. Thirty-six percent believed prescribed marijuana should be legal and 26% were neutral to the proposition. Non-moralistic attitudes toward substance use were significantly associated with support for physician prescription, as was internal medicine and obstetrics-gynecology specialization. Physicians are, in general, less supportive than the general American public regarding the use of medical marijuana. Charuvastra, A., Friedmann, P. and Stein, M. Physician Attitudes Regarding The Prescription Of Medical Marijuana. J Addict Dis, 24(3), pp. 87-93, 2005.

Financial Transfers Reduce Help-Seeking Behavior

This article examines the factors affecting the help-seeking behavior for HIV-related social services among a sample of HIV+ urban poor individuals. The author examines how financial transfers from friends and family affect the decision to seek HIV social services from public and community organizations. The effect of transfers on the help-seeking behavior is examined while controlling for sociodemographic factors, Acquired Immunodeficiency Syndrome (AIDS) status, and HIV+ status. The results showed that financial transfers from friends and family had a negative effect on individual's help-seeking behavior for social HIV-services, especially for supportive services. The results also showed that sociodemographic factors and HIV-transmission mode were significant determinants in the help-seeking behavior for HIV-services. The significance of such findings imply an informed public health policy should include the balanced combination of transfers as well as appropriately targeted public funds. Montoya, I. D. Help-Seeking Behavior for HIV-Related Social

Services Among the Urban Poor. Int'L J. Self Help & Self Care, 2(4), pp. 271-283, 2004.

Research Agenda For Economic Evaluation of Substance Abuse Services

Economic analyses of substance abuse interventions play a critical role in informing the decision makers involved in funding these programs. In May 2003, a blue ribbon task force (BRTF) was formed to assess the status of addiction health services research at the National Institute on Drug Abuse and to develop recommendations to strengthen their research portfolio. The recommendations presented in this article develop and expand the economic perspective. With the emergence of new and more effective interventions, the adoption of costlier services still demands justification based on economic evidence. Updated and more rigorous economic information allows patients, health care professionals, insurance companies, policymakers, and others to allocate scarce resources more efficiently. To prepare for the next wave of addiction health services research, this article presents background information on the economics of addiction health services, reviews recent empirical and methodological contributions, and provides 15 research recommendations. French, M.T. and Drummond, M.F. A Research Agenda for Economic Evaluation of Substance Abuse Services. J Subst Abuse Treat, 29(2), pp. 125-137, 2005.

Economic Methods For Adolescent Substance Abuse Treatment

Only a few economic evaluations have been conducted for adolescent-specific treatments. This is the first article to present rigorous methodological guidelines for estimating the economic costs and benefits of adolescent substance abuse treatments, while also addressing the potential challenges associated with such research activities. A representative case study of two adolescent substance abuse treatment programs (one residential and one outpatient) is presented to show some of the initial steps of a comprehensive economic evaluation (e.g., cost analyses, selection of treatment outcome measures, and valuation of outcome measures via monetary conversion factors). Cost data were collected and analyzed using the Drug Abuse Treatment Cost Analysis Program. Monetary conversion factors were obtained and presented for a variety of treatment outcomes. The methodological guidelines, discussion of analytic challenges, and recommendations set forth in this article provide a foundation for future economic studies on adolescent substance abuse treatments. Zavala, S., French, M., Henderson, C., Alberga, L., Rowe, C. and Liddle, H. Guidelines and Challenges for Estimating the Economic Costs and Benefits of Adolescent Substance Abuse Treatments. J Subst Abuse Treat, 29(3), pp. 191-205, 2005.

Challenges In Conducting International Health Research

The Comprehensive Drug Research Center (CDRC) at the University of Miami was established in the early 1970s. Through the decades, investigators from the CDRC have worked with investigators from several countries to establish joint research efforts. Countries often do not have the infrastructure or monetary resources to carry out research on their own. Collaborating with institutions in these countries to build a sustainable capacity for research is a worthwhile and satisfying endeavor, and it presents a method for initiating research and building the necessary research structures. However, working with other countries presents a unique set of challenges and ethical dilemmas. This article presents some of the specific challenges encountered in these research efforts and describes what has done to resolve the problems and work more effectively and efficiently with foreign investigators. McCoy, C., Achi, R., Wolfe, H. and Crandall, L. The CDRC Principles of International Health

Research. J Urban Health, 82(3-4), pp. iv5-iv8, 2005.

Immunologic Function And Virologic Suppression Among Children With Perinatally Acquired HIV Infection On HAART

The goal of highly active antiretroviral therapy (HAART) has been to stabilize and reconstitute immune function and suppress viral replication to the greatest degree possible. Suppression of HIV viral replication has been associated with improved long-term and short-term prognosis. Limited data are available on the level of virologic suppression and immune function of pediatric patients followed in clinical settings in the HAART era. The objective of this study was to assess the level of virologic suppression and immune function in a cohort of children with perinatally acquired HIV infection followed at dedicated HIV specialty care sites. This study comprised a cohort study of HIV-infected children and adolescents. Study subjects consisted of 263 HIV-positive children (< or=17 years old), on HAART, with at least one outpatient visit and CD4 test recorded in 2001 seen at 4 U.S. HIV primary pediatrics and specialty care sites (2 eastern, 1 southern, and 1 western). Measures consisted of all plasma HIV-1 RNA levels < or=400 during calendar year 2001. Two hundred sixty-three patients received HIV-related treatment during 2001, with a mean age of 8.5 years. Sixty-eight percent were black, 54% were females, and the majority (85%) was insured by Medicaid. A total of 28.6% had a class C AIDS diagnosis. A total of 23.5% and 34% of patients maintained viral suppression at <50 copies per milliliter (cpm), or <400 cpm, respectively, for the calendar year; 32.5% and 38.8%, respectively, fulfilled the criteria if one "blip" to <5000 cpm was allowed. Forty-eight percent maintained all viral loads <5000 cpm, and 74.9% overall had HIV-1 RNAs < or=15,000 cpm. Eighty-seven percent of patients had CD4% >25; only 4.2% had CD4 <15%. Overall, 12.5% of patients had either CD4% <15 or severely decreased absolute CD4 counts (adjusted for age). A total of 4.6% of patients had HIV-1 RNAs >100,000 cpm and severe immunosuppression. Patients who were less likely to achieve virologic suppression to <400 cpm included those with CD4 count <200 cells/mm(3) (odds ratio [OR], 0.06; 95% confidence interval [CI], 0.007-0.46), those with AIDS (OR, 0.5; 95% CI, 0.28-0.94), and those with moderate (OR, 0.42; 95% CI, 0.22-0.79), or severe immunologic suppression (OR, 0.14; 95% CI, 0.046-0.43) based on CD4%. CONCLUSION: In this multisite, pediatric cohort, the rate of near-complete virologic suppression (<50 or <400 cpm) was low. However, the majority of patients have near-normal CD4 counts and viral loads <15,000 cpm. Follow up will be critical to assess the implications of ongoing low-level viral replication with near-normal CD4 values. Rutstein, R., Gebo, K., Flynn, P., Fleishman, J., Sharp, V., Siberry, G., and Spector, S. Immunologic Function and Virologic Suppression Among Children with Perinatally Acquired HIV Infection on Highly Active Antiretroviral Therapy. Med Care, 43(9), pp. 15-22, 2005.

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

Research Findings - Intramural Research

Development and Plasticity Section, Cellular Neurobiology Research Branch

Genomic Alterations in Cultured Human Embryonic Stem Cells Cultured human embryonic stem cell (hESC) lines are an invaluable resource because they provide a uniform and stable genetic system for functional analyses and therapeutic applications. Nevertheless, these dividing cells, like other cells, probably undergo spontaneous mutation at a rate of 10(-9) per nucleotide. Because each mutant has only a few progeny, the overall biological properties of the cell culture are not altered unless a mutation provides a survival or growth advantage. Clonal evolution that leads to emergence of a dominant mutant genotype may potentially affect cellular phenotype as well. IRP investigators assessed the genomic fidelity of paired early- and late-passage hESC lines in the course of tissue culture. Relative to early-passage lines, eight of nine late-passage hESC lines had one or more genomic alterations commonly observed in human cancers, including aberrations in copy number (45%), mitochondrial DNA sequence (22%) and gene promoter methylation (90%), although the latter was essentially restricted to 2 of 14 promoters examined. The observation that hESC lines maintained in vitro develop genetic and epigenetic alterations implies that periodic monitoring of these lines will be required before they are used in in vivo applications and that some late-passage hESC lines may be unusable for therapeutic purposes. Maitra, A., Arking, D.E., Shivapurkar, N., Ikeda, M., Stastny, V., Kassauei, K., Sui, G., Cutler, D.J., Liu, Y., Brimble, S.N., Noaksson, K., Hyllner, J., Schulz, T.C., Zeng, X., Freed, W.J., Crook, J., Abraham, S., Colman, A., Sartipy, P., Matsui, S., Carpenter, M., Gazdar, A.F., Rao, M. and Chakravarti, A. Nature Genetics, 37, pp. 1099-1103, 2005.

Reactive Oxygen Species and p38 Phosphorylation Regulate the Protective Effect of Delta9-tetrahydrocannabinol in the Apoptotic Response to NMDA NMDA causes oxidative stress in neurons, and produces cell death involving elements of both necrosis and apoptosis. To examine the neuroprotective mechanism of Delta9-tetrahydrocannabinol (THC) in NMDA-induced death of AF5 cells, IRP researchers measured reactive oxygen species (ROS) formation after exposure to NMDA. ROS generation was increased by NMDA, and NMDA-induced ROS generation was significantly decreased by THC. Western blotting revealed an increase in phosphorylated p38 MAPK after NMDA treatment, which was also blocked by pretreatment with THC. The time course of ROS generation and activation of MAPK signaling pathways were similar. SB203580, a p38 inhibitor, partially blocked glutamate excitotoxicity in AF5 cells. The present data suggest that THC protects against NMDA-induced apoptosis in AF5 cells by blocking ROS generation and inhibiting the activation of p38-MAPK. Chen, J., Errico, S.L. and Freed, W.J. Neuroscience Letters, 389,

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pp. 99-103, 2005.

NTera2: A Model System to Study Dopaminergic Differentiation of Human Embryonic Stem Cells NTera2, a human embryonal carcinoma (EC) stem cell line, shares many characteristics with human embryonic stem cells (hESCs). To determine whether NTera2 can serve as a useful surrogate for hESCs, IRP scientists compared global gene expression between undifferentiated NTera2, multiple undifferentiated hESC cell lines, and their differentiated derivatives, and showed that NTera2 cells share multiple markers with hESCs. Similar to hESCs, NTera2 cells differentiated into TH-positive cells that express dopaminergic markers including AADC, DAT, Nurr1, TrkB, TrkC, and GFRA1 when co-cultured with PA6 cells. Flow cytometry analysis showed that tyrosine hydroxylase (TH) and neural cell adhesion molecule (NCAM) expression increased, whereas SSEA4 expression decreased as cells differentiated. Medium conditioned by PA6 cells stimulated differentiation of NTera2 cells to generate TH-positive cells that expressed dopaminergic markers. Flow cytometry selected polysialylated (PSA-NCAM) cells responded to medium conditioned by PA6 cells by differentiating into TH-positive cells and expressed dopaminergic markers. Sorted cells differentiated for 4 weeks in PA6 cell conditioned media included functional neurons that responded to neurotransmitters and exhibited electronic excitability. Therefore, NTera2 cell dopaminergic neuronal differentiation and PSA-NCAM enrichment provides a useful system for the future study of hESCs. Schwartz, C.M., Spivak, C.E., Baker, S.C., McDaniel, T.K., Loring, J.F., Nguyen, C., Chrest, F.J., Wersto, R., Arenas, E., Zeng, X., Freed, W.J., and Rao MS. Stem Cells and Development, 14, pp. 517-534, 2005.

Electrophysiology Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Species and Strain Differences in the Expression of a Novel Glutamate-Modulating Cannabinoid Receptor in the Rodent Hippocampus A novel, non-CB1 cannabinoid receptor has been defined by the persistence of inhibition of glutamatergic EPSPs by the cannabinoid receptor agonist WIN55,212-2 in mice lacking the cloned CB1 receptor (CB1-/-) (Hajos et al., 2001). This novel receptor was also distinguished from CB1 by its sensitivity to the antagonist SR141716A and its insensitivity to the antagonist AM251 (Hajos & Freund, 2002). The authors have chosen to refer to this putative receptor as CBsc due to its identification on Schaffer collateral axon terminals in the hippocampus. These IRP researchers examined properties of CBsc receptors in Sprague Dawley (SD) rats and two strains of wild-type (WT) mice (C57BL/6J and CD1) used as backgrounds for two independent lines of CB1-/- mice (Ledent et al., 1999; Zimmer et al., 1999). The inhibition of synaptic glutamate release by WIN55,212-2 was observed in hippocampal slices from WT CD1 mice and SD rats but was absent in WT C57 mice. The authors also found that AM251 and SR141716A antagonized the effect of WIN55,212-2 in hippocampal slices from CD1 mice and SD rats demonstrating a lack of selectivity of these ligands for CB1 and CBsc receptors in these animals. The results indicate that the glutamate-modulating CBsc cannabinoid receptor is present in the hippocampi of CD1 mice and SD rats but not in C57BL/6J mice. Thus, the authors have identified animal models that may permit the study of cannabinoids independently of the novel CBsc receptor (C57CB1+/+), the CBsc receptor independently of the cloned CB1 receptor (CD1CB1-/-), or in the absence of both receptors (C57CB1-/-). Hoffman, A.F., Macgill, A.M., Smith, D., Oz, M. and Lupica, C.R. European Journal of Neuroscience 22, pp. 2387-2391, 2005.

Proteomics Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

In Situ Structural Characterization of Phosphatidylcholines in Brain

Staff Highlights

Grantee Honors

Tissue using MALDI-MS/MS Phosphatidylcholine (PC) is one of the most abundant classes of phospholipids and is a major component of membranes in biological systems. Recently, PCs have been detected by direct tissue analysis using MALDI-TOFMS. However, these studies did not allow for the structural characterization of PCs in tissue. In the current study, an in situ method for detection and structural analysis of PC species in brain tissue was developed using a MALDI-TOF/TOF mass spectrometer. Initial profiling of lipids in tissue is performed by MALDI-TOFMS, which allows for the assignment of PC species. However, to confirm the structure of the PC species detected in tissue, MALDI-MS/MS analysis was employed. In this work, protonated, sodiated, and potassiated PC species were detected in brain tissue using DHA matrix. MALDI-MS/MS analysis of these species yielded fragments that verified a phosphocholine head group, but did not supply any fragments that would permit the identification of acyl substituents. To obtain more structural information, lithium adducts of PC species were produced using DHA matrix dissolved in 100 mM lithium chloride. MALDI-MS/MS analysis of lithiated PC species produced fragments that allowed for the identification and positional assignment of acyl groups in PC species. Jackson, S.N., Wang, H.Y., and Woods, A.S. Journal of the American Society for Mass Spectrometry 16, pp. 2052-2056, 2005.

Localization and Analyses of Small Drug Molecules in Rat Brain Tissue Sections Traditional detection of drugs in tissue requires tissue homogenization, which precludes the mapping and localization of drugs. The use of autoradiography could compensate for such shortcomings. However, it requires expensive custom-synthesized radioactive drugs. Recent improvement in sample preparation for matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) and MALDI-MS/MS provides an alternative approach for in situ drug detection. In this work, rat brains were collected after intracranial injection of chlorisondamine or intraperitoneal injection of cocaine and snap frozen. MALDI matrixes were applied directly to 14-mum brain cryosections and spectra acquired. The identity of the drugs was further confirmed by MS/MS. Careful matrix selection and tissue preparation allows for the successful detection of drugs and the mapping of their relative abundance across various regions of the brain. This new method is simple, safe, accurate, fast, cost-effective, and low in sample consumption and shows potential for imaging, pharmacokinetics, and toxicology applications. Wang, H.Y., Jackson, S.N., McEuen, J. and Woods, A.S. Analytical Chemistry, 77, pp. 6682-6686, 2005.

Clinical Psychopharmacology Section, Medications Discovery Research Branch

Regulation of the Rat Brain Endothelin System by Endogenous Beta-endorphin Several lines of evidence indicate that the central endogenous opioid and endothelin (ET) system regulate each other. To explore this idea further, IRP researchers determined the effect of intracerebroventricular (i.c.v.) administration of anti-beta-endorphin IgG (rabbit) on the expression level of the opioid, corticotropin-releasing hormone and endothelin receptors, and tissue concentration of ET-1. Three days after implanting cannula into the lateral ventricle, male Sprague-Dawley rats were administered 10mul (i.c.v.) of either control rabbit IgG (2.5 ug/mul) or anti-beta-endorphin IgG (2.5mug/mul) on days 1, 3 and 5. On day 6, animals were euthanized and caudate, cortex and hippocampus collected for Western blot analysis. Anti-beta-endorphin IgG down-regulated ET-A receptor protein expression in the caudate (51%), but had no effect on the expression of mu, delta, kappa opioid, ET-B, CRH-1 and CRH-2 receptors in any brain region. Anti-beta-endorphin IgG increased tissue ET-1 levels in the caudate by 30.3%. [(35)S]GTP-gamma-S binding assays demonstrated that anti-beta-endorphin IgG increased the efficacy of [d-Ala(2)-MePhe(4),Gly-ol(5)]enkephalin without altering its potency

in caudate. Control experiments showed that there was no detectable rabbit IgG in caudate, cortex and hippocampus samples. These results suggest that beta-endorphin in the CSF coordinately regulates ET-1 levels and the ET-A receptor in rat caudate. These findings support the hypothesis that CSF neuropeptides have regulatory effects and further demonstrate a link between opioid and ET system. Wang, X., Xu, H. and Rothman, R.B. Regulation of the Rat Brain Endothelin System by Endogenous Beta-endorphin. Peptides. [Epub ahead of print], 2005.

Medicinal Chemistry Section, Medications Discovery Research Branch

N-8-Substituted-Benztropinamine Analogs as Selective Dopamine Transporter Ligands A series of N-8-substituted benztropinamines was synthesized and evaluated for binding at the dopamine (DAT), serotonin (SERT), norepinephrine (NET) transporters, and muscarinic M1 receptors. In general, the isosteric replacement of the C-3 benzhydrol ether of benztropine by a benzhydryl amino group was well tolerated at these binding sites. However, for certain N-8 substituted derivatives, selectivity over muscarinic M1 receptor affinity was reduced. Behavioral evaluation of selected compounds in this series, in animal models of cocaine abuse, is underway. Grundt, P., Kopajtic, T., Katz, J.L. and Newman, A.H. Bioorganic Medicinal Chemistry Letters 15, pp. 5419-5423, 2005.

Neurobiology of Relapse Section, Behavioral Neuroscience Research Branch

The Novel mGluR2/3 Agonist LY379268 Attenuates Cue-induced Reinstatement of Heroin Seeking In humans, drug-associated stimuli can provoke heroin relapse during abstinence. In rats, cues paired with heroin self-administration reinstate heroin seeking in a relapse model. The neurobiological mechanisms involved in this reinstatement, however, are largely unknown. Here, IRP scientists determined the effect of LY379268, an mGluR2/3 agonist which decreases evoked glutamate release, on cue-induced reinstatement of heroin seeking. Systemic injections of LY379268 attenuated reinstatement of heroin seeking induced by exposure to a discrete tone-light cue that was previously paired with heroin infusions during self-administration training. In contrast, LY379268 had no effect on heroin self-administration. Results indicate that glutamate plays an important role in cue-induced reinstatement of heroin seeking and suggest that mGluR2/3 agonists should be considered for the treatment of opiate relapse. Bossert, J.M., Busch, R.F. and Gray, S.M. Neuroreport 16, pp. 1013-1016, 2005.

Differential Long-term Neuroadaptations of Glutamate Receptors in the Basolateral and Central Amygdala after Withdrawal from Cocaine Self-administration in Rats Humans and laboratory animals remain highly vulnerable to relapse to cocaine seeking after prolonged periods of withdrawal from the drug. It has been hypothesized that this persistent cocaine relapse vulnerability involves drug-induced alterations in glutamatergic synapses within the mesolimbic dopamine reward system. Previous studies have shown that cocaine self-administration induces long-lasting neuroadaptations in glutamate neurons of the ventral tegmental area and nucleus accumbens. Here, IRP investigators determined the effect of cocaine self-administration and subsequent withdrawal on glutamate receptor expression in the amygdala, a component of the mesolimbic dopamine system that is involved in cocaine seeking and craving induced by drug-associated cues. Rats were trained for 10 d to self-administer intravenous cocaine (6-h/d) or saline (a control condition) and were sacrificed after 1 or 30 withdrawal days. Basolateral and central amygdala tissues were assayed for protein expression of the AMPA receptor subunits (GluR1, GluR2) and the NMDA receptor subunits (NR1, NR2A and

NR2B). In the basolateral amygdala, GluR1, but not GluR2, levels were increased on days 1 and 30, NR2A levels were increased on day 1, and NR2B levels were decreased on day 30 of withdrawal from cocaine. In the central amygdala, GluR2, but not GluR1, levels were increased on days 1 and 30, NR1 levels were increased on day 30, and NR2A or NR2B levels were not altered after withdrawal from cocaine. These results indicate that cocaine self-administration and subsequent withdrawal induces long-lasting and differential neuroadaptations in basolateral and central amygdala glutamate receptors. Lu, L., Dempsey, J., Shaham, Y. and Hope, B.T. Journal of Neurochemistry 94, pp. 161-168, 2005.

Behavioral Neuroscience Section, Behavioral Neuroscience Research Branch

The Supramammillary Nucleus Mediates Primary Reinforcement via GABA(A) Receptors The supramammillary nucleus (SUM), a dorsal layer of the mammillary body, has recently been implicated in positive reinforcement. The present study examined whether GABA(A) receptors in the SUM or adjacent regions are involved in primary reinforcement using intracranial self-administration procedures. Rats learned quickly to lever-press for infusions of the GABA(A) antagonist picrotoxin into the SUM. Although picrotoxin was also self-administered into the posterior hypothalamic nuclei and anterior ventral tegmental area, these regions were less responsive to lower doses of picrotoxin than the SUM. The finding that rats learned to respond selectively on the lever triggering drug infusions is consistent with picrotoxin's reinforcing effect. Coadministration of the GABA(A) agonist muscimol disrupted picrotoxin self-administration, and another GABA(A) antagonist, bicuculline, was also self-administered into the SUM; thus, the reinforcing effect of picrotoxin is mediated by GABA(A) receptors. Since rats did not self-administer the GABA(B) antagonist 2-hydroxysaclofen into the SUM, the role of GABA(B) receptors may be distinct from that of GABA(A) receptors. Pretreatment with the dopamine receptor antagonist SCH 23390 (0.05 mg/kg, i.p.) extinguished picrotoxin self-administration into the SUM, suggesting that the reinforcing effects of GABA(A) receptor blockade depend on normal dopamine transmission. In conclusion, the blockade of GABA(A) receptors in the SUM is reinforcing, and the brain 'reward' circuitry appears to be tonically inhibited via supramammillary GABA(A) receptors and more extensive than the meso-limbic dopamine system. Ikemoto, S. Neuropsychopharmacology, 30(6), pp. 1088-1095, 2005.

A Five-minute, but not a Fifteen-minute, Conditioning Trial Duration Induces Conditioned Place Preference for Cocaine Administration into the Olfactory Tubercle The establishment of conditioned place preference (CPP) with intracranial injections requires specific injection sites, drug doses, and conditioning trial durations. IRP scientists examined the role of conditioning trial duration in CPP with cocaine injections into the medial olfactory tubercle. Only those rats that had spent 5 min in the compartments showed CPP for cocaine, while rats that had been removed immediately or spent 15 min following cocaine injections did not show CPP. Effective conditioning trial durations for CPP induced by intracranial cocaine injections are apparently much shorter than those typically used for intracranial injections of other drugs of abuse. Ikemoto, S. and Donahue, K.M. Synapse 56(1), pp. 57-59, 2005.

The Functional Divide for Primary Reinforcement of D-amphetamine Lies Between the Medial and Lateral Ventral Striatum: Is the Division of the Accumbens Core, Shell, and Olfactory Tubercle Valid? When projection analyses placed the nucleus accumbens and olfactory tubercle in the striatal system, functional links between these sites began to emerge. The accumbens has been implicated in the rewarding effects of psychomotor stimulants, whereas recent work suggests that the medial accumbens shell and

medial olfactory tubercle mediate the rewarding effects of cocaine. Interestingly, anatomical evidence suggests that medial portions of the shell and tubercle receive afferents from common zones in a number of regions. Here, IRP investigators report results suggesting that the current division of the ventral striatum into the accumbens core and shell and the olfactory tubercle does not reflect the functional organization for amphetamine reward. Rats quickly learned to self-administer D-amphetamine into the medial shell or medial tubercle, whereas they failed to learn to do so into the accumbens core, ventral shell, or lateral tubercle. The present results suggest that primary reinforcement of amphetamine is mediated via the medial portion of the ventral striatum. Thus, the medial shell and medial tubercle are more functionally related than the medial and ventral shell or the medial and lateral tubercle. The current core-shell-tubercle scheme should be reconsidered in light of recent anatomical data and these functional findings. Ikemoto, S., Qin, M and Liu, Z.H., Journal of Neuroscience, 25(20), pp. 5061-5065, 2005.

Cocaine Experience Establishes Control of Midbrain Glutamate and Dopamine by Corticotropin-releasing Factor: A Role in Stress-induced Relapse to Drug Seeking Footshock stress can reinstate cocaine-seeking behavior through a central action of the stress-associated neurohormone corticotropin-releasing factor (CRF). Here IRP scientists report (1) that footshock stress releases CRF in the ventral tegmental area (VTA) of the brain, (2) that, in cocaine-experienced but not in cocaine-naive rats, this CRF acquires control over local glutamate release, (3) that CRF-induced glutamate release activates the mesocorticolimbic dopamine system, and (4) that, through this circuitry, footshock stress triggers relapse to drug seeking in cocaine-experienced animals. Thus, a long-lasting cocaine-induced neuroadaptation, presumably at the level of glutamate terminals in the VTA, appears to play an important role in stress-induced relapse to drug use. Similar neuroadaptations may be important for the comorbidity between addiction and other stress-related psychiatric disorders. Wang, B., Shaham, Y, Zitzman, D, Azari, S., Wise, R.A. and You, Z.B., Journal of Neuroscience, 25(2), pp. 5389-5396, 2005.

Study of the Interaction of Chlorisondamine and Chlorisondamine Analogues with an Epitope of the Alpha-2 Neuronal Acetylcholine Nicotinic Receptor Subunit Chlorisondamine (CHL), a neuronal nicotinic ganglionic blocker, when injected in the cerebral ventricle of rats chronically blocks the increase in locomotion and rearing by subcutaneous nicotine injection. The blocking of the ion channel(s) prevents nicotine from exerting its rewarding effects on the CNS. When administered intraperitoneally, a dose 400-500 times the intracerebroventricular one is needed to cross the blood-brain barrier and to generate the same level of nicotine antagonism, resulting in severe side-effects, thus making it unlikely to be used as a therapeutic compound. Three CHL analogues, 2-(indolin-1-yl)-N,N,N-trimethylethanaminium iodide, 2-(1,3-dioxoisoindolin-2-yl)- N,N,N-trimethylethanaminium iodide, and 2-(1H-indole-3-carboxamido)- N,N,N-trimethylethanaminium iodide, were synthesized in the hope of circumventing the parent compound's shortcomings. They all share a modified indole ring, lack the four chlorines CHL carries, and have one tertiary amine and one quaternary amine. The CHL analogues form noncovalent complexes with an epitope of the alpha-2 nicotinic receptor subunit, GEREE(p)TEEEEEEEDEN, previously proposed as the possible site of CHL interaction. Complexes were analyzed using matrix-assisted laser desorption/ionization mass spectrometry for comparison with CHL. Overall, all three analogues showed better affinity than CHL for complex formation with both the nonphosphorylated and phosphorylated epitopes. Wang, H.Y., Taggi, A.E., Meinwald, J., Wise, R.A. and Woods, A.S. Journal of Proteome Research 4(2), pp. 532-539, 2005.

Brain Stimulation and Morphine Reward Deficits in Dopamine D2 Receptor-deficient Mice The rewarding effects of lateral hypothalamic brain

stimulation, various natural rewards, and several drugs of abuse are attenuated by D1 or D2 dopamine receptor (D1R or D2R) antagonists. Much of the evidence for dopaminergic involvement in rewards is based on pharmacological agents with limited or "relative" selectivity for dopamine receptor subtypes. Genetically engineered animal models provide a complementary approach to pharmacological investigations. In the present study, IRP researchers explored the contribution of dopamine D2Rs to (1) brain stimulation reward (BSR) and (2) the potentiation of this behavior by morphine and amphetamine using D2R-deficient mice. Wild-type (D2Rwt), heterozygous (D2Rhet), and D2R knockout (D2Rko) mice were trained to turn a wheel for rewarding brain stimulation. Once equivalent rate-frequency curves were established, morphine-induced (0, 1.0, 3.0, and 5.6 mg/kg s.c.) and amphetamine-induced (0, 1.0, 2.0, and 4.0 mg/kg i.p.) potentiations of BSR were determined. The D2Rko mice required approximately 50% more stimulation than the D2Rwt mice did. With the equi-rewarding levels of stimulation current, amphetamine potentiated BSR equally across the three genotypes. In contrast, morphine potentiated rewarding stimulation in the D2Rwt, had no effect in the D2Rhet, and antagonized rewarding stimulation in the D2Rko mice. D2R elimination decreases, but does not eliminate, the rewarding effects of lateral hypothalamic stimulation. After compensation for this deficit, amphetamine continues to potentiate BSR, while morphine does not. Elmer, G.I., Pieper, J.O., Levy, J., Rubinstein, M., Low, M.J., Grandy, D.K. and Wise, R.A. Psychopharmacology, 182, pp. 33-44, 2005.

Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch

Nicotine as a Typical Drug of Abuse in Experimental Animals and Humans Tobacco use through cigarette smoking is the leading preventable cause of death in the developed world. Nicotine, a psychoactive component of tobacco, appears to play a major role in tobacco dependence, but reinforcing effects of nicotine often are difficult to demonstrate directly in controlled laboratory studies with animal or human subjects. The objective of the present study was to review the major findings obtained with various procedures developed to study dependence-related behavioral effects of nicotine in experimental animals and humans, i.e., drug self-administration, conditioned place preference, subjective reports of nicotine effects and nicotine discrimination, withdrawal signs, and ratings of drug withdrawal. Results showed thst nicotine can function as an effective reinforcer of drug-seeking and drug-taking behavior both in experimental animals and humans under appropriate conditions. Interruption of chronic nicotine exposure produces withdrawal symptoms that may contribute to relapse. Difficulties encountered in demonstrating reinforcing effects of nicotine under some conditions, relative to other drugs of abuse, may be due to weaker primary reinforcing effects of nicotine or to a more critical contribution of environmental stimuli to the maintenance of drug-seeking and drug-taking behavior with nicotine than with other drugs of abuse. Further experiments are also needed to delineate the role other chemical substances inhaled along with nicotine in tobacco smoke play in sustaining smoking behavior. The authors conclude that nicotine acts as a typical drug of abuse in experimental animals and humans. LeFoll, B. and Goldberg, S.R. Psychopharmacology (Berlin), October 5, 2005, Epubmed ahead of print, PMID 16205918.

A Detailed Behavioral Analysis of the Acute Motor Effects of Caffeine in the Rat: Involvement of Adenosine A1 and A2A Receptors Currently, there is no consensus on the contribution of adenosine A1 and A2A receptor blockade to motor-activating effects of caffeine. The aim of the present study was to use a detailed and continuous observational method to compare the motor effects induced by caffeine with those induced by selective A1 and A2A receptor antagonists. The behavioral repertoire induced by systemic

administration of caffeine (3, 10, and 30 mg/kg), A1 receptor antagonist 8-cyclopentyl-1,3-dimethylxanthine (CPT; 1.2, 4.8 and 7.2 mg/kg), and A2A receptor antagonist 3-(3-hydroxypropyl)-8-(m-methoxystyryl)-7-methyl-1-propargylxanthine phosphate disodium salt (MSX-3; 1, 3, and 10 mg/kg) was analyzed. The effects of pretreatment with the selective A1 receptor agonist N 6-cyclopentyladenosine (CPA; 0.1 mg/g) and the selective A2A receptor agonist 2-p-(2-carboxyethyl)phenethylamino-5¶Î-N-ethylcarboxyamidoadenosine (CGS 21680; 0.2 mg/kg) on the pattern of motor activation induced by caffeine, CPT, or MSX-3 were also examined. Results showed that the pattern of behavioral activation induced by caffeine was better mimicked by CPT than by MSX-3. Coadministration of CPT and MSX-3 gave different results depending on the dose and the type of behavioral response. CPA was more effective at decreasing the activating effects of caffeine and CPT than those of CGS 21680. On the other hand, CGS 21680 was more effective at decreasing the activating effects of MSX-3 than those of caffeine or CPT. Factor analysis revealed a complex three-dimensional behavioral profile for caffeine that was similar to the profile for CPT and was different from the profile for MSX-3. The results indicate a predominant role for A1 receptors in the motor-activating effects of acutely administered caffeine. Antoniou, K., Papadopoulou-Daifoti, Z., Hyphantis, T., Papathanasiou, G., Bekris, E., Marselos, M., Panlilio, L, MŸller, C.E., Goldberg, S.R. and Ferré, S. Psychopharmacology (Berlin), October 5, 2005, Epubmed ahead of print, PMID 16205915.

Ethanol Does Not Affect Discriminative-Stimulus Effects of Nicotine in Rats The effects of ethanol were evaluated in rats trained to discriminate 0.4 mg/kg of nicotine from saline under a fixed-ratio 10 schedule of food delivery. Ethanol (0.1-1 g/kg, i.p.) did not produce any nicotine-like discriminative effects and did not produce any shift in the dose-response curve for nicotine discrimination. Thus, the ability to discriminate nicotine's effects does not appear to be altered by ethanol administration. However, the high dose of 1 g/kg ethanol, given either alone or in combination with nicotine, markedly depressed food-maintained responding. This later effect was associated in some rats with an attenuation of the discriminative-stimulus effects of the training dose of nicotine. This suggests that previous reports of increased tobacco smoking following ethanol consumption in humans are connected, in some way, with an increase in motivation to consume nicotine that is produced by ethanol, rather than with a decrease in the subjective response to nicotine. LeFoll, B. and Goldberg, S.R. European Journal of Pharmacology, 519, pp. 96-102, 2005.

The Dopamine D3 Receptor and Drug Dependence: Effects on Reward or Beyond? Abused drugs (alcohol, heroin, cocaine, tetrahydrocannabinol and nicotine) elicit a variety of chronically relapsing disorders by interacting with brain reward systems. All of these drugs increase dopamine levels in the shell of nucleus accumbens, a structure that has been involved in their hedonic and reinforcing properties. Dopamine D3 receptors (DRD3) are predominantly expressed in the nucleus accumbens, but also in the ventral tegmental area and in the amygdala, brain structures implicated in drug dependence. Moreover, converging pharmacological, human post-mortem and genetic studies have suggested the involvement of the DRD3 in drug dependence. Based on early studies using non-selective DRD3 ligands, the DRD3 was proposed as having a direct role in the rewarding effects of psychostimulants. However, recent studies using highly selective DRD3 ligands and the DRD3-deficient mice have revealed that the DRD3 is not implicated in the direct reinforcing effects of drugs of abuse. In contrast, the DRD3 appears to be implicated in the motivation to self-administer drugs under schedules where the response requirements are high. This is consistent with a behavioral economic analysis, with the effects of DRD3 ligands revealed only in situations with high prices for drug. Drug-self administration and relapse are strongly controlled by environmental stimuli. The DRD3 strongly modulates the influence of these environmental stimuli on drug-seeking behavior. DRD3

blockade disrupts the reactivity to drug-associated stimuli in various paradigms, such as second-order schedules of drug-self administration, conditioned place preference and Pavlovian conditioning procedures. In several paradigms, the involvement of the DRD3 has been confirmed by using DRD3-deficient mice. On the contrary, reactivity to stimuli associated with natural reinforcers, such as food, appears unaffected by modulation of the DRD3. All these findings suggest that DRD3 ligands may represent a useful strategy for decreasing relapse in abstinent drug-abusers. Le Foll, B., Goldberg, S.R. and Sokoloff, P. Neuropharmacology, 49, pp. 525-541, 2005.

Existence and Theoretical Aspects of Homomeric and Heteromeric Dopamine Receptor Complexes and their Relevance for Neurological Diseases Dopamine (DA) and other receptors physically interact in the plasma membrane of basal ganglia neurons forming receptor mosaics (RMs). Two types of RMs are discussed, homomers formed only by DA-receptor (DA-R) subtypes and heteromers formed by DA-R associated with other receptors, such as A2A, A1, mGluR5, N-methyl-D-aspartate (NMDA), gamma-aminobutryic acid (GABA)-A, and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid. By being part of horizontal molecular networks, RMs tune multiple effector systems already at membrane level, such as G protein regulated inward rectifying potassium channels and dopamine transporter activity. Also, ligand-gated ion channels such as GABA-A and NMDA receptors are modulated by DA-R, e.g., in the striatal GABA output neurons through the formation of heteromeric complexes with these receptors. Thus, intramembrane DA-R-receptor interactions play an important role in the information handling in the basal ganglia. On this basis, functional implications of DA RM in physiological and pathological conditions are discussed. The effects of temperature on RM are discussed not only because receptor-decoding mechanisms are temperature sensitive, but also in view of the suggestion that possible ordering effects (i.e., changes in the entropy of a receptor complex) induced by a ligand are as a result of alterations in the receptor oligomerization (i.e., are related to rearrangements of the RM). Hence, brain temperature may have profound effects on brain integrative functions not only because its effects on the kinetics of biochemical reactions, but also for its effects on receptor geometry, building up of RM, and alterations in protein expression, as is the case of H-channels following febrile seizures. Agnati, L.F., Ferre, S., Burioni, R., Woods, A., Genedani, S., Franco, R. and Fuxe, K. Neuromolecular Medicine, 7, pp. 61-78, 2005.

Partners for Adenosine A1 Receptors G protein-coupled receptors (GPCRs) are targets for therapy in a variety of neurological diseases. Using adenosine A1 receptors (A1Rs) as paradigm of GPCRs, this review focuses on how protein-protein interactions, from monomers to heteromers, can contribute to hormone/neurotransmitter/neuromodulator regulation. The interaction of A1Rs with other membrane receptors, enzymes, and adaptor and scaffolding proteins is relevant for receptor traffic, internalization, and desensitization, and A1Rs are extremely important in driving signaling through different intracellular pathways. There is even the possibility of linking together GPCR heteromeric complexes with ion channel receptors in a receptor mosaic that might have special integrative value and might constitute the molecular basis for learning and memory. Franco, R., Ciruela, F., Casado, V., Cortes, A., Canela, E.I., Mallol, J., Agnati, L.F., Ferre, S., Fuxe, K. and Lluis, C. Journal of Molecular Neuroscience, 26, pp. 221-232, 2005.

Receptor-Receptor Interactions, Receptor Mosaics, and Basic Principles of Molecular Network Organization: Possible Implications for Drug Development The phenomenon of receptor-receptor interactions was hypothesized by Agnati and Fuxe in the 1980s, and several indirect proofs were provided in the following years by means of in vitro binding experiments and in vivo experiments in physiological and pathological animal models. This paper aims to outline some of the most important features and consequences of this

phenomenon in the frame of the structural and functional aspects of molecular networks. In particular, the concepts of receptor mosaic (RM), and of horizontal and vertical molecular networks (HMNs, VMNs, respectively) are illustrated. To discuss some aspects of the functional organization of molecular networks, not only new data on protein-protein interactions but also the biochemical mechanism of cooperativity will be used. On this basis, some theoretical deductions can be drawn that allow a tentative classification of the RMs and the proposal of the extension of the concept of branching point introduced for enzymes to the possible switching role of some RMs in directing signals to various VMNs. Finally, the cooperativity phenomenon and the so-called symmetry rule will be used to introduce a proper mathematical approach that characterizes RMs as to their receptor composition, receptor topography, and order of receptor activation inside the RM. These new data on G protein-coupled receptors and molecular network organization indicate possible new approaches for drug development. Agnati, L.F., Tarakanov, A.O., Ferre, S., Fuxe, K. and Guidolin, D. Journal of Molecular Neuroscience, 26, pp. 193-208, 2005.

Dimer-based Model for Heptaspanning Membrane Receptors The existence of intramembrane receptor-receptor interactions for heptaspanning membrane receptors is now fully accepted, but a model considering dimers as the basic unit that binds to two ligand molecules is lacking. Here, IRP scientists propose a two-state-dimer model in which the ligand-induced conformational changes from one component of the dimer are communicated to the other. Our model predicts cooperativity in binding, which is relevant because the other current models fail to address this phenomenon satisfactorily. Our two-state-dimer model also predicts the variety of responses elicited by full or partial agonists, neutral antagonists and inverse agonists. This model can aid our understanding of the operation of heptaspanning receptors and receptor channels, and, potentially, be important for improving the treatment of cardiovascular, neurological and neuropsychyatric diseases. Franco, R., Casado, V., Mallol, J., Ferre, S., Fuxe, K., Cortes, A., Ciruela, F., Lluis, C. and Canela, E.I. Trends Biochemical Science 30, pp. 360-366, 2005.

Smoking Cessation Guidelines: Evidence -based Recommendations of the French Health Products Safety Agency Tobacco use is the leading preventable cause of death in developed countries. Millions of smokers are willing to stop, but few of them are able to do so. Clinicians should only use approaches that have demonstrated their efficacy in helping patients to stop smoking. This article summarizes the evidence-based major findings and clinical recommendations for the treatment of tobacco dependence of the French Health Products Safety Agency (AFSSAPS). Clinicians should enquire about the smoking status of each patient and provide information about health consequence of smoking and effective treatments available. These treatments include counseling (mainly individual or social support and behavioral and cognitive therapy) and pharmacological treatment with either nicotine replacement therapy (NRT) or bupropion LP. Pharmacological treatments should be used only for proven nicotine dependence, as assessed by the Fagerstrom test for Nicotine Dependence. The choice of pharmacologic treatment depends on the patient's preference and history and of the presence of contra-indications. The clinician should start with a single agent, but these treatments may be used in combination. Smoking behavior is a chronic problem that requires long-term management and follow-up. Access to intensive treatment combining pharmacological treatment and extensive behavioral and cognitive therapy should be available for highly dependent patients. LeFoll, B., Melihan-Cheinin, P., Rostoker, G., Lagrue, G. Working Group of AFSSAPS European Psychiatry, 20, pp. 431-441, 2005.

Intravenous Butyrylcholinesterase Administration and Plasma and Brain Levels of Cocaine and Metabolites in Rats Butyrylcholinesterase is a major cocaine-metabolizing enzyme in humans and other primates, catalyzing

hydrolysis to ecgonine methylester. Increasing butyrylcholinesterase activity may be a treatment for cocaine addiction. IRP researchers evaluated the effect of 30-min pretreatment with horse-derived butyrylcholinesterase (5-15,000 U i.v.) or with the selective butyrylcholinesterase inhibitor cymserine (10 mg/kg i.v.) on the metabolism of cocaine (17 mg/kg i.p.) in anesthetized rats. Venous blood samples were collected for two hours after cocaine administration and later assayed for cocaine and metabolites by gas chromatography/mass spectroscopy. Whole brains were collected after the last blood sample and similarly assayed. Butyrylcholinesterase significantly increased plasma and brain ecgonine methylester levels and decreased cocaine plasma half-life from 26.2 min (saline) to 16.4 min (15,000 U). Butyrylcholinesterase had no significant effect on plasma or brain cocaine or benzoylecgonine levels. Cymserine had no effect on any variable. These findings suggest that butyrylcholinesterase treatment may have benefits in enhancing cocaine metabolism and in increasing levels of ecgonine methylester, which may have a protective action against cocaine. Carmona, G.N., Schindler, C.W., Greig, N.H., Holloway, H.W., Jufer, R.A., Cone, E.J. and Gorelick, D.A. European Journal of Pharmacology, 517, pp. 186-190, 2005.

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

Shorter Time to First Cigarette of the Day in Menthol Adolescent Cigarette Smokers Menthol smoking is thought to contribute to the addictiveness of smoking. Given the high prevalence of menthol smoking among youth, the aim of the current analysis was to examine differences in consumption and tobacco dependence, including smoking urgency among menthol and non-menthol adolescent smokers. Data for the current analysis were collected from telephone interviews with adolescent smokers applying to a cessation treatment study. Of 572 adolescent smokers (mean age=15.6+/-1.6 years; 55.1% female; 46.9% African American, 48.2% European American), 531 smoked menthol cigarettes and 41 smoked non-menthol as their usual brand. Analysis using Fisher's Exact (one-tailed) Test revealed that menthol smokers had a significantly shorter time to first (TTF) cigarette of the day compared to non-menthol smokers (smoking within the first 5 min of the day, 45% vs. 29%, respectively; $p<0.04$). Independent t tests revealed no significant difference in number of cigarettes per day (CPD) (mean=12.2+/-8.5 vs. 11.4+/-8.8; $p<0.28$) or Fagerstrom Test for Nicotine Dependence (FTND) scores (3.4+/-1.4 vs. 3.2+/-1.3; $p<0.23$). While preliminary, authors findings suggest greater smoking urgency among menthol compared to non-menthol adolescent cessation-treatment seekers. Further study in a broader sample of adolescent smokers is warranted to elucidate the mechanisms underlying the effects of menthol smoking for youths. Collins, C.C. and Moolchan, E.T. Addictive Behaviors November 19, 2005; [Epub ahead of print].

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

International Research

Research Supported by International Program Supplement Suggests Emancipatory Research Can Promote Recovery

Dr. Alexandre Laudet, National Development and Research Institutes, Inc. (NDRI), and Mr. Gordon Storey, Self-help Addiction Resource Center, Melbourne, presented their research, "Emancipatory Research In The Addiction Field: A Partnership To Promote Empowerment And To Understand The Recovery Process" at the September 2005 Congress of the World Federation for Mental Health in Cairo, Egypt. The authors conclude that emancipatory research can promote recovery by empowering patients, compiling experiential expertise into a credible knowledge base, and improving access to services. Dr. Laudet and Mr. Storey are conducting a pilot study to identify and compare recovery-promoting factors and various paths to resolving harmful drug use in Australia and the United States, supported by an International Program Administrative Supplement, R01-DA014409-03S1.

DISCA-Supported Research Examines Genetic Link to Smoking Cessation

2004 NIDA Distinguished International Scientist Dr. Ivan Berlin, Groupe Haspitalier Universitaire Pitié-Salpêtrière, France, and his DISCA partner, Dr. Liro S. Covey, New York State Psychiatric Institute, have published their joint research in Nicotine & Tobacco Research, 7(5), pp. 725-728, 2005. The authors report on their studies of a polymorphism in the D2 dopamine receptor and its predictive value for the likelihood of successfully quitting smoking.

DISCA-Supported Research Demonstrates Effectiveness of HIV/AIDS Prevention Education in a Chinese Drug Abuse Treatment Setting

2005 NIDA Distinguished International Scientist Dr. Min Zhao, China, and her DISCA partner, Dr. Clyde B. McCoy, University of Miami, have published their joint research in the Journal of Urban Health, Volume 82, Number 3, Supplement 4, iv84-91. The authors found that HIV/AIDS prevention education increased HIV knowledge, improved understanding of HIV prevention methods, and changed attitudes toward HIV/AIDS among a population of injection drug users undergoing treatment in Shanghai.

Research Publications by International Program Alumni Alumni of the NIDA International Program research training and exchange programs authored or coauthored the following recent articles indexed by PubMed:

Former NIDA INVEST Drug Abuse Research Fellows

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Staff Highlights

Grantee Honors

Clinical Characterization of Use of Acamprosate and Naltrexone: Data from an Addiction Center in India

Basu, D., Jhirwal, O.P., Mattoo, S.K. Am J Addict. 14(4), pp. 381-395, July-September 2005. (INVEST Fellow: Debasish Basu, India, 2001-2002). There are several queries on the effectiveness of acamprosate in pharmacoprophylaxis of alcohol dependence despite studies conducted over the last decade regarding its efficacy. In this retrospective chart review, 62 patients with ICD-10-diagnosed alcohol dependence who received treatment from an addiction center in India were studied to compare those on acamprosate or naltrexone versus those on no prophylactic drugs with regard to their demographic and clinical background and short-term outcome after treatment. Compared to those on naltrexone or no drugs, significantly more patients on acamprosate came from higher socioeconomic strata and had fewer family/marital complications and less comorbid use of opioids and other drugs; however, they also had more liver function impairment and alcoholic liver disease and a higher average duration of relapse in the past ($p < 0.05$ or less in each case). The group on no drugs had significantly less family/social support ($p = 0.006$) and poorer motivation rating ($p < 0.001$) than the other two groups on drugs. Intent-to-treat analysis showed that there was a non-significant trend of a higher proportion of acamprosate patients remaining abstinent (77%) than those on naltrexone (36%) or no drug (50%). At follow-up, acamprosate patients had significantly better functioning in several areas. However, because many of the baseline patient characteristics might themselves have influenced the outcome, no conclusion should be drawn from this data regarding the efficacy of the drug. Logistic regression analysis showed that both family/social support and acamprosate appeared to contribute modestly toward explaining the variance in short-term outcome.

Anti-Allodynic Interactions Between NMDA Receptor Channel Blockers And Morphine Or Clonidine In Neuropathic Rats

Malyshkin, A.A., Medvedev, I.O., Danysz, W., Bespalov, A.Y. Eur J Pharmacol. 519(1-2):80-85, September 5, 2005. (INVEST Fellow: Anton Bespalov, Russia, 1994-1995). Previous studies suggested that combining N-methyl-d-aspartate (NMDA) receptor antagonists with either mu-opioid agonist morphine or alpha2-adrenoreceptor agonist clonidine results in the significant synergistic enhancement of analgesic activity in the animal models of acute and neuropathic pain. When given alone, NMDA receptor antagonists, morphine and clonidine are capable of attenuating tactile allodynia associated with chronic nerve injury. The present study aimed to assess anti-allodynic effects of these compounds and to test additivity of these interactions using isobolographic analysis. Adult male Wistar rats with unilateral loose ligation of sciatic nerve developed significant tactile allodynia (between-paw difference of about 18-20 g). In separate groups of animals, dose-dependent anti-allodynic activity was confirmed for memantine (1.8-17.8 mg/kg), neramexane (1.8-17.8 mg/kg), morphine (1-10 mg/kg) and clonidine (0.01-0.1 mg/kg). In a subsequent series of experiments, memantine (or neramexane) and morphine (or clonidine) were co-administered at the fixed equi-effective dose ratios (six dose levels per drug combination). None of the tested combinations produced supra-additive, synergistic effects. In fact, memantine+clonidine, neramexane+clonidine and morphine+neramexane were producing simple additive effects, while morphine+memantine was characterized as the infra-additive combination. Thus, despite expectations based on previous studies, NMDA receptor channel blockers, memantine and neramexane, produce no synergistic interactions with either morphine or clonidine when administered acutely to rats with nerve injury-induced tactile allodynia.

Multi-level Analysis of Causal Attribution of Injury to Alcohol and

Modifying Effects: Data from Two International Emergency Room Projects

Cherpitel ,C.J., Bond, J., Ye,Y., Borges, G., Room, R., Poznyak, V. and Hao, W. Drug Alcohol Depend. October 26, 2005 [Epub ahead of print] (INVEST Fellow: Guilherme Borges, Mexico, 1997-1998). Although alcohol consumption and injury has received a great deal of attention in the literature, less is known about patient's causal attribution of the injury event to their drinking or factors which modify attribution. Hierarchical linear modeling is used to analyze the relationships of the volume of alcohol consumed prior to injury and feeling drunk at the time of the event with causal attribution, as well as the association of aggregate individual-level and socio-cultural variables on these relationships. Data analyzed are from 1955 ER patients who reported drinking prior to injury included in 35 ERs from 24 studies covering 15 countries from the combined Emergency Room Collaborative Alcohol Analysis Project (ERCAAP) and the WHO Collaborative Study on Alcohol and Injuries. Half of those patients drinking prior to injury attributed a causal association of their injury with alcohol consumption, but the rate of causal attribution varied significantly across studies. When controlling for gender and age, the volume of alcohol consumed and feeling drunk (controlling for volume) were both significantly predictive of attribution and this did not vary across studies. Those who drink at least weekly were less likely to attribute causality at a low volume level, but more likely at high volume levels than less frequent drinkers. Attribution of causality was also less likely at low volume levels in those societies with low detrimental drinking patterns, but more likely at high volume levels or when feeling drunk compared to societies with high detrimental drinking patterns. These findings have important implications for brief intervention in the ER if motivation to change drinking behavior is greater among those attributing a causal association of their drinking with injury.

Forensics: Age Written In Teeth By Nuclear Tests

Spalding, K.L., Buchholz, B.A., Bergman, L.E., Druid, H. and Frisen, J. Nature. 437(7057), pp. 333-334, September 15, 2005. (INVEST Fellow: Henrik Druid, Sweden, 2000-2001). Establishing the age at death of individuals is an important step in their identification and can be done with high precision up to adolescence by analysis of dentition, but it is more difficult in adults. Here we show that the amount of radiocarbon present in tooth enamel as a result of nuclear bomb testing during 1955-63 is a remarkably accurate indicator of when a person was born. Age is determined to within 1.6 years, whereas the commonly used morphological evaluation of skeletal remains and tooth wear is sensitive to within 5-10 years in adults.

Toxicological Findings And Manner Of Death In Autopsied Users Of Anabolic Androgenic Steroids

Petersson, A., Garle, M., Holmgren, P., Druid, H., Krantz, P. and Thiblin, I. Drug Alcohol Depend. August 29, 2005 [Epub ahead of print] (INVEST Fellow: Henrik Druid, Sweden, 2000-2001). With the aims of characterizing patterns in toxicological profile and manner of death in deceased users of anabolic androgenic steroids (AAS), a retrospective autopsy protocol study of 52 deceased users of AAS was undertaken. The AAS users were compared to 68 deceased users of amphetamine and/or heroin who were consecutively tested and found to be negative for AAS. Use of AAS was in the majority of cases (79%) associated with concomitant use of psychotropic substances. AAS-related deaths differed in several respects from deaths among users of heroin or amphetamine, most strikingly with regard to: (a) the median age at death, which was significantly lower for AAS users (24.5 years) than for users of heroin and/or amphetamine (34 and 40 years, respectively); (b) the manner of

death, with AAS users dying significantly more often from homicide or suicide than users of other drugs; and (c) the body mass index (BMI), with AAS users exhibiting significantly higher BMI than users of other drugs. These results support the earlier reported association between use of AAS and use of other psychoactive substances. In addition, the data suggest that AAS users are more likely to become involved in incidents leading to violent death and have a higher risk of dying at a younger age than users of other drugs.

mu Opioid Receptor Agonist DAMGO-Induced Suppression Of Saccharin Intake In Lewis and Fischer Rats

Liu, C. and Grigson, P. Brain Res. October 27, 2005 [Epub ahead of print] (INVEST Fellow: Chuang Liu, China, 2000-2001). Rats suppress intake of a saccharin cue when paired with a drug of abuse such as morphine or cocaine. Relative to Lewis rats, Fischer rats exhibit greater avoidance of a saccharin cue following saccharin-morphine pairings. Thepresent study used the mu agonist, [d-Ala(2),N-MePhe(4),Gly-ol(5)]enkephalin (DAMGO), to test whether strain differences in sensitivity of the mu receptor contribute to this effect. Water-deprived Lewis and Fischer rats were given 5 min access to 0.15% saccharin followed by an icv injection of either DAMGO (0.5 microg/1 microl/rat) or an equal volume of saline. There were six taste-drug pairings occurring at 48 h intervals. The results showed that, relative to the saline treated controls, all rats reduced intake of the saccharin cue following saccharin-DAMGO pairings. No differences occurred between strains. These data suggest that greater morphine-induced suppression of saccharin intake by the Fischer rats is not likely mediated by differences in sensitivity of the mu receptor. Other mechanisms are implicated.

Systemic And Site-Specific Effects Of A-425619, A Selective TRPV1 Receptor Antagonist, On Wide Dynamic Range Neurons In CFA-Treated and Uninjured Rats

McGaraughty, S., Chu, K.L., Faltynek, C.R. and Jarvis, M.F. J Neurophysiol. September 14, 2005 [Epub ahead of print] (INVEST Fellow: Steve McGaraughty, Canada, 1995-1996). Systemic administration of A-425619, a potent and selective TRPV1 receptor antagonist that does not readily enter the CNS, produces antinociception in several rat models of pathological nociception, including complete Freund's adjuvant (CFA)-induced thermal hyperalgesia. In order to further understand the peripheral mechanisms of TRPV1-related antinociception, we examined the effects of systemic and site-specific injections of A-425169 on evoked and spontaneous firing of spinal wide dynamic range (WDR) neurons in uninjured rats and rats with peripheral inflammation (CFA, 48 hrs). In uninjured rats, capsaicin-evoked (1 microg) WDR activity was completely blocked by intraplantar administration of A-425619 (3-100 nmol). Systemic injection of A-425619 (3-30 micromol/kg, i.v.) reduced WDR responses to thermal stimulation in both CFA-inflamed (47 degrees C) and uninjured (52 degrees C) rats. However, the efficacy of A-425619 to attenuate thermal-evoked WDR activity was significantly greater ($P < 0.01$) in CFA-treated rats. Both intra-dorsal root ganglion (DRG, L5, 20 nmol) and intraplantar (30-300 nmol) injection of A-425619 reduced WDR responses to thermal stimulation. While the effectiveness of A-425619 was similar between CFA-inflamed and uninjured rats following intraplantar injection, the effects of A-425619 after intra-DRG injection were enhanced in the inflamed rats (compared to the uninjured rats). Spontaneous WDR discharges were unaltered by systemic or site-specific injections of A-425619. Thus, noxious thermal stimulation triggers the transmission of TRPV1-related signals to spinal WDR neurons in both inflamed and uninjured animals. The apparent increase in TRPV1 signaling to WDR neurons following injury may be the result of changes to the distribution/sensitization of peripheral TRPV1 receptors.

Substance Use and Multiple Victimization Among Adolescents In South Africa

Morojele, N.K. and Brook, J.S. Addict Behav. October 24, 2005 [Epub ahead of print] (INVEST Fellow: Neo Morojele, South Africa, 1998-1999). The aims of the study were to examine the relationship between multiple victimization and drug use, and the role of drug use and other intra-personal, peer, parental and environmental factors in predicting multiple victimization among adolescents in South Africa. A cross-sectional design was employed. The participants comprised 1474 male and female adolescents aged between 12 and 17 years, from Durban and Cape Town. They completed questionnaire measures assessing demographic characteristics; self, peer and parental drug use; self and peer delinquency; parental child-centeredness and rules; and community drug availability and exposure to violence on television. A measure of multiple victimization assessed whether or not the respondents had experienced two or more different types of violence in their lifetime. There was a significant association between frequency of tobacco, alcohol and marijuana use and multiple victimization. Significant predictors of multiple victimization in multiple logistic regression analyses were variables within intra-personal, peer, parental and environmental domains. Victimization prevention programs in South Africa should be comprehensive and target adolescents' drug use as well as their other psychosocial risk factors.

Predictors Of Cigarette Use Among South African Adolescents

Brook, J.S., Morojele, N.K., Brook, D.W. and Rosen, Z. Into J Behav Med. 12(4), pp. 207-217. (INVEST Fellow: Neo Morojele, South Africa, 1998-1999). This study assessed the interrelation among domains of ethnic factors; the individual's sense of well-being; personality, attitudes, and behaviors; sibling and peer smoking; and adolescent smoking behavior. The sample consisted of 1,468 South African adolescents selected from 4 ethnic groups self-identified as defined by current South African usage: Black (mainly Zulu and Xhosa), Indian, White, and Colored (mixed ancestry). In accordance with family interactional theory, there was a sequence of patterning from ethnic factors and the individual's sense of well-being to adolescent personality, attitudes, and behaviors and models of smoking. All of the 4 domains in the model also had a direct effect on adolescent smoking behavior. The findings suggest 4 possible targets of therapeutic or preventive intervention with regard to adolescent smoking: ethnic factors; the individual's sense of well being; personality, attitudes, and behaviors; and smoking within the peer group.

Interactive Skills Of Infants With Their High-Risk Mothers

Savonlahti, E., Pajulo, M., Ahlqvist, S., Helenius, H., Korvenranta, H., Tamminen, T. and Piha J. Nord J Psychiatry. 59(2), pp. 139-147, 2005. (INVEST Fellow: Marjaterttu Pajulo, Finland, 2003-2004). In this pilot study, the interactive skills of infants with their high-risk, substance-dependent mothers were explored in residential treatment from pregnancy until the infant was 6 months of age. Fourteen mother-infant pairs were videotaped in feeding and free play situations at 6 months after birth. A comparison, low-risk group consisted of 12 ordinary Finnish mother-infant pairs with minimal clinical risks. The findings show significantly higher levels of dyadic interactive deficiencies among the high-risk mother-infant pairs compared to the low-risk pairs, displayed especially in the feeding situation as lack of mutuality and flat, empty, constricted affective tone of interaction. Also, more interactive deficiencies were found among the high-risk infants compared to the low-risk infants, but the differences were not significant. In this study, this finding might reflect the reduced amount of somatic complications and the benefits of treatment, the impacts of which were not explored. The differences between

the high- and low-risk infants were displayed as more withdrawal, depressed mood and avoiding behavior and as less alertness and attentional abilities, robustness and focus on parent's emotional state among the high-risk group.

Multidrug Resistance Polypeptide 1 (MDR1, ABCB1) Variant 3435C>T Affects mRNA Stability

Wang, D., Johnson, A.D., Papp, A.C., Kroetz, D.L. and Sadee, W. Pharmacogenet Genomics. 15(10), pp. 693-704, October 2005. (INVEST Fellow: Danxin Wang, China, 1996-1997). ABCB1 (multidrug resistance 1 polypeptide, MDR1, Pgp) is a multispecific efflux transporter of drugs and xenobiotics. Among numerous polymorphisms in human ABCB1, the synonymous SNP 3435C > T has been associated with decreased mRNA and protein levels, via unknown mechanisms. To search for cis-acting polymorphism affecting transcription or mRNA processing, 3435C > T was used as a marker single nucleotide polymorphism (SNP), for measuring differences in allelic mRNA expression. Ratios of allelic abundance in genomic DNA and mRNA (after conversion to cDNA) were measured quantitatively with a primer extension assay, in human liver samples. mRNA expression of the 3435C allele was significantly higher than that of the 3435T allele (3435C/3435T ratios ranging from 1.06-1.61). Cotransfection of equal amounts of ABCB1 expression plasmids containing 3435C or 3435T also revealed higher 3435C mRNA expression. Increasing 3435C/3435T ratios after cessation of transcription indicated that the 3435C > T substitution decreases mRNA stability. 3435C > T is in strong linkage disequilibrium with two other coding SNPs (1236C > T and 2677G > T) forming two abundant haplotypes (ABCB1*1 and ABCB1*13). Transfection of all possible combinations of these three SNPs demonstrated that only 3435T is associated with lower mRNA levels. Calculations of mRNA folding, using Mfold, suggested an effect on mRNA secondary structure. Authors concluded that the abundant 3435C > T SNP appears to be a main factor in allelic variation of ABCB1 mRNA expression in the liver, by changing mRNA stability.

The Novel Dopamine D(3) Receptor Antagonist NGB 2904 Inhibits Cocaine's Rewarding Effects and Cocaine-Induced Reinstatement of Drug-Seeking Behavior in Rats

Xi, Z.X., Newman, A.H., Gilbert, J.G., Pak, A.C., Peng, X.Q., Ashby, C.R., Gitajn, L. and Gardner, E.L. Neuropsychopharmacology. October 5, 2005 [Epub ahead of print](INVEST Fellow: Zhengxiong Xi, China, 1995-1996). Accumulating evidence indicates that dopamine (DA) D(3) receptor antagonists appear highly promising in attenuating cocaine reward and relapse in preclinical models of addiction. In the present study, authors investigated the effects of the novel D(3)-selective antagonist NGB 2904 (N-(4-[4-{2,3-dichlorophenyl}-1-piperazinyl]butyl)-3-fluorenylcarboxamide) on cocaine self-administration, cocaine-enhanced brain stimulation reward (BSR), and cocaine-triggered reinstatement of drug-seeking behavior in male Long-Evans rats. Results showed that: (1) acute intraperitoneal (i.p.) administration of NGB 2904 (0.1-10 mg/kg) failed to alter cocaine self-administration (0.5 mg/kg/infusion) under fixed-ratio 2 (FR2) reinforcement, but 1 or 5 mg/kg NGB 2904 significantly lowered the break-point for cocaine self-administration under progressive-ratio (PR) reinforcement; (2) cocaine (1, 2, and 10 mg/kg) significantly enhanced electrical BSR (decreased brain reward thresholds), while NGB 2904 significantly inhibited the enhancement of BSR elicited by 2 mg/kg, but not 10 mg/kg of cocaine; (3) NGB 2904 alone neither maintained self-administration behavior nor altered brain reward thresholds; and (4) NGB 2904 significantly inhibited cocaine-triggered reinstatement of extinguished drug-seeking behavior, but not sucrose-plus-sucrose-cue-triggered reinstatement of sucrose-seeking behavior. Overall, these data show that the novel D(3)-selective antagonist NGB 2904 attenuates cocaine's rewarding

effects as assessed by PR self-administration, BSR, and cocaine-triggered reinstatement of cocaine-seeking behavior. Owing to these properties and to its lack of rewarding effects (as assessed by BSR and by substitution during drug self-administration), NGB 2904 merits further investigation as a potential agent for treatment of cocaine addiction. Neuropsychopharmacology advance online publication, 5 October 2005; doi:10.1038/sj.npp. 1300912.

Simultaneous Intra-Accumbens Remifentanil and Dopamine Kinetics Suggest That Neither Determines Within-Session Operant Responding

Crespo, J.A., Sturm, K., Saria, A. and Zernig, G. Psychopharmacology (Berl). October 12, 2005, 1-9 [Epub ahead of print] (INVEST Fellow: Gerald Zernig, Austria, 1993-1994). The ultra-short-acting mu opioid agonist analgesic/anesthetic remifentanil (RMF) is extremely rapidly eliminated from blood (half-life in rats, 0.3-0.7 min). This extremely fast elimination is thought to be the main reason why RMF maintains such high rates of responding in animal operant-conditioning models of drug addiction. The present study investigated if such a fast elimination of RMF also occurs in the extracellular space of the brain, i.e., in the pharmacokinetic compartment that is thought to be ultimately mediating the reinforcing effect, and hence, the abuse liability of drugs. Nucleus accumbens (NAC) RMF and dopamine (DA) were simultaneously quantified by in vivo microdialysis followed by tandem mass spectrometry both in rats that traversed an alley to receive intravenous injections of 0.032 mg kg(-1) RMF in an operant runway procedure (contingent RMF) and in rats that passively received RMF in the runway (noncontingent RMF). Regardless of the mode of administration (i.e., contingent or noncontingent), intra-accumbens RMF peaked in the first 10-min sample and decreased exponentially with a t(1/2) of 10.0+/-1.2 min (N=31). RMF-stimulated DA peaked in the 10-min sample immediately after the RMF peak and decreased with a time course very similar to that of RMF. Crosscorrelation of the NAC RMF and NAC DA curves showed them to be tightly synchronized. Noncontingent single-dose RMF was eliminated from the whole brain with a half-life of 1.1+/-0.2 min and from blood with a half-life of 0.3 min or less. The comparison of blood-vs.-brain RMF pharmacokinetics with rat RMF self-administration behavior, either in operant runway (present study) or in lever-press-based operant-conditioning procedures, suggests that titration of blood RMF, whole-brain RMF, intra-accumbens RMF, or accumbal DA levels (assessed with the limited temporal resolution of in vivo microdialysis) does not determine a rat's decision to reemit a response during a multiple-injection drug self-administration session.

The AGNP-TDM Expert Group Consensus Guidelines: Focus on Therapeutic Monitoring of Antidepressants

Baumann, P., Ulrich, S., Eckermann, G., Gerlach, M., Kuss, H.J., Laux, G., Muller-Oerlinghausen, B., Rao, M.L., Riederer, P., Zernig, G. and Hiemke, C. Dialogues Clin Neurosci.7(3), pp. 231-247. 2005. (INVEST Fellow: Gerald Zernig, Austria, 1993-1994). Therapeutic drug monitoring (TDM) of psychotropic drugs such as antidepressants has been widely introduced for optimization of pharmacotherapy in psychiatric patients. The interdisciplinary TDM group of the Arbeitsgemeinschaft fur Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) has worked out consensus guidelines with the aim of providing psychiatrists and TDM laboratories with a tool to optimize the use of TDM. Five research-based levels of recommendation were defined with regard to routine monitoring of drug plasma concentrations: (i) strongly recommended; (ii) recommended; (iii) useful; (iv) probably useful; and (v) not recommended. In addition, a list of indications that justify the use of TDM is presented, e.g., control of compliance, lack of clinical response or adverse effects at recommended doses, drug interactions, pharmacovigilance programs, presence of a genetic particularity concerning drug metabolism, and children,

adolescents, and elderly patients. For some drugs, studies on therapeutic ranges are lacking, but target ranges for clinically relevant plasma concentrations are presented for most drugs, based on pharmacokinetic studies reported in the literature. For many antidepressants, a thorough analysis of the literature on studies dealing with the plasma concentration-clinical effectiveness relationship allowed inclusion of therapeutic ranges of plasma concentrations. In addition, recommendations are made with regard to the combination of pharmacogenetic (phenotyping or genotyping) tests with TDM. Finally, practical instructions are given for the laboratory practitioners and the treating physicians how to use TDM: preparation of TDM, drug analysis, reporting and interpretation of results, and adequate use of information for patient treatment TDM is a complex process that needs optimal interdisciplinary coordination of a procedure implicating patients, treating physicians, clinical pharmacologists, and clinical laboratory specialists. These consensus guidelines should be helpful for optimizing TDM of antidepressants.

Former Hubert H. Humphrey Drug Abuse Research Fellows

Opioids and Abnormal Pain Perception: New Evidence From A Study Of Chronic Opioid Addicts and Healthy Subjects

Pud, D., Cohen, D., Lawental, E. and Eisenberg, E. Drug Alcohol Depend. October 13, 2005 [Epub ahead of print] (HHH Fellow: Eli Lawental, Israel, 1993-1994). Recent evidence reported on increased pain sensitivity in animals following parenteral opioid administration and in humans subsequent to intravenous administration of short-acting opioids and possibly in drug addicts. The aims of the present study were to explore the possibilities that (1) pain perception is altered in chronic opioid addicts (OAs); (2) if indeed so, the cessation of opioid consumption resets their altered pain perception. Sixty heroin or methadone OAs who attended a 4-week inpatient detoxification program were exposed to the cold pressor test (CPT) upon entrance to the program, at 7 and 28 days subsequent to the cessation of opioid consumption (verified by repeated urine toxicology tests). Latency of pain onset (s), pain intensity (0-100 VAS), and tolerance (time for hand withdrawal) in response to the CPT were measured. In comparison with 70 healthy controls, the OAs demonstrated prolonged latency (6.6+/-3.5s versus 10.9+/-7.7s; $p<0.0001$); decreased VAS (74+/-16 versus 55+/-20; $p<0.0001$); shorter tolerance (56.4+/-51.3s versus 31.7+/-40.7s; $p=0.001$). No differences between the three time points in any of the three measures were detected in the OAs. The results provide further evidence of opioid-induced hyperalgesia in the OA population, as manifested by their quicker hand withdrawal. In addition, it appears that detoxification from opioids does not reset pain perception for at least 1 month.

Adoption Of The New Antimalarial Drug Policy In Tanzania - A Cross-Sectional Study In the Community

Eriksen, J., Nsimba, S.E., Minzi, O.M., Sanga, A.J., Petzold, M., Gustafsson, L.L., Warsame, M.Y. and Tomson, G. Trop Med Int Health. 10(10), pp. 1038-1046, October 2005. (HHH Fellow: Stephen Nsimba, Tanzania, 2005-2006). The objective of this study was to assess the diffusion of the change of first line antimalarial drug from chloroquine (CQ) to sulphadoxine/pyrimethamine (SP) at household level in a rural district of Tanzania less than a year after the policy implementation. Caretakers in 729 households were interviewed on knowledge of the new policy, home stocking of antimalarials, home-treatment practices of children younger than 5 years with fever, health-seeking behavior and experience of SP. SP and CQ levels in blood were analyzed from 328 children younger than 5 years in the households. Twelve focus group discussions (FGD) were performed with mothers, fathers and health workers. About 51% of the population knew that SP was the first line antimalarial. Only

8% of mothers stocked antimalarials, and only 4% stated self-treatment as the first action. We estimated that 84% of the children who had had fever during the last 4 weeks sought care at public health facilities. SP was detectable in 18% of the total child population and in 32% of those with reported fever, CQ in only 5% and 7%, respectively. The FGDs revealed negative perceptions of SP and fear of severe adverse reactions with mass media reported as key informant. Authors concluded that the policy had diffused to the communities in the sense that CQ had been changed to SP, which was well known as first line treatment. Moreover, there was a reported dramatic change from self-treatment with CQ to seeking care at public health facilities where SP was given under observation.

Comparative Study Of Drug Use Among Undergraduate Students At The University Of Sao Paulo - Sao Paulo Campus In 1996 and 2001

Stempliuk, Vde A., Barroso, L.P., Andrade, A.G., Nicastri, S. and Malbergier, A. Rev Bras Psiquiatr.27(3), pp. 185-193, September 2005. Epub 2005 Oct 4. (HHH Fellows: Vladimir Stempliuk, Brazil, 2003-2004; Sergio Nicastri, Brazil, 1997-1998; and Arthur Guerra de Andrade, Brazil, 1991-1992). The objective of this study was to compare the rate of drug use prevalence and to investigate opinions regarding such use among undergraduate students at the University of Sao Paulo - Sao Paulo campus in 1996 and again in 2001. Both studies followed the same procedures of sampling and data collection. A random sample of undergraduate students, divided into the areas of Humanities, Exact Sciences and Biologic Sciences, responded to an anonymous and self-report survey regarding the use of licit and illicit drugs within the last 30 days, within the last 12 months, and over the lifetime of the subject. The two surveys were compared through the construction of (95%) confidence intervals for the prevalence differences for each substance by area and by total number of students. The Wald test for homogeneity was applied in order to compare the prevalences. High approval of regularly trying and using cocaine, crack, amphetamines, and inhalants was observed. The drugs that showed statistic significant increasing were: lifetime use: alcohol, tobacco, marijuana, inhalants, hallucinogens, amphetamines, anticholines, barbiturics, and any illicit drug; last-12-month use: marijuana, inhalants, amphetamines, hallucinogens, and any illicit drug; last-30-day use: marijuana, inhalants, amphetamines, and any illicit drug. The observed difference in the use of some drugs between the two surveys appears to be a consequence of the higher rates of favorable opinions regarding trying and regularly using some psychoactive substances, a finding that mirrors global trends in drug use.

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

Program Activities

New NIDA PAs and RFAs

NIDA has reissued the **International Research Collaboration on Drug Addiction Program Announcement** soliciting collaborative research proposals on drug abuse and addiction that take advantage of unusual talent, resources, populations, or environmental conditions in other countries; speed scientific discovery; and meet NIDA research priorities. Applicants may propose investigations using the NIH Research Project (R01) mechanism. The new announcement, **PA-06-050**, uses standard receipt dates and expires January 3, 2009.

On November 9, 2005, NIDA issued a Program Announcement (**PAS-06-066**) entitled **Design, Synthesis, and Preclinical Testing of Potential Treatment Agents for Drug Addiction**. The purpose of this PA is to support research for the design, synthesis and pharmacological evaluation of new classes of compounds as potential treatment agents for cocaine, methamphetamine or cannabinoid addiction based on novel pharmacological interventions and molecular targets other than biogenic amine transporters.

On December 7, 2005, **NIDA issued a Program Announcement (PA) entitled NIDA Phase II Small Business Innovation Research (SBIR [R44]) Competing Renewal Awards (PA-06-036)**. This PA solicits Small Business Innovative Research (SBIR) grant applications from small business concers (SBCs) that propose the advance stage development of pharmacological treatment agents for drug and nicotine abuse and dependence.

On December 9, 2005, NIDA released a PA entitled **Imaging - Science Track Award for Research Transition (I/START) (R03) (PAR-06-092)**. This PA is intended to facilitate the entry of investigators to the area of neuroimaging, including both new investigators and established investigators seeking to adopt neuroimaging methodologies in their research programs.

On November 8, 2005, NIDA issued an RFA entitled **Developmental Centers for Translational Research on the Clinical Neurobiology of Drug Addiction (P20) (RFA-DA-06-006)**. This solicitation invites applications for the development of Translational Research Centers on the neurobiology of drug abuse and addiction. For purposes of this RFA, a Translational Research Center is defined as an entity with a primarily clinical/human neurobiology focus in which the preclinical research directly informs or provides a mechanistic foundation for the clinical research, and the preclinical science is informed and modified by the outcomes of the clinical research. Letter of Intent Receipt Date for this RFA: January 23, 2006; Application Receipt Date: February 23, 2006.

Two program announcements were released as a result of the work of the

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African American Initiative. One, which focuses on HIV/AIDS developed in collaboration with AIDS Program Office, is entitled **Health Disparities in HIV/AIDS: Focus on African Americans (R01) (PA-06-069)** (issued with NIMH). The other, which focuses on criminalization is entitled **Drug Abuse as a Cause, Correlate, or Consequence of Criminal Justice Related Health Disparities among African Americans (R01) (PA-06-068)**.

In response to a call for **Administrative Supplements for Research on the Intersection of Drug Use and Criminal Justice Consequences in the African American Population**, NIDA awarded supplements to six grantees.

PAs and RFAs Issued With Other NIH Components/Agencies

On September 9, 2005, NIDA joined with NIMH in its issuance of **PA-05-164**, entitled **Recent HIV Infection: New Prevention Challenges and Opportunities**. This PA solicits innovative basic or applied HIV prevention science research to extend knowledge of the biological processes and behavioral risk contexts of acute and early HIV disease, and to identify and develop effective responses to specific prevention needs of highly infectious, newly HIV infected persons, who may account for a disproportionate share of secondary HIV transmissions.

On November 9, 2005, NIDA and NIMH jointly issued a PA entitled **Non-Injection Drug Abuse and HIV/AIDS (R01) (PAS-06-054)**. The purpose of this PA is to encourage drug abuse research that elucidates the contribution of non-injection drug abuse to the acquisition and/or transmission and/or disease progression of HIV/AIDS. Specifically, it seeks to: 1) investigate how, where, why and among whom HIV/AIDS is spreading through non-injection drug use associated high-risk sexual behavior; 2) develop effective prevention and treatment interventions for non-injection drug users at risk for or infected with HIV; 3) and improve accessibility and utilization of evidence-based, integrated care for non-injection drug abuse, risky sexual behavior, and HIV/AIDS and other infectious diseases.

On December 15, 2005, NIDA and several other NIH Institutes released a PA entitled **Parenting Capacities and Health Outcomes in Youths and Adolescents (R01) (PA-06-097)**. This PA solicits research applications aimed at increasing the parenting skills and capacities of parents and caregivers to improve the health outcomes of their young and adolescent children. This is important because childhood, and particularly adolescence, is a time for the development of health habits that can last a lifetime. Moreover, adolescence is a transitional period during which experimentation and high-risk health behaviors may be displayed. Parents and similarly situated caregivers of children 10-to-18 years of age are the targets of this initiative.

On December 15, 2005, NIDA and several other NIH Institutes released a PA entitled **Parenting Capacities and Health Outcomes in Youths and Adolescents (R21) (PA-06-098)**. This PA solicits research applications aimed at increasing the parenting skills and capacities of parents and caregivers to improve the health outcomes of their young and adolescent children. This is important because childhood, and particularly adolescence, is a time for the development of health habits that can last a lifetime. Moreover, adolescence is a transitional period during which experimentation and high-risk health behaviors may be displayed. Parents and similarly situated caregivers of children 10-to-18 years of age are the targets of this initiative.

On December 27, 2005, NIDA and several other NIH Institutes issued a PA entitled **Research on Pathways Linking Environments, Behaviors and HIV/AIDS (R01) (PAR-06-114)**. This PA calls for research studies on the relationships among social environments, individual behaviors and the incidence and prevalence of HIV/AIDS in populations.

Staff Highlights

Grantee Honors

On October 4, 2005, NIDA and numerous other NIH components issued a PA entitled **Mentored Research Scientist Development Award (K01) (PA-06-001)**. The purpose of this PA is to provide support and "protected time" (three, four or five years) for an intensive, supervised career development experience in the biomedical, behavioral or clinical sciences leading to research independence.

On October 17, 2005, NIDA and numerous other NIH and DHHS components, issued a PA entitled **Small Business Innovation Research Program Parent Announcement (SBIR [R43/R44]): Electronic Submission of Grant Applications through Grants.gov. (PA-06-006)**. The purpose of this Funding Opportunity Announcement (FOA) is to invite eligible US small business concerns (SBCs) to submit SBIR Phase I, Phase II, and Fast-Track grant applications through Grants..

On October 17, 2005, NIDA and numerous other NIH and DHHS components, issued a PA entitled **Small Business Innovation Research Program Parent Announcement (STTR [R41/R42]): Electronic Submission of Grant Applications through Grants.gov. (PA-06-007)**. The purpose of this Funding Opportunity Announcement (FOA) is to invite eligible US small business concerns (SBCs) to submit SBIR Phase I, Phase II, and Fast-Track grant applications through Grants.gov.

On October 18, 2005, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Small Business Innovation Research to Improve the Chemistry and Targeted Delivery of RNAi Molecules (STTR[R43/R4]) (PA-06-003)**. Through this PA, the participating NIH Institutes invite the small business community to apply cutting edge technology to develop new approaches and chemical modifications that will increase the long term stability, delivery and targeting of siRNAs in cells and tissues for laboratory and therapeutic applications.

On October 18, 2005, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Small Business Innovation Research to Improve the Chemistry and Targeted Delivery of RNAi Molecules (SBIR[R41/R42]) (PA-06-004)**. Through this PA, the participating NIH Institutes invite the small business community to apply cutting edge technology to develop new approaches and chemical modifications that will increase the long term stability, delivery and targeting of siRNAs in cells and tissues for laboratory and therapeutic applications.

On October 18, 2005, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Bioengineering Nanotechnology Initiative (STTR[R41/R42]) (PA-06-008)**. This Funding Opportunity Announcment (FOA), issued as an initiative of the trans-NIH Bioengineering Consortium (BECON) on behalf of the participating Institutes and Centers, invites Small Business Technology Transfer (STTR) grant applications for projects for developing and applying nanotechnology to biomedicine.

On October 18, 2005, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Bioengineering Nanotechnology Initiative (SBIR[R43/R44]) (PA-06-009)**. This Funding Opportunity Announcment (FOA), issued as an initiative of the trans-NIH Bioengineering Consortium (BECON) on behalf of the participating Institutes and Centers, invites Small Business Innovation Research (SBIR) grant applications for projects for developing and applying nanotechnology to biomedicine.

On October 20, 2005, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Manufacturing Processes of Medical, Dental, and Biological Technologies (STTR[R41/R42]) (PA-06-012)**. Through this PA, NIH is responding to Executive Order 13329 (requiring agencies, to the extent possible, to expand the focus of their SBIR and STTR

programs to manufacturing-related research and development) by encouraging eligible US small business concers to submit STTR Phase I, Phase II and Fast-Track grant applications whose biomedical research is related to advanced processing, manufacturing processes, equipment and systems, and manufacturing workforce skills and protection.

On October 20, 2005, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Manufacturing Processes of Medical, Dental, and Biological Technologies (SBIR[R43/R44]) (PA-06-013)**. Through this PA, NIH is responding to Executive Order 13329 (requiring agencies, to the extent possible, to expand the focus of their SBIR and STTR programs to manufacturing-related research and development) by encouraging eligible US small business concerns to submit SBIR Phase I, Phase II and Fast-Track grant applications whose biomedical research is related to advanced processing, manufacturing processes, equipment and systems, and manufacturing workforce skills and protection.

On October 17, 2005, NIDA and several other NIH Institutes jointly issued a PA entitled **Development of PET and SPECT Ligands for Brain Imaging (SBIR[R43/R44]) (PA-06-017)**. This initiative is intended to stimulate the commercial development of noval radioligands for positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging in human brain, and to incorporate pilot or clinical feasibility evaluation in pre-clinical studies, model development, or clinical studies. The NIH Institues sponsoring this FOA are specifically interested in the development of radioligands for molecular targets (e.g., receptors, cell adhesion molecules, intracellular messengers, and disease-related proteins) that are of broad interest to the scientific community. These radiotracers will be used for neuroimaging as well as potential biological markers and surrogate endpoints for translational and clinical research, drug discovery and development, and clinical trials. Also appropriate for this FOA are applications proposing research and development of new technologies for radiotracer development.

On October 17, 2005, NIDA and several other NIH Institutes jointly issued a PA entitled **Development of PET and SPECT Ligands for Brain Imaging (STTR[R41/R42]) (PA-06-018)**. This initiative is intended to stimulate the commercial development of noval radioligands for positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging in human brain, and to incorporate pilot or clinical feasibility evaluation in pre-clinical studies, model development, or clinical studies. The NIH Institues sponsoring this FOA are specifically interested in the development of radioligands for molecular targets (e.g., receptors, cell adhesion molecules, intracellular messengers, and disease-related proteins) that are of broad interest to the scientific community. These radiotracers will be used for neuroimaging as well as potential biological markers and surrogate endpoints for translational and clinical research, drug discovery and development, and clinical trials. Also appropriate for this FOA are applications proposing research and development of new technologies for radiotracer development.

On November 14, 2005, NIDA, along with a number of other NIH components, released a PA entitled **Dissemination and Implementation Research in Health (R01) (PAR-06-0039)**. This PA encourages investigators to submit research grant applications that will identify, develop, and refine effective and efficient methods, structures and strategies that test models to disseminate and implement research-tested health behavior change interventions and evidence-based prevention, early detection, diagnostic, treatment, and quality of life improvement services into public health and clinical practice settings.

On November 14, 2005, NIDA, along with a number of other NIH components, released a PA entitled **Dissemination and Implementation Research in Health (R03) (PAR-06-071)**. This PA encourages investigators to submit research grant applications that will identify, develop, and refine effective and

efficient methods, structures and strategies that test models to disseminate and implement research-tested health behavior change interventions and evidence-based prevention, early detection, diagnostic, treatment, and quality of life improvement services into public health and clinical practice settings.

On November 14, 2005, NIDA, along with a number of other NIH components, released a PA entitled **Dissemination and Implementation Research in Health (R21) (PAR-06-072).** This PA encourages investigators to submit research grant applications that will identify, develop, and refine effective and efficient methods, structures and strategies that test models to disseminate and implement research-tested health behavior change interventions and evidence-based prevention, early detection, diagnostic, treatment, and quality of life improvement services into public health and clinical practice settings.

On October 26, 2005, NIDA, in conjunction with numerous other NIH components, issued a PA entitled **NIH Support for Conferences and Scientific Meetings (R13/U13) (PA-06-041)**. This funding opportunity provides updated guidelines for NIH support of conferences and scientific meetings.

On October 26, 2005, NIDA, in conjunction with numerous other NIH components, issued a PA entitled **Academic Research Enhancement Award (AREA) (R15) (PA-06-042)**. The purpose of the Academic Research Enhancement Award (AREA) is to stimulate research in educational institutions that provide baccalaureate or advances degrees for a significant number of the Nation's research scientists, but that have not been major recipients of NIH support. These AREA grants create opportunities for scientists and institutions otherwise unlikely to participate extensively in NIH programs, to contribute to the Nation's biomedical and behavioral research effort.

On December 1, 2005, NIDA, in collaboration with a number of other NIH components, issued a PA entitled **Research on Social Work Practice and Concepts in Health (R01) (PA-06-081)**. The ultimate goal of this PA is to encourage the development of empirical research on social work practice, concepts and theory as these relate to the NIH public health goal of improving health outcomes for persons with medical and behavioral disorders and conditions.

On December 1, 2005, NIDA, in collaboration with a number of other NIH components, issued a PA entitled **Research on Social Work Practice and Concepts in Health (R03) (PA-06-082)**. The ultimate goal of this PA is to encourage the development of empirical research on social work practice, concepts and theory as these relate to the NIH public health goal of improving health outcomes for persons with medical and behavioral disorders and conditions.

On December 1, 2005, NIDA, in collaboration with a number of other NIH components, issued a PA entitled **Research on Social Work Practice and Concepts in Health (R21) (PA-06-083).** The ultimate goal of this PA is to encourage the development of empirical research on social work practice, concepts and theory as these relate to the NIH public health goal of improving health outcomes for persons with medical and behavioral disorders and conditions.

On December 2, 2005, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Mentored Qualitative Research Development Award (K25) (PA-06-087)**. The purpose of this award is to attract to NIH-relevant research those investigators whose quantitative science and engineering research has thus far not been focused primarily on questions of health and disease.

On December 19, 2005, NIDA, in collaboration with numerous other NIH

components, issued a PA entitled **Innovations in Biomedical Computational Science and Technology Initiative (SBIR [R43/R44]) (PAR-06-088)**. This announcement solicits Small Business Innovation Research (SBIR) grant applications from small business concerns (SBCs) that propose innovative research in biomedical computational science and technology to promote the progress of biomedical research.

On December 19, 2005, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Innovations in Biomedical Computational Science and Technology Initiative (STTR [R41/R42]) (PAR-06-089)**. This announcement solicits Small Business Innovation Research (SBIR) grant applications from small business concerns (SBCs) that propose innovative research in biomedical computational science and technology to promote the progress of biomedical research.

On January 20, 2006, NIDA, in collaboration with numerous other NIH and DHHS components, issued a PA entitled **PHS 2006-02 Omnibus Solicitation of the NIH, CDC, and FDA for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44]) (PA-06-120)**. The purpose of this PA is to invite eligible US small business concerns (SBCs) to submit Small Business Innovation Research (SBIR) Phase I, Phase II, Fast-Track, and Phase II Competing Renewal grant applications through Grants.gov.

On January 20, 2006, NIDA, in collaboration with numerous other NIH and DHHS components, issued a PA entitled **PHS 2006-02 Omnibus Solicitation of the NIH, CDC, and FDA for Small Business Innovation Research Grant Applications (Parent STTR [R41/R42]) (PA-06-121)**. The purpose of this PA is to invite eligible US small business concerns (SBCs) to submit Small Business Technology Transfer (STTR) Phase I, Phase II, Fast-Track, and Phase II Competing Renewal grant applications through Grants.gov.

On November 10, 2005, NIDA, in collaboration with several other NIH Institutes and the Canadian Institutes of Health Research (CIHR), issued an RFA entitled **Social Neuroscience (RFA-DA-06-004)**. The purpose of this RFA is to stimulate investigations of the cognitive/behavioral processes and neurobiological mechanisms of social behavior relevant to alcohol and drug abuse (NIDA/NIAAA) and decision making judgement over the life course (NIA). Clinical and preclinical research will be supported by this initiative. Letter of Intent Receipt Date for this RFA: January 23, 2006; Application Receipt Date: February 23, 2006.

On October 2, 2005, NIDA, in collaboration with the Canadian Institutes of Health Research (CIHR), issued an RFA entitled **Epigenetics of Neurobiology and Addiction (RFA-DA-06-007)**. The goal of this RFA is to solicit applications that will link epigenetics changes to other biological changes (i.e., neuroplasticity) from gene expression to behavior (i.e., addiction). This RFA will also support the acquisition of preliminary data on epigenetic mechanisms related to addiction through a modified R03 funding mechanism. Letter of Intent Receipt Date for this RFA: December 23, 2005; Application Receipt Date: January 23, 2006.

On November 18, 2005, NIDA, in collaboration with the National Institute on Aging (NIA) and the National Institute of Dental and Craniofacial Research (NIDCR), issued an RFA entitled **Prescription Opioid Use and Abuse in the Treatment of Pain (R01, R03, R21, R25) (RFA-DA-06-005)**. This RFA solicits new applications that examine risk and protective factors regarding the onset of opioid abuse and addiction in the context of pain, develop pain treatment protocols that are tailored to reduce the probability of these negative health consequences, and develop ways to ameliorate these problems when they occur. Letter of Intent Receipt Date for this RFA: January 23, 2006; Application Receipt Date: February 23, 2006.

On September 16, 2005, NIDA, in collaboration with a number of other NIH components, issued an RFA entitled **Development and Improvement of Inbred ES Cell Lines for Use in Generation of Mouse Mutants (RFA-DA-06-009)**. The goal of this RFA is to improve the efficiency of germline transmission of C57BL/6 ES lines to an extent that permits the use of C57BL/6 ES cell for high throughput gene targeting and the efficient production of C57BL/6 mice carring a null mutation. Letter of Intent Receipt Date for this RFA: October 20, 2005; Application Receipt Date: November 22, 2005.

On November 15, 2005, NIDA, in collaboration with a number of other NIH components, issued an RFA entitled International Clinical, Operational and Health Services Research Training Award (ICOHRTA) [D43] (RFA-TW-06-002). This award will support advanced training in collaborative, multidisciplinary, international clinical, operational, health services and prevention science research on non-communicable disorders and diseases for health researchers from low- and middle-income countries. Letter of Intent Receipt Date for this RFA: December 26, 2005; Application Receipt Date: January 25, 2006.

On November 10, 2005, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **course Development in the Neurobiology of Disease (R25) (RFA-DA-06-006)**. This RFA is an initiative of the NIH Blueprint for Neuroscience Research, a trans-NIH partnership to accelerate neuroscience research. Fifteen Institutes and Centers are participating in the Neuroscience Blueprint. This funding opportunity supports the development and initiation or the significant expansion of courses on the neurobiology of disease for graduate students receiving basic neuroscience training. It is expected that each course will span a breadth of diseases and disorders affecting the nervous system, emphasizing links and common themes across diseases/disorders, and addressing both the pathology af these diseases/disorders and their basic science underpinnings. Letter of Intent Receipt Date for this RFA: January 17, 2006; Application Receipt Date: February 16, 2006.

On September 29, 2005, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Neuroscience Blueprint Interdisciplinary Center Core Grants (RFA-NS-06-003)**. This RFA is an initiative of the NIH Blueprint for Neuroscience Research, a trans-NIH partnership to accelerate neuroscience research. Fifteen Institutes and Centers are participating in the Neuroscience Blueprint. Neuroscience Blueprint Interdisciplinary Center Core Grants will support centralized resources and facilities shared by neuroscience investigators. Each Center will be composed of one or more research cores, each of which will enrich the effectiveness of ongoing research and promote new research directions. Letter of Intent Receipt Date for this RFA: December 19, 2005; Application Receipt Date: January 19, 2006.

On November 9, 2005, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Training in Translational Research in Neurobiology of Disease (T32) (RFA-DA-06-008)**. This RFA is an initiative of the NIH Blueprint for Neuroscience Research, a trans-NIH partnership to accelerate neuroscience research. Fifteen Institutes and Centers are participating in the Neuroscience Blueprint. Through this RFA, NIH will award Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Research Training Grants (T32) to eligible institutions to support research trainees in translational research neurobiology of disease. Letter of Intent Receipt Date for this RFA: January 23 2006; Application Receipt Date: February 22, 2006.

On December 16, 2005, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Training in Computational Neuroscience: From Biology to Model and Back Again (T90) (RFA-DA-06-010)**. This RFA is an initiative of the NIH Blueprint for Neuroscience

Research, a trans-NIH partnership to accelerate neuroscience research. Fifteen Institutes and Centers are participating in the Neuroscience Blueprint. This RFA will be administered by NIDA on behalf of the Neuroscience Blueprint. This funding opportunity will support integrated research education and research training programs that provide interdisciplinary training in basic neuroscience and the theoretical and technological approaches of computational neuroscience. Letter of Intent Receipt Date for this RFA: February 13, 2006; Application Receipt Date: March 13, 2006.

On December 23, 2005, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled *Training in Neuroimaging: Integrating First Principles and Applications (T90) (RFA-DA-06-011)*. This RFA is an initiative of the NIH Blueprint for Neuroscience Research, a trans-NIH partnership to accelerate neuroscience research. Fifteen Institutes and Centers are participating in the Neuroscience Blueprint. This funding opportunity will enable the development of novel, interdisciplinary training programs that integrate comprehensive training in basic neuroscience, the physical and biological bases of neuroimaging, the technologies and analytic methods on in vivo neuroimaging, and the application of these technologies to understanding questions in neuroscience across the lifespan. Letter of Intent Receipt Date for this RFA: February 13, 2006; Application Receipt Date: March 13, 2006.

On November 18, 2005, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Development of Recombinase-Expressing ("Driver") Mouse Lines for Studying the Nervous System (U01) (RFA-MH-06-007).** This RFA is an initiative of the NIH Blueprint for Neuroscience Research, a trans-NIH partnership to accelerate neuroscience research. Fifteen Institutes and Centers are participating in the Neuroscience Blueprint. This funding opportunity supports the design, creation and characterization of recombinase-expressing C57BL/6 mouse lines to aid in studies of nervous system development and/or function. These so-called "driver lines" should specify expression in distinct cell types and/or other useful temporospatial expression patterns in the nervous system. Letter of Intent Receipt Date for this RFA: December 17, 2005; Application Receipt Date: January 19, 2006.

Other Program Activities

CTN Update

A total of 22 protocols and surveys have been initiated since 2001. A total of 11,314 patients were screened and 6,877 enrolled in studies as of December 14, 2005. Of these studies, 11 have completed enrollment and locked the data. Eleven protocols are currently active, and are summarized below:

Protocol CTN 0003 (Bup/Nx: Comparison of Two Taper Schedules) began enrollment June 30, 2003, data collection completed on November 3rd, 2005. Data lock is expected in March 2006.

Protocol CTN 0010 (Buprenorphine/Naloxone Facilitated Rehabilitation for Opioid Dependent Adolescents/Young Adults) began enrollment in July 2003. Enrollment is at 72% of the projected target.

Protocol CTN 0013 (Motivational Enhancement Therapy to Improve Treatment Utilization and Outcome In Pregnant Substance Abusers) began enrollment in November 2003 and has enrolled 90% of the projected target enrollment.

Protocol CTN 0014, Brief Strategic Family Therapy for Adolescent Drug Abusers (BSFT), has been implemented at 8 sites. The study has reached 44% enrollment.

Protocol CTN 0015 (Women's Treatment for Trauma and Substance Use

Disorder: A Randomized Clinical Trial) began in March 2004. The study has reached its enrollment target, and follow-up continues.

Protocol CTN 0017 (HIV and HCV Intervention in Drug Treatment Settings). The study began enrollment in November 2004 and enrollment has reached 85% of the target goal. This study is enrolling at 8 community treatment sites across 5 Nodes.

CTN 0018 (Reducing HIV/STD Risk Behaviors: A Research Study for Men in Drug Abuse Treatment) began enrolling in April 2004 and has reached its target. The study is now in follow-up phase.

CTN 0019 (Reducing HIV/STD Risk Behaviors: A Research Study for Women in Drug Abuse Treatment) began enrollment in May 2004 and has reached its target. The study is now in follow-up phase.

CTN 0020 (Job Seekers Training for Substance Abusers). The protocol began enrollment in October 2004 and will have completed its enrollment goal as of December 31, 2005. This study is also being conducted in a Navajo American Indian site, the Na'nizhoozhi Center, Inc. in Gallup, New Mexico, the first CTN study to be conducted there.

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

Protocol CTN-0029: A Pilot Study of Osmotic-Release Methylphenidate (OROS MPH) in Initiating and Maintaining Abstinence in Smokers with Attention Deficit Hyperactivity Disorder (ADHD). Enrollment began at 3 sites in November 2005. The first patient was randomized on December 13, 2005. This study is being carried out at 6 CTPs across 5 Nodes.

Two protocols have recently locked their data sets and are at the analysis stage. Those include:

Protocol CTN 0004 (Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome in Subjects Seeking Treatment for Substance Abuse). Protocol CTN 0008 (Assessment of the National Drug Abuse Clinical Trials Network: A Baseline for Investigating Diffusion of Innovation) - The first group of publications is being reviewed internally by the Publications Committee prior to submission to peer reviewed journals.

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

Protocol CTN 0012 (Characteristics of Screening, Evaluation, and Treatment of HIV/AIDS, Hepatitis C Viral Infections, and Sexually Transmitted Infections in Substance Abuse Treatment Programs) - The first publications from this study are being reviewed internally by the Publications Committee prior to submission to peer reviewed journals.

Four additional Protocols are currently being developed for the Network.

- Protocol CTN 0027: Starting Treatment with Agonist Replacement Therapies (START) is a randomized, open-label, multi-center study that was developed in collaboration with the Division of Pharmacotherapies & Medical Consequences of Drug Abuse (DPMCDA). Implementation is planned for April 2006.
- 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). The protocol

implementation is planned for February 2006.

- Protocol CTN 0030: Prescription Opioid Addiction Treatment Study (POATS) is a randomized 2-phases, open-label, multi-center study in outpatient treatment settings. Implementation is planned for Spring 2006.
- Protocol CTN 0031: Twelve Step Facilitation: Evaluation of an Intervention to Increase 12-Step Involvement and Improve Substance Abuse Treatment. This activity is at the concept development stage.

In addition to the primary CTN trials, there are 12 studies supported by independent grants or as supplements that use CTN studies as a platform.

NIDA's New and Competing Continuation Grants Awarded Since September 2005

Abdala, Nadia -- Yale University
Identifying HIV-Bridge-Population In STI Clinics, Russia

Andrews, Judy A. -- Oregon Research Institute
Substance Use & Girls: Stress, Hormones & Puberty

Astur, Robert S. -- Hartford Hospital
Cocaine-Induced Place Preference Using Virtual Reality

Avison, Malcolm J. -- Vanderbilt University
Neural Bases Of ADHD In Fetal Drug Or Alcohol Exposure

Beer, Jennifer S. -- University of California, Davis
Regulating Approach Impulses: Implications of Orbitofrontal Function For Addiction

Benowitz, Neal L. -- University of California, San Francisco
Pharmacogenetics of Nicotine Addiction and Treatment

Black, Maureen M. -- University of Maryland Baltimore Professional School
Prenatal Drug Exposure: Effects On Adolescent Brain

Booze, Rosemarie M. -- University of South Carolina at Columbia
HIV/Cocaine Neurotoxicity In Females

Brody, Arthur L. -- Brentwood Biomedical Research Institute
Nicotine Receptor Density & Dopamine System Function

Carroll, Frank I. -- Research Triangle Institute
Kappa Opioid Antagonist For Cocaine Addiction

Caton, Carol L. -- Columbia University Health Sciences
HIV Risk Among Homeless Mothers

Chang, Linda -- University of Hawaii at Manoa
Early Brain Development After Prenatal "Ice" Exposure: A Longitudinal MR Study

Colfax, Grant N. -- Public Health Foundation Enterprises
Acceptability Of Pharmacologic Treatment For Methamphetamine Dependence Among MSM

Crano, William D. -- Claremont Graduate University
Marijuana Use Patterns: Temporal Change In Predictors

De Bellis, Michael D. -- Duke University
Frontal Function In Adolescent Cannabis Use Disorders

De La Torre, Rafael -- Municipal Institute of Medical Research

Metabolism and Pharmacogenetics In MDMA-Induced Toxicity

Deisseroth, Karl A. -- Stanford University
Calcium Channels, Newborn Neurons, and CNS Circuit Dynamics

Dewey, Stephen L. -- Brookhaven Science Associates-Brookhaven Lab
Optimizing Intensity and Duration of GVG Pharmacotherapy

Dougherty, Donald M. -- Wake Forest University Health Sciences
Impulsivity and Information Processing In Adolescent Cannabis Abuse

Ducharme, Lori J. -- University of Georgia (UGA)
Comparison of Methadone Units Within and Outside The CTN

Dutta, Aloke K. -- Wayne State University
Dopamine Transporter Agents Against Cocaine Dependence

Dwoskin, Linda P. -- University of Kentucky
Nicotinic Receptor Regulation of Dopamine Transporter

Dwoskin, Linda P. -- University of Kentucky
Development of Novel Therapies for Methamphetamine Abuse

Farrelly, Matthew C. -- Research Triangle Institute
Macro-Social & Parent Influence On Adolescents' Drug Use

Fiez, Julie A. -- University of Pittsburgh at Pittsburgh
Neural Bases of Executive Control In Addiction

Fillmore, Mark T. -- University of Kentucky
Neurocognitive Consequences of Adolescent Drug Use

Fisher, Celia B. -- Fordham University
Participant Perspectives On Drug Use/HIV Research Ethics

Fisher, Philip A. -- Oregon Social Learning Center, Inc.
Kits: School Readiness In Foster Care Efficacy Trial

Fox, Howard S. -- Scripps Research Institute
Perilous Effects of Methamphetamine On SIV/AIDS

Fuller, Crystal -- Columbia University Health Sciences
Social Predictors For Transition Into Injection Drug Use

Gilman, Stephen -- Harvard University School of Public Health
Race, Socioeconomic Status, and Trajectories of Substance Use Disorders

Glass, Jennifer M. -- University of Michigan at Ann Arbor
Neurocognitive Risks & Consequences of Smoking

Gnegy, Margaret E. -- University of Michigan at Ann Arbor
Pharmacology of Dopamine Release By Amphetamine

Goodman, Richard H. -- Oregon Health & Science University
Gene Targets for Morphine and Other Drugs of Abuse

Goodwin, Renee D. -- Columbia University Health Sciences
Role of Depression and Anxiety In the Tobacco Epidemic

Green, Sarah A. -- Michigan Technological University
Identification of Short-Lived Radicals In Tobacco Smoke

Grigson, Patricia Sue -- Pennsylvania State University Hershey Medical Center
Drugs of Abuse and Learned Aversions: Solving A Paradox

Hart, Carl L. -- New York State Psychiatric Institute
Intranasal Methamphetamine: A Pharmacotherapy Model

Hauser, Kurt F. -- University of Kentucky
Mechanisms of Opiate Drug-HIV-Induced Neurodegeneration

Hook, Michelle A. -- Texas A&M University System
The Effects of Morphine On Sensory and Motor Functions After A Spinal Cord Injury

Huffman, John W. -- Clemson University
Synthesis of Cannabinoids, Analogues and Metabolites

Husbands, Stephen M. -- University of Bath
Discovery of New Treatments for Drug Abuse

Izenwasser, Sari -- University of Miami-Medical
Cocaine Behavior: Regulation By K-Opioids and Serotonin

Jacobsohn, Lela S. -- University of Pennsylvania
The Boomerang Effect of the Anti-Drug Media Campaign

Johnson, Bankole A. -- University of Virginia Charlottesville
Novel Pharmacotherapy For Dual Dependence

Johnson, Eric O. -- Research Triangle Institute
Pathway Among Co-Occurring Mental/Substance Use Disorder

Kabbaj, Mohamed -- Florida State University
Individual Differences In Anxiety In Females

Kalechstein, Ari D. -- University of California, Los Angeles
Methamphetamine Dependence: Treating Cognition Disorder

Karno, Mitchell P. -- University of California, Los Angeles
Factor Associated W/ Help-Seeking & Change In Drug Abuse

Kiehl, Kent A. -- Hartford Hospital
Neurocognitive Change Associated With Behavioral Treatment

King, Tamara -- University of Arizona
Effects of Sustained Opiates On Bone Metastasis and Pain

Kippin, Tod E. -- University of California, Santa Barbara
Sex Differences and Incubation of Cocaine Craving

Kopin, Alan S. -- New England Medical Center Hospitals
Molecular Analysis of Dopamine 2 Like Receptor Function

Kosobud, Ann E. -- Indiana University-Purdue University at Indianapolis
Role of Circadian Entrainment In Drug Intake and Abuse

Lai, Shenghan -- Johns Hopkins University
China Macs: An Exploratory Study

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

Latimer, William -- Johns Hopkins University
Adapt IFCBT Into HIV Prevention Intervention

Lee, Buyean -- University of California, Los Angeles
Vervet Monkey Model For Methamphetamine-Induced Deficits In Response Inhibition

Lejuez, Carl W. -- University of Maryland, College Park

Behavioral Depression Treatment For Smoking Cessation

Lester, Henry A. -- California Institute of Technology
Nicotinic Ligands For Smoking Cessation

Liberty, Hilary J. -- National Development & Res Institutes
Understanding Self-Reports of Drug Use In Pregnant Women

London, Edythe D. -- University of California, Los Angeles
Neural Systems, Inhibitory Control, and Methamphetamine Dependence

Lucas, Gregory M. -- Johns Hopkins University
Directly Administered HIV Therapy In Methadone Clinics

Luongo, Peter F. -- Maryland State Department of Health and Mental Hygiene
Enhancing Adoption of Science-Based Practices

Lynch, Wendy J. -- University of Virginia, Charlottesville
Sex, Hormones and Cocaine Self-Administration

Martinez, Diana -- New York State Psychiatric Institute
Imaging ihe Neurobiology of A Behavioral Treatment

Martins, Silvia Saboia -- Johns Hopkins University
Predictors of Adolescent Ecstasy Use In The National Survey of Parents and Youth

Marvizon, Juan Carlos G. -- University of California, Los Angeles
Spinal Neurokinin and Opioid Release In Nociception

Matsueda, Ross L. -- University of Washington
Life Course Trajectories of Substance Use and Crime

McKay, Mary -- Mount Sinai School of Medicine of New York University
HIV/Drug Abuse Prevention For Homeless Youth & Families

McMahon, Thomas J. -- Yale University
Parent Intervention For Drug-Abusing Fathers

Newlin, David B. -- Research Triangle Institute
Weak Prefrontal Dc Stimulation and Tobacco Craving

Newton, Thomas F. -- University of California, Los Angeles
Laboratory Models of Cocaine Self-Administration

Nicosia, Nancy -- Rand Corporation
Impact of Amphetamine Abuse on Health and Crime

Patten, Christi A. -- Mayo Clinic College of Medicine, Rochester
Tobacco Cessation Treatment For Pregnant Alaska Natives

Picciotto, Marina R. -- Yale University
Nicotine Addiction In Mice Lacking The Neuronal nAChR

Potenza, Marc N. -- Yale University
fMRI of CBT and CM for Cocaine Dependence

Price, Rumi K. -- Washington University
Disentangling Substance Use and Psychiatric Disorder Comorbidity

Prisinzano, Thomas E. -- University of Iowa
Investigation of Neoclerodanes as Novel Opioid Ligands

Proudfit, Herbert K. -- University of Iowa
Dendritic Varicosities Regulate Neuronal Excitability

Ramsey, Susan E. -- Rhode Island Hospital, Providence, RI
Reducing HIV Risk Among Pregnant Women In Drug Treatment

Rasenick, Mark M. -- University of Illinois at Chicago
Structural Basis For Reciprocal Regulation of the Gtpases Tubulin and Gsalpha

Renshaw, Perry F. -- Mc Lean Hospital, Belmont, MA
Magnetic Resonance, EEG, and Behavior After Cocaine

Roberts, David C. -- Wake Forest University Health Sciences
Animal Models of Cocaine Addiction

Rush, Craig R. -- University of Kentucky
Preventing Cocaine Relapse: Developing Pharmacotherapies

Samaras, Dimitrios -- State University of New York, Stony Brook
CRCNS: Machine Learning for Analysis of fMRI

Schutzer, Steven E. -- University of Medicine/Dentistry of NJ-NJ Medical School
Complete Proteome Of Cerebrospinal Fluid

Shadel, William G. -- Rand Corporation
Adolescents' Responses To Anti-Smoking PSAs

Silverman, Kenneth -- Johns Hopkins University
Employment-Based Depot Naltrexone Clinical Trial

Sircar, Ratna -- Rutgers The State University of New Jersey, New Brunswick
Neurobehavioral Effects Of Adolescent GHB

Skosnik, Patrick D. -- Indiana University Bloomington
Sensory Processing Deficits In Cannabis Use

Smelson, David A. -- University of Medicine/Dentistry NJ-RWJ Medical School
Cue-Elicited Craving /Genetics In Relapse In Cocaine Use

Stein, Michael D. -- Rhode Island Hospital, Providence, RI
Insomnia and Drug Relapse Risk

Stenken, Julie -- Rensselaer Polytechnic Institute
Neuropeptide Affinity Enrichment Microdialysis Sampling

Strathdee, Steffanie A. -- University of California, San Diego
Epidemiology of HIV and BBVs Among IDUs In Tijuana

Sullivan, Maria A. -- New York State Psychiatric Institute
Predictors of Relapse To Prescription Opioid Abuse

Taxman, Faye S. -- Virginia Commonwealth University
Assessment and Referral Technologies In Juvenile Justice

Terzian, Arpi -- Johns Hopkins University
Physical Functioning In Women With HIV

Thomas, David L. -- Johns Hopkins University
HIV/HCV Coinfection Antiviral Therapy and Fibrosis

Turner, R Jay. -- Florida State University
Ethnic Contrasts In Mental Health and Substance Problems

Varga, Eva V. -- University of Arizona
Trafficking In Human CB1 Cannabinoid Receptor Signaling

Walkup, John T. -- Johns Hopkins University
In-Home Prevention Of SA Risks For Native Teen Families

Wallis, Jonathan D. -- University of California, Berkeley
The Neural Representation of Reward In Working Memory

Waters, Andrew J. -- University of Texas MD Anderson Cancer Center
Cognitive Processes In Smoking Cessation

Watson, Donnie W. -- Friends Research Institute, Inc.
Cognitive Behavioral Therapy For South Africa

Wechsberg, Wendee M. -- Research Triangle Institute
Woman-Focused HIV Prevention With Pregnant African-Americans In Treatment

Xie, Xiang-Qun -- University of Houston
A Public Cannabinoid Molecular Information Repository

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

Extramural Policy and Review Activities

Receipt, Referral, and Review

NIDA received 1214 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 736 applications.

OEA arranged and managed 18 grant review meetings in which 244 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 3 contract proposal reviews and 3 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 14 Special Emphasis Panels for a variety of reasons:

Conflicts with the chartered committees
Center Grant Applications
Program Project Grant applications
Mechanism For Time-Sensitive Research Opportunities
Behavioral Science Track Award for Rapid Transition (B/START)
Imaging Science Track Awards for Research Transition (I/START)
Conference Grants (R13)

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

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

- N01DA-5-9909: Residential Research Support Services

SBIR Phase II

- N44DA-6-8843: Automatic Delineation and Quantification of WMSH
- N44DA-6-8851: Multi-focal Cortical Thinning in Drug and Alcohol Abuse

R&D Concept Reviews

- N01DA-6-7758: Synthesis and Distribution of Opioid and Related Peptides
- N01DA-6-8866: Development & Manufacture of Pharmaceutical Products for Addiction Treatment
- N01DA-6-9910: NIDA IRP Recruitment Services

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Grantee Honors

The CTN Data and Safety Monitoring Board (DSMB) conducted a review of CTN 0027: Starting Treatment with Agonist Replacement Therapies (START) on November 17, 2005. START is a randomize d, open-label, multi-center study in outpatient settings.

Certificates of Confidentiality

Dr. Paul Coulis manages the processing of Certificates of Confidentiality. Between August 12, 2005 and December 06, 2005, 102 new certificates, 34 extensions, and 23 amendments were processed.

Extramural Outreach

Dr. Levitin, Director, OEA, is the newly appointed NIDA liaison to the Peer Review Advisory Committee (PRAC), a committee established late in 2004 to provide guidance on trans-NIH review policy and operations to the NIH Director and Deputy Director of Extramural Research, to provide guidance to the Center for Scientific Review Director on CSR-specific policy and operations and to assist other IC Directors on IC-specific questions of review policy and operations, as needed.

Dr. Levitin continues to serve as the NIDA liaison to the NIH Director's Pioneer Award Implementation Committee, one of the NIH Roadmap activities. She was also a member of the NIH Director's Pioneer Award Evaluation Advisory Committee which reviewed the evaluation of the first year of the Pioneer Award program.

In October 2005, Dr. Levitin was a plenary speaker at the Society of Experimental Social Psychology annual meeting where she presented some of the social psychological research supported at NIDA and showed how research on drug abuse could be enriched by a social psychological perspective.

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

Dr. Gerald McLaughlin, OEA, attended the first meeting of a NINDS/NIMH/NIDA committee led by Dr. Serena Chu of NIMH, to discuss options for inter-Institute meetings regarding operating procedures and training for review activities between these three Institutes.

OEA staff working at the NIDA booth at the Society for Neuroscience meeting in Washington D.C., included Drs. Gerald McLaughlin, Mark Green, Meenaxi Hiremath, Rita Liu and Ms. Loretta Beuchert.

Dr. Murat Oz, OEA, attended the Society for Neuroscience meeting in Washington D.C., and presented 6 abstracts.

Dr. Gerald McLaughlin is the NIDA Liaison to the NIH-wide committee dealing with all aspects of the transition to electronic grant submission. He has also given a talk on this topic at the OEA Symposium Series.

Dr. Gerald McLaughlin participates in the NIH-wide Mitochondria Interest Group (MIG).

Dr. Gerald McLaughlin participates in the D.C. area Iowa Alumni Club. He has been a representative for three of its College Fairs in the greater Washington DC area.

Ms. Loretta Beuchert, OEA, served on a trans-NIH workgroup responsible for implementing the time line for electronic receipt of applications and working

out procedures for converting existing grant mechanisms into the electronic 424 format.

Dr. Mark Swieter, OEA, attended NIDA's Bridging Science and Culture Conference in Atlanta on October 24-26,2005, where he organized and chaired two Grant Writing Workshops that included Kathy Sanders Phillips, Martin Iguchi, Aria Crump, Cece Spitznas, and Suman Rao King.

Dr. Meenaxi Hiremath, OEA, attended the Addiction Health Services Research Conference in Santa Monica, California at the end of October 2005. Dr. Meenaxi Hiremath participated in the trans-NIH workgroup dealing with public members participating in peer review meetings.

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

Dr. Mark Green serves on the NIH-wide workgroup developing the transition of the R03, R21, R33 and R34 grant mechanisms to electronic submission format.

Dr. Mark Green presented an NIH overview and grant writing workshop on November 2, 2005, at the Edward Via Virginia College of Osteopathic Medicine in Blacksburg, Virginia.

Staff Training and Development

The OEA Symposium Series, a forum for staff training and sharing of ideas and information, continued through the winter and spring. Topics addressed have included: a presentation by Jerry McLaughlin on the SF 424 roll out and use. Other topics led by Mark Swieter included NIDA's Policy Update on K Awards; NIH responses to hurricane Katrina and NIDA's participation in PAR-05-150: Mechanism for Time-Sensitive Research Opportunities; NIH Request for Information concerning updating the Standards of Care and Use of Laboratory Animals; Implementation of Policy on Enhancing Public Access to Archived Publications Resulting from NIH-funded Research; Request for Information on the Plan to Recognize Multiple Principal Investigators on NIH Grants; New Closeout Feature in the eRA Commons and Reminder to Grantees of Required Closeout Reports for NIH Assistance Awards; Notice of Change for Fiscal Year 2006 Competing Applications for Ruth L. Kirschstein National Research Service Award (NRSA) T32 Institutional Training Grant Support; and Guidelines for Inclusion of Clinical Practice Compensation in Institutional Base Salary Charged to NIH Grants and Contracts.

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

Congressional Affairs (Prepared January 25, 2006)

BUDGET FY 2006

In late December, the Congress concluded its action on the Labor, Health and Human Services, and Education Appropriations Bill with an NIH Budget Authority level of $28.617 billion. They also concluded action on the Department of Defense Appropriations Bill that contains a 1% across-the-board cut to non-emergency, non-discretionary programs. The NIH share of this cut is $286 million.

NIDA's FY 2006 budget is $1,000,029,000, a decrease of 0.6% from the FY 2005 level. This figure includes funds set aside for NIH Roadmap and Neuroscience Blueprint initiatives.

Other Hearings and Briefings of Interest

Congressional Meth Caucus Roundtable Discussion

September 25, 2005 - Two dozen members of the Congressional Caucus to Fight and Control Methamphetamine hosted a roundtable discussion with several federal agency representatives. NIDA Director Dr. Nora Volkow joined executive branch colleagues from the Office of National Drug Control Policy, Drug Enforcement Administration, Substance Abuse and Mental Health Services Administration, Department of Homeland Security, Department of State, and the Environmental Protection Agency in discussing with Caucus members a variety of methamphetamine related issues.

HIV/AIDS and Drug Abuse Hill Briefing Sponsored by the Friends of NIDA

October 25, 2005 - Behaviors associated with drug use have been shown to be among some of the most prominent and robust predictors of HIV transmission in the United States. In fact, injection drug use has directly and indirectly accounted for more than one-third (36 percent) of AIDS cases in the United States. Drug use also affects judgment about sexual risks and thereby increases the likelihood of transmitting or acquiring HIV through unprotected sex. Evidence suggests, however, that drug abuse treatment can help prevent the spread of HIV/AIDS, especially when combined with prevention and community-based outreach programs for at-risk individuals. Because these efforts can reduce or eliminate drug use and drug-related HIV risk behaviors, the Friends of NIDA hosted an educational briefing on Capitol Hill to raise awareness about the relationship between drug use and HIV infection.

The briefing, entitled "Drug Use and HIV/AIDS: Breaking the Cycle of Infection," was the third in a series this year organized and sponsored by the

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Friends of NIDA. As with past briefings, this event was designed to educate congressional staff and other policymakers on an important drug abuse and addiction research topic. The Friends of NIDA coordinated with the Chairs of the Addiction, Treatment and Recovery Caucus to find space and garner support for the briefing. Attendance was strong, with a standing room only crowd of over 100 guests.

NIDA Director Nora Volkow, MD, provided an overview of NIDA's HIV/AIDS research portfolio, noting, among other issues, the alarming change in patterns of transmission disproportionately affecting African American women. Psychologist Robert Booth, PhD, a Professor of Psychiatry at the University of Colorado School of Medicine, described his experiences as an HIV prevention researcher leading the community-based SAFE program in Denver. Finally, Ms. Patricia Nalls, Founder and Executive Director of a Washington, D.C.-based nonprofit organization, The Women's Collective, provided her personal perspective as an HIV-positive woman helping other women deal with HIV-related issues.

For further information and some photographs of the event, go to http://www.apa.org/ppo/spin/1005.html.

Methamphetamine Hearing

November 17, 2005 - The House Education and the Workforce Subcommittee on Education Reform conducted a hearing on "Combating Methamphetamines through Prevention and Education." Subcommittee Chairman Michael Castle (R-DE) provided an opening statement before Subcommittee Member Tom Osborne (R-NE) took the chair at the hearing. Among the witnesses providing testimony was NIDA grantee Richard Spoth, Ph.D., Director, Partnerships in Prevention Science Institute at Iowa State University.

Representative Castle expressed that this hearing was intended to give Subcommittee members the opportunity to learn about effective programs operating around the country. Congressman Osborne, leading the hearing, spoke specifically about the impact of methamphetamine addiction on children and families, and also highlighted the direct and indirect costs of methamphetamine use and addiction. In his later comments, Congressman Osborne also advocated for age-appropriate prevention efforts where messages are targeted at younger children, noting that drug use often starts before a young person is 13 years old. Congressman Mark Souder (R-IN) framed the nation's problem with methamphetamine as a health crisis. Asserting that a focus on the supply of drugs is critical to the nation's drug control policy, Congressman Souder also argued that illicit drug use cannot be eradicated without prevention, treatment and research. Dr. Spoth discussed results from studies of drug prevention programs that have demonstrated the effectiveness of a number of school- and community-based prevention efforts. In identifying factors that result in better outcomes, Dr. Spoth highlighted using existing school infrastructure, forging and reinforcing strategic partnerships, and using evidence-based interventions in prevention and education programming.

U.S. Senators' National Town Hall on Methamphetamine Awareness and Prevention

January 23, 2006 - To address the dangers methamphetamine abuse and addiction exact on our nation's communities and families, Senators Norm Coleman (R-MN), Conrad Burns (R-MT), Max Baucus (D-MT), Mark Pryor (D-AR), and Chuck Hagel (R-NE) hosted a National Town Hall on Methamphetamine Awareness and Prevention. U.S. Attorney General Alberto Gonzales and Drug Czar John Walters of the Office of National Drug Control Policy made opening remarks and during the three panel sessions during the town hall, the Senators were joined by state and national panelists. NIDA Director Dr. Nora Volkow was on one panel, and made remarks and responded

to questions from the Senators and members of the public. According to the Senate sponsors, the event was assembled as a national forum in which to understand the use and widespread impact of the drug, as well as seek ways to inform the public, deter use, and examine possible legislative initiatives to further combat meth.

PASSED BILLS OF INTEREST — 109th Congress

H.R. 3 - This law was originally introduced by Representative Young (R-AK) as the "Transportation Equity Act: A Legacy for Users," a bill to authorize funds for federal aid for highways, highway safety programs, and transit programs. The original House version of this bill included language (Section 2013 "Drug Impaired Driving Research and Prevention Act") that would require the development of a model statute for States relating to drug impaired driving. The model would include threshold levels of impairment for a controlled substance; methods for detecting the presence of controlled substances; and penalties for drug impaired driving. It would be based on recommendations contained in a report to be developed by NIH and submitted to Congress not later than 18 months after the date of enactment. The final version of the law maintains the requirements for model statute development, and for a report to be developed on the problem of drug-impaired driving. The Secretary of Transportation will develop the report, "in cooperation with the National Institutes of Health." The President signed the bill into law (109-59) on August 10, 2005.

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

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

S. 518/H.R. 1132 - Senator Sessions (R-AL) in the Senate and Representative Whitfield (R-KY) in the House introduced identical bills, the "National All Schedules Prescription Electronic Reporting Act of 2005." This law (P.L. 109-60) will provide for the establishment of a controlled substance monitoring program in each State; it was signed by the President on August 11, 2005.

BILLS OF INTEREST - SENATE

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

S. 103 - Senator Talent (R-MO) introduced on January 24, 2005 the "Combat Meth Act of 2005," a bill to respond to the illegal production, distribution, and

use of methamphetamine in the United States, and for other purposes. Among many things, the bill would have SAMHSA establish a methamphetamine research, training, and technical assistance center "Éin consultation with the Director of the National Institutes of HealthÉ" The bill was passed by the Senate on September 9, 2005, in the form of an amendment to the Commerce, Justice, Science FY 2006 appropriation bill (HR 2662). Subsequent legislative action saw the bill attached to the USA Patriot Act, an effort to get it passed late in the session. Ultimately, the language was removed from the conference report on the Patriot Act. Floor action is expected early in 2006. Related Bills: See H.R. 314, H.R. 3889.

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

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

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

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

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

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

clinical activities related to special focal areas of substance abuse, and provide opportunities for interdisciplinary collaboration in curriculum development, clinical practice, research and policy analysis. Committee: Health, Education, Labor and Pensions.

S. 666 - Senator DeWine (R-OH) introduced on March 17, 2005 the "Family Smoking Prevention and Tobacco Control Act," a bill to protect the public health by providing the FDA with certain authority to regulate tobacco products. Committee: Health, Education, Labor and Pensions.

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

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

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

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

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

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

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

S. 1722 - On September 19th, Senator Lisa Murkowski (R-AK) introduced S. 1722, the "Advancing FASD Research, Prevention, and Services Act." This legislation would amend the Public Health Service Act to reauthorize and extend the Fetal Alcohol Syndrome prevention and services program. S. 1722 would require the Secretary of Health and Human Services, acting through the

Director of the National Institutes of Health and in coordination with the Interagency Coordinating Committee on Fetal Alcohol Syndrome to establish a research agenda for Fetal Alcohol Spectrum Disorders (FASD) and award grants, contracts, or cooperative agreements to public or private nonprofit entities to pay all or part of carrying out research under such agenda. Committee: Health, Education, Labor, and Pensions. Related bill HR 4272.

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

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

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

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

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

BILLS OF INTEREST - HOUSE

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

H.R. 314 - Representative Blunt (R-MO) introduced on January 25, 2005 the "Combat Meth Act of 2005," a bill to respond to the illegal production, distribution, and use of methamphetamine in the United States, and for other purposes. In part the bill would authorize funds to provide training to State and local prosecutors and law enforcement agents for the investigation and prosecution of methamphetamine offenses. Committees: Judiciary, Subcommittee on Crime, Terrorism, and Homeland Security; Energy and Commerce, Subcommittee on Health. Related Bills: See S. 103, H.R. 3889.

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

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

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

H.R. 864 - Representative Roybal-Allard (D-CA) introduced on February 16, 2005 a bill to provide for programs and activities with respect to the prevention of underage drinking. Committee: Energy and Commerce, Subcommittee on Health. Related Bills: See S. 408.

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

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

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

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

H.R. 1106 - Representative Kennedy (D-RI) introduced on March 3, 2005 the "Veterans Medical Research Assistance Voluntary Option Act of 2005," a bill to increase the number of well-trained mental health service professionals (including those based in schools) providing clinical mental health care to

children and adolescents, and for other purposes. Committees: Energy and Commerce, Subcommittee on Health; Ways and Means. Related Bills: See S.537.

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

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

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

H.R. 1357 - Representative Weldon (R-FL) introduced on March 17, 2005, the Human Cloning Prohibition Act of 2005, a bill to prohibit human cloning. Committee: House Judiciary, Subcommittee on Crime, Terrorism, and Homeland Security.

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

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

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

H.R. 1446 - Representative Souder (R-IN) introduced on March 17, 2005 the "Methamphetamine Abuse Prevention Act of 2005," a bill to eliminate the safe-harbor exception for certain packaged pseudoephedrine products used in the manufacture of methamphetamine, Committees: Energy and Commerce,

Subcommittee on Health; Judiciary. Related Bills: See H.R.1350.

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

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

H.R. 1704 - Representative Portman (R-OH [now resigned from the House]) introduced on April 19, 2005 the "Second Chance Act: Community Safety Through Recidivism Prevention Act of 2005," which would reauthorize the grant program of the Department of Justice for reentry of offenders into the community, to establish a task force on Federal programs and activities relating to the reentry of offenders into the community, and for other purposes. Committees: Judiciary; Education and the Workforce. Related bill: see S. 1934.

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

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

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

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

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

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

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

H.R. 2565* ** - Representative Davis (R-VA) on May 24, 2005, introduced the "Office of National Drug Control Policy Reauthorization Act," to reauthorize the Office of National Drug Control Policy Act and to establish minimum drug

testing standards for major professional sports leagues. Committees: Government Reform, Energy and Commerce, Education and the Workforce.

H.R. 2829* - Representative Souder (R-IN) introduced on June 9, 2005, the "Office of National Drug Control Policy Reauthorization Act of 2005." The bill expands and enhances certain authorities of the Office. Committees: Government Reform, Judiciary, Energy and Commerce, Select Intelligence.

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

H.R. 3196 - On June 30, 2005, Representative Henry Waxman (D-CA) introduced H.R. 3196, the Fair Access to Clinical Trials Act (FACT). The measure would require sponsors of privately and publicly funded studies of drugs, biologics, or medical devices to register using a database that builds on the National Library of Medicine's www.clinicaltrials.gov. It would provide public access to basic information on studies before they begin, such as the disease or condition with which the trial is concerned, the hypothesis being tested, the sponsor and principal investigator, and the sources of funding. Public access to the results of clinical studies, including primary and secondary outcomes and significant adverse events, would also be permitted under the legislation. H.R. 3196 also would authorize the Secretary of HHS to impose penalties for noncompliance, including revoking a sponsor's eligibility for further Federal funding and imposing civil money penalties. Committee: Committee on Energy and Commerce.

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

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

H.R. 3889 - On September 22, 2005, Representative Mark Souder introduced H.R. 3889, the "Methamphetamine Epidemic Elimination Act," to further

regulate and punish illicit conduct relating to methamphetamine, and for other purposes. Status: passed by the House. Related bill and legislative action: see S. 103, H.R. 314.

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

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

H.R. 4212 - On November 2, 2005, Representative Frank Pallone (D-NJ) introduced the Advancing FASD Research, Prevention, and Services Act, to amend the Public Health Service Act to reauthorize and extend the Fetal Alcohol Syndrome prevention and services program, and for other purposes. Committees: Energy and Commerce; Education and the Workforce. Related bill: see S. 1722.

H.R. 4272 - On November 9, 2005, Representative Sam Farr (D-CA) introduced H.R. 4272, the Steve McWilliams Truth in Trials Act, to amend the Controlled Substances Act to provide an affirmative defense for the medical use of marijuana in accordance with the laws of the various states, and for other purposes. Committees: Judiciary; Energy and Commerce.

***** - Note: House Leadership and Committee chairs say they are still working to resolve the differences in these bills regarding steroids, and intend to have one bill that they will consider moving through the legislative process to focus on steroids issues.**

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

International Activities

NIDA-Sponsored Meetings

NIDA, Fogarty Sponsor International Effort to Build Inhalant Research Agenda
The NIDA International Program and the Fogarty International Center, together with the Canadian Institute of Aboriginal Peoples' Health and the Mexican Consejo Nacional Contra Las Addicciones (CONADIC), cosponsored the meeting Inhalant Abuse Among Children and Adolescents: Consultation on Building an International Research Agenda November 7-9, 2005, at the NIH Neuroscience Center in Rockville, Maryland. This meeting provided important updates on inhalant abuse research and highlighted the need to increase awareness about the issue among researchers, health care providers, and the general public. The following priority research areas emerged from the discussion: (1) standardizing and adapting existing surveillance methods to better measure the extent of inhalant abuse; (2) designing, implementing, and evaluating treatment and prevention interventions tailored to inhalant abuse; (3) expanding basic science studies to better understand the mechanisms of action of inhalants on young brains; and (4) separating the effects of precursors of inhalant abuse from the consequences of that abuse. Meeting participants expressed particular interest in qualitative research, longitudinal studies to compile data about subjects before they begin using inhalants, and research that explores chronic vs. episodic and isolated vs. communal use patterns. The participants recommended that an international workgroup of pharmacologists and epidemiologists be created to classify substances and develop questions for use in screening instruments and surveys, and that international communications be improved through tools such as listservs, Web portals, or Web-casts.

ROSITA Meeting Assesses Drugged Driving Research
NIDA Scientific Director, Dr. Barry Hoffer, opened the ROSITA 2 International Collaboration Meeting where U.S. and European Union scientists exchanged results on research assessing new detection devices for drugged drivers. Discussions focused on data collection issues and the legal requirements for sensitivity and specificity of roadside testing devices. The meeting, which was held December 5-6, 2005, in Baltimore, Maryland, was hosted by The Walsh Group in collaboration with NIDA. ROSITA is a collaborative effort between the United States and the European Union to identify the requirements for roadside testing equipment and assess roadside testing result validity, equipment reliability, practicality, and usage costs in four U.S. states and six European countries. The Walsh Group coordinates the U.S. effort and Dr. Alain Verstraete, University of Ghent, Belgium, coordinates the EU efforts. The project is supported by ONDCP, NIDA, NHTSA, and the European Union.

U.S. - Mexico Bi-National Research Symposium Explores Migration and Substance Use Disorders

Staff Highlights

Grantee Honors

NIDA supported the participation of three U.S. researchers at the Bi-National Research Symposium held during the U.S. - Mexico 6th Bi-National Drug Demand Reduction Conference, November 30 - December 1, 2005, in Mexico City, Mexico. Dr. Joshua Breslau, Harvard Medical School, discussed the impact of migration on substance use disorders along the Mexico-U.S. border using data from two surveys conducted as part of the World Health Organization's World Mental Health Survey Initiative. The results suggest that migration is associated with increased risk of substance use disorders among Mexican populations on both sides of the border. Dr. Antonio Cepeda-Benito, Texas A&M University, and Chair, International Research Collaboration Committee, National Hispanic Science Network (NHSN) on Drug Abuse, described the subcommittee's functions, activities, and goals. He also reviewed issues related to substance abuse and Hispanics in the United States. Dr. Jane Maxwell, University of Texas, reported on the collaborative Border Epidemiology Work Group and presented data on treatment admissions, discussing similarities and differences in programs on both sides of the border and highlighting the risk of HIV/AIDS due to patterns of drug use in the cross-border treatment population. The Bi-National Research Symposium also featured a presentation by Dr. Carmen Lara, Mexican Institute of Psychiatry.

NIDA, National Hispanic Science Network Explore Latin American Regional Network to Exchange Data and Promote Research
As part of the September 2005 National Hispanic Science Network on Drug Abuse Conference, NIDA Director, Dr. Nora Volkow, hosted a meeting for researchers from Latin America, NHSN officials, and NIDA staff to review research infrastructure, data gathering, and research capabilities in Latin American countries and explore the possible creation of an integrated regional network to facilitate information sharing and research. Presentations focused on methamphetamine abuse, the connections between HIV and drug abuse, and smoking. Presenters included: José Capece, Argentina; Mariano Montenegro Corona, Chile; Ximena Burbano, Colombia; Giselle Amador, Costa Rica; Maria-Elena Medina-Mora, Mexico; Marina Piazza-Ferrand, Peru; Miguel Angel Torres, Valenciana, Spain; Pedro Delgado, Venezuela; and Jose Francisco Cumsille, Organization of American States-CICAD.

NIDA Hosts Foresight Brain Science, Addiction and Drugs Project
Representatives from Foresight, the British government's science-based think tank, presented results from the group's Brain Science, Addiction, and Drugs Project at a NIDA Director's Seminar on September 26, 2005, at NIDA headquarters. The Brain Science, Addiction, and Drugs Project involved more than 50 experts to explore how future scientific and technological advances will affect our understanding of addiction and drug use. Presenters at the NIDA Director's Seminar included Dr. Trevor Robbins, Professor of Experimental Psychology, University of Cambridge, and Editor, Psychopharmacology; Dr. Gerry Stimson, Executive Director, International Harm Reduction Association, and Emeritus Professor of the Sociology of Health Behaviour, Imperial College London; and Mr. Andrew Jackson, Foresight Deputy Director. Foresight considered the implications of future advances in 15 areas of basic and social sciences, concluding that within the near future, scientists will better understand how the brain functions, which may help researchers develop: (1) revolutionary treatments for drug abuse, mental illness, or neurodegenerative diseases and (2) novel psychoactive drugs with fewer harms and lower risks of addiction than the substances currently available. Potential drug abuse treatment advances include new or improved behavioral therapies; cognitive therapies; vaccines; and pharmacotherapies that target glutamate neurotransmitters or neuropeptides, manage craving and relapse, improve cognitive function, or tailor therapeutic drugs to address specific genetic and environmental variables. Foresight predicted that the development of new ligands for key neurotransmitters, including serotonin, glutamate, and acetylcholine, could improve significantly the current understanding of brain operations. The Brain Science, Addiction, and Drugs Project also considered the

implications these scientific advances will have on individuals, families, and communities and outlined strategic choices, opportunities, and challenges facing researchers, industry, and policymakers. The complete report is available on the Foresight Web page, http://www.foresight.gov.uk.

NIDA Hosts Poster Session at Society for Neuroscience Research Meeting
Drs. Susan Volman, DBNBR, and Steven W. Gust, IP, co-chaired an Early Career Investigators Poster Session on Friday, November 11, 2005, as part of NIDA's mini-convention on Frontiers in Addiction Research at the Society for Neuroscience Research meeting in Washington, D.C. The invited poster session showcased drug abuse and drug-related neuroscience research by: Victoria Eugenia Mendiz‡bal, Argentina; Kelly J. Clemens, Australia; Isabel Marian Hartmann de Quadros and Sionaldo Ferreira, Brazil; Candace Contet and Marcello Solinas, France; Abraham Zangen, Israel; Michela Ferrucci, Silvana Gaetani, Gloria Lazzeri, Isabel Matias, and Raffaela Tonini, Italy; Bronwyn Kivell and Regan Wisnewski, New Zealand; Marina Rubio, Spain; Camilla Bellone, Switzerland; Y Hakan Dogan and Gorkem Yarabas, Turkey; and Christopher Bailey, Jonathan Lee, and Amy Milton, United Kingdom. The International poster presenters were supported, in part, by NIDA and the: International Union of Pharmacology, International Brain Research Organization, International Narcotics Research Conference, College on Problems of Drug Dependence, International Cannabinoid Research Society, and International Drug Abuse Research Society.

Research Training and Exchange Programs

Distinguished International Scientist Collaboration Awards (DISCA)
The 2005 NIDA Distinguished International Scientists have completed their research visits to the United States. The competitive DISCA awards provide support to senior scientists during research exchange visits of 1 to 3 months so that applicants and their partners can cooperate on drug abuse research.

- **Dr. Luc Denoroy**, Université Claude Bernard, Lyon, France, worked with Dr. Toni Shippenberg, IRP, to establish a research initiative combining Dr. Denoroy's technique to monitor rapid changes in the extracellular concentration of neurotransmitters with IRP animal studies using microdialysis and intravenous drug self-administration. The capillary electrophoresis with laser-induced fluorescence detection (CE-LIFD) system was installed in the IRP Behavioral Neuroscience Branch, and two protocols were developed and validated to determine neurotransmitter levels in brain microdialysates. CE-LIFD permits the accurate and simultaneous measurement of gamma-amino butyric acid (GABA), glutamate, and aspartate in small-volume brain microdialysates. NIDA scientists now routinely use CE-LIFD for operant drug self-administration and other studies, and Dr. Denoroy's laboratory is using NIDA protocols to conduct microdialysis studies in the freely moving mouse. The NIDA and French researchers are continuing their collaboration, writing journal articles, sharing French technology to quantify neurotransmitters with NIDA scientists, and training French students in NIDA's behavioral analysis methods.
- **Dr. Min Zhao**, Shanghai Mental Health Center, China, and Dr. Clyde B. McCoy, University of Miami, have filed an R01 research grant application to study gender differences of HIV risk behaviors among Chinese injection drug users (IDUs). The researchers propose a longitudinal study employing both qualitative and quantitative studies to explore the effects of gender on changes in HIV risk behaviors, identify the factors that contribute to HIV infection, and establish the prevalence and incidence of HIV and hepatitis infections in Shanghai. Drs. Zhao and McCoy also finalized plans to have the Shanghai Mental Health Center apply for the NIDA Research Center Grant Consolidated Program, which would allow the Shanghai institution to join

the University of Miami's multi-country drug abuse and HIV/AIDS research center, where each participating research site designs, tests, adapts, and evaluates culturally appropriate, evidence-based HIV prevention strategies and drug abuse intervention efforts among IDUs. The research team also completed a scientific article that has been submitted for publication, and Dr. Zhao received certification in human subjects protections from the University of Miami's Collaborative IRB Training Initiative.

INVEST, Humphrey Fellows Meet NIDA Officials
NIDA hosted an orientation on Friday, October 28, 2005, for the 2005-2006 NIDA INVEST and Hubert H. Humphrey Drug Abuse Research Fellows. The group met with Ms. Dale Weiss, IP; former NIDA Humphrey Fellow and Distinguished International Scientist Dr. Petra Exnerova, DESPR; and with program officers who work with the Fellows' U.S. mentors. The Fellows also toured the National Library of Medicine and the Fogarty International Center. The NIDA INVEST Fellows included Dr. Oscar Quintela, Spain, and Dr. Tsafrir Loebl, Israel. Dr. Quintela met with Dr. J. Michael Walsh, The Walsh Group, and Dr. Loebl met with Dr. Betty Tai, CCTN. Ten Hubert H. Humphrey Fellows from Johns Hopkins University participated in the NIDA orientation. Dr. Anna Tkachenko, Russia, and Ms. Nataliya Vlasova, Ukraine, met with Dr. Peter Hartsock, DESPR. Dr. Fadi Hammal, Syria, met with Dr. Allison Chausmer, DBNBR. Ms. Alexandra Hill, El Salvador, met with Ms. Ana Anders, NIDA Special Populations Office. Dr. Danesh Gupta, India, met with Dr. Larry Seitz, DESPR. Dr. Abdallah Mansour, Egypt, met with Dr. Ahmed Elkashef, DPMCDA. Dr. Stephen Nsimba, Tanzania, met with Dr. Jerry Flanzer, DESPR. Dr. Benjamin Oaikhena, Nigeria, met with Dr. Lois Cohen, Office of International Health, National Institute of Dental and Craniofacial Research. Dr. Islam Miftari, Kosov, and Ms. Patricia Schmid, Brazil, met with Dr. Exnerova.

Humphrey Fellows Tour IRP
The 2005-2006 Hubert H. Humphrey Drug Abuse Research Fellows toured the NIDA Intramural Research Program in Baltimore, Maryland, on November 4, 2005. The following IRP staff members met with the Fellows: Kenzie Preston, Ph.D., Chief, Clinical Pharmacology and Therapeutics Research Branch, overview of the IRP; Stephen Heishman, Ph.D., Chemistry and Drug Metabolism Section, nicotine addiction; Marilyn Huestis, Ph.D., Chief, Chemistry and Drug Metabolism Section, application of toxicology methods to research on cannabinoids, Ecstasy, and in-utero drug exposure; Eliot Stein, Ph.D., Chief, Neuroimaging Branch, MRI scanner; Alane Kimes, Ph.D., PET Center; Ron Herning, Molecular Neuropsychiatry Section, the neuropsychiatric effects of prolonged drug abuse; Steven Goldberg, Ph.D., Chief, Preclinical Pharmacology Section, cannabinoid research; Eric Moolchan, M.D., Chief, Teen Tobacco Addiction Research Clinic; and David Epstein, Ph.D., Treatment Section, Archway Clinic, contingency management.

Travel and Meeting Support

- IP Director Dr. Steven W. Gust participated in the Annual Meeting of the Society for Psychophysiological Research, held September 21-24, 2005, in Lisbon, Portugal. While in Lisbon, Dr. Gust also met with colleagues at the European Monitoring Centre for Drugs and Drug Addiction.
- NIDA provided travel support to Dr. Patricia Molina, University of Louisiana-New Orleans, for participation in the Congresso en Cordoba, held October 27-29, 2005, in Cordoba, Argentina.
- NIDA provided travel support to Professor Filippo Drago, Department of Experimental and Clinical Pharmacology, University of Catania, Italy, to present his research, "The Endogenous Cannabinoid System and Its Possible Role in Psychiatric Disorders," at the IRP Seminar Series on November 1, 2005.

International Visitors

On November 14, 2005 a group of 10 participants in the U.S. Department of State, International Visitor Leadership Program visited NIDA as part of a multi-regional project in substance abuse education, treatment and prevention. The 10 countries represented include Burma, Canada, Germany, India, Iraq, Maldives, Pakistan, Philippines, Saudi Arabia and Serbia. Drs. Liz Ginexi, Richard Denisco and Ms. Gina Hijjawi of the Division of Epidemiology, Services and Prevention Research and Ms. Dale Weiss of the International Program met with the group.

Ms. Carmen Cecilia Villanueva Brach, General Coordinator for the United Nationals Office of Drugs and Crime Mexico International Relations visited NIDA on November 19, 2005. Dr. Steven Gust and Ms. Dale Weiss, NIDA International Program, met with Ms. Villanueva to discuss drug treatment work being done in Mexico and Central America.

As part of the U.S. - Netherlands Demand Reduction Exchange Meeting, NIDA hosted a visit of Netherlands researchers on December 8, 2005. The visit included a morning tour of the NIH campus and in the afternoon the delegation visited the NIDA offices for presentations and discussions. Attending for NIDA were Dr. Steven Gust, NIDA International Program, Drs. Elizabeth Robertson, Yonette Thomas, and Redonna Chandler, Division of Epidemiology, Services and Prevention Research, and Cecelia McNamara Spitznas, Division of Clinical Neuroscience and Behavioral Research. The visitors from the Netherlands included J.A. Walburg and Maurice Galla, Trimbos Institute, Marcel de Kort, Netherlands Ministry of Health, Welfare and Sport, Maria Magdalena Riper, Center of Prevention and Brief Interventions, Margriet Van Laar, National Drug Monitor, Chistina M. van der Felitz-Cornelis, Programme for Diagnosis and Treatment, Andre Gageldonk, Senior Research Fellow, and Dirk Ruwaard, Netherland Embassy.

A group of visitors from the Netherlands organization De Hoop (The Hope) visited NIDA on December 12, 2005. The visitors included Teun Stortenbeker, managing director De Hoop, Leo van der Wild, treatment supervisor (executive) De Hoop, Leendert van den Brink, treatment coordinator (policy) De Hoop, Guy Thijskens, psychiatrist (in education) De Hoop, Frans Koopmans, staff worker communications De Hoop and Wouter van Twillert, Director Treatment Center Krusada, Bonaire (Netherlands Antilles). Attendees from NIDA included Drs. Beverly Pringle, Redonna Chandler, Dionne Jones, Richard Denisco and Eve Reider from the Division of Epidemiology, Services and Prevention Research, and Dr. Lisa Onken, Division of Clinical Neuroscience and Behavioral Research.

Dr. Wilson Compton, Director, DESPR, presented at the International Conference on Drug Epidemiology and Prevention, September 20-22, 2005, Taipei, Taiwan.

Dr. Wilson Compton met with participants in the international satellite session to the meeting of the National Hispanic Science Network on Drug Abuse, Miami, Florida, September 13-16, 2005.

Dr. Elizabeth Robertson, DESPR, gave a presentation to the Organization of American States substance abuse prevention subcommittee on September 12 in Ottawa, Canada. The title of her presentation was Measuring Outcomes: The Role of Attitudes in Predicting Drug Use Behaviors - A Cautionary Tale.

Moira O'Brien, DESPR, chaired the Border Epidemiology Work Group Meeting (BEWG), September 15-16, 2005, in San Antonio, Texas. Participants included representatives from the Mexican Ministry of Health, Mexican Institute of Psychiatry, National Council Against Drug Abuse Mexico and in 4 U.S. Border States.

Dr. Jag Khalsa, DPMCDA, presented a mini-symposium on Metabolic and Endocrine Disorders and Interventions in Drug Abusers Co-infected with HIV and HCV at the XIII World Psychiatry Congress, in Cairo, Egypt, September 10-15, 2005. Speakers (Dr. Adrian Dobs of JHU, Dr. Tim Flanigan of Brown University, Dr. Charles Hinkin of UCLA, and Christine Wanke of Tufts) presented current research findings on the subject. A brief summary of the symposium will be placed on NIDA's website.

Dr. Jag Khalsa, Dr. Jacques Normand, Director, Office on AIDS, Dr. Pat Needle, and the NIH OAR Staff presented an Indo-US Workshop on AIDS and Drug Abuse, New Delhi, India, October 27-30, 2005. NIDA/NIH supported researchers including Drs. Strathdee, Wanke, Flanigan and many others also exchanged current research with the Indian counterparts, fostered collaborations, and discussed ways to facilitate approval of research protocols by the respective approval authorities. The meeting was a great success. Dr. Normand will further brief the council.

Dr. Ivan Montoya, DPMCDA, was a guest speaker at the annual meeting of the Colombian Psychiatric Association, in Cartagena, Colombia. Dr. Ivan Montoya was invited to speak at the annual meeting of the Italian Federation of Substance Abuse, in Palermo, Italy.

Dr. Frank Vocci, Director, DPMCDA, attended the World Psychiatric Association meeting in Cairo, Egypt from September 10-14, 2005. He presented on the Neurobiology of Marijuana at a symposium and chaired a symposium titled: Addiction is a Brain Disease: Implications for Treatment. At this symposium Dr. Richard Rawson spoke about Cognitive behavioral therapy for the treatment of methamphetamine dependence; Dr. Bankole Johnson spoke about Alcohol dependence therapies, Dr. Ahmed Elkashef, DPMCDA, spoke about Pharmacotherapies for stimulant dependence, and Dr. Frank Vocci spoke about the Neurobiology of addiction.

Dr. Frank Vocci attended the Italian FederSerD meeting in Palermo, Sicily from November 30 through December 2, 2005. He presented on Addiction and action mechanisms relating to cocaine addiction.

On November 3, 2005, Dr. Peter Hartsock met with NIDA Russian grantees, the Russian Attaché for Science and Health, and representatives from NIAID, Fogarty, and NIH/OAR in Washington, D.C., to discuss planning for the next G-8 Summit, to be held for the first time in Russia. Public health, especially related to drug abuse and HIV/AIDS, is expected to play a larger role than at any previous G summits.

Dr. Peter Hartsock met with Humphrey Fellows Dr. Nataliya Vlasova from Ukraine and Dr. Anna Tkachenko from Russia as part of the Humphrey Fellows Orientation Program, in Bethesda, MD, on October 28, 2005.

Dr. Peter Hartsock participated with members of the Department of Justice and Department of Defense in a meeting at the German Embassy dealing with narco-terrorism, in Washington, D.C., on November 2, 2005.

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Meetings/Conferences

NIDA hosted its second Health Disparities Conference, **Bridging Science and Culture to Improve Drug Abuse Research in Minority Communities** at the Hyatt Regency in Atlanta, Georgia, October 24-26, 2005. Conference highlights included plenary sessions on genetic research, health disparities within rural communities, HIV/AIDS and the criminal justice system, and gender issues associated with drug abuse research. Participants also had the opportunity to attend a poster session and smaller symposia on numerous drug abuse research concerns, including social, cognitive, behavioral, health and medical consequences as they related to minority populations. NIDA staff was heavily involved in the conference, serving in roles as conference planners, session/symposia moderators, chairs of grant writing workshops, poster session judges, travel award coordinators, etc. Staff participants included: Lula Beatty, Ph.D., Ana Anders, Pamela Goodlow, LeKhessa Doctor, Flair Lindsey, Charlotte Annan, Don Vereen, M.D., Wilson Compton, M.D., Carmen Rosa, Aria Crump, Ph.D., Belinda Sims, Ph.D., Mark Swieter, Ph.D., Nate Appel, Ph.D., Pushpa Thadani, Ph.D. Gloria Lester, Suman Rao King, Ph.D., Paul Schnur, Ph.D., David Anderson, Jessica Campbell, Ph.D. and CeCe McNamara Spitznas, Ph.D.

On November 17 - 18, 2005, NIDA convened the first meeting of the **Basic Science Review Work Group** in Bethesda, Maryland. This meeting was coordinated by Dr. Denise Pintello, OSPC, and chaired by Dr. Linda Porrino, who is a member of the National Advisory Council on Drug Abuse. The purpose for this Work Group is to conduct a comprehensive review of NIDA's basic science research portfolio and to provide recommendations to effectively address the future direction of basic science research at NIDA. The Work Group members will prepare a written report for the National Advisory Council on Drug Abuse in 2006.

The Work Group examining **NIDA's Approach to Grant-Making** held its first meeting on December 6-7, 2005 to review NIDA's current grant-making practices and will determine if any new actions or policies are needed. The Work Group membership is composed of experts in the field of drug abuse research and is chaired by Dr. Constance Weisner. Based on their findings and recommendations, it is anticipated that the Work Group members will complete their recommendations and final report in 2006.

On November 29th NIDA held a joint press conference and science meeting at the National Press Club on **Drug Abuse and HIV/AIDS: The Complexities of Linked Epidemics**. During this event NIDA launched its newest public service announcement designed to urge teens to learn the link between drug abuse and HIV/AIDS.

On October 24, 2005, NIDA sponsored a one-day symposium titled: **The NIH Roadmap: Inviting Drug Abuse and Addiction Researchers to**

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Contribute to the Clinical Research Enterprise. The purpose of this symposium was to inform clinical and translational researchers about future scientific opportunities within the Roadmap. Dr. Timothy P. Condon, NIDA Deputy Director welcomed the several hundred participants and presented "NIH Roadmap for Medical Research: Inviting Drug Abuse and Addiction Researchers to Contribute to the Clinical Research Enterprise." The symposium was held in North Bethesda, Maryland and coordinated by Dr. Denise Pintello, OSPC and Ronald Dobbins, CCTN.

Drs. Minda Lynch and Allison Chausmer, DBNBR, co-organized and chaired a symposium entitled **Adolescent Drug Abuse: Brain Development, Cognition and Vulnerability** as part of NIDA's Frontiers in Addiction Research Mini-Convention Satellite to November's Society for Neuroscience Annual Meeting. The session focused on developmental processes that may contribute to increased vulnerability, including cortical development and a discussion of how brain maturation supports the emergence of abstract thought, goal planning, and behavioral inhibition. Speakers included Drs. Judith Rapoport from NIMH, Bea Luna, Linda Spear, and P.V. Piazza.

Drs. Susan Volman and David Shurtleff, DBNBR, co-organized and chaired a symposium entitled **Neurobiological Basis for Co-Occurring Substance Abuse and Mental Illness** as part of NIDA's Frontiers in Addiction Research Mini-Convention Satellite to November's Society for Neuroscience Annual Meeting. The symposium presented studies of psychiatric illness in humans and in animal models that seek to explain the neurobiological basis of comorbidity. Speakers included Drs. Sherry Leonard, R. Andrew Chambers, Jean King, and Robin Murray.

Dr. Susan Volman, DBNBR, and Dr. Barbara Sorg (Washington State University) co-organized and chaired a symposium entitled **Reconsolidation of Memory: A New Approach To Treat Drug Addiction?** as part of NIDA's Frontiers in Addiction Research Mini-Convention Satellite to November's Society for Neuroscience Annual Meeting. The symposium featured recent research on the behavioral, neural, and molecular basis of the reconsolidation of fear conditioning and drug-related memory, and addressed the question of whether a better understanding of the process of reconsolidation could shed light on how to disrupt the memory for drug addiction. Speakers included Drs. Karim Nader, Cristina Alberini, Barry Everitt, and Barbara Sorg.

Dr. Susan Volman, DBNBR, and Dr. Steve Gust, IP, organized an **Early Career Investigators Poster Session** as part of NIDA's Frontiers in Addiction Research Mini-Convention Satellite to November's Society for Neuroscience Annual Meeting. Poster presenters were selected from a diverse group of early career investigators, and for the first time this year, international presenters were sponsored in partnership with six international organizations: IUPHAR, IBRO, INRC, CPDD, ICRS, and IDARS.

Dr. Paul Schnur, DBNBR, and Dr. Joe Frascella, DCNBR, organized and chaired a symposium entitled **Addiction and Obesity-Brain System Commonalities** as part of NIDA's Frontiers in Addiction Research Mini-Convention Satellite to the 2005 Society for Neuroscience Annual Meeting. This session explored obesity and drug addiction through their common neurobiological processes and neuronal systems. Speakers included Daniele Piomelli, Ph.D., University of California, Irvine, Ann E. Kelley, Ph.D., University of Wisconsin, Edmund T. Rolls, D.Sc., University of Oxford and Nora D. Volkow, M.D., NIDA.

Dr. Allison Chausmer, DBNBR, organized and chaired a symposium entitled **mGluR: A Substrate in the Neurobiology of Addiction** as part of NIDA's Frontiers in Addiction Research Mini-Convention Satellite to November's Society for Neuroscience Annual Meeting. This session focused on how the modulation of mGluR function results in neurobiological and behavioral changes, and how these changed are associated with drug challenged. Speakers included Drs.

Paul J. Kenny (Scripps Research Institute), Karen Szumlinski (University of California, Santa Barbara), and Carl Lupica (NIDA Intramural Program).

Drs. Eve Reider and Elizabeth Robertson, Prevention Research Branch, DESPR, convened a meeting, **Bi-directional Influences of Drug Abuse and Child Abuse and Neglect**. The meeting was sponsored by NIDA's Office of Science Policy and Communication in conjunction with the Child Welfare League of America; it was held on October 27, 2005 at the Holiday Inn Select in Bethesda, Maryland.

The NIDA Special Populations Office and the AIDS Program Office cosponsored a seminar on December 6, 2005 with the NIMH Office of Special Populations and the NINDS Minority Research Office on **HIV/AIDS in Minority Populations**. The NIDA speaker was Dr. Maureen Miller, who spoke on Community Academic Partnerships.

CTN-Related Meetings/Conferences

A **CTN New Node Orientation Meeting** was held September 19-20, 2005 in Gaithersburg, MD. At this meeting, members of the Long Island and Ohio Valley Nodes joined the CCTN in briefing members of the two newest Nodes (Texas and Appalachian Tri-State) on CTN activities, policies and procedures.

National CTN Steering Committee (SC) Meetings were held October 25-26, in Bethesda, Maryland. Dr. Nora Volkow, NIDA Director, outlined goals for the CTN over the next five years, identified steps the CTN might take to meet increasing resource challenges, and identified additional opportunities for the CTN. Dr. Timothy Condon, NIDA Deputy Director, provided an update on blending research and practice dissemination, describing collaboration with SAMHSA's ATTCs to disseminate strategies and products, which are dovetailed with the CTN protocols. Dr. Condon also discussed the opportunity for a convergence of NIDA Networks in order to do more with the same or fewer resources. The SC approved the revised By-Laws and the new governance structure for the CTN. Several NIDA presenters included: 1) Lynda Erinoff, Ph.D., discussed NIDA's HIV/AIDS Research Program and Counsil recommendations; 2) Jamie Biswas, Division of Pharmacotherapies and Medical Consequences of Drug Abuse, gave an overview of NIDA Initiatives in Medication Development.

Dr. Betty Tai, Director of the CCTN, presented at the 4th SINO-US Symposium on Medicine in the 21st Century, San Francisco, California, August 19-21, 2005. She spoke on Clinical Research and the NIH Roadmap.

CCTN staff and CTN investigators presented two sessions at the **NIDA Health Disparities Conference** on October 24-26, 2005, in Atlanta, Georgia. The panels were: Implementation of Multi-Site Trials with Hispanic Minorities (CTN in Spanish) - The focus of the panel was on the experience of the CTN in implementing randomized clinical trials in Hispanic-serving, community based, drug treatment programs. The panelists were Dr. Rafaela Robles (Chair), Dr. Lourdes Suarez, Dr. Viviana Horigian, Dr. Edna Quinones, and Carmen Rosa, M.S. The title of the second panel was "What We Are Learning About Drug Abuse Treatment for Minorities: The CTN Experience". This panel presented a review of the findings for ethnic Minorities in studies affiliated with the CTN. The panelists were Dr. Kathy Burlew (Chair), Carmen Rosa, and Dr. Kathy Magruder.

The CTN Data and Safety Monitoring Board met November 17-18, 2005, in Bethesda, Maryland. The group reviewed the continuing progress of the CTN's active protocols and new protocols.

The CCTN sponsored two workshops at the 16th Annual Meeting & Symposium of AAAP (American Academy of Addiction Psychiatry) in Scottsdale, Arizona,

December 9-11, 2005. The first session, entitled "The Interface between Pain and Addiction: New Horizons", was chaired by Dr. Petra Jacobs, CCTN NIDA, and Dr. Roger Weiss, Northern New England Node. Dr. Petra Jacobs also presented on "Blending Research and Practice: NIDA Perspectives on Bipolar Disorder and Addiction". This presentation was developed as a collaborative effort between CCTN and DESPR (Dr. Wilson Compton). In addition, Dr. Petra Jacobs presented a poster entitled "What is the connection between physical and psychological pain and the clinical implications of this relationship?"

The CCTN sponsored an all day pre-conference brainstorming symposium entitled "The Methamphetamine Menace: Treatment Approaches for a National Problem" as a satellite conference at the American College of Neuropsychopharmacology (ACNP) Annual Conference on December 10, 2005, in Waikoloa, Hawaii Dr. Volkow, Director of NIDA and Dr. Betty Tai co-chaired the meeting. Presenters discussed possible treatment interventions and implications for methamphetamine addiction.

On November 28th, 2005, Dr. Betty Tai was invited by the Treatment Research Center at University of Pennsylvania, Department of Psychiatry, for a seminar on an update of the National Drug Abuse Treatment Clinical Trials Network and NIH roadmap initiatives on reengineering the clinical trials enterprise. During her visit, she had meetings with faculty members from the department to exchange information on current scientific status on drug abuse treatments.

The findings and implications for clinical practice from three CTN protocols were presented in a Symposium at the December 2005 Annual Meeting of the American Academy of Addiction Psychiatry (AAAP) chaired by Dr. Edward Nunes. Dr. Maxine Stitzer (PI for studies CTN 0006 and 0005) presented on Motivational Incentives, Dr. Leslie Amass (Co-PI for studies CTN 0001 and 0002) presented on Buprenorphine-Naloxone for Short-Term Opioid Detoxification, and Dr. Bob Forman (PI for study CTN 0016) presented findings from Patient Feedback: A Quality Improvement System for Outpatient Clinics.

In collaboration with NIAAA and CSAT, new CCTN staff member Dr. Harold Perl organized an invited expert panel workshop titled "State-of-the-Science on Dissemination and Implementation of Evidence-Based Practice" on January 9-10, 2006 in North Bethesda, MD. The goals of this workshop included delineating current knowledge on implementation science in addictions and other health-related areas, identifying critical gaps in knowledge and recommending an agenda for future research on implementation.

January 29- February 2, 2006, Dr. Betty Tai, Director, CCTN, chaired a session to highlight CTN research results at the 11th International Conference on Treatment of Addictive Behaviors (CTAB-11) in Santa Fe, New Mexico. The symposium was titled, "The First Four Studies: Bridging the Gap between Research and Practice", and included presentations by Dr. Dennis McCarty (PI for study 0008), Dr. Kathleen Carroll (PI for studies CTN 0004 and 0005), Dr. Maxine Stitzer (PI for CTN 0006 and 0007), and Dr. Walter Ling (PI for studies CTN 0001 and 0002).

Dr. Timothy P. Condon, Deputy Director, NIDA, presented "Addiction as a Brain Disease: Blending Research and Practice" at the Illinois Alcoholism and Drug Dependence Association Annual Conference: Partners in Action: Forging Our Future on September 18, 2005 in Oak Brook, Illinois.

Dr. Timothy P. Condon presented "Advances in Drug Abuse and Addiction Research: Implications for Prevention" at the Southwest Regional Prevention Conference on September 28, 2005 in Dallas, Texas.

Dr. Timothy P. Condon gave the keynote address "Drug Addiction: A Brain Disorder" at the American Academy of Child and Adolescent Psychiatry

conference on October 21, 2005 in Toronto, Canada.

Dr. Timothy P. Condon presented "Network of NIDA's Networks" at the CTN National Steering Committee meeting on October 25, 2005 in North Bethesda, Maryland.

Dr. Timothy P. Condon presented "Addiction as a Brain Disease: Blending Research and Practice" at the 36th Annual MAARCH Chemical Health Conference on October 26, 2005 in St. Paul, Minnesota.

Dr. Timothy P. Condon presented "Methamphetamine: The Science of Addiction" to the Minnesota Supreme Court Chemical Dependency Task Force on October 28, 2005 in St. Paul, Minnesota.

Dr. Timothy P. Condon presented a judicial training session entitled "It's a Brain Disease: Beyond a Reasonable Doubt: The Neuroscience of Addiction & Judicial Decision Making," at the Circuit Court of Cook County Criminal Division, Cook County, Illinois on November 15, 2005 in Chicago, Illinois.

Dr. Timothy P. Condon presented "Advances in Drug Abuse and Addiction Research: Implications for Prevention" at the 17th Annual Ohio Prevention and Education Conference on November 17, 2005 in Columbus, Ohio.

Dr. Timothy P. Condon presented the keynote address entitled "Bringing the Power of Science to Bear on the Care of Addicted Patients" at the American Academy of Addiction Psychiatry 16th Annual Meeting and Symposium on December 9, 2005, in Scottsdale, Arizona.

Dr. Cindy Miner, Deputy Director, OSPC, participated in an Advisory Work Group Meeting at TASC on September 15, 2005 in Chicago, Illinois.

Dr. Cindy Miner gave the Opening Plenary on "The Science of Addiction" at a Conference for Family Court Judges, Masters and Staff on September 23, 2005 in Timonium, Maryland.

Dr. Cindy Miner participated in a Grantwriting Workshop at the 2005 American Academy of Child & Adolescent Psychiatry Conference on October 19, 2005 in Toronto, Canada.

Dr. Cindy Miner was a Keynote Speaker on "Just INCASE You Didn't Know: Drug Addiction is a Brain Disease" at the INCASE Conference on October 28, 2005 in Silver Spring, Maryland.

Dr. Suman Rao King, Science Policy Branch, OSPC, presented on the NIH Loan Repayment Program in the Grant Writing Workshop at the Health Disparities Conference on October 24-25, 2005 in Atlanta, GA.

On December 15, 2005, Drs. Susan Weiss and Ruben Baler, Science Policy Branch, OSPC, co-chaired a panel at the 44th Annual Meeting of the American College of Neuropsychopharmaco-logy in Waikoloa, Hawaii, entitled "Plastic Changes in the Addicted Brain: A Glimpse at the Next Generation of Pharmacotherapies." The panel, organized by OSPC, brought together four leading researchers investigating some of the molecular changes triggered by drugs of abuse in the brain. The panel discussed several cutting-edge strategies aimed at using the new understanding of the processes underlying drug addiction toward the development of better addiction treatments.

On October 4, 2005, Dr. Ruben Baler made a presentation at the School of Public Health and Health Services, Department of Exercise Science, at George Washington University. The lecture was part of the "Drug Awareness" course offered every semester to incoming freshmen; it was entitled "Addiction is a Brain Disease" and highlighted NIDA's mission, strategies and achievements.

Mr. David Anderson, OSPC, made a presentation on research-practice

collaboration at "Persistently Safe Schools 2005", the annual conference of the Hamilton Fish Institute of George Washington University, held on September 11, 2005 at the Wyndham Plaza Hotel, Philadelphia.

Ms. Sheryl Massaro, OSPC, presented at the NIH-wide communications workshop, Taking Action: Health Promotion and Outreach with American Indians and Alaska Natives, on November 1, 2005 at the Natcher Conference Center, NIH. She presented lessons learned from creating, disseminating, and evaluating NIDA's Walking a Good Path Calendars, including advice on how to begin such outreach, approach community members, form partnerships, conduct meetings and research, and develop messages and materials.

Dr. Cathrine Sasek, Office of Science Policy and Communications, presented a symposium titled "How to Improve Neuroscience Education and Literacy" on November 14, at the 2005 Society for Neuroscience Meeting. Also presenting were Drs. David Friedman, Rochelle Schwartz-Bloom, and David Vannier.

Dr. Donald Vereen, Jr., OD, presented at the DC Drug Summit, sponsored by the Mayor's Interagency Task Force on Drug Prevention, Treatment, and Control on September 29, 2005 in Washington, DC.

Dr. Donald R. Vereen, Jr. presented "Drug Abuse and Addiction" and served on a panel with the NIH Deputy Director at the Men's Health Conference at the Howard University Hospital on October 1 and 2, 2005 in Washington, D.C.

Dr. Donald R. Vereen, Jr. presented the "Science of Addiction" to the Florida Supreme Court and associated personnel on October 6, 2005 in Orlando, FL.

Dr. Donald R. Vereen, Jr. presented a keynote address to the Advanced Science and Technology Adjudication Resource Center (ASTAR), entitled the Science of Drug Abuse and Addiction and on October 9, 2005 in Airlie, VA.

Dr. Donald R. Vereen, Jr. made a plenary presentation to the American Academy of Pediatrics on October 10, 2005 in Washington D.C.

Dr. Donald R. Vereen, Jr. made a presentation on drug abuse and addiction research findings to the Alliance of Concerned Black Men, on October 12, 2005 in Washington, D.C.

Dr. Donald R. Vereen, Jr. gave a presentation on drug abuse and addiction research to the Drug Enforcement Administration demand reduction staff on October 14, 2005 in Arlington, VA.

Dr. Donald R. Vereen, Jr. presented an overview of drug abuse and addiction research to the D.C. Safe Schools and Communities Coalition General Body on October 19, 2005.

Dr. Donald R. Vereen, Jr. delivered the keynote address at the annual Washington State Prevention Summit on October 20, 2005.

Dr. Donald R. Vereen, Jr. opened the NIDA sponsored "Bridging Science and Culture to Improve Drug Abuse Research in Minority Communities" and moderated a panel, October 24-26, 2005 in Atlanta GA.

Dr. Donald R. Vereen, Jr. was the keynote speaker for the Second Annual Corrections Mental Illness Awareness Week Program on October 28, 2005 in Boyds, MD.

Dr. Donald R. Vereen, Jr. co-led a panel at the ASAM "State of the Art" Conference on October 29, 2005 in Washington D.C.

Dr. Donald R. Vereen, Jr. was a plenary presenter at the Annual Biomedical Research Conference for Minority Students on November 3, 2005 in Atlanta, GA.

Dr. Donald R. Vereen, Jr. was the keynote presenter at the Nebraska Prevention Leadership Institute on November 7, 2005 in Lincoln NE.

Dr. Donald R. Vereen, Jr. participated in the Disparities Focus Group Meeting of the National Association of Drug Court Professionals on November 9-10, 2005 in Chicago, IL.

Dr. Donald R. Vereen, Jr. participated in the American Psychiatric Association sponsored "Black Psychiatrists Dialogue" on November 13, 2005 in Washington, D.C.

Dr. Lula Beatty, Chief, Special Populations Office, met with the American Psychological Association's Committee on AIDS to discuss HIV/AIDS programs at NIDA and to discuss possible collaborations on preparing racial/ethnic minority scientists to become involved in HIV/AIDS research, September, 2005.

Dr. Lula Beatty gave a presentation, "Disparities in Drug Abuse: Priorities and Funding Opportunities at the National Institute on Drug Abuse," at the Institute for the Elimination of Health Disparities, University of Medicine and Dentistry of New Jersey, School of Public Health, November 2005.

Dr. Lula Beatty gave a presentation, "HIV/AIDS, Drugs, and Criminalization in African Americans," at the Africa Studies Department, Central Connecticut University, November 2005.

Dr. Lula Beatty gave a presentation, "Health Disparities Research at the National Institute on Drug Abuse," at the University of New Mexico, Albuquerque, November 2005.

Ana Anders, Senior Advisor on Special Populations, participated in the National Hispanic Science Network on Drug Abuse annual conference in Miami, Florida, September 14-17, 2005.

Ana Anders was a speaker at the Latino Behavioral Health Institute (LBHI) annual conference, September 20-22, 2005.

Ana Anders represented NIDA at the CSAT Hispanic Stakeholders meeting in Los Angeles, California, September 21, 2005.

Ana Anders attended a working meeting of the National Hispanic Science Network on Drug Abuse in Miami, Florida, November 29 - December 1, 2005.

Flair Lindsey, Program Analyst, Special Populations Office, coordinated the ninth annual Summer Research with NIDA program. The program allowed high school and undergraduate students to engage in drug abuse research with NIDA grantees for 8-10 weeks over the summer. In 2005, 84 students and 32 grantees participated in the program.

Dr. Wilson Compton, Director, DESPR, presented a keynote presentation to the American Psychiatric Association meeting of Chief Residents in Psychiatry, San Diego, California, October 5, 2005. He also presented a keynote plenary at the South Carolina Community Methamphetamine Summit, Myrtle Beach, South Carolina, November 28, 2005.

Dr. Wilson Compton chaired a plenary symposium on HIV/AIDS at the NIDA Health Disparities Conference-"Bridging Science and Culture", Atlanta, Georgia, October 24, 2005.

Dr. Wilson Compton presented to the Addictions Health Services Research conference on "Future Directions in Health Services Research", Santa Monica, California, October 26, 2005.

Dr. Wilson Compton presented to the NIDA meeting, Enhancing Linkages with

the Drug Abuse Treatment System: The Role of Faith Leaders, Communities, and Organizations, Bethesda, Maryland, November 1, 2005.

Dr. Wilson Compton presented to the ECRI Conference on Opioids and Pain, November 3, 2005.

Dr. Wilson Compton presented at the American College on Neuropychopharmacology (ACNP) a poster on Pain and Opioid Abuse, Kailua, Hawaii, December 12, 2005.

Dr. Elizabeth Robertson, DESPR, is the NIDA representative to the State Prevention Framework - State Incentive Grant Internal Workgroup on Evaluation. On September 28, 2005, she addressed the program evaluators from the 27 participating states and territories on developing and using community level instruments for evaluation.

Drs. Elizabeth Ginexi, Eve Reider and Elizabeth Robertson, all of DESPR, attended a conference on substance abuse and foster care from September 14-16, 2005, in Eugene, OR. They also conducted multiple site visits with prevention projects housed at the Oregon Social Learning Center and Oregon Research Institute.

Dr. Elizabeth Robertson is the NIDA representative to the State Prevention Framework - State Incentive Grant Evidence-based workgroup. The group is in the process of writing a document for use by states and communities on assessing the evidence for prevention programs, policies and practices.

Dr. Shakeh Kaftarian, Prevention Research Branch, DESPR, was invited by Vanderbilt University to be a guest speaker for the "Interdisciplinary Colloquium Series: Teaching and Conducting Community-based Participatory Research" attended by faculty, administrators and graduate students. Her two presentations were titled: "Participatory Research and Empowerment Evaluation Approaches" and "Funding Opportunities at the National Institute on Drug Abuse for Community-based Participatory Research." Dr. Kaftarian also consulted with graduate students and faculty interested in training and grant opportunities at NIDA.

Dr. Eve Reider chaired a panel on October 26, 2005 at Johns Hopkins University at the meeting New Directions for Mental Health and Drug Abuse Effectiveness and Dissemination Trial Research and Methodology. The panel title was From Efficacy to Practice in the Child Welfare System: Methodologic and Logistic Challenges.

At NIDA's recent "Bridging Science and Culture" meeting in Atlanta, GA, October 24 - 26, 2005, Dr. Jessica Campbell represented DESPR's Epidemiology Research Branch and moderated a session on "Drug Abuse Research in Minority Communities: Focus on Youth."

Dr. Peter Hartsock, DESPR, participated with NIDA Grantee Dr. Andrei Kozlov in the National Library of Medicine's "Global Health Histories Conference," November 3-5, 2005, in Bethesda, MD.

Dr. Peter Hartsock met on October 13, 2005 with the founding faculty of the new University School of Public Health and scientists from the NASA Goddard Space Flight Center, in College Park, MD, to discuss research plans involving remote sensing and monitoring of opiate cultivation, trade routes, and the correspondence between trade routes and the spread of HIV.

Dr. Peter Hartsock attended the symposium, "Approaches of Clinical Research in Disaster and Defense Medicine," in Washington, D.C., on October 18, 2005. The meeting was sponsored by the Department of Defense and NATO.

Dr. Peter Hartsock participated in a round-table discussion with Russian drug

abuse researchers during the Conference of the U.S. Society of Neuroscience, in Washington, D.C., on November 14, 2005.

Drs. Cartwright, Chandler, Denisco, Hilton, Jones, Flanzer, and Pringle, all of DESPR, provided technical assistance at a workshop held to assist eligible applicants in developing and submitting their proposals for RFA #06-001, Enhancing Practice Improvement in Community-Based Care for Prevention and Treatment of Drug Abuse or Co-Occurring Drug Abuse and Mental Disorders on Tuesday, October 11, 2005 at the Neuroscience Conference Center.

Dr. William Cartwright, DESPR, advised the SAMHSA/CSAT Evaluation of the Buprenorphine Waiver Program Expert Panel on October 3, 2005.

Dr. Jerry Flanzer, DESPR, presented a paper and moderated a panel at the 2005 Addictions Health Services Research Conference, reviewing findings based on the HIV/AIDS Treatment Adherence, Health Outcomes, and Cost Study, October 26, 2005, Los Angeles, CA.

Dr. Jerry Flanzer spoke about the importance of community based research partnerships at the opening session of the World Conference of Oxford Houses, Alexandria, VA., October 14, 2005.

Dr. Redonna K. Chandler, DESPR, gave the plenary address entitled, Integration Drug Abuse Services into Criminal Justice Settings at the 29th Annual National Conference for the Association for Medical Education & Research in Substance Abuse, Bethesda, MD, October 27, 2005.

Dr. Redonna K. Chandler presented a paper entitled, Data & Safety Monitoring in Clinical Trials in Intervention and Drug Abuse Services Research at the Addiction Health Services Research meeting, Santa Monica, CA, October 25, 2005.

Dr. Redonna K. Chandler, DESPR, presented for the Leadership Plenary: Charting a Collaborative Path to Success at the 12th National TASC Conference, Cleveland, OH, September 13, 2004.

Dr. Thomas Hilton, DESPR, represented NIDA at the initial planning committee meeting for the Government-Wide Conference on Returning Veterans at SAMHSA headquarters in Gaithersburg, MD on September 21, 2005.

Dr. Thomas Hilton attended the 2005 Oxford House World Conference held in Alexandria, VA October 13th -16th 2005 where he participated in a symposium overviewing NIDA-funded research examining the role of Oxford Houses in post-treatment addiction recovery.

Dr. Nicolette Borek, DCNBR, co-chaired a symposium on "The Neurobiology of the Adolescent Brain and Increased Risk for Experimentation", and presented a talk on NIDA research funding opportunities at the "Research Seminar for Early Investigators" at the 52nd annual meeting of the American Academy of Child & Adolescent Psychiatry, October 18-23, 2005 in Toronto.

Dr. Nicolette Borek, DCNBR, participated as a scientific staff collaborator in the Network Meeting of the Adolescent Trials Network for HIV/AIDS Interventions in Rockville, MD, October 25-28, 2005. The ATN is a collaborative network cosponsored by NICHD, NIDA, NIMH, and NIAAA.

Drs. Nicolette Borek, Karen Sirocco, and Vincent Smeriglio of the Behavioral and Brain Development Branch, DCNBR, participated in the Study Assembly Meeting of the National Children's Study (NCS) that was held November 29-30, 2005 in Washington, DC. Entitled "Implementing the National Children's Study: Scientific Progress, Challenges, and Opportunities", the meeting included introduction of the Vanguard Centers and the Coordinating Center of the NCS, as well as several sessions on current implementation issues and future

planning for the NCS.

Dr. Laurence Stanford, DCNBR, participated in the NIH MRI Study of Normal Human Brain Development Annual Workshop on November 17 and 18, 2005. The MRI Study of Normal Human Brain Development is a multi-site project designed to develop a database of the development of human brain and behavior from birth through late adolescence.

Dr. Steven Grant, DCNBR, was a discussant at the first annual conference of the Society for Impulsivity Research held in Washington, DC on November 10, 2005.

Drs. Steven Grant and Harold Gordon staffed the NIDA booth at the Society of Neuroscience meeting in Washington, DC on November 12 -16, 2005.

Dr. Steven Grant represented NIDA at the conference on NeuroAcupuncture in Bethesda, MD, November 17-18, 2005.

Dr. Steven Grant was chair and discussant at a symposium panel titled "What Does Dopamine Say: Clues from Computational Modeling" at the annual meeting of the American College of Neuropsychopharmacology in Waikoloa, Hawaii, December 11-15, 2005. The participants in the symposium were, Read Montague, Baylor University, Paul Glimcher, New York Universty, A. David Redish, University of Minnesota and Jonathan Cohen, Princeton University.

On October 21, 2005, Dr. Melissa W. Racioppo, DCNBR, attended the satellite meeting of the K12-supported trainees sponsored by the American Academy of Child and Adolescent Psychiatry (AACAP). Trainees give bi-annual updates on their progress to the AACAP K12 Executive Committee, and mentors and other presenters offer guidance. Dr. Racioppo presented a brief update on NIDA's program priorities as part of this meeting.

On October 22, 2005, Dr. Melissa W. Racioppo chaired a symposium at the annual meeting of the American Academy of Child and Adolescent Psychiatry (AACAP) entitled "Cutting-Edge Treatments for Adolescent Substance Abuse" in Toronto, Canada. NIDA-funded researchers Ken C. Winters, John R. Knight, Roger A. Roffman, Lynda Stein, and Eric T. Moolchan presented their work on adolescent substance abuse screening, engagement, and treatment.

On October 24th & 25th, 2005, Dr. Cece McNamara Spitznas, DCNBR, gave presentations in a NIDA led grant workshop entitled, "Grant Writing Tips From A NIH Program Official's Perspective" at the NIDA Health Disparities Conference in Atlanta, GA.

On November 9, 2005, Dr. Cece McNamara Spitznas participated as a discussant on Subjective and Objective Measures and PET scanning and Ecological Momentary Assessment for measuring Adverse Events at the NIMH Workshop on Assessing Suicidality During SSRI Antidepressant Treatment in Bethesda, MD.

On November 17, 2005, Dr. Melissa W. Racioppo participated in a panel of Federal grants officers, addressing several special interest groups as part of the annual meeting of the Association for the Advancement of Behavior Therapy (now ABCT) in Washington, D.C. Representatives from NIDA, NIAAA, NIMH, and the Academy for Children and Families spoke with clinical researchers with interests in child maltreatment and neglect, childhood anxiety disorders, and couples and family therapy about Federal funding opportunities.

On November 19 2005, Dr. Lisa Onken, DCNBR, co-chaired a workshop with Dr. Michael Otto, "Writing National Institutes of Health (NIH) Grants: Practical Strategies for Success," at the annual convention of the Association for Behavioral and Cognitive Therapies in Washington, D.C.

Dr. Cora Lee Wetherington, DBNBR and NIDA's Women & Gender Research Coordinator, chaired Session IV: Metabolism and Session V: Hormonal Regulation at the NIH Office of Research on Women's Health meeting, Second Annual Interdisciplinary Women's Health Research Symposium. October 20, 2005, Bethesda, MD.

Dr. Cora Lee Wetherington chaired Sessions III and IV: Interdisciplinary SCOR Presentations, at the NIH Office of Research on Women's Health, Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health: Center Directors Meeting, October 21, 2005, Bethesda, MD.

Dr. Cora Lee Wetherington gave an invited plenary address, "The Pervasiveness of Male-Female Differences in Drug Abuse," at the annual meeting of the International Council on Alcohol and Addictions, Conference on Addictions, October 23-28, 2005, Budapest, Hungary.

Dr. Cora Lee Wetherington gave an invited talk, "Sex/Gender Differences in Drug Abuse and Dependence," at the Health Resource and Services Administration (HRSA), November 9, 2005, Rockville, MD.

Dr. Cora Lee Wetherington was co-facilitator (with Kimberly Yonkers, M.D., Yale University) of the Biological & Developmental Factors Workgroup as part of the working meeting, The Surgeon General's Workshop on Women's Mental Health, November 29-December 1, 2005, Denver, CO.

Dr. David Shurtleff, Director, DBNBR, gave a presentation on "Research Funding Opportunities for Inhalant Abuse Research at NIDA" at the National Institute on Drug Abuse Sponsored Conference: "Inhalant Abuse Among Children: Consultation on Building an International Research Agenda," Rockville, MD, November 7-9, 2005.

Dr. Jonathan D. Pollock, DBNBR, organized and co-chaired a session with Dr. James Kennedy at the World Congress on Psychiatric Genetics, entitled, "Can Genetic Variation Be Imaged? Boston, MA, October 17, 2005.

Dr. Christine Colvis and Dr. Jonathan D. Pollock, DBNBR, co-chaired an invited symposium at the 35th Annual Meeting of the Society for Neuroscience, entitled, " Epigenetic Mechanisms and Gene Networks in the Nervous System. Washington, D.C. November 15, 2005.

Dr. Joni Rutter, DBNBR, chaired the NIDA Genetics Consortium Meeting, November 29-30, 2005. Rockville, MD.

Dr. Jonathan D. Pollock, DBNBR, co-chaired with Dr. Lorna Role (Columbia University College of Physicians and Surgeons) a panel, entitled, "Molecular Mechanisms of Synaptic Alterations Associated with Neuropsychiatric Disorders and Addiction", at the annual meeting of The American College of Neuropsychopharmacology (ACNP), Waikoloa, HI, December 14, 2005.

Dr. Frank Vocci, Director, DPMCDA, spoke on Medications Development Programs at the NIH at the American Clinical Pharmacology Units meeting in Bethesda on October 18, 2005.

Dr. Frank Vocci organized, co-moderated and spoke at the October 27, 2005 evening session of the American Society of Addiction Medicine's State of the Art Conference in Addiction Medicine 2005 in Washington, D.C. The session was titled: An Update on New and Pipeline Anti-Addiction Medications. Speakers and topics were: Dr. Bankole Johnson: Acamprosate and other medications for alcohol addiction and relapse prevention; Dr. Robert Anthenelli: Rimonabant for smoking cessation; Dr. Helen Pettinati: Depot naltrexone: A first in addiction pharmacotherapy; Dr. Ahmed Elkashef: New and promising medications for the treatment of cocaine addiction; and Dr. Frank Vocci: Emerging medications: From the bench to the clinic.

Dr. Frank Vocci presented on New pharmacotherapies for assisting smokers in their cessation efforts at the Increasing Consumer Demand for Cessation Products and Services meeting on December 7, 2005 in Washington, D.C.

Dr. Frank Vocci presented Psychiatry Grand Rounds at the University of Hawaii in Honolulu on December 9, 2005. His presentation was titled: Improving Methamphetamine Treatment Through Cognitive Enhancement and Better Decision-Making. Dr. Vocci also spoke to the Psychiatry residents at the University of Hawaii on December 9, 2005 on neuroimaging technologies (PET/SPECT/MRI).

Dr. Frank Vocci attended the ACNP meeting in Waikoloa, Hawaii. He was a discussant at a panel session titled: Novel Pharmacological Approaches to the Treatment of Drug Addiction: Animal and Human Studies. Drs. Laura Peoples, Bert Weiss, Peter Kalivas, and Charles O'Brien spoke at the session.

Dr. Ivan Montoya, DPMCDA, co-chaired with Mike Sesma from NIMH at Grant Writing workshop at the Latino Mental Health Conference, in Princeton, New Jersey.

Dr. Ivan Montoya participated in the NIMH workshop on Tobacco Use and Cessation in Psychiatric Disorders, in Bethesda, MD.

On October 24, 2005, Dr. Nathan M. Appel of DPMCDA chaired a session entitled "How High, Understanding Addiction" at the Bridging Science & Culture to Improve Drug Abuse Research in Minority Communities conference in Atlanta, GA.

At the invitation of the University of Minnesota School of Medicine, Minneapolis, Center for Infectious Disease and Microbiology Translational Research, Dr. Jag Khalsa, DPMCDA, presented a Seminar on Medical /Clinical Consequences of Drug Abuse and Co-occurring Infections Research, funding opportunities, and possible collaborations at NIDA/NIH on December 21, 2005.

At the invitation of School of Medicine, Ohio State University, Columbus, OH, Dr. Jag Khalsa, DPMCDA, presented a seminar on Medical Consequences of Drug Abuse and Co-occurring Infections (HIV, HCV) and funding opportunities at NIDA. New projects on drug-drug interactions were discussed/planned.

Dr. Amy Newman, IRP, was invited to give a seminar at the NIH/NIDDK Chemistry Interest Group, in Bethesda, September 2005.

Dr. Santosh Kulkarni, IRP, was invited to give a seminar at the Department of Medicinal Chemistry, School of Pharmacy, University of Kansas, November 2005.

Dr. Amy Newman was invited to participate in the American College of Neuropsychopharmacology 44th Annual meeting in Waikoloa, HI, December 2005.

Dr. Eric Moolchan, IRP, gave the following invited talks: Framing the Risk Benefit Ratio of Pharmacotherapy for Treating Adolescent Addiction, Annual Meeting of the American Academy of Child and Adolescent Psychiatry, Toronto, November, 2005; Adolescent Tobacco Addiction: Treatment Relevant Studies for the Addiction Research Foundation Tobacco Transdiciplinary Rounds, Toronto, November, 2005; and Nicotine Replacement and Other Pharmacological Therapies: Focus on Adolescents with Chronic Disorders, St. Jude Hospital Memphis, October, 2005.

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

Media and Education Activities

Press Releases

November 29, 2005 - NIDA Unveils Campaign to Send Teens the Message about the Link between Drug Abuse and HIV.
"Drug Abuse and HIV: Learn the Link" is the message of a new public awareness campaign announced by NIDA. "Drug abuse prevention is HIV prevention," says NIDA Director Dr. Nora D. Volkow. "Research has shown that a significant proportion of young people are not concerned about becoming infected with HIV. In recent years, the number of young people in the United States diagnosed with AIDS rose substantially. Because drug use encourages risky behaviors that can promote HIV transmission, NIDA views drug abuse treatment as essential HIV prevention."

October 28, 2005 - NIDA NewsScan #39 - Special Health Disparities Issue

- Gang Membership, Length of Incarceration Related to Injection Drug Abuse Among Jailed Puerto Rican Drug Injectors
- Abuse of Cocaine, Heroin, and Other Drugs Is a Key Factor in Hispanic Teen Suicide
- Designing Effective Drug Abuse and HIV Preventive Interventions for Hispanic Adolescent Subgroups
- HIV Risk Behaviors Differ Among Homeless Drug Injectors in Puerto Rico
- Bridging Cultural Divides Can Help Achieve Field Research Goals
- Highly Active Antiretroviral Therapy Is an Effective Form of Treatment for Minority Injection Drug Users with Late-Stage HIV
- Depression and Therapy Side Effects May Influence Antiretroviral Adherence in Adolescents with Late-Stage HIV
- Additional Examples from NIDA's Ongoing Research into Health Disparities and Drug Abuse

October 12, 2005 - Motivational Incentive Program is an Effective Treatment for Stimulant Drug Abuse.
The chance to win even small rewards in a prize-based Motivational Incentive program can motivate cocaine and methamphetamine abusers to stay in treatment and be drug-free for a longer period, according to a new study funded by the National Institute on Drug Abuse (NIDA), National Institutes of Health. The study, led by Dr. Nancy Petry of the University of Connecticut School of Medicine and Dr. Maxine Stitzer of Johns Hopkins University School of Medicine, was published in the October 2005 issue of the *Archives of General Psychiatry*.

Staff Highlights

Grantee Honors

October 12, 2005 - NIDA and Scholastic Continue to Reach Tweens with Information About Methamphetamine and Other Drugs.
Through a continuing partnership, NIDA and SCHOLASTIC, the global children's publishing and media company, will distribute information on the health effects of methamphetamine to nearly 2 million middle and high school students and their teachers. Methamphetamine's devastating effects on the brain and body, as well as the environmental and social impact of its manufacture, will be covered in an article in the fall issues for the 2005-6 school year in Scholastic Classroom Magazines' Junior Scholastic®, Science World®, CHOICES®, SCOPE®, ACTION®, and UPFRONT®. Additional articles for the 2005-6 school year will cover inhalants, prescription drugs, and drugs that may be encountered in social settings.

September 8, 2005 - NIDA NewsScan #38 - Special Back-to-School Issue

- New Study Provides Insight to the Human Brain's Response to Methamphetamine Abuse
- Drinking, Drug Abuse Higher in Fraternities and Sororities
- A Healthy Start: Some Parenting Practices May Protect Youth From Early Marijuana Use
- Adolescents Also Can Experience Marijuana Withdrawal Symptoms; Differences In Severity Between Teens, Adults Noted
- Co-Occurring Substance Abuse, Mental Disorders Increase AIDS Risk in Delinquent Youth
- New Research Highlights Patterns of Drug Abuse in Hispanic-American Youth
- Televised Anti-Tobacco Advertising Decreases Smoking in U.S. Youth
- Adolescent Smoking Cessation: Is Motivation Enough?
- Rat Study Shows Isolation During Infancy Causes Brain, Behavioral Responses to Cocaine
- Buprenorphine Is Effective in Treating Opiate Withdrawal in Newborns of Opiate-Addicted Mothers

August 25, 2005 - Researchers Identify a Brain Chemical That Plays a Key Role in Food and Drug-Seeking Behavior.
New research performed in rats suggests that orexin, a brain chemical involved in feeding behavior, arousal, and sleep, also plays a role in reward function and drug-seeking behavior. This study suggests that orexin may be a factor in modulating the reward-seeking characteristic of substance abuse. The findings help to better identify neural pathways involved in drug abuse, craving and relapse, which may ultimately help scientists find more effective therapies. This study was published online August 14, 2005 in the journal Nature.

August 23, 2005 - NIDA NewsScan #37

- Therapists Don't Live By Treatment Manuals Alone
- Mouse Study Reveals Promising Compound for Treating Cocaine Abuse
- Smoking Marijuana Alters Blood Flow in the Brain
- Scientists Modify Fly Behavior Through Remote Control
- Long-Term Methamphetamine Abuse Impairs Selective Inhibition
- Heavy Abuse of Marijuana Linked to Inferior Decision-making Skills, Altered Brain Activity

August 11, 2005 - Methamphetamine Abuse, HIV Infections Cause Changes in Brain Structure.
New research published in the August 2005 issue of the *American Journal of Psychiatry* indicates that methamphetamine abuse and HIV infection cause

significant alterations in the size of certain brain structures and in both cases the changes may be associated with impaired cognitive functions, such as difficulties in learning new information, solving problems, maintaining attention and quickly processing information. Co-occurring methamphetamine abuse and HIV infection appears to result in greater impairment than each condition alone.

Articles of Interest

August 2005, *Ladies Home Journal* - "The Deadliest Drug you've Never Heard Of" - Interview with Joseph Frascella, Ph.D.

December 2, 2005, *The Washington Times* - "Ad Links Teen HIV Infection, Drug Use" - Interview with Donald R. Vereen, M.D.

Dr. Frank Vocci, Director, DPMCDA, was interviewed by Ms. Jane Spencer of the Wall Street Journal on the therapeutic potential of vaccines and monoclonal antibodies in the treatment of addiction on September 15, 2005.

Dr. Frank Vocci was interviewed by Ms. Vicki Brower, a freelance writer, on targets for addiction pharmacotherapies on September 22, 2005.

Dr. Frank Vocci was interviewed by Ms. Rita Rubin of the USA Today staff on medications to treat drug cravings on September 22, 2005.

Dr. Frank Vocci was interviewed by Ms. Ann Stanton, a freelance writer, on the current status of research on Ibogaine as an addiction treatment on November 18, 2005.

Educational Activities

Heads Up: Real News About Drugs and Your Body. Through a continuing partnership, NIDA and SCHOLASTIC INC, the global children's publishing and media company, distributed information on the health effects of methamphetamine to nearly 2 million students and teachers in grades 5 through 10 nationwide. Methamphetamine's devastating effects on the brain and body, as well as the environmental and social impact of its manufacture, were covered in an article-insert in the first issues for the 2005-2006 school year in October, in Scholastic Classroom Magazines' *Junior Scholastic®, Science World®, CHOICES®, SCOPE®, ACTION®,* and *Up Front®*. An article-insert on Inhalants followed in November with the same distribution.

In advance of World AIDS Day, NIDA launched *Drug Abuse and HIV: Learn the Link*, a new awareness campaign about the connection between drug abuse and HIV infection. On Tuesday, November 29, 2005, NIDA launched the new TV public service announcements and conducted a science meeting about the issue. NIDA is building a coalition of partners to help get the message out, with groups such as the American Academy of Child and Adolescent Psychiatry, and the United Negro College Fund, Special Programs Corporation. Besides distributing the spots to television stations around the country, NIDA approached movie theaters, film festivals, niche markets, public transit systems, and other commercial outlets asking them to air the ads, especially around World AIDS Day. For more information about the campaign, go to www.hiv.drugabuse.gov.

NIDA Free Post Card Program. From December 1 (World AIDS Day) through December 31, 2005 NIDA's latest HIV/AIDS awareness post cards were distributed to the general public in free venues nationwide. More than 300,000 cards went to 12 cities with the highest population of teens: Washington, DC; Atlanta, GA; Los Angeles, CA; San Francisco, CA; New York City; Chicago, IL; Philadelphia, PA; Dallas, TX; Columbus, OH; Miami, FL; Boston, MA; and

Detroit, MI. Most distribution sites included movie theaters, pizza parlors, arcades, and skating rinks.

Brain Power! The NIDA Junior Scientists Program for kindergarten and first grade has been selected as a winner in the 2005 National Health Information Awards honoring the Nation's Best Consumer Health Information Programs and Materials. In May and June, more than 1,000 entries for the 12th annual National Health Information Awards were judged by a specially selected panel of health information experts. Entries were grouped and judged by Class, Division, and Category, with the target audience noted. Using a rating scale of one to 100, each judge evaluated entries for health information content, creativity, and overall excellence. The scores were then totaled and averaged. Gold, Silver, Bronze, and Merit Certificates were awarded on the basis of these averaged scores. Brain Power! won a Gold Award. This recognition program is organized by the Health Information Resource Center, a national professional clearinghouse for consumer health information. You can find more information about this program by visiting www.healthawards.com.

NIDA has just released the latest in our Brain Power series, a comprehensive educational curriculum on drugs and the brain for 4-5th grade students and teachers, entitled Brain Power! The NIDA Junior Scientists Program: Grades 4-5, this curriculum follows the successful similar materials developed for grades K-1 and 2-3. NIDA is currently working on a similar program for middle school students.

CTN-Related Media and Education Activities

On September 13, 2005, Dr. Dennis Dixon, Mathematical Statistician at NIAID and President, Society for Clinical Trials, was invited to present the CCTN Classroom Series. The topic was *"Discussion on Clinical Trials and the Definition of Efficacy vs. Effectiveness as Related to Clinical Research."*

The CCTN in collaboration with the CTN Clinical Coordinating Center (EMMES) has created a web version of GCP training. The program is available on-line for all CTN staff that need training or refresher courses in GCP topics. This training consists of 12 modules, each module taking between 20 and 60 minutes to complete. Questions for each module are listed on the last page of the module.

The New York Node, Long Island Node, Northeast ATTC, and New York Office of Alcohol, Substance Abuse Services sponsored a conference entitled, "Bringing Contingency Management (CM) to Clinics" on October 18, 2005 in New York City. This free conference was targeted at helping clinicians to implement contingency management in their clinics.

Training on the Comprehensive Adolescent Severity Index (CASI) was held in Rockville, MD on October 17-18, 2005. Dr. Kathy Meyers, who developed the measure, led the sessions.

On November 8, 2005, Dr. Carl Pieper, Assistant Research Professor, Department of Biometry and Bioinformatics, Duke University, presented in the CCTN Classroom Series on "Large-Scale Simple Trials: Implications for Clinical Research".

The CTN Clinical Coordinating Center (EMMES Corp.) arranged for National Risk Behaviors Survey (RBS) training for interviewers on November 16, 2005. This event was open to all staff across the CTN.

Addiction Severity Index (ASI) interviewer training was held in Gaithersburg on December 13 and 14, 2005.

Conferences/Exhibits

Latino Behavioral Health Institute 11th Annual Meeting -- September 20-22,

2005

American Academy of Pediatrics National Conference and Exhibition -- October 8-11, 2005

Employee Assistance Professionals Association Annual Conference -- October 15-17, 2005

American Academy of Child and Adolescent Psychiatry -- October 18-23, 2005

American School Health Association Annual Conference -- October 19-23, 2005

Bridging Science & Culture to Improve Drug Abuse Research in Minority Communities -- October 24-26, 2005

American Public Health Association Annual Meeting and Exposition -- November 5-9, 2005

National Association for the Education of Young Children -- December 7-10, 2005

Society for Social Work and Research -- January 12-15, 2006

Community Anti-Drug Coalitions of America -- February 14-16, 2006

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Planned Meetings

NIDA is planning to hold a large conference on **Drug Abuse and HIV/AIDS** on September 25, 2006 in Bethesda, Maryland. This meeting will bring together leading researchers in the field with the intention of drawing attention to multiple links between drug abuse and HIV/AIDS.

Yonette Thomas, Ph.D., Chief of DESPR's Epidemiology Research Branch, and Douglas Richardson, Ph.D., Executive Director of the Association of American Geographers (AAG), are planning a symposium on **Geography and Addiction**, to be held March 8, 2006 in conjunction with the 2006 Annual Meeting of the AAG in Chicago, Illinois. The NIDA-AAG sponsored research symposium is an opportunity for medical researchers, epidemiologists, geographers, and others interested in geographical dimensions of drug addiction to address such themes as spatial patterns of drug use and addiction, interactions of social and environmental factors with biochemical processes of addiction, the use of GIS to better understand and respond to patterns of drug use and addiction, spatial diffusion modeling of addictive drug use and its changing characteristics, including predictive modeling, and much more.

A NIDA sponsored symposium entitled **Adolescent Brain Development: Implications for Psychiatric Treatment** has been accepted in the program for the American Psychiatric Association's Annual Meeting in Toronto, Ontario during May of 2006. The session will be chaired by Minda Lynch (BCSRB/DBNBR), with introductory remarks from David Shurtleff (OD/DBNBR). Larry Stanford (OD/DCNBR) will be the discussant. Speakers will discuss the prolonged maturation of frontal regions involved in decision making, judgment, and complex cognitive processes of executive function and attention. Neurobehavioral development in emotional regulation, behavioral inhibition, risk assessment, and the influence of "hot" and "cold" states of emotional arousal will be considered for potential clinical implications. Speakers include Drs. Ronald Dahl, Leslie Jacobsen, Isabelle Rosso and Bea Luna.

A NIDA sponsored meeting entitled **National Cooperative Drug Discovery Groups for Nicotine Addiction - A Synthesis Meeting** will be held on Feb 15, 2006 as a satellite to the Society for Research on Nicotine and Tobacco's Annual Meeting in Orlando, Florida. The meeting will be chaired by Dr. William Corrigall (NIDA consultant), with introductory remarks by Drs. David Shurtleff (OD/DBNBR), and Allison Chausmer (BCSRB/DBNBR). Dr. Frank Vocci (OD/DPMCDA) will serve as a discussant. This NIDA-sponsored meeting will highlight research funded under the National Cooperative Drug Discovery Groups (NCDDG) initiative, which focuses on the need for mechanism-of-action based medications in nicotine addiction, for molecular tools for discovery research, and to facilitate partnerships between academic and pharmaceutical industry groups. Speakers include Drs. Linda Dwoskin, Maurizio Fava, Athina Markou, Frank I. Carroll, Palmer Taylor and Henry Lester.

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Dr. Susan Volman, DBNBR, will chair a NIDA-sponsored symposium entitled **Neurobiological Basis for Co-Occuring Substance Abuse and Other Psychiatric Disorders** that has been accepted in the program for the American Psychiatric Association's Annual Meeting in Toronto, Ontario during May of 2006. The presentations will include human clinical and genetic studies and research using recently developed animal models of psychiatric illness that seek a neurobiological understanding for the high prevalence of concurrent substance abuse and other psychiatric disorders. Discussion will focus on how a better biological understanding could lead to improved treatment of dual-diagnosis disorders.

On March 26 - 29, 2006, Program Officers from several NIDA Divisions will participate in the Joint Meeting on Adolescent Treatment Effectiveness (JMATE) in Baltimore, MD. Multiple symposia and workshops are planned for this second annual meeting of clinicians and researchers with an interest in adolescent substance abuse treatment.

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

National CTN Steering Committee Meetings are planned for the following dates and locations: March 20-23, 2006, in Dallas, Texas, and October 2006 in Seattle, Washington.

The CTN has three invited sessions for the 27th Annual Meeting of the Society for Clinical Trials May 21-24, 2006, in Orlando, Florida: 1) **Analytical Issues Unique to Multi-Site Trials: Which Are Resolved and Which Are Still Controversial?**; 2) **Group Therapeutic Interventions for Drug Dependence and Mental Health: What questions to ask and how to design trials to answer them?**; and 3) **a workshop on Clinical Trials Networks**.

Two CTN workshops will be held at the College on Problems of Drug Dependence (CPDD) Annual Meeting June 17-22, 2006, in Scottsdale, AZ. The workshops are entitled, 1) **HIV/AIDS Research in the NIDA Clinical Trials Network: Emerging Results**, and 2) **Addressing Health Disparities Research in the CTN**.

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Publications

The Cell Biology of Addiction Eds. Bertha K. Madras, Christine M. Colvis, Jonathan D. Pollock, Joni L. Rutter, David Shurtleff, and Mark Von Zastrow, Cold Spring Harbor Laboratory Press. Cold Spring Harbor, NY, 2006.

NIDA Publications

Epidemiologic Trends in Drug Abuse - Community Epidemiology Work Group - Advance Report - June 2005
NIH Pub. No.: 06-5280A
The report provides descriptive information on the most recent significant trends, emerging problems and populations at risk.

Epidemiologic Trends in Drug Abuse - Community Epidemiology Work Group - Volume I - June 2005
NIH Pub. No.:06-5281A
This report provides an ongoing assessment of drug abuse in major metropolitan areas of the United States with the purpose of keeping both public and private sector policymakers and researchers informed with current and accurate data.

Epidemiologic Trends in Drug Abuse - Community Epidemiology Work Group - Volume II - June 2005
NIH Pub. No. 06-5282A
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 Science & Practice Perspectives, Volume 3, Number 1
NIH Pub. No.: 06-5768
In this issue, the journal offers Research Reviews on the neurobiology of cocaine addiction and on the common co-occurrence of mood disorders and substance abuse disorders. The issue's two Clinical Perspectives present a veteran clinician's reflections on the status of methadone treatment 40 years after it was introduced and a summary of the broad array of institutional and individual stakeholders in one well-established Oregon treatment program. Also featured is a multi-voiced narrative of a research-practice collaboration between researchers at RAND Corporation and the community treatment providers at Behavioral Health Services in Los Angeles.

Monitoring the Future National Survey Results on Drug Use, 1975-2004: Volume I Secondary School Students 2004
NIH Pub. No. 05-5727
This annual monograph reports the prevalence of drug use among American

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secondary students (specifically 8th, 10th and 12th graders). The trends are used for understanding the changing drug abuse problems and for formulating the appropriate intervention (prevention/treatment) policies.

Monitoring the Future National Survey Results on Drug Use, 1975-2004: Volume II College Students and Young Adults Ages 19-45, 2004
NIH Pub. No. 05-5728
This annual monograph reports trends in drug use by populations based on gender, college plans, regions of the country, population density, race/ethnicity, and parents' education. The trends are used for understanding the changing drug abuse problems and for formulating the appropriate intervention (prevention/treatment) policies.

NIDA Notes

NIDA Notes Volume 20 Issue No. 3 (Archives)
NIH Pub. No. 05-3478
NCADI #NN0077
The Director's Column addresses the alarming upward trend of inhalant abuse among teenagers. Even though the level of overall drug abuse among teenagers has declined, according to the Monitoring the Future survey, inhalant abuse is a notable exception. In the past 2 years, the percentage of eighth-graders who have abused inhalants even once has increased to 17.3 percent. To help parents spot the signs of abuse and get the information and help they need, NIDA has created a new website devoted to the dangers of inhalants: http//inhalants.drugabuse.gov. The site offers readers science-based information on inhalant abuse so that adults can learn the facts and communicate with children in a way that guides them toward healthy life choices. In addition, NIDA joined leaders of the Community Anti-Coalitions of America to discuss the magnitude of youth inhalant abuse, and participated in the National Inhalant Prevention Coalition's National "Inhalants & Poisons Awareness Week" in March of this year.

The lead story is an analysis of the cost-effectiveness of expanded HIV testing on a routine basis in outpatient health care settings, and a comparison of the costs with other routine health tests. Drs. Gillian Sanders and A. David Paltiel used computer models to determine whether it would be cost-effective to extend routine voluntary screening to subpopulations with a moderate prevalence of infection, or to the whole population. The study updates previous models by incorporating the use of state-of-the-art antiretroviral treatment for HIV. The analysis found that the cost-effectiveness of a one-time HIV test was about $15,078 for every year of life gained in a hypothetical population, taking reduced transmission to partners into account; when compared with the cost-effectiveness of other routine tests, such as mammograms or colon cancer tests, the HIV testing was considerably less expensive. When the researchers then compared current practice with routine voluntary HIV testing among populations with varying prevalences of HIV infection, they concluded that voluntary testing every 3 to 5 years in all populations except those with the lowest prevalence would increase survival at a comparatively attractive cost by U.S. standards.

Other research findings include:

- NIDA-supported investigators have identified a pair of proteins, called thrombospondins, that direct the formation of synapses-the cell-to-cell connections that control the flow of information through the brain. Addictive drugs disrupt communication in the brain in part by altering the synapses. Understanding how thrombospondins contribute to synapse formation may lead to improved treatment for drug addiction, which is characterized in part by an excess of synapses in the brain.
- A single meeting with a peer addiction counselor during a routine medical visit has been shown to help out-of-treatment cocaine and opiate abusers

Staff Highlights

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attain abstinence. A study conducted at three Boston clinics revealed that a motivational interview conducted by individuals from the same ethnically mixed communities as the drug abusers helped more abusers remain abstinent from cocaine and opiates than those who simply received printed information on how to seek treatment. A similar percentage from both groups sought drug treatment in the six months after the encounters, thus the higher rates of abstinence among the group who received the interview suggests that the interview itself is beneficial, not simply a means to get abusers into treatment.

- New evidence shows that acetaldehyde, a chemical constituent of tobacco smoke, is a factor in the heightened vulnerability of adolescents to tobacco addiction. A NIDA-supported animal study showed that the combination of acetaldehyde and nicotine had a stronger reinforcing effect on adolescent rats than on adult rats, and a stronger effect than either acetaldehyde or nicotine alone. By testing rats of various ages in self- administration of nicotine, acetaldehyde, a combination of the two, or saline researchers found that the youngest rats demonstrated the greatest preference for the combination, and that this preference diminished with age.

The Bulletin Board covers the results of the 9th annual PRISM Awards, which aired September 4 on the FX cable channel. The movie Ray won the award in the wide release feature film category for its realistic portrayal of singer Ray Charles's drug abuse. Jamie Foxx won for his performance in the film's title role. Another Bulletin Board reports on NIDA Director Dr. Nora D. Volkow's discussion on drugs and crime in a Capitol Hill briefing sponsored by the Friends of NIDA, a coalition of private-sector organizations in the drug abuse field that support NIDA's mission. The Tearoff highlights NIDA's website on HIV/AIDS and drug abuse, hiv.drugabuse.gov.

CTN-Related Publications

Two MIEDAR papers have recently been accepted for publication from the CTN 0006 and 0007 (Motivational Incentives in Drug Free and Methadone Clinics) studies: Accepted in *Archives of General Psychiatry* - J. Peirce et al. "Lower Cost Incentives Increase Stimulant Abstinence in Methadone Maintenance Treatment" accepted by *American Journal of Psychiatry* - J. Roll et al. "Contingency Management for the Treatment of Methamphetamine Use Disorders".

Nancy Petry, Jessica Peirce, Maxine Stitzer, Jack Blaine, et al., "Prize-Based Incentives Improve Outcomes of Stimulant Abusers in Outpatient Psychosocial Treatment Programs: A National Drug Abuse Treatment Clinical Trials Network Study," published in the *Archives of General Psychiatry*, October 5, 2005 edition. This paper presents the primary outcome of CTN 0006.

Kathleen Carroll, Samuel Ball, Charla Nich, et al., "Motivational Interviewing to Improve Treatment Engagement and Outcome in Individuals Seeking Treatment for Substance Abuse: A Multisite Effectiveness Study", to be published in *Drug and Alcohol Dependence*, (available online September 28, 2005). This paper presents the primary outcome of CTN 0005.

During the months August - December, 2005, eight editions of the CTN Bulletin Board were distributed. The Bulletin Board is an electronic report on the progress of the protocols, committees, and node activity in the CTN.

A patient recruitment brochure was translated to Spanish and submitted for approval for CTN Protocol - Brief Strategic Family Therapy (CTN-0014) for distribution throughout the Network.

A patient recruitment brochure was developed and submitted for approval for CTN Protocol - Smoking Cessation Study for Smokers with ADHD (CTN-0029)

for distribution throughout the Network.

A patient recruitment brochure was developed and is pending submission for CTN Protocol - Randomized Control Trial for ADHD in Adolescents with Substance Use Disorders (CTN-0028).

A pamphlet listing General Interviewing Guidelines for CTN clinical staff was developed and is pending submission for approval before distribution throughout the Network.

International Program E-News Letter

The NIDA International Program issues an E-News Letter every other month to inform the international drug abuse research community about recent events, funding opportunities, NIDA's research training and exchange programs for international scientists, and forthcoming meetings.

- October 2005 - This issue reported on the reissued Program Announcement supporting International Research Collaboration on Drug Addiction, PA-05-050; the NIDA Director's Seminar featuring the Foresight Brain Science, Addiction and Drugs Project; and announced the abstract deadlines for the 2006 NIDA International Forum.
- December 2006 - This issue reported on the inhalant abuse meeting cosponsored in November by the NIDA International Program, the Fogarty International Center, and partner agencies in Canada and Mexico.

Other Publications

Colvis, C.M., Pollock, J.D., Goodman, RH., Impey, S., Dunn, J., Mandel, G., Champagne, F.A., Mayford, M., Korzus, E., Kumar, A., Renthal, W., Theobald, D.E. and Nestler, E.J. Epigenetic Mechanisms and Gene Networks in the Nervous System. J Neurosci. 25(45), pp. 10379-10389, November 9, 2005.

Beatty, L., Jones, D. and Doctor, L. (Eds.) Reducing HIV/AIDS and Criminal Justice Involvement in African Americans as a Consequence of Drug Abuse. Journal of Health Care for the Poor and Undeserved, 16, 4 (Supplement B), 2005.

Montoya, I.D., Herbeck, D.M., Svikis, D S. and Pincus, H.A. Identification and Treatment of Patients with Nicotine Problems in Routine Clinical Psychiatry Practice. Am. J.Addict., 14, pp. 441-454, 2005.

Vocci, F. and Ling, W. Medications Development: Successes and Challenges. Pharmacology and Therapeutics 108, pp. 94-108, 2005. This publication was part of a special issue devoted to medications development for addictive disorders. Dr. Vocci served as the guest editor for the issue.

Compton, W.M., Stein, J.B., Robertson, E.B., Pintello, D., Pringle, B. and Volkow, N.D. Charting A Course for Health Services Research at the National Institute on Drug Abuse. Journal of Substance Abuse Treatment 29(3), pp. 167-172, 2005.

Compton, W.M., Thomas, Y., Conway, K.P. and Colliver, J.D. Developments in the Epidemiology of Drug Use and Drug Use Disorders. American Journal of Psychiatry 162(8), pp. 1494-1502, 2005.

Compton, W.M. Applying A Public Health Approach To Drug Abuse Research. Journal of Drug Issues 35(3), pp. 461-468, 2005.

Compton, W.M., Conway, K.P., Stinson, F.S., Colliver, J.D. and Grant, B.F. Prevalence and Comorbidity of DSM-IV Antisocial Personality Syndromes and Specific Substance Use Disorders in the United States: Results from the

National Epidemiologic Survey on Alcohol and Related Conditions. Journal of Clinical Psychiatry 66(6), pp. 677-685, 2005.

Compton, W.M. and Volkow ND. Major Increases in Opioid Analgesic Abuse: Concerns and Strategies. Drug and Alcohol Dependence 81(2), pp. 103-107, 2006. (e-pub July 14, 2005.)

Desai, R., Kopajtic, T., French, D., Newman, A.H. and Katz, J.L. Relationship Between In Vivo Occupancy at the Dopamine Transporter and Behavioral Effects of Cocaine, GBR 12909 and Benztropine Analogues. J. Pharmacol. Exp. Ther. 315, pp. 397-404, 2005.

Campbell, V.C., Kopajtic, T.A., Newman, A.H. and Katz, J.L. Assessment of the Influence of Histaminergic Actions on Cocaine-like Effects of 3a-Diphenylmethoxytropane Analogues. J. Pharmacol. Exp. Ther. 315, pp. 631-640, 2005.

Xi, Z.-X, Newman A.H., Gilbert, J.G., Pak, A.C., Peng, X.-Q., Ashby, C.A., Gitajn, L. and Gardner, E.L. The Novel Dopamine D3 Receptor Antagonist NGB 2904 Inhibits Cocaine's Rewarding Effects and Cocaine-induced Reinstatement of Drug Seeking Behavior in Rats. Neuropsychopharmacology pp. 1-13, 2005.

Grundt, P., Kopajtic, T., Katz, J.L. and Newman, A.H. N-8-Substituted-Benztropinamine Analogs as Selective Dopamine Transporter Ligands. Bioorg. Med. Chem. Lett. 15, pp. 5419-5423, 2005.

Collins, C.C. and Moolchan, E.T. Shorter Time to First Cigarette of the Day in Menthol Adolescent Cigarette Smokers. Addict Behav. November 19, 2005 [Epub ahead of print].

Kacinko, S.L., Barnes, A.J., Schwilke, E.W., Cone, E.J., Moolchan, E.T. and Huestis, M.A. Disposition of Cocaine and its Metabolites in Human Sweat after Controlled Cocaine Administration. Clin Chem. 51(11), pp. 2085-2094, November 2005. Epub September 15, 2005.

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

Staff Highlights

Honors and Awards

The following awards were bestowed on NIDA staff members at NIDA's Annual Awards Ceremony held October 31, 2005.

NIDA DIRECTOR'S AWARD OF MERIT

Carol Cushing, CCTN
Carmen L. Rosa, CCTN
Christie Baxter, DBNBR
Allison Chausmer, DBNBR
Jonathan Pollock, DBNBR
Rao Rapaka, DBNBR
Joyce Williams, DBNBR
Melissa W. Racioppo, DCNBR
Redonna Chandler, DESPR
Elizabeth M. Ginexi, DESPR
Bennett Fletcher, DESPR
Dionne Jones, DESPR
Elizabeth Y. Lambert, DESPR
Moira O'Brien, DESPR
Eve E. Reider, DESPR
Larry A. Seitz, DESPR
Amrat Patel, DPMCDA
Satoshi Ikemoto, IRP
Susan Schlossberg, OD
Linda B. Thomas, OD
Mark Green, OEA
Rita Liu, OEA
Pamela Stokes, OEA
Dave S. Daubert, OPRM
Michael Wright, OPRM
Gayathri Dowling, OSPC
Geoffrey Laredo, OSPC
Jan Lipkin, OSPC
Lucinda Miner, OSPC
Michelle Person, OSPC
Sara Rosario Wilson, OSPC
Susan Weiss, OSPC
Pamela Goodlow, SPO

Group Award: CTN Coordinating Centers Team
Carol A. Cushing, CCTN
Kenneth Goodling, OPRM
Pedro Godinez, OA
Nancy Hurd, OPRM
Diane Loeb, OPRM
Jeng-Jong Pan, CCTN
Paul G. Wakim, CCTN

Group Award: NIH Blueprint Neuroscience Information Framework Group
Nancy Hurd, OPRM
Diane Loeb, OPRM
Karen Skinner, DBNBR
Eric Zatman, OPRM

Group Award: NIH Genetics

Group Award: NIDA's Neuroscience Consortium
Jane Acri
Tom Aigner
Nathan Appel
Kursheed Ashgar
Lula Beatty
Loretta Beuchert
Nicolett Borek
Allison Chausmer
Christine Colvis
Hirsch Davis
Lynda Erinoff
Joseph Frascella
Jerry Frankenheim
Harold Gordon
Pamela Goodlow
Stephen Gust

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Consortium (NGC) Retreat
Kevin Conway, DCNBR
Jim Glass, DPMDCA
Joni Rutter, DBNBR
Kay Wanke, NCI

Group Award: DESPR Genetic Epidemiology Portfolio Review Team
Naimah Weinberg, DESPR
Kevin P. Conway, DCNBR

Group Award: DESPR Health Disparities Workgroup
Jessica Campbell, DESPR
William Cartwright, DESPR
Aria Crump, DESPR
Dionne Jones, DESPR

Group Award: DESPR HIV/AIDS Workgr
Jessica Campbell, DESPR
Jerry Flanzer, DESPR
Dionne Jones, DESPR
Elizabeth Lambert, DESPR
Eve Reider, DESPR

Group Award: RTX Development Project Team
Roberta Kahn, DPMCDA
James B. Terrill, DPMCDA

Group Award: Molecular Neurobiology Human Genetics Workgroup
Tomas Drgon, IRP
Catherine Johnson, IRP
Qing Rong Liu, IRP
George R. Uhl, IRP
Donna M. Walther, IRP

Group Award: (APA) Planning Team
Meyer Glantz, DESPR
Lula Beatty, SPO
Teresa Levitin, OEA
Minda Lynch, DBNBR
Lisa Onken, DCNBR
Kenzie Preston, IRP
Melissa Racioppo, DCNBR
David Shurtleff, DBNBR
Cora Lee Wetherington, DBNBR
Jane Smither, OSPC

Group Award: Blending Conference Planning Team
Timothy Condon, OD/OSPC
Suman Rao King, OSPC
Jan Lipkin, OSPC
Lucinda Miner, OSPC
Michelle Person, OSPC
Denise Pintello, OSPC
Jane Smither, OSPC
Susan Weiss, OSPC
Sara Rosario Wilson, OSPC
Steven Grant
Monica Jones
Barbara Hermn
Geraline Lin
Cheryl Kassed
Rita Liu
Yu Lin
Minda Lynch
David McCann
Lucinda Miner
Mary Ellen Michel
Joan Nolan
Nancy Pilotte
Jonathan Pollock
Rao Rapaka
Cathrine Sasek
Paul Schnur
David Shurtleff
Hari Singh
Laurence Stanford
Pushpa Thadani
David Thomas
Susan Volman
Deborah Wertz
Susan Weiss
Cora Lee Wetherington
Joyce Williams
Berhane Yitbarek

Group Award: The African American Initiative Committee
Lula Beatty, SPO
Jean Lud Cadet, IRP
Redonna Chandler, DESPR
Gayathri Dowling, OSPC
Dionne Jones, DESPR
Steven Oversby, DPMCDA
Carmen Rosa, CCTN
Paul Schnur, DBNBR
Don Vereen, OD

Nominated by *NIDA DIRECTOR for* Katrina Awards
Volunteer Service
Janice Carico, IRP
Redonna Chandler, DESPR
Betty Jo Salmeron, IRP
Edwina Smith, IRP

Deployed
Ivan Montoya, DPMCDA

Volunteer Jerry Flanzer, DESPR

EEO Awards
Allison Chausmer, DBNBR
Aria Crump, DESPR
Stacy Gardner, OPRM
John Hamill, OPRM
Hari H. Singh, DBNBR

Staff Highlights

Grantee Honors

Group Award: Blueprint Research Training Team Beth Babecki, DBNBR Allison Chausme, DBNBR Gayathri Dowling, OSPC Steven Grant, DCNBR Suman Rao King, OSPC Teresa Levitin, OEA Charles Sharp, DBNBR David Shurtleff, DBNBR Karen Skinner, DBNBR Laurence Stanford, DCNBR Susan Volman, DBNBR Susan Weiss, OSPC	

COMMISSIONED CORPS AWARDS

The Achievement Medal
CAPTAIN Anthony J. Brooks, IRP
COMANDER Paul J. Na, IRP

LENGTH OF SERVICE AWARDS

30 Year Length of Service
Patricia A. Ballerstadt, IRP
Thomas F. Hilton, DESPR
Donna M. Jones, OPRM
Teresa E. Levitin, OEA
Marguerite M. Lewis, OPRM
Tina McDonald-Bennett, OPRM

40 Year Length of Service
Helen K. Cesari, OSPC
Nancy A. Hurd, OPRM

Dr. Thomas F. Hilton of the Services Research Branch, DESPR, attended a reception in his honor hosted by the University of Georgetown International School of Public Health on September 15, 2005, in recognition of his mentorship of international students on the development and administration of substance abuse health services research programs.

Dr. Redonna K. Chandler, DESPR was deployed to New Orleans, LA, September 19 - October 1, 2005 to provide mental health support to first responders as part of the NIH response to Hurricane Katrina.

Dr. Teruo Hayashi, IRP, was the recipient of 2005 Sarai Award sponsored by Kyumon-kai, Hiroshima, Japan.

Dr. Amy Newman, IRP, filed the following patent on August 24, 2005. Newman, A.H., Zou, M-F. and Katz, J.L. N- and 2-Substituted Benztropines as Therapeutic Agents for CNS Disorders.

Staff Changes

Dr. Kevin P. Conway joined the Division of Clinical Neuroscience and Behavioral Research (DCNBR) as Associate Director in October 2005. Dr. Conway comes to DCNBR from the Epidemiology Research Branch, Division of Epidemiology, Services, and Prevention Research (NIDA), where he served as a Program Director and as the Deputy Branch Chief of Epidemiology Research Branch.

Dr. Karen Sirocco joined the Division of Clinical Neuroscience and Behavioral Research in the Behavioral and Brain Development Branch in October 2005. Dr. Sirocco is a developmental psychologist, and came to NIDA from the NIH Center for Scientific Review (CSR) where she was the chief of the biobehavioral and behavioral processes integrated review group. Prior to joining CSR, Dr. Sirocco spent 10 years in the Laboratory of Clinical Studies, NIAAA, where she was involved in basic and clinical biobehavioral research into the causes, prevention, and treatment of alcoholism.

Jennifer Elcano joined the Science Policy Branch in the Office of Science Policy and Communications in October 2005 as a science writer. For 12 years before coming to NIDA, Ms. Elcano served as president of her small business Elcano Communications, working mainly as a science and marketing writer on Federal Government contracts, including NIDA and other health/science organizations. She has also held writing positions with consulting firms and communications magazines, and served a stint with the U.S. Resolution Trust Corporation in the 1990's. Ms. Elcano, has a masters degree in English-Professional Writing and Editing, and, with her partners, has developed, and is preparing to publish, a writing curriculum titled "7 Steps to Better Writing." She is a singer-songwriter in her other life and performs with several groups in the area.

Harold I. Perl, Ph.D. recently joined the CCTN as Senior Team Leader for Behavioral and Social Science, which includes behavior therapy research, dissemination, and training. Previously, he had been on staff of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) for 16 years, where he helped establish NIAAA's Health Services Research Branch and subsequently became its Branch Chief in 2001. At NIAAA, Dr. Perl developed and managed programs that focused on alcohol-related health services research, the incorporation of screening and brief interventions for alcohol problems in medical care settings, community-based research demonstrations for treating homeless persons with alcohol and drug abuse problems, and, most recently, the dissemination and implementation of scientific findings into real-world practice. Prior to coming to NIAAA, Dr. Perl served as Program Director of the Prevention Research Center in the Department of Mental Hygiene at the Johns Hopkins University School of Hygiene and Public Health. Dr. Perl earned a doctorate in Clinical/Community Psychology from the University of Maryland and has maintained a clinical practice since 1988.

Raul Mandler, M.D. was recently appointed as senior medical officer for the CCTN. Dr. Mandler came from George Washington University where he had been a professor of Neurology and Neurosurgery since 1999. He was trained in neurology at the Cleveland Clinic and in neuroscience at NINDS IRP through the 1980's. He is certified in Neurology from the American Board of Psychiatry and Neurology and a Fellow of the American Neurological Association and American Academy of Neurology. Dr. Mandler was an awardee of many NIH grants, including a 5-year grant for the study of basic neurobiology of ALS, and clinical studies in multiple sclerosis, peripheral neuropathies and neurological complications of infections. His expertise and experience in basic neuroscience and clinical aspects of neuro-inflammatory disorders will definitely enrich the CCTN program. One specific area he will be involved in is HIV/HCV, which is a serious co-morbid infectious disease in the substance abuse patient population. He is the CCTN's representative in NIDA's genetic workgroup. In addition, his clinical experience with many of the neuroleptic medications will contribute to future medications trials for stimulant abusers.

Murat Oz, Ph.D. Oz recently joined OEA as a Scientific Review Administrator (SRA). He comes to OEA from NIDA's intramural program, where he studied the effects of drugs of abuse on neurotransmitter-gated ion channels and cellular excitability. Oz received a medical degree from the University of Ankara, Turkey and a Ph.D. from the Department of Pharmacology, University

of Alberta, Canada. While a postdoctoral researcher at NIAAA, he studied physiological and pharmacological aspects of neurotransmitter-gated ion channels. He joined the NIDA intramural program in 2000 as a Staff Fellow, and his research there has implicated several new molecular targets for drugs of abuse. In his new role as a SRA in the Training and Special Projects Review Branch, Oz will be responsible for a variety of review activities in many scientific areas.

Gerald (Jerry) McLaughlin, Ph.D. joined NIDA in May 2005 as Chief of the Grants Review Branch of the Office of Extramural Affairs. The Grants Review Branch includes the centers, treatment, services and medications development scientific review groups. Jerry was previously a Scientific Review Administrator at the National Institute of Allergy and Infectious Diseases (NIAID), where he helped arrange reviews for many complex grant and contract initiatives during a time of rapid growth and change within NIAID. Jerry also brings extensive experience as an academic, clinical and government scientist, a research and clinical laboratory director, a teacher and an administrator. He was the recipient of grants and contracts from NIH and other federal agencies as well as pharmaceutical and biotechnology companies. As a teacher, he developed and taught classes at undergraduate, graduate and professional levels. Jerry's administrative service has included co-directing clinical laboratories for hospitals as well as academic and society appointments. After academics and before NIH, he worked at a Gaithersburg MD biotechnology company. Jerry's doctoral work was at the University of Iowa, and his postdoctoral positions included a NIH postdoctoral traineeship at Notre Dame and an NSF Research Associate position at Texas A&M University School of Medicine. In his academic positions, including that of Associate Professor/Co-Director of Clinical Laboratories at the Indiana University School of Medicine, Indianapolis, his research led to several improved molecular diagnostics and drugs as well as insights regarding immunity, vaccines, and disease processes.

John Satterlee, Ph.D. joined the Genetics and Molecular Neurobiology Research Branch, DBNBR in November 2005 as program director for the Synaptic Plasticity and Model Organism Genetics Program. Dr. Satterlee received his B.S. in Biology from Cornell University in 1986 and was awarded a Masters in Science Education from Syracuse University in 1987. He then taught high school chemistry for one year. He subsequently became a research specialist in biochemistry and protein chemistry working on fat biosynthetic enzymes at SUNY-Upstate Medical University where he remained until 1991. He subsequently went on to do doctoral work in the Department of Cell and Molecular Biology at the University of Wisconsin-Madison with Dr. Michael Sussman where he was awarded his Ph.D. in 1997 for his work on plant signal transduction and calcium stimulated protein kinases. He then became a postdoctoral fellow at Brandeis University with Dr. Piali Sengupta until 2003. As a post-doctoral fellow he genetically and molecularly identified four genes required for proper development and function of thermosensory neurons in the model animal C. elegans. After completing his post-doctoral work Dr. Satterlee became Co-director of C. elegans Core Facility at Massachusetts General Hospital Cancer Research Center, Harvard Medical School until 2005. As co-director of the C. elegans Core Facility he utilized C. elegans techniques and resources to illuminate a variety of biological processes, including aspects of cancer biology, regulation of the cell cycle, regulation of fat biosynthesis, and neurodegenerative disease.

Michelle Person, NIDA's press officer, left NIDA in December to work with the Office of Justice programs, in the Department of Justice, where she will be working with law enforcement agencies at the state and local level to develop and implement campaigns like the Amber Alert program. In addition, she will have other communications duties such as speechwriting. Michelle joined OSPC six and a half years ago to take on the role of NIDA press officer. Prior to that, she was a press officer at the Federal Trade Commission. During her time here

at OSPC, Michelle has, of course, been involved in all of our outreach initiatives.

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Grantee Honors

Dr. Nicholas S. Ialongo was recently named Professor in the Department of Mental Hygiene at the Johns Hopkins University Bloomberg School of Public Health. Dr. Ialongo is the PI of a NIDA-funded research study titled "Development and Malleability from Childhood to Early Adulthood" which was recently recognized with a MERIT Award from NIDA's Prevention Research Branch, Division of Epidemiology, Services and Prevention Research.

Dr. Sheppard Kellam, American Institutes for Research, was invited to speak at the Helping America's Youth Conference, in October 2005, hosted by First Lady, Laura Bush. The conference focused on best practices for reducing risky behaviors in youth, and promoting successful youth development. Dr. Kellam presented on the Good Behavior Game, a program for first graders, which has demonstrated evidence for reducing risk for substance use and increasing school success.

Dr. J. David Hawkins, University of Washington, was invited to speak at the Helping America's Youth Conference, in October 2005, hosted by First Lady, Laura Bush. The conference focused on best practices for reducing risky behaviors in youth, and promoting successful youth development. Dr. Hawkins presented on principles of successful programs.

Dr. Gene Brody, University of Georgia, Athens, was invited to attend the Helping America's Youth Conference, in October 2005, hosted by First Lady, Laura Bush. The conference focused on best practices for reducing risky behaviors in youth, and promoting successful youth development.

Dr. Mark Greenberg, Pennsylvania State University, was invited to attend the Helping America's Youth Conference, in October 2005, hosted by First Lady, Laura Bush. The conference focused on best practices for reducing risky behaviors in youth, and promoting successful youth development.

Dr. John Reid, Oregon Social Learning Center, was invited to attend the Helping America's Youth Conference, in October 2005, hosted by First Lady, Laura Bush. The conference focused on best practices for reducing risky behaviors in youth, and promoting successful youth development.

Dr. Richard Spoth, Iowa State University, was invited to attend the Helping America's Youth Conference, in October 2005, hosted by First Lady, Laura Bush. The conference focused on best practices for reducing risky behaviors in youth, and promoting successful youth development.

Dr. Linda Dwoskin was named University Research Professor at the University of Kentucky for 2005-2006.

Dr. Julia H. Arnsten was promoted to Chief, Division of General Internal Medicine, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx,

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NY.

Dr. James McKay was promoted to full professor at the University of Pennsylvania.

Dr. Kathleen Brady, PI of the Southern Consortium Node, was recently appointed as the Director of the Medical University of South Carolina's General Clinical Research Center (GCRC) and Associate Dean for Clinical Research.

Dr. Sohee Park has been promoted to full professor at Vanderbilt University.

Virtual Reality Medical Center (PI's Drs. Brenda and Mark Wiederhold) won one year of commercialization support from the National Institutes of Health Commercialization Assistance Program (NIH-CAP), beginning September 2005.

Staff Highlights

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