Director's Report to the National Advisory Council on Drug Abuse - February, 2007

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Director's Report to the National Advisory Council on Drug Abuse - February, 2007

Research Findings - Basic Neuroscience Research

Paternal Cocaine Exposure & Its Consequences

In a recent study, NIDA supported researchers, Dr. Michael Lidow and his associates report that paternal cocaine abuse may have a significant negative impact on offspring development and that such paternal impact could be brought about by long-term cocaine exposure of males prior to coitus. This study conducted using a novel drug inhalation model revealed that male mice were capable of learning self-administration of cocaine via inhalation route as well as achieving and maintaining blood levels of this drug during daily inhalation sessions comparable to that reported for females. Authors also noted a reduction in biparietal head diameter in newborn pups sired by cocaine-inhaling males suggesting a decreased cerebral volume. Most importantly, they observed a greater negative impact in female offspring compared to males with respect to working memory and light stimulus duration. This study also showed that chronic cocaine exposure in male mice did not result in substantial breakage of spermatozoal DNA, but significantly altered expression of DNA methyltransferase 1 and 3a in the germ cell-rich seminiferous tubules of the testis. Since these enzymes are essential for generating and maintaining parental gene imprinting in germ cells, the authors' observations point to an intriguing possibility that cocaine may cause paternally induced neuroteratological effects by interfering with gene-imprinting patterns in male gametes. He, F., Lidow, I.A., and Lidow, M.S. Consequences of Paternal Cocaine Exposure in Mice, Neurotoxicology and Teratology, 28, pp. 198-209, 2006.

Supraspinal Brain-derived Neurotrophic Factor Acts at the TrkB Receptor to Produce

Pain Sensitivity Brain-derived neurotrophic factor, or BDNF, plays a critical role in learning and memory by actions at the TrkB receptor. NIDA grantees Drs. Ronald Dubner and Ke Ren (University of Maryland, Baltimore) and colleagues now report that BDNF-TrkB signaling also plays a critical role within the brain to produce pain hypersensitivity. They found that after tissue injury, the BDNF-TrkB complex in the brain stem triggers pain facilitating signals to the spinal cord. This facilitating signal causes the amplification and spreads the pain. This discovery not only helps us understand the mechanisms of chronic pain, but suggests the possibility of targeting the BDNF-TrkB complex in the development of novel pain therapies. Guo, W., Robbins, M.T., Wei, F., Zou, S., Dubner, R., and Ren, K. Supraspinal Brain-Derived Neurotrophic Factor Signaling: A Novel Mechanism for Descending Pain Facilitation, Journal of Neuroscience, 26(1), pp. 126-137, 2006.

Buprenorphine Pharmacokinetics

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Buprenorphine, a partial mu agonist, was approved by the Food and Drug Administration in 2001, in part for the treatment of dependence on opioids such as heroin, morphine, and oxycontin. It is formulated under the trade name Suboxone, consisting of a sublingual tablet of 2 or 8 mg buprenorphine, together with 0.5 or 2 mg naloxone as a mu antagonist. In work supported by NIDA awards to the University of Utah and the Virginia Commonwealth University, Dr. David Moody and Dr. Elinore McCance-Katz have recently collaborated to determine the in-vivo pharmacokinetics of this formulation in human plasma and urine samples. Five opioid-dependent subjects were treated with sixteen mg daily doses of buprenorphine for twenty-one days, with collection of blood and urine (twenty-four hour) samples obtained. These clinical samples were treated with appropriate deuterated internal standards, centrifuged in the case of blood samples, and the supernatants applied to solid phase extraction cartridges for extraction, solvent removal, and reconstitution. Separation of four particular analytes, buprenorphine, norbuprenorphine, and the three position glucuronides of both buprenorphine and norbuprenorphine, was carried out. The pharmacokinetic data indicated that norbuprenorphine-3-glucuronide was the predominant metabolite found in both urine and plasma, and that buprenorphine was converted to its glucuronide and to norbuprenorphine in approximately the same time frame (i.e, one hour after administration). Huang, W., Moody D.E., and McCance-Katz, E.F. The In-vivo Glucuronidation of Buprenorphine and Norbuprenorphine Determined by Liquid Chromatography-Electrospray Ionization-Tandem Mass Spectrometry, Therapeutic Drug Monitoring, 28(2), pp. 245-251, 2006.

Tritiation of the Cannabinoid Receptor Antagonist SR144528 Involving Lithium Aluminum Tritide Reduction; Assessment of the Kinetic Isotope by 3H-NMR

The pyrazole caboxamide SR144528 is a selective antagonist at the peripheral cannabinoid CB2 receptor. The potential value of this compound to researchers for pharmacological studies of the CB2 receptor and its potential role in immune function prompted the synthesis of the tritiated compound. In this paper the authors reported the synthesis of this compound and used an approach that enabled the incorporation of highly specific activity tritium label while circumventing the liability of the target compound to catalytic hydrogenation. Lithium aluminum tritide of less than maximum specific activity was employed to introduce tritium, resulting in hydride/tritide incorporation indicative of non kinetic isotope effect for the hydride/tritide reduction of a methyl benzoate. Seltzman, H.H., Foster, M.C., Wyrick, C.D., Burgess, J.P. and Carroll, F.I. Tritiation of the Cannabinoid Receptor Antagonist SR144528 Involving Lithium Aluminum Tritide Reduction; Assessment of the Kinetic Isotope Effect by 3H-NMR, Journal of Labeled Compounds and Radiopharmaceuticals, 48, pp. 589-596, 2005.

Marijuana Smoke and Rimonabant Precipitated Withdrawal

The goals of the present study were to assess whether the CB1 antagonist SR 141716 (rimonabant) precipitates withdrawal in mice that had been repeatedly exposed to marijuana smoke, and to compare these precipitated withdrawal effects to those elicited following intravenous administration of its chief psychoactive component _9-tetrahydrocannabinol _9-THC. SR 141716 elicited a significant increase in paw tremors in mice that were repeatedly dosed with either marijuana or _9-THC. Unexpectedly, the blood and brain concentrations of _9-THC following marijuana exposure were considerably lower than those found following _9-THC injection when comparing an equivalent magnitude of paw tremors in both conditions. Finally, _9-THC dose-dependently alleviated SR 141716-induced paw tremors in marijuana-dependent mice, but marijuana

itself failed to reverse the precipitated withdrawal effect. It is likely that marijuana exposure generated insufficient _9-THC brain levels to reverse the withdrawal signs compared with the brain levels following intravenous injection. These findings taken together indicate that mice exposed repeatedly to marijuana smoke exhibit similar precipitated withdrawal effects as _9-THC-injected mice. Wilson, D.M., Varvel, S.A., Haroe, J.P., Martin, B.R., and Lichtman, A.H. SR 141716 (Rimonabant) Precipitates Withdrawal in Marijuana-Dependent Mice, Pharmacology Biochemistry and Behavior, 85(1), pp. 105-113, 2006.

AMPA Receptor Subunits in the Shell of the Nucleus Accumbens Regulate Brain Reward

Although it is known that drugs of abuse alter the expression of AMPA-type glutamate receptor subunits (GluRs) in the nucleus accumbens (NAc), the impact of this regulation on general motivational states is unclear. Dr. Carlezon and his colleagues used herpes simplex virus vectors to examine how transient increases in the expression of GluR1 or GluR2 protein in the shell of the NAc affect the rewarding impact of electrical stimulation of the medial forebrain bundle, as reflected by intracranial self-stimulation (ICSS) thresholds in rats. After they raised the densities of GluR1 in NAc shell, they saw increased ICSS thresholds, an effect that was similar to what is seen after treatments that cause anhedonia and dysphoria (prodepressive effects) in rats and humans (e.g., drug withdrawal). In contrast, elevated GluR2 decreased the ICSS thresholds, an effect similar to that seen after rewarding treatments (e.g., drugs of abuse). To confirm that viral vector-mediated elevations of GluR1 in the NAc shell produced molecular consequences that were different from those produced by elevated GluR2, they used quantitative PCR to examine the expression of a set of drug-regulated genes 3 days after treatment. Elevated GluR1 was accompanied by sustained increases in the gene for GluR1, whereas elevated GluR2 was accompanied by decreases in prodynorphin. These data suggest that GluR1 and GluR2 in the NAc shell play opposing roles in the regulation of motivated behavior. Todtenkopf, M.S., Parsegian, A., Naydenov, A., Neve, R.L., Konradi, C., and Carlezon Jr., W.A. Brain Reward Regulated by AMPA Receptor Subunits in Nucleus Accumbens Shell. The Journal of Neuroscience, 26(45), pp. 11665-11669, 2006.

Tuned for Reconfiguration: New Forms of Intrinsic, Negative-Feedback Regulation of Activity-and Experience-Dependent Neural Plasticity Stabilize Synaptic Strengths and are Present During Neural Development

Signal transmission between neurons and within neural networks occurs at synapses where efferent signals from one presynaptic neuron are integrated and coded into firing discharges of the postsynaptic responding neurons. The inputs received by the postsynaptic neuron may change dramatically in response to specific patterns of correlated synaptic activity that occur during learning and development, and these patterns depend on the strength and flexibility of the synapses. Long-lasting changes in synaptic strength, also known as LTP and LTD, reflect a persistent reinforcement of the synaptic activities. It is one major way to store information in neural circuits, promoting learning and memory formation. However, these are very dynamic states, and even in the face of dramatic changes in activity, the neurons and circuits must maintain a degree of stability in their firing properties to prevent the synapse from firing at increasingly higher rates with every instance of excitatory input. NIDA grantee Dr. Gina Turrigiano has discovered that the neurons achieve this self-regulation by using homeostatic synaptic plasticity, which includes new forms of intrinsic negative-feedback regulation of activity- and experience-dependent neural plasticity. She found that activity of a neuron could be tuned

up and down according to the strength of synaptic connections, a phenomenon called synaptic scaling, and showed that between cortical pyramidal neurons, increased activity would decrease synaptic strengths, and vice versa. Her experiments indicate that the negative feedback regulation of activity/experience-dependent neural plasticity is an event intrinsic to the postsynaptic neuron. Such 'synaptic scaling' has been observed early in development using cultured neurons, but she found that these properties were retained even after the neuron became more mature. In addition to the synaptic scaling, blockade of activity blockade with TTX induced a large increase in the frequency of mEPSCs, and this was associated with an increased density of excitatory synapses due to elevation of presynaptic vesicle trafficking and increased presynaptic vesicle release in response to electrical stimulation. These results raise the intriguing possibility that the expression mechanism of homeostatic plasticity can be tailored to the needs of the network during different stages of development or in response to different challenges to network function. Wierenga, C.J., Walsh, M.F., and Turrigiano, G.G. Temporal Regulation of the Expression Locus of Homeostatic Plasticity. Journal of Neurophysiology, 96, pp. 2127-2133, 2006. and Maffei, A., Nataraj, K., Nelson, S.B., and Turrigiano, G.G. Potentiation of Cortical Inhibition by Visual Deprivation. Nature, 443, pp. 81-84, 2006.

Endocannabinoid-Mediated Synaptic Plasticity in the CNS

Changes in synaptic efficacy are essential for neuronal development, learning, and memory formation. Dr. Pablo Castillo studies how synapses modify their efficacy as well as the functional impact of such changes in a neural network. One of the main goals of his work is to elucidate both the specific molecular events that underlie various forms of synaptic plasticity and the exact modifications in synaptic proteins that are responsible for the observed, short- and long-lasting changes in synaptic efficacy. While most of the current knowledge on long-term synaptic plasticity is derived from studies at excitatory synapses, he has recently reported that endogenous cannabinoids mediate long-term plasticity at inhibitory synapses in the hippocampus. He demonstrated a temporal and spatial relationship at hippocampal synapses between the depolarization-induced suppression of inhibition (DSI) and the long-term synaptic inhibition, which can be generated by electric brain stimulation that mimics physiologically relevant brain theta activity. In addition, the DSI facilitated the subsequent induction of long-term potentiation (LTP) at nearby excitatory inputs. This study provides functional evidence that the synaptic integration at focal points of brain circuitry between excitatory and inhibitory inputs and the endocannabinoid signaling are important modulators of activity-dependent synaptic plasticity. A single exposure to _9THC can disrupt functional plasticity mediated by endocannabinoid in the hippocampus and suggests that endogenous cannabinoid and their receptors in the hippocampus and other brain areas may be important in tuning the synaptic activity and plasticity of neurons. Chevaleyre, V., Takahashi, K.A., and Castillo, P.E. Endocannabinoid-Mediated Synaptic Plasticity in the CNS. Annual Review of Neuroscience, 29, pp. 37-76, 2006. and Castillo, P.E., and Khodakhah, K. Biochemical Confinements without Walls in Aspiny Neurons. Nature Neuroscience, 6, pp. 719-720, 2006.

Increased Susceptibility to Methamphetamine-Induced Dopamine Neurotoxicity by HIV-Tat and Tumor Necrosis Factor-alpha

Methamphetamine abuse is a major risk factor for HIV transmission due to sharing of contaminated needles and increased high risk sexual activity. Previous studies have shown synergistic increases in neurotoxicity, particularly in dopamine neurons, by the combination of HIV infection (or HIV proteins) in the brain and MA exposure. Possible mechanisms of this effect include oxidative stress, microglial and astrocyte activation, and release of pro-

inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha), all of which are correlated with neuropathology in the context of HIV infection. In a study published in Neurobiology of Disease, Dr. William Maragos and colleagues showed that TNF-alpha mediates the interaction between Tat and methamphetamine. In Sprague-Dawley rats, injections of Tat caused a small but significant increase in striatal TNF-alpha levels, whereas MA resulted in no change. The increase in TNF-alpha induced by Tat and methamphetamine was not significantly different from that induced by Tat alone. Temporal analysis of TNF-alpha levels revealed a 50-fold increase 4 h after Tat administration. In C57BL/6 mice, Tat and methamphetamine induced a 50% decline in striatal dopamine levels, which was significantly attenuated in mice lacking both receptors for TNF-alpha. TNF-alpha synthesis inhibitors significantly attenuated Tat and methamphetamine neurotoxicity in hippocampal neuronal culture. The results suggest that Tat-induced elevation of TNF-alpha may predispose the dopaminergic terminals to subsequent damage by methamphetamine. Theodore, S., Cass, W.A., Nath, A., Steiner, J., Young, K., and Maragos, W.F. Inhibition of Tumor Necrosis Factor-alpha Signaling Prevents Human Immunodeficiency Virus-1 Protein Tat and Methamphetamine Interaction. Neurobiology of Disease, 23(3), pp. 663-668, 2006.

Unlimited Access to Heroin Self-Administration as a Rat Model of Opiate Dependence

A major goal in addiction research is to develop an animal model that can be used to study the mechanisms of opiate dependence. Dr. George Koob and colleagues at The Scripps Research Institute addressed this issue using a paradigm of unlimited access to intravenous heroin self-administration combined with responding for food and water to characterize the transition from exposure to drug dependence. Male Wistar rats were allowed to lever press for heroin and nose-poke for food and water in consecutive, daily 23-h sessions. Daily heroin intake increased over days, reaching significance by Day 14. Drug-taking increased across the circadian cycle, reflected as increases in both the nocturnal peak and diurnal nadir of heroin intake. Changes in the circadian pattern of food intake and meal patterning preceded and paralleled the changes in heroin intake. By Day 7, the circadian amplitude of feeding was blunted. Nocturnal food intake decreased because rats consumed smaller and briefer meals. Diurnal intake increased due to increased meal frequency, whereas total daily food intake decreased. To control for time or experience in the self-administration boxes, rats with saline (no drug) tethers were tested and did not show significant changes in food intake pattern. Body weight gain slowed slightly in rats taking heroin relative to saline controls. Separate groups of rats revealed that significant physical dependence as measured by physical signs of opiate withdrawal following a naloxone injection was reached by Day 14. Significant increases in heroin intake could be produced using low doses of naloxone on days 28-31 of heroin access. After 6 weeks of heroin self-administration, rats injected with buprenorphine, an FDA approved medication for opiate addiction, showed a dose-dependent reduction in heroin intake. Changes in the pattern of drug and food intake in the present unlimited heroin access model may serve as independent motivational markers for the transition to a drug-dependent state. Chen, S.A., O'Dell, L.E., Hoefer, M.E., Greenwell, T.N., Zorrilla, E.P., and Koob, G.F. Unlimited Access to Heroin Self-Administration: Independent Motivational Markers of Opiate Dependence. Neuropsychopharmacology, 31, pp. 2692-2707, 2006.

Planaria Model Demonstrates Reduced Withdrawal Effects from Poly-Drug Exposure

Many drug abusers engage in 'polydrug' abuse, the co-incident use of more than one controlled substance. Specific combinations of substances are used, possibly because they maximize the euphoric effect. An alternative view is that

the combination might result in less intense withdrawal during periods of abstinence. In a recent issue of Brain Research, Dr. Robert Raffa of Temple University measured responses to withdrawal from fixed ratio combinations of cocaine and a _-opioid agonist in *Planaria*, which are useful for studying drug interactions because of their permeable exteriors and their relevant neurotransmitter systems (e.g., dopaminergic, opioid, and serotonergic). In this study, the investigators used "joint-action" analysis as a mathematical method to quantify interactions between drugs. The D_{50} (concentration producing half-maximal effect) for cocaine and U-50,488H was 10.3 and 1.02 _g, respectively. The D50 for 19:1 or 1:19 combinations did not differ significantly ($p > 0.05$) from expected additive values (11.6 ± 3.0 vs. 9.9 ± 1.4 and 1.1 ± 0.2 vs. 1.5 ± 0.1, respectively), but the 3:1, 1:1, and 1:3 ratios did (34.5 ± 6.9 vs. 7.7 ± 1.1; 55.1 ± 10.0 vs. 5.7 ± 0.7; and 40.8 ± 8.9 vs. 3.3 ± 0.4, respectively), indicating subadditive interaction at these ratios. The finding of "subadditivity" in this model suggests that abstinence-induced withdrawal from the combination is less intense than that predicted from the individual drug potencies. The concept that certain combinations of drugs lead to attenuated withdrawal might generalize to humans. Raffa, R.B., Stagliano, G.W., and Tallarida, R.J. Subadditive Withdrawal from Cocaine/_-opioid Agonist Combinations in Planaria. Brain Research, 1114(1), pp. 31-35, 2006.

In studies of neuroAIDS, brain levels of the chemokine CCL2 (or MCP-1) are highly elevated compared to serum levels as well as levels from brains of HIV-negative subjects. CCL2 is believed to stimulate inflammatory responses and/or recruit infected monocytes to the brain in neuroAIDS, as well as in Alzheimer's disease, Multiple Sclerosis, and possibly other neurodegenerative diseases. Illicit drug use is a common cofactor in HIV transmission, and there is evidence that opioids and stimulants exacerbate the neurological damage associated with HIV infection. Previous work by Dr. Kurt Hauser and colleagues at the University of Kentucky has demonstrated that opioids and HIV-Tat protein synergistically increase neuronal dysfunction and glial activation in a rodent model system. In a recent study published in the Journal of Neuroimmunology, Dr. Hauser's group found that CCR2, the primary receptor for CCL2, is important for the glial activation resulting from Tat and opioid exposure. The effects of systemic morphine and intrastriatal HIV-1 Tat on macrophage/microglial and astroglial activation were assessed in wild type and CCR2 null mice. Tat and/or morphine additively increased the proportion of CCL2 immunoreactive astroglia. The effects of morphine were prevented by the opioid antagonist naltrexone. Glial activation was significantly reduced in CCR2(_/_) versus wild-type mice following Tat or morphine plus Tat exposure. Thus, CCR2 contributes to local glial activation caused by Tat alone or in the presence of opiates, implicating CCR2 signaling in HIV-1 neuropathogenesis in drug abusers and non-abusers. El-Hage, N., Wu, G., Ambati, J., Bruce-Keller, A.J., Knapp, P.E., and Hauser, K.F. CCR2 Mediates Increases in Glial Activation Caused by Exposure to HIV-1 Tat and Opiates. Journal of Neuroimmunology, 178, pp. 9-16, 2006.

Combined Chronic Stress and MDMA Enhances Mesoaccumbens Dopamine

MDMA acutely releases serotonin and dopamine, and produces long-term damage to serotonin terminals in animals. It is also known that MDMA-induced dopamine release is dampened by serotonin. Since stress activates the mesolimbic dopamine pathway, Bryan Yamamoto's group hypothesized that chronic stress after exposure to neurotoxic doses of MDMA may enhance the effect of a subsequent challenge dose of MDMA on dopamine release in the nucleus accumbens shell (NAcc(sh)). The present study used in vivo microdialysis to assess changes in mesolimbic responses to MDMA in rats with prior exposure to a neurotoxic regimen of MDMA and/or chronic unpredictable stress (CUS). Rats were pretreated with a neurotoxic regimen of MDMA. Seven

days later, the rats were subjected to 10 days of CUS and the dopamine release in the NAcc(sh) and serotonin in the VTA were measured after a challenge injection of MDMA. Pretreatment with MDMA or CUS alone blunted MDMA-induced serotonin release in the VTA. As predicted, pretreatment with MDMA + CUS enhanced MDMA-stimulated dopamine release in the NAcc(sh). The augmentation of MDMA-induced dopamine release in rats pretreated with MDMA + CUS was attenuated by perfusion of the 5HT1B antagonist, GR127935, into the VTA prior to the MDMA challenge injection. This is the first demonstration that CUS after previous exposure to neurotoxic doses of MDMA alters mesolimbic dopamine and serotonin release, suggesting that stress can alter the neuronal mechanisms associated with MDMA reward. Pre-exposure to MDMA and stress is not simply additive but synergizes to augment mesolimbic dopamine neurotransmission in a manner that is both quantitatively and qualitatively different from either the effects of MDMA or stress alone. Further, stress exposure after a neurotoxic regimen of MDMA did not affect the neurotoxicity of MDMA, as indicated by unaltered long-term depletion of serotonin tissue content. Thus, the effects of stress exposure after MDMA are not the result of added damage to serotonergic neurons. Finally, the serotonin receptor-1B receptor is newly implicated as a mediator of chronic stress-induced changes in the effects of MDMA. These results suggest that prior exposure to neurotoxic doses of MDMA can augment the reactivity of the dopamine-mediated reward system to chronic stress via a serotonin receptor-1B mechanism that might increase the vulnerability to drug abuse in the future. Amato, J.L., Bankson, M.G., and Yamamoto, B.K. Prior Exposure to Chronic Stress and MDMA Potentiates Mesoaccumbens Dopamine Release Mediated by the Serotonin receptor-1B. Neuropsychopharmacology, 2 August 2006 (Epub ahead of print).

MDMA Increases Cocaine Reward in Adolescent Rats and Decreases It in Adults

Adolescent rats at postnatal day (PND) 33 and adult rats at PND 60 were exposed to MDMA or saline for 7 days. Exposing adolescent rats to MDMA resulted in cocaine becoming reinforcing, but not for adolescent rats exposed to saline. In contrast, the reinforcing effects of cocaine were diminished after MDMA exposure in adult rats. These findings suggest that exposure to MDMA during adolescence may carry a greater risk for subsequent stimulant abuse. Åberg, M., Wade, D., Wall, E., and Izenwasser, S. Effect of MDMA (Ecstasy) on Activity and Cocaine Conditioned Place Preference in Adult and Adolescent Rats. Neurotoxicoly and Teratology, 14 September 2006 (Epub ahead of print).

Opiate Actions on Immunity via the Dopa System

Morphine is known to modulate immune function and interacts with neurotransmitter systems to modulate specific immune parameters. To approach an understanding of the basis of the interaction of these two systems, this study investigated whether dopaminergic projections to the nucleus accumbens are involved in morphine-induced suppression of splenic natural killer (NK) cell activity. Administration of the dopamine D-1 antagonist SCH-23390 into the nucleus accumbens shell blocked morphine's suppressive effect on NK activity in male Lewis rats. In addition, morphine's effects were also prevented by intra-accumbens microinfusions of the dopaminergic immunotoxin anti-DAT-saporin or the administration of the dopamine D-1 agonist SKF-38393. These results indicate a critical role for dopamine D-1 receptors in the modulation of NK activity and that dopaminergic inputs to the nucleus accumbens are involved in opioid-induced immunosuppression. Thus opioid-induced increases in dopamine D-1 receptor activation may have adverse consequences on immune status. Saurer, T.B., Carrigan, K.A., Ijames, S.G., and Lysle, D.T. Suppression of Natural Killer Cell Activity by Morphine Is Mediated by the Nucleus Accumbens Shell. Journal of Neuroimmunology, 173,

pp. 3-11, 2006.

From the Genome to the Proteome: Uncovering Peptides in the Apis Brain

The honey bee is an excellent model system for studying biological systems including social behavior and gene environment interactions. As a model system, the honey bee is relatively inexpensive when compared to a rodent model, yet still possesses some of the complex attributes such as a social structure and the ability of individuals to learn and communicate with other members of its society. These characteristics make it particularly attractive as a model for studying neurobiology. While possessing these complex attributes, at the same time, the honey bee is a simpler biological model than a higher order animal and as such, offers an increased likelihood for identifying biological molecules or collections of molecules involved in the condition of interest. This can be extremely valuable for dissecting the underlying causes for health and disease when those molecules or collections of molecules have human orthologs. In October of this year, the first draft of the honey bee genome was published in the journal Nature. As with other species, sequencing of the genome is the first and critical step toward more advanced genetic and proteomic studies such as identifying gene networks, biomarkers, candidate genes of diseases, etc. One of the more challenging classes of molecules to identify is biologically significant peptides including neuropeptides. The challenge is a result of the way in which neuropeptides are generated by the cell. Neuropeptides are generally produced by targeted cleavage of a larger protein into smaller parts, the neuropeptides. In this Science article, researchers report development of a computer algorithm that looks for repetitive sequences in the genome. Using this algorithm in conjunction with homology searching, they are able to infer neuropeptides even in an unannotated genome. They then use mass spectrometry to analyze biological samples from the animal to see if they are able to detect the predicted peptides. Using this approach, they have inferred more than 200 peptides and confirmed the presence of 100 peptides from 20 precursor genes in the honey bee. The researchers have made the neuropeptide prediction tool freely available at neuroproteomics.scs.uiuc.edu. This tool, used in conjunction with homology searching and verification techniques like mass spectrometry should aid researchers who are looking for new neuropeptides or neuropeptides in model organisms that are not as well annotated as mouse and human for example. This should greatly facilitate research on these otherwise elusive but highly important biomolecules. Hummon, A.B., Richmond, T.A., Verleyen, P., Baggerman, G., Huybrechts, J., Ewing, M.S., Vierstraete, E., Rodriquez-Zas, S.L., Schoofs, L., Robinson, G.E., and Sweedler, J.V. From the Genome to the Proteome: Uncovering Peptides in the Apis Brain. Science, 314, pp. 647-649, 2006.

Mutation of the RhoGAP18B Gene, a Likely Regulator of Actin Cytoskeletal Dynamics, Makes Flies Resistant to the Intoxicating Effects of Ethanol, Cocaine, and Nicotine

Individuals that are resistant to the intoxicating effects of a drug have an increased risk of developing drug dependence. What are the genes that regulate intoxication, and how are these genes involved in addiction? The Drosophila model system is particularly useful for gene identification because: 1)fruit fly genetics is rapid and powerful, 2) no prior assumptions need to be made about the identities of the genes involved, and 3) genes and processes frequently are evolutionarily conserved between species. To identify genes involved in drug intoxication, Dr. Ulrike Heberlein and coworkers used a mutagen to disrupt the genes of a large number of flies. The animals were then sorted to identify the very rare individuals that were resistant to the intoxicating effects of ethanol. The gene responsible for the mutant phenotype

of these rare animals was identified using a molecular genetic strategy. In this case, the mutated gene identified was completely unexpected: RhoGAP18B, a putative regulator of actin cytoskeletal dynamics. Dr. Heberlein found that RhoGAP18B encodes several mRNA varieties or isoforms (A, B, C, and D). Interestingly, the A isoform regulates the locomotor stimulating effects of ethanol, while the C isoform regulates the sedating effects of ethanol. Furthermore, mutants in RhoGAP18B were also resistant to the intoxicating effects of nicotine and cocaine, revealing a role for RhoGAP18B in regulation of the intoxicating effects of multiple drugs. Although it is unclear exactly how RhoGAP18B modulates resistance to acute drug exposure, Dr. Heberlein and co-workers hypothesize that RhoGAP18B regulates actin cytoskeletal dynamics critical for reorganization of neuronal dendrites and axons which in turn leads to altered synaptic plasticity in response to drug exposure. In a companion paper strengthening Dr. Heberlein's hypothesis, Dr. Di Fiore and colleagues found that mutation of the mouse Eps8 gene (which normally regulates neuronal actin dynamics in response to NMDA glutamate receptor activation) increased ethanol resistance as well as ethanol consumption (Cell, 127:213-226, 2006). Identification of a role for RhoGAP18B in drug resistance has several potential outcomes: 1) the human homolog of RhoGAP18B could be studied to see if it plays a role in human drug resistance or dependence, 2) the role of RhoGAP18B and neuronal actin cytoskeletal remodeling can be further investigated to see if this process is an important biological underpinning of addiction, and 3) modulation of neuronal actin cytoskeletal remodeling by novel medicinal agents might be a useful therapeutic approach to treat drug addiction. Rothenfluh, A., Threlkeld, R.J., Bainton, R.J., Tsai, L.T-Y., Lasek, A.W. and Heberlein, U. Distinct Behavioral Responses to Ethanol are Regulated by Alternate RhoGAP18B Isoforms. Cell 127, pp. 199-211, 2006.

A Worm Model for Genetic Analysis of Nicotine-Dependent Behavior: Regulation by TRPC Family Calcium Channels

Genetically tractable organisms such as the roundworm or the fruit fly can facilitate the experimental examination of addictive processes, as well as allow the identification and characterization of new genes involved in these processes. In work initiated in NIDA grantee Dr. Paul Sternberg's lab, Dr. Shawn Xu developed a worm model for nicotine-dependent behavior. Using a worm locomotion tracking system, Dr. Xu and co-workers quantified worm movement in response to nicotine exposure and found that worms, like vertebrates, show acute behavioral response to nicotine as well as nicotine tolerance, withdrawal, and sensitization. In mammals, nicotinic acetylcholine receptors (ACRs) are required for nicotine behavioral responses so Dr. Xu tested all available mutants in worm ACRs (20 out of 28 total), and found that two of them, ACR-15 and ACR-16, were required for acute behavioral response to nicotine. Dr. Xu found that the mouse 42 ACR can functionally replace worm ACR-16 when it is expressed in a particular subset of worm interneurons. Dr. Xu's lab then decided to try to identify new genes involved in nicotine-dependent behaviors. He found that two members of the TRPC family of calcium channel, TRP-1 and TRP-2, were required for behavioral response to acute nicotine, while mutants in several other TRP channels had normal responses to nicotine. Again, Dr. Xu found that TRP-1 and TRP-2 were required in a particular subset of interneurons within the worm, and that the human TRPC3 channel can functionally replace TRP-2 when expressed in this subset of neurons. Where are the nicotinic acetylcholine receptors functioning with the TRPC channels to regulate acute behavioral response to nicotine? To narrow down precisely where the ACR and TRP genes were required, Dr. Xu used a laser to kill pairs of interneurons, and then tested the animals for acute response to nicotine. He found that killing a single pair of interneurons (the AVA neuron pair) abolished the acute nicotine response, indicating that these two neurons are required for acute behavioral response to nicotine. How do the nicotinic acetylcholine receptors function with the TRPC calcium channels to

regulate acute behavioral response to nicotine? Dr. Xu and coworkers expressed a genetically encoded calcium sensor to look at AVA interneuron function in living animals. Acute nicotine exposure caused a robust increase in calcium levels in the AVA neurons, chronic nicotine exposure reduced calcium levels in the AVA neurons, but animals that were previously sensitized to nicotine had very strong calcium responses. Animals lacking ACR-15 had little or no calcium response in the AVA neurons, as did animals lacking TRP-1 or TRP-2. These data suggest that acute behavioral response to nicotine requires specific ACRs and TRPC calcium channels, and that these proteins function together to regulate neuronal calcium levels in response to nicotine. This research is important for several reasons: 1) it shows that nicotine-dependent behavior and the molecular apparatus necessary for this response is evolutionarily conserved, 2) this model system provides a rapid and inexpensive means for functional testing of genes and gene variants implicated in nicotine responses in humans and other organisms, and 3) it provides an elegant way to experimentally characterize the molecular genetic basis of nicotine behavioral responses and, perhaps ultimately, addiction itself. Feng, Z., Li, W.,Ward, A., Piggot, B.J., Larkspur, E.R., Sternberg, P.W. and Xu, X.Z.S. A. C. elegans Model of Nicotine-dependent Behavior: Regulation by TRP-family Channels. Cell, 127, pp. 621-633, 2006.

Novel Genes Identified for Nicotine Dependence: A Hybrid Design Using a High Density Genome Wide Association Scan and a Candidate Gene Approach

Dr. Laura Bierut and Dr. Scott Saccone have completed a hybrid study to identify nicotine dependence loci through a whole genome association scan using 2.4 million single nucleotide polymorphisms (SNPs) along with a candidate gene approach targeting 3,713 SNPs in 348 genes. The study was carried out in a two-stage design. In the first stage, genotyping was completed in case (smokers) and control pools. In the second stage, SNPs were selected for individual genotyping of based on the most significant allele frequency differences between cases and controls pooled results. Individual genotypes were performed in 1050 cases (smokers) and 879 controls using 31,960 selected SNPs. For the candidate gene study, 3,713 SNPs were added to the 31,960 SNPs selected from the whole genome scan and screened together. The whole genome study nominates several novel genes, such as Neurexin 1, while also identifying a known gene, the B3 nicotinic receptor. Overall, there were 35 SNPs that were more commonly observed in the smokers than the "non-smokers", some of which highlighted several genes not previously implicated in the development of nicotine dependence. The candidate gene study showed several cholinergic nicotinic receptor genes among the top signals, namely CHRNB3, CHRNA5, KCNJ6, and GABRA4. Overall there were 39 top SNPs, five of which were SNPs within nicotinic receptor genes. Most significant was the CHRNA5 SNP(rs16969968). Compared to having no copies, the odds ratio for having 1 copy and 2 copies of the A allele was 1.1 (95% CI 0.9-1.4) and 1.9 (95% CI 1.4-2.6), respectively. Thus, individuals with the AA genotype were nearly twice as likely to be nicotine dependent as those with 1 or no copies of this A allele. The study was performed in collaboration with Perlegen Sciences, Inc. and the results are published in back-to-back papers. Bierut, L.J., Madden, P.A.F., Breslau, N., Johnson, E.O., Hatsukami, D., Pomerleau, O.F., Swan, G.E., Rutter, J., Bertelsen, S., Fox, L., Fugman, D., Goate, A.M., Hinrichs, A.L., Konvicka, K., Martin, N.G., Montgomery, G.W., Saccone, N.L., Saccone, S.F., Wang, J.C., Chase, G.A., Rice, J.P., Ballinger, D.G. Novel Genes Identified in a High Density Genome Wide Association Study for Nicotine Dependence. Human Molecular Genetics (epub ahead of publication), 2006.

Director's Report to the National Advisory Council on Drug Abuse - February, 2007

Research Findings - Basic Behavioral Research

Combined Inhibition of Dopaminergic and Serotonergic Transporters as a Cocaine Treatment Approach

The dopamine transporter is thought to play a critical role in mediating the reinforcing efficacy and subjective effects of cocaine. It has been known for many years that the affinity of drugs for this transporter is positively correlated with their capacities to maintain self-administration behavior in animals. Dopamine transport inhibitors are now generally considered to demonstrate potential as cocaine treatment medications. Dr. Leonard Howell and his colleagues at the Yerkes National Regional Primate Research Center combined these observations with those of studies showing that inhibitors of the serotonin transporter can mitigate the reinforcing effects of psychomotor stimulants in animals. He and his colleagues examined the effectiveness of combining the selective dopamine transporter inhibitor RTI-336 with either of two serotonin transporter inhibitors, fluoxetine or citalopram, and found that cocaine self-administration was completely suppressed without affecting dopamine transporter occupancy (as measured by PET neuroimaging). Additionally, the reduction in self-administration with the drug combinations was greater than that of the RTI compound alone. Dr. Howell interpreted these findings to indicate that combined inhibition of the dopamine and serotonin transporters merits further study as a cocaine treatment medication. Howell, L.L., Carroll, F.I., Votaw, J.R., Goodman, M.M. and Kimmel, H.L. Effects of Combined Dopamine and Serotonin Transporter Inhibitors on Cocaine Self-Administration in Rhesus Monkeys. Journal of Pharmacology and Experimental Therapeutics, Online Published November 14, 2006.

Brain Reward Systems are Activated by Acute Nicotine and Produce Long-Lasting Increases in Reward Sensitivity

Changes in intracranial self-stimulation (ICSS) thresholds have been used to monitor the effects of drugs of abuse on brain reward systems: the lower the ICCS threshold after drug treatment, the greater the sensitivity to rewarding effects of the drug. NIDA grantee Dr. Athina Markou investigated the short- and long-term actions of nicotine consumption on the sensitivity of brain reward systems. Rats were first trained to lever press to receive ICSS. Two experimental groups were then given 1h or 12h access to intravenous nicotine for 20 consecutive days. ICSS thresholds were assessed before and after each nicotine self-administration session. After nicotine self-administration, ICSS thresholds were lowered (indicating increased sensitivity to reward) for 36 days in both 1h and 12h nicotine self-administration groups. Short-term effects of nicotine on reward thresholds were blocked by DHE, indicating that this effect is mediated by nicotine receptors. It is interesting to note that, unlike cocaine or morphine, access to nicotine did not result in escalation of drug intake, and

decreases in reward sensitivity were not attenuated over time. These findings reveal that nicotine produces short- and long-term effects on reward hypersensitivity. Kenny, P.J. and Markou, A. Nicotine Self-administration Acutely Activates Brain Reward Systems and Induces a Long Lasting Increase in Reward Sensitivity. Neuropsychopharmacology, 31, pp. 1203-1211, 2006.

Gestational Nicotine Exposure Changes Basal Neuronal Activity in Areas Associated with Motivated Behavior

Dr. Frances Leslie and colleagues investigated whether nicotine, infused into a pregnant dam during gestation, would affect the neuronal response to acute nicotine during adolescence. One of three challenge doses of nicotine, or saline, was administered during postnatal days 38-40 (i.e., adolescence in the rat), and c-fos mRNA was used as a measure of neuronal activity. Gestational exposure to nicotine did not alter response to acute nicotine challenge during adolescence. The highest dose of acute nicotine challenge, however, did result in a significant increase in c-fos mRNA in the nucleus accumbens, the superior colliculus and the dorsolateral geniculate nucleus. Stress-sensitive areas of the lateral bed nucleus of the stria terminalis and the paraventricular nucleus also showed increased neuronal activity in response to acute nicotine. Two brain areas showed significant increases in c-fos mRNA as a result of gestational treatment, independently of nicotine challenge during adolescence: the infralimbic cortex and the nucleus accumbens core. These regions are important mediators of executive function and inhibitory control. These data suggest that gestational nicotine exposure results in long-term changes in neuronal activity, that it does not interact with acute adolescent exposure, but that the neuronal activity of adolescent rats can be significantly altered by a single, acute dose of nicotine. Park, M.K., Loughlin, S.E. and Leslie, F.M. Gestational Nicotine-Induced Changes in Adolescent Neuronal Activity. Brain Research, 1094, pp. 119-126, 2006.

Salvinorin-A, a K-Opioid Hallucinogen, Produces Time- and Dose-Dependent Neuroendocrine Effects

Salvinorin A is a potent kappa-opioid agonist in vitro and salvinorin A-containing products have been emerging as drugs of abuse for their hallucinogenic effects. NIDA researcher Dr. Eduardo Butelman recently tested the drug for kappa effects in vivo using serum prolactin levels as biomarkers of efficacy, and also cloned the Macaca mulatto (M. mulatto) OPRK1 gene, which codes for the kappa opioid receptor. He treated M. mulattos with salvinorin A, U69,593 (a kappa-agonist) or vehicle, followed by blood sampling at 5-120 minutes post-injection. Both kappa agonists produced robust, dose-and time-dependent increases in prolactin levels in males. U69,593 produced a longer-lasting effect; however the maximum effect and potency were the same as produced by salvinorin A. In females in the follicular phase, salvinorin A produced robust prolactin release. This was longer lasting, and had a faster onset than in males. In antagonist challenge studies the opioid antagonist nalmefene and/or the serotonin antagonist ketanserin was administered prior to a dose of salvinorin A. In both males and females, antagonist pretreatment with nalmefene produced robust antagonism of salvinorin A-stimulated prolactin release at the high, but not low, dose. Ketanserin produced no antagonism and did not affect prolactin levels, indicating that serotonin receptors were not involved. In these studies, salvinorin A was shown to be a potent kappa agonist, and was effective in both males and females. Butelman, E.R., Mandau, M., Prisinzano, T.E., Yuferov, V. and Kreek, M.J. Effects of Salvinorin A, a K-Opioid Hallucinogen, on a Neuroendocrine Biomarker Assay in Non-human Primates with High k-Receptor Homology to Humans. Journal of Pharmacology and Experimental Therapeutics, e-pub, 2006.

Planned Meetings

Publications

Staff Highlights

Grantee Honors

Subthreshold Smokers Experience Nicotine Withdrawal

Dr. Joseph DiFranza and colleagues investigated an understudied population of smokers: those who smoke 5 or fewer cigarettes per day, so-called "subthreshold" smokers. The first of two studies used a convenience sample of young adult smokers who met these criteria. Smokers were asked open-ended questions about their withdrawal experiences. Symptoms that were not specifically mentioned in the open-ended responses were further explored so that all 9 listed symptoms (craving, restless, irritable, anxious/nervous, difficulty concentrating, headache, sad/blue, angry, hungry) were considered. Time before symptom onset was also explored, as were strategies for coping with symptoms. Subjects reported on the 9 listed symptoms, as well as some additional ones (e.g., sensitivity to stress). All 36 subjects reported at least one withdrawal symptom, with 29 subjects reporting a specific set duration of abstinence that predictably resulted in the experience of withdrawal. Most reported symptoms within 1-2.4 days, with an average of a single cigarette providing relief. There was an inverse relationship between weekly cigarette consumption and the latency to withdrawal symptom onset. That is, the higher the weekly cigarette consumption, the faster the latency to symptom onset. There were no differences in the number of withdrawal symptoms between those subjects who previously smoked more than 5 cigarettes per day, and those who didn't. In a second study, secondary data analysis of findings from the 2004 NYTS, which surveyed over 27,000 individuals, aged 9-21 years old, was performed. Most of these subjects were subthreshold smokers (78.5%), and only these data were included in the secondary data analysis. These smokers were more likely to be intermittent, rather than daily, smokers. About half of the subjects reported craving, and most reported at least one withdrawal symptom, most notably restlessness and irritability. There was a negative correlation between monthly cigarette consumption and latency to 'need a cigarette'. Taken together, these studies suggest that although subthreshold smokers are often excluded from smoking studies, both children and adults with low rates of smoking experience withdrawal symptoms in a reliable, time-related manner. Fernando, W.W.S.A , Wellman, R.J., and DiFranza, J.R. The Relationship between Level of Cigarette Consumption and Latency to the Onset of Retrospectively Reported Withdrawal Symptoms. Psychopharmacology, 188, pp. 335-342, 2006.

Increases of Endogenous Cannabinoids Accelerate Extinction

Extinction of learned responses and behaviors is considered a form of inhibitory learning, rather than an unlearning of the original response. Recently, there has been considerable interest in developing pharmacotherapeutic approaches to enhance or accelerate extinction processes as a potential treatment for disorders such as phobias, post-traumatic stress, and drug abuse. Drs. Aron Lichtman, Stephen Varvel, and their colleagues have been investigating whether manipulations of the endogenous cannabinoid system can alter extinction of conditioned fear or spatial memory in the Morris water maze task. Previous studies have shown that disruption of signaling via the CB1 cannabinoid receptor impairs extinction of learned responses in these paradigms. Now, in this report, the investigators tested the hypothesis that elevating brain levels of the endogenous cannabinoid anandamide would potentiate extinction in the water maze task. They used two approaches to elevate anandamide levels: genetic deletion and pharmacological inhibition of its primary catabolic enzyme fatty-acid amide hydrolase (FAAH). FAAH (-/-) mice and mice treated with the FAAH inhibitor OL-135, did not display any memory impairment or motor disruption, but they did exhibit a significant increase in the rate of extinction. The CB1 receptor antagonist SR141716 (Rimonabant) delayed extinction when given alone (as they had previously shown), and blocked the effects of OL-135 on extinction. These results indicate that endogenous anandamide plays a facilitatory role in extinction through a

CB1 receptor mechanism of action. In contrast, the primary psychoactive constituent of marijuana, _9-tetrahydrocannabinol, did not affect extinction rates, which suggests that FAAH is a more effective target than a direct acting CB1 receptor agonist, for facilitating extinction. These findings suggest that FAAH inhibition represents a promising pharmacological approach to treat psychopathologies characterized by an inability to extinguish maladaptive behaviors, such as post-traumatic stress syndrome, obsessive-compulsive disorder, and cue-induced relapse to drug seeking. Varvel, S.A., Wise, L.E., Niyuhire, F., Cravatt, B.F., and Lichtman, A.H. Inhibition of Fatty-Acid Amide Hydrolase Accelerates Acquisition and Extinction Rates in a Spatial Memory Task. Neuropsychopharmacology, [Oct 18, Epub ahead of print], 2006.

Dopamine Tone Affects the Motivation to Perform Goal-Directed Responses

Dopamine has been implicated in both learning and motivation. There are two general, not mutually exclusive, interpretations of dopamine function. One is that dopamine, particularly phasic dopamine release, facilitates reinforcement learning and stimulus-reward associations by providing a reward prediction error. The other is that dopamine enhances the energizing or motivating effect of reward or reward-predicting cues. This hypothesis predicts that dopamine modulates the expression of learned behavior by scaling the response to previously established associations. In the current study, Dr. Zhuang and his colleagues designed a genetic approach for manipulating dopamine signaling to address the question of whether dopamine can directly scale performance of a learned task in the absence of new learning. They developed an inducible dopamine transporter (DAT) knockdown mouse line in which they could reduce DAT expression, and thereby enhance tonic dopamine levels, without affecting phasic dopamine activity, as assessed by electrophysiology. The inducible knockdown allowed them to isolate the putative performance scaling effects of dopamine from learning effects by training the mice prior to inducing the genetic alteration. The knockdown was induced by giving the mutant mice doxycycline (Dox), which turned off the expression of the DAT gene. Three groups of mice were used for all behavioral testing: wild type mice, which were given Dox as a control, mutant mice given Dox to knockdown DAT, and mutant mice not given Dox as a genetic control group. For the first behavioral test, all mice were first trained on a progressive ratio schedule (PR7, where the number of lever presses increased by 7 after each food reward). Then half the mutant mice and all the wild type mice were fed Dox. Whereas prior to the Dox treatment, all groups exhibited similar numbers of lever presses, after treatment the mutant Dox group responded with almost twice as many presses. Importantly, this difference was seen only when the animals were food deprived; when they were sated, again all groups performed similarly. Then a concurrent choice task was used as a second behavioral measure. In this task, animals learn to press a lever (FR30 schedule) for a preferred food (chocolate-flavored pellets). On alternate days, they either obtained all their food by operant responding (no-choice condition), or by choosing between freely available regular chow and the chocolate pellets for which they had to work (choice condition). On no-choice days, and on choice days before Dox, all groups lever pressed about the same amount. But after Dox, the mutant animals with elevated dopamine again worked almost twice as hard as the others to receive the preferred food. These data provide evidence that dopamine directly scales behavioral performance on goal-directed tasks, in the absence of new learning. Cagniard, B., Beeler, J.A., Britt, J.P., McGehee, D.S., Marinelli, M., and Zhuang, X. Dopamine Scales Performance in the Absence of New Learning, Neuron, 51, pp. 541-547, 2006.

Repeated Cocaine Self-Administration Alters Processing of Cocaine-Related Information in Rat Prefrontal Cortex

Cocaine addicts persist in compulsive drug seeking in the face of known harm. The hypofrontality hypothesis suggests that long-term cocaine exposure reduces the ability of the prefrontal cortex (PFC) to control behavior. A more complex suggestion about PFC function in drug addiction is that lower basal activity may serve to amplify responses to drugs and drug conditioned stimuli, allowing them to exert greater control over behavior. Drs. Sun and Rebec carried out experiments in a rat animal model to examine changes in PFC activity after drug exposure. They monitored the electrophysiological activity of PFC neurons during three weeks of cocaine self-administration. Rats were trained to press a lever to self-administer cocaine in daily 2 hour sessions. In each session, basal activity was measured before the first infusion, and then activity in response to cocaine was measured throughout the session at a time point after each infusion when cocaine effects were maximal (10s), and after the associated environmental stimuli no longer influenced neuronal responses (a period of less than 1s, determined from previous experiments by these investigators). They analyzed the data by comparing neural activity from the first self-administration session with activity from sessions 10-12 and sessions 19-21. In the first self-administration session, the overall firing rate and burst rate of PFC neurons were significantly decreased after cocaine infusions relative to the period immediately before the session (i.e., the basal response). These effects disappeared after 10 days of drug self-administration and were replaced by a significant increase in burst duration and firing rate within a burst. However, the level of basal activity was significantly decreased after multiple weeks of cocaine exposure. These data support the view that repeated sessions of cocaine self-administration decrease basal PFC activity, but at the same time, burst-related firing in response to cocaine infusions is increased. Thus, the data are consistent with the hypothesis that processing of cocaine-related information is enhanced after chronic exposure and may contribute to increased control by cocaine over cocaine-seeking behavior. Collectively, these findings and others indicate that increased dopamine D1 receptor-mediated signaling in the PFC after chronic exposure to cocaine may be an important mechanism underlying compulsive cocaine seeking. Sun, W. and Rebec, G.V. Repeated Cocaine Self-Administration Alters Processing of Cocaine-Related Information in Rat Prefrontal Cortex. Journal of Neuroscience, 26, pp. 8004-8008, 2006.

Environmentally Enriched Conditions Reduce Impulsivity in an Animal Model

Rats reared in an enriched environment (EE) show enhanced cortical plasticity and improved learning. EE also protects against the development of drug abuse behavior in animal models of vulnerability such as i.v. self-administration. As socially isolated (SI) rats react more intensely to light and sound stimuli, they may more easily acquire self-administration because they are more emotionally responsive. A recent study by Dr. George Rebec suggests that either greater arousal, or impaired cognitive function, on the part of SI reared animals interferes with learning a complex appetitive task. In this study all rats were initially cross-fostered to a single mother to control for effects of rearing. At post-natal day 45, they were food deprived to 85% body weight and subjected to three sequential phases of an experiment as follows: Phase I. Associate licking sucrose from a spout with the feeder cue (tone + light). Phase II. Train contingent nose poke responses to elicit this feeder cue; when the light was illuminated animals could nose poke into either of two holes where sucrose was delivered and the tone was provided. Phase III. Only one nose poke hole was lit and nose pokes into that hole activated the feeder cue, followed by sucrose delivery. EE and SI animals showed no differences in learning during Phases I and II, but during phase III SI animals made significantly more "bad nose pokes" (in the incorrect hole) so their mean number of sessions to learn the task was significantly greater. As this group was not hyperactive in the task it appears that the difference is due to an inability to withhold anticipatory

responses. In support of this interpretation, SI rats also performed more nose pokes during inter-trial intervals when sucrose was not available. SI and EE groups did not differ in consummatory behavior, as lick measures were no different during any part of the session. The investigators infer that for animals reared in SI conditions, salience of rewarding stimuli is increased and these animals are less able to inhibit approach responding. This interpretation is compatible with the previous finding of greater drug self-administration by SI animals. Wood, D.A., Siegel, A.K. and Rebec, G.V. Environmental Enrichment Reduces Impulsivity During Appetitive Conditioning, Physiology & Behavior, 88, pp. 132-137, 2006.

Adolescent Rats are Less Sensitive to Aversive Properties of Drug and Natural Rewards

Adolescence is a time when individuals are likely to initiate drug use. It is also known that whether the initial experiences are positive or negative can contribute to the likelihood of subsequent drug abuse. Recently, investigators using animal models to study reward sensitivity during adolescence have shown that, compared to older rats, younger rats are more sensitive to the rewarding effects of drugs and less sensitive to the aversive effects of withdrawal. Additional findings suggest that adolescent rats are less sensitive to the aversive properties of drugs such as nicotine and amphetamine. NIDA researcher Dr. Cynthia Kuhn and colleagues used conditioned taste aversion (CTA) procedures to examine developmental differences in aversive properties of cocaine and lithium chloride (LiCl). Male adolescent and adult rats were conditioned with 0.2% saccharin followed by saline, cocaine (10, 20 or 40 mg/kg), or LiCl (19 or 76mg/kg). All groups were also tested in an elevated plus maze for individual differences in anxiety, for response to novelty, and peripheral blood was collected for corticosterone. Cocaine aversions were significantly less in adolescent rats only for the 10 and 20 mg/kg doses. Adolescent rats were also less sensitive to LiCl aversions. Neither anxiety, response to novelty, or basal corticosterone predicted the magnitude of CTA to cocaine when conditioned with a single dose of 10 mg/kg. Multiple regression analysis of variables known to predict vulnerability to the reinforcing effects of drugs revealed a significant effect only for age. Thus, individual differences associated with vulnerability to the rewarding effects of drugs of abuse do not appear to influence cocaine's aversive properties. Separate animals were used to measure corticosterone stimulation with 15 mg/kg cocaine. As corticosterone was found to be significantly greater in adolescent rats than in adult rats, investigators suggest that differences in stress reactivity may be responsible for the diminished CTA seen in the adolescents. It is possible that protection from aversive experiences contributes to increased risk taking and greater impulsivity during adolescent development. Schramm-Sapyta, N.L., Morris, R.W. and Kuhn, C.M. Adolescent Rats Are Protected from the Conditioned Aversive Properties of Cocaine and Lithium Chloride, Pharmacology, Biochemistry and Behavior, 84, pp. 344-352, 2006.

Impulsivity in Methamphetamine Abusers is Correlated with Cognitive Impairment

Methamphetamine dependent individuals show impairments of verbal memory and cognitive inhibition. On the basis of these and other findings it has been argued that drug dependence is characterized by decreased response inhibition and heightened impulsivity. As impulsivity has been observed to predict relapse, it is important to understand the mechanisms of poor cognitive inhibition in drug abusers. Dr. Suzanne Mitchell and her collaborators have been using delay discounting to measure impulsivity in methamphetamine - dependent subjects recruited from treatment programs in Portland, Oregon. Prior studies with this procedure reveal that drug-dependent individuals compared to non-users show greater impulsivity by selecting small immediate

rewards over larger delayed rewards. Forty-one subjects meeting DSM-IV criteria for methamphetamine dependence were rated for psychiatric symptoms and took battery of standard neuropsychological tests to assess cognition. Performance on the delayed discounting task was measured by "indifference point", the point at which preference switches from immediate to delayed rewards. Indifference points for a given reward value (e.g., $100) can be fit with an indifference curve that represents more impulsive choices by steeper gradients. Results indicated greater severity of psychiatric symptoms in chronic methamphetamine users, and that methamphetamine subjects were more rigid than controls. Severity of use, duration of use, average daily use and duration of abstinence were not correlated with these measures. Methamphetamine and control subjects differed on tests suggesting memory impairment in the methamphetamine group. Substantial group differences were seen in the extent to which subjects discounted delayed rewards. For all delays tested indifference points for the methamphetamine group were significantly less than for controls and methamphetamine gradients were significantly greater; thus, methamphetamine subjects discounted future rewards more. This measure was not related to use history, severity or time since last use. The researchers suggest that greater impulsivity seen in methamphetamine dependence may result from impairments of working memory. While increased working memory load does lead to greater impulsivity, it is also possible that methamphetamine subjects may differ from non-users in the incentive salience of rewards. Hoffman, W.F., Moore, M., Tamplin, R., McFarland, B., Hitzemann, R.J. and Mitchell, S.H. Neuropsychological Function and Delay Discounting in Methamphetamine-Dependent Individuals, Psychopharmacology, 188, pp. 162-170, 2006.

Sex Differences in Decision Making on the Iowa Gambling Task

On the Iowa Gambling Task subjects choose cards from four decks that provide monetary gains or monetary losses. Selections from two of the decks result in an overall net gain, but choices from the other two produce an overall net loss. Optimal performance requires the subject to identify and select from a low pay/low loss deck, and men typically select significantly more cards from these advantageous decks whereas women consistently choose more cards from disadvantageous decks with high penalties. Successful performance depends on integrity of the prefrontal cortex (PFC) and measurement of PFC activation during the task reveals that men activate bilateral areas of the dorsolateral PFC, right lateral orbital PFC, and right parietal lobe. By contrast, women activate a smaller region of the left medial orbital PFC. Recently, Dr. William Overman conducted a study to determine if a task known to activate dorsolateral PFC areas might improve IGT performance in women. One task that activates this region is deliberation of moral personal dilemmas. In the present study, 200 participants were divided into three groups and asked to contemplate a scenario every 10 trials - either a moral personal dilemma, a moral impersonal dilemma, or a nonmoral dilemma. Results show that sex differences on the Iowa Gambling Task were eliminated in groups contemplating PM whereas men in the other two conditions selected a significantly greater proportion of cards from advantageous decks than did the women. Finally, in order to test whether improvement might be due to generalized emotional arousal, another 229 students were tested after moral personal dilemma deliberation on a Wisconsin Card Sort Task that relies upon dorsolateral and dorsomedial PFC substrates. Wisconsin Card Sort Task scores were unaffected by moral personal dilemma deliberation suggesting that improvement by females on the Iowa Gambling Task is due to a shift in activation of PFC regions and enhanced cognitive control over an emotional response to rewards in the disadvantageous decks. Overman, W., Graham, L., Redmond, A. Eubank, R., Boettcher, L., Samplawski, O. and Walsh, K. Contemplation of Moral Dilemmas Eliminates Sex Differences on the Iowa Gambling Task. Behavioral Neuroscience, 120, pp. 817-825, 2006.

Cannabinoid Receptors Modulate Morphine Reinforcement through Ventral Pallidal GABA

Previous research has demonstrated that endogenous cannabinoid-1 (CB-1) receptors are involved in the reinforcing effects of opiates but not of the psychostimulant, cocaine. However, the mechanism responsible for this modulation is not known. Dr. Loren Parsons has been investigating the role of GABAergic transmission in the ventral pallidum (VP) and dopaminergic activity in the nucleus accumbens (NAS) in the ability of a CB-1 antagonist, SR 141716 (SR, or Rimonabant) to block heroin reinforcement. He tested SR effects on: 1) morphine decreases in VP GABA, 2) morphine increases in NAS dopamine, 3) cocaine decreases in VP GABA, 4) cocaine increases in NAS DA, 5) heroin (self-administration after SR infusion into the VP or NAS, and 6) cocaine self-administration after peripheral SR treatment. An additional study assessed effects of the CB-1 agonist, WIN 55,212, on VP GABA release and determined if the opiate mu antagonist, naloxone, could block WIN 55,212 effects. The investigator found that while SR blocked morphine-induced decreases in VP GABA, it was without effect on morphine-induced dopamine increase in the NAS. Conversely, SR had no effect on cocaine-induced decreases of VP GABA, and increases in NAS DA. SR infused centrally into the NAS but not the VP, attenuated heroin self-administration. Peripherally administered SR was without effect on cocaine self-administration. However, when SR was peripherally administered, it significantly decreased VP GABA and this effect could be blocked by prior naloxone administration. These findings suggest that CB-1 receptors modulate opiate, but not cocaine, reward by changing VP GABAergic activity. Since CB-1 antagonist infusions into the NAS decreased heroin self-administration, it appears that CB-1 attenuation of opiate reward is accomplished by altering GABA in the VP. The neural mechanisms by which NAS CB-1 receptors alter opiate-induced decreases of VP GABA are yet to be determined, but the authors speculate that cyclic-AMP, and/or changes in NAS glutamate, may be involved. Caille, S. and Parsons, L.H. Cannabinoid Modulation of Opiate Reinforcement through the Ventral Striatopallidal Pathway, Neuropsychopharmacology, 31, pp. 804-813, 2006.

Conditioned Psychostimulant Effects Are Moderated by Age and Sex

Individual differences in locomotor response to novelty predict the behavioral activating effects and self-administration of psychomotor stimulants. Rats that are more reactive in a novel environment (high responders, HR) show greater drug-induced stimulation and more readily acquire self-administration of amphetamine, cocaine, and nicotine, than their low-responding (LR) counterparts. Dr. Michael Bardo and colleagues recently completed a study to determine if individual differences in novelty response predict: 1) Locomotor sensitization to the psychostimulant, methylphenidate or 2) methylphenidate-conditioned locomotion in the drug-paired environment. Moreover, they sought to determine if novelty response would predict behavioral change differentially for male versus female rats and for adolescent (25 days old) versus adult (60 days old). A median split between HR and LR rats was based on locomotor counts and time spent in a novel compartment. Rats were then treated with saline, 3.0 or 10.0 mg/kg methylphenidate, for 10 days. After 14 days of withdrawal animals were assessed for conditioned locomotor activity with saline and for sensitization with a single 10.0mg/kg methylphenidate injection in the test cage. The investigators found: 1) adolescent rats selected novelty in a free choice situation significantly more than adults; however, choice did not predict methylphenidate sensitization or conditioning; 2) HR showed greater methylphenidate behavioral activation and adult females had greater dose-dependent activity than adult males; 3) Adolescent rats developed sensitization at 3.0 mg/kg METH, whereas adults only sensitized to 10 mg/kg; 4) only HR

adult females had increased sensitization to 5) All animals showed a methylphenidate conditioned to the test environment except the adult males; 6) HR rats showed an greater methylphenidate conditioned locomotor activity but a HR>LR difference was only significant for adolescent males and adult females; 6) only HR adult feamlaes showed greater sensitization on the methylphenidate challenge. These findings suggest that: 1) Gender differences in sensitization emerge during development; 2) adolescent rats in general are more sensitive to psychomotor stimulant sensitization; 3) Initial response to novelty predicts methylphenidate -induced conditioned locomotion to the test chamber and sensitized behavioral response to methylphenidate; and 4) This individual difference is moderated by both age and gender. Wooters, T.E., Dwoskin, L.P. and Bardo, M.T. Age and Sex Differences in the Locomotor Effect of Repeated Methylphenidate in Rats Classified as High or Low Novelty Responders. Psychopharmacology, 188, pp. 18-27, 2006.

Escalation of Cocaine Self-Administration Is not Associated with Neuroadaptations in Dopamine Transporter

Neuroadaptations produced by continued cocaine exposure are believed to be important in the mechanisms underlying addiction. Investigators at the University of California in Santa Barbara recently sought to determine if extended access to cocaine resulted in alterations of the dopamine transporter (DAT). Rats were trained to self-administer 0.25 mg cocaine per infusion in daily 1 h sessions until their responding was stable. They were then assigned to 1 h or 6 h cocaine self-administration group for 8 consecutive days of cocaine self-administration, followed by 14 days of abstinence. Following the abstinence period, receptor autoradiography was used to quantify membrane DAT. Animals in the 6 h group showed significant increases in cocaine infusions over eight days, while 1 h access rats maintained steady intake. However, rats in the1 h condition showed higher densities of DAT in the nucleus accumbens core and the dorsal striatum, relative to rats not exposed to cocaine and rats exposed to cocaine for 6 h per day. There were no differences in DAT densities in the nucleus accumbens shell, the medial prefrontal cortex, or the ventral tegmental area among the groups. These findings suggest that escalation to uncontrollable cocaine intake is associated with different kinds of neuroadaptations than have been observed in pre-synaptic regions of the central dopamine system. Ben-Shahar, O., Moscarello, J.M. and Ettenberg, A. One Hour, but not Six Hours, of Daily Access to Self-Administered Cocaine Results in Elevated Levels of the Dopamine Transporter, Brain Research, 1095, pp. 148-153, 2006.

Menstrual Cycle Phase Effects on Nicotine Withdrawal and Cigarette Craving: A Review

Research over the past several years has uncovered numerous male-female differences in cigarette smoking. In studies of quitting, for example, women are less successful than men, and there is clinical and laboratory evidence that nicotine versus non-nicotine factors play a differential role in smoking for men versus women. The menstrual cycle has been shown to be a factor in smoking for women with several studies finding more smoking in the luteal phase (post-ovulation/premenstrual) of the cycle than in the follicular phase (menses/pre-ovulation). Researchers at the Medical University of South Carolina conducted a literature review to examine whether this higher level of smoking in the luteal phase reflects greater nicotine withdrawal and craving. Using MEDLINE and PsychInfo databases, a total of 13 studies were identified, of which 3 examined the naturalistic time course of withdrawal and craving under ad libitum smoking, 6 examined these measures under laboratory conditions of abstinence, and 4 conducted comparisons of the two conditions. The review yielded mixed results although there was evidence for greater withdrawal and craving in the luteal phase. The authors conclude that "the most striking

implication from this review is the need for further research," noting that inconsistencies in outcomes among studies could be due to heterogeneity of methods including differences in statistical power to detect cycle effects, inconsistency in identification and corroboration of menstrual cycle phase, definition of cycle phase (two phases versus four-phases), and inclusion versus exclusion of women with a history of premenstrual dysphoric disorder. The authors recommend that future research in this area uses hormonal verification of menstrual phase status and follows a four-phase conceptualization: early follicular, late follicular, early luteal, and late luteal. This area of research has important clinical implications for choice of quit date for nicotine cessation and thus warrants future study. Carpenter, M.J., Upadhyaya, H.P., LaRowe, S.D., Saladin, M.E., and Brady, K.T. Menstrual Cycle Phase Effects on Nicotine Withdrawal and Cigarette Craving. A Review. Nicotine & Tobacco Research, 8, pp. 627-638, 2006.

Director's Report to the National Advisory Council on Drug Abuse - February, 2007

Research Findings - Behavioral and Brain Development Research

Effects of Prenatal Methamphetamine Exposure, Polydrug Exposure, and Poverty on Intrauterine Growth

Methamphetamine use among pregnant women is an increasing problem in the United States. Effects of methamphetamine use during pregnancy on fetal growth have not been reported in large, prospective studies. Dr. Barry Lester and his colleagues at four clinical centers in California, Oklahoma, Hawaii and Iowa examined the neonatal growth effects of prenatal methamphetamine exposure. Of 13,808 subjects screened, 1,618 were eligible and consented, among which 84 were methamphetamine exposed, and 1,534 were unexposed. Both groups included prenatal alcohol, tobacco, or marijuana use, but excluded use of opiates, LSD, PCP or cocaine only. The methamphetamine exposed group was 3.5 times more likely to be small for gestational age than the unexposed group. Mothers who used tobacco during pregnancy were nearly two times more likely to have small-for-gestational-age infants. In addition, less maternal weight gain during pregnancy was more likely to result in a small-for-gestational-age infant. Birth weight in the methamphetamine exposed group was lower than the unexposed group. These findings suggest that prenatal methamphetamine use is associated with fetal growth restriction after adjusting for covariates. Continued follow-up will determine if these infants are at increased risk for growth and/or neurodevelopmental deficits in the future. Smith, L.M., LaGasse, L.L., Derauf, C., Grant, P., Shah, R., Arria, A., Huestis, M., Haning, W., Strauss, A., Della Grotta, S., Liu, J., and Lester, B.M. The Infant Development, Environment, and Lifestyle Study: Effects of Prenatal Methamphetamine Exposure, Polydrug Exposure, and Poverty on Interuterine Growth, Pediatrics, 118(3), pp. 1149-1156, 2006.

Neuroimaging of Frontal White Matter and Executive Functioning in Cocaine-Exposed Children

Researchers at the University of Florida have reported on the use of Diffusion Tensor Imaging (DTI) to assess frontal white matter development in prenatally cocaine-exposed and non-exposed children, and also have reported on associations between frontal white matter development and executive functioning in these children. DTI uses magnetic resonance imaging (MRI) to investigate white matter microstructure by measuring the movement, or diffusion, of water molecules in tissues. Using different DTI quantification indices, researchers study maturation of white matter tracts. Executive functioning is a concept that describes a diverse set of skills involved in goal-directed behavior such as problem solving, and includes skills such as attention control, inhibition abilities, and management of cognitive, emotional, and behavioral functions. Executive functioning was assessed using two frequently

used instruments (the Stroop color and word test and the Trail Making Test). The sample for these analyses (tested and scanned in the age range 9.6 to 12.2 years) was drawn from an ongoing longitudinal study of development following prenatal cocaine exposure, and involved 28 cocaine-exposed children and 25 non-exposed children with similar sociodemographic characteristics. The investigators conclude that prenatal cocaine exposure, alone and in combination with exposure to other drugs, is associated with slightly poorer executive functioning and with subtle microstrucural characteristics that may suggest less mature development of frontal white matter pathways. They also state that the relative contribution of postnatal environmental factors (e.g., caregiving environment) on brain development and behavioral functioning in polydrug-exposed children awaits further research. Warner, T.D., Behnke, M., Eyler, F.D., et al. Diffusion Tensor Imaging of Frontal White Matter and Executive Functioning in Cocaine-Exposed Children. Pediatrics, 118, pp. 2014-2024, 2006.

Discrete Opioid Gene Expression Impairment in the Human Fetal Brain Associated with Maternal Marijuana Use

The most commonly used illicit drug by pregnant women is marijuana. In light of the strong interactions between the cannabinoid and Opioid systems, Dr. Yasmin Hurd and her colleagues investigated the effects of in utero marijuana exposure on expression levels of Opioid-related genes in the human fetal forebrain. The Opioid peptide precursors (preprodynorphin and preproenkephalin (PENK)) and receptor (mu, kappa and delta) mRNA expression were assessed in distinct brain regions in 42 midgestation fetuses from saline-induced voluntary abortions and the effects of prenatal cannabis exposure was analyzed while controlling for confounding variables such as maternal alcohol and cigarette use, fetal age, sex, growth measure and post-mortem interval. Prenatal cannabis exposure was found to be significantly correlated with increased mu receptor expression in the amygdala, reduced kappa receptor mRNA in mediodorsal thalamic nucleus and reduced preproenkephalin expression in the caudal putamen. Prenatal alcohol exposure was found to primarily influence kappa receptor mRNA, with reduced levels in the amygdala, claustrum, putamen and insula cortex. No significant effect of prenatal nicotine exposure was seen in the analyses performed. These results indicate that maternal cannabis and alcohol exposure during pregnancy differentially affect opioid-related genes in distinct brain circuits; alterations that may have long-term effects on cognitive and emotional behaviors. Wang, X., Dow-Edwards, D., Anderson, V., Minkoff, H., and Hurd, Y.L. Discrete Opioid Gene Expression Impairment in the Human Fetal Brain Associated with Maternal Marijuana Use. Pharmacogenomics Journal, 6(4), pp. 255-264, 2006.

Prenatal Cocaine Exposure and Risk for Developing Learning Disabilities

Dr. Emmalee Bandstra and her colleagues at the University of Miami examined prenatal cocaine exposure and risk for developing a learning disability (LD) or impaired intellectual functioning by age seven in a sample of 409 children (212 cocaine-exposed, 197 non-cocaine-exposed) born full term and enrolled prospectively at birth. LDs were categorized based on ability-achievement discrepancy scores. The cocaine-exposed children had 2.8 times greater risk of developing a LD by age seven than non-cocaine-exposed children. No differences were found in the estimate of relative risk for impaired intellectual functioning (IQ below 70) between children with and without prenatal cocaine exposure. Results remained stable with adjustment for multiple child and caregiver covariates including but not limited to maternal education, caregiver substance use, the home environment, and attendance in Head Start/prekindergarten suggesting that children with prenatal cocaine exposure are at increased risk for developing a learning disability by age seven when

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compared to their non-cocaine-exposed peers. Morrow, C.E., Culbertson, J.L., Accornero, V.H., Xue, L., Anthony, J.C., and Bandstra, E.S. Learning Disabilities and Intellectual Functioning in School-Aged Children with Prenatal Cocaine Exposure. Developmental Neuropsychology, 30(3), pp. 905-931, 2006.

Prenatal Smoking Exposure and Developmental Patterns of Conduct Problems in Boys

There are reports in the research literature of associations between prenatal smoking exposure and increased risk of conduct problems among offspring. This report examines associations of prenatal smoking exposure with oppositional defiant disorder (ODD) and attention-deficit/hyperactivity disorder (ADHD) in young boys (during first grade), and with developmental patterns of delinquent behavior during adolescence. Researchers from the University of Illinois at Chicago and from the University of Pittsburgh examined data from the Pittsburgh Youth Study, a prospective, population-based study of conduct problems in boys. In the analyses for this report, prenatal smoking exposure was examined relative to the presence of ODD and ADHD, singly and as comorbid conditions at age 7 years. Also investigated was the association of prenatal exposure with the timing of onset of both mild and more serious conduct problems, using in-depth measures of delinquency administered prospectively from early school age through age 19 years. Multiple potentially confounding factors were controlled in multivariate analyses. The investigators report that exposed boys were more likely to show evidence of ODD and comorbid ODD-ADHD, but not ADHD alone. They also report that exposed boys were more likely to have an earlier onset of significant delinquent behavior. The authors note that whether prenatal smoking plays an etiological role in, or is a marker for risk of antisocial behavior, it is clear that the offspring of prenatal smokers as a group are at increased risk for an early-starter pathway to antisocial behavior that is evident as early as first grade. Wakschlag, L.S., Pickett, K.E., Kasza, K.E., and Loeber, R. Is Prenatal Smoking Associated with a Developmental Pattern of Conduct Problems in Young Boys? Journal of the American Academy of Child and Adolescent Psychiatry, 45, pp. 461-467, 2006.

Prenatal Cannabis Exposure Increases Heroin Seeking with Allostatic Changes in Limbic Enkephalin Systems in Adulthood

Very little is known about the long-term consequences of prenatal cannabis exposure on behavior and neural systems. Dr Yasmin Hurd and her colleagues used an animal model to study the effects of prenatal exposure to _9-tetrahydrocannabinol (THC) on heroin self-administration behavior and opioid neural systems in adult male rats (postnatal day 62) that were exposed to THC from gestational day five to postnatal day two. They found that THC-exposed rats exhibited shorter latency to pressing a lever for heroin, responded more for low heroin doses, and had more readily sought heroin when stressed and during drug extinction. Neurobiologically, they found that THC exposure reduced preproenkephalin (PENK) mRNA expression in the nucleus accumbens during early development, but this was elevated in adulthood. PENK mRNA was also increased in the central and medial amygdala in adult THC-exposed animals. Finally, THC animals had reduced heroin-induced locomotor activity and nucleus accumbens _ opioid receptor coupling. This study demonstrates that the effects of prenatal THC exposure endure into adulthood and that these effects are evident on heroin-seeking behavior and in changes in mesocorticolimbic PENK systems relevant to drug motivation/reward and stress responses. Spano, M.S., Ellgren, M., Wang, X., and Hurd, Y.L. Prenatal Cannabis Exposure Increases Heroin Seeking with Allostatic Changes in Limbic Enkephalin Systems in Adulthood. Biological Psychiatry, July 27, 2006.

Intrauterine Growth Restriction and Prenatal Substance Exposure

in Term Infants and Risk for Hypertension at Age Six

Researchers from the Maternal Lifestyle Study, a prospective longitudinal multi-site study of prenatal cocaine and opiate exposure, investigated the association between intrauterine growth restriction (IUGR) status at birth among full-term infants, exposure to substance use during pregnancy, and risk of hypertension at six years of age. Of the 1,388 infants (600 cocaine exposed, 781 non-exposed, and seven indeterminate, matched by gestational age, race, and sex), enrolled in this study, 950 children (415 exposed, 535 non-exposed) completed the age six assessment, 891 had blood pressure data and of these, 516 were born at full term. One hundred and forty-four (28%) of the 516 children had a diagnosis of IUGR at birth. At six years of age, 93 (19%) of 516 children had hypertension, defined as either systolic or diastolic blood pressure higher than the 95th percentile for sex, age, and height. Of 144 children with IUGR, 35 (24%) had hypertension as compared with 58 (16%) of 372 children without IUGR. The study did not find any association with cocaine, opiate, marijuana, tobacco, or alcohol use during pregnancy and hypertension at 6 years of age. Twenty percent of cocaine-exposed children had hypertension as compared with 16% of nonexposed children. Intrauterine growth restriction status at birth was significantly associated with hypertension adjusting for site; maternal race, education, and tobacco, marijuana, alcohol, and cocaine use during pregnancy; and child's current body mass index. In term infants, IUGR is linked to risk of hypertension in early childhood, which may be a marker for adult cardiovascular disease. Shankaran, S., Das, A., Bauer, C.R., Bada, H., Lester, B., Wright, L., Higgins, R., and Poole, K. Fetal Origin of Childhood Disease: Intrauterine Growth Restriction in Term Infants and Risk for Hypertension at Age Six. Archives of Pediatrics and Adolescent Medicine, 160(9), pp. 977-981, 2006.

Perinatal HIV Infection, In Utero Substance Exposure and Cognitive Development in Young Children

Researchers from the Women and Infants transmission study examined the effect of HIV in combination with other health and social factors including in utero exposure to drugs on the development of cognitive abilities of children perinatally exposed to HIV and substances of abuse. Serial cognitive assessments were performed for 117 children who were infected vertically and 422 children (50% African American, 32% Hispanic, and 12% Caucasian) who were exposed to but not infected with HIV. Forty-one percent of the children were exposed to cocaine, heroin, or methadone in utero as measured by self-report and/or urine screen and 63% were exposed to alcohol, tobacco, or marijuana as measured by self-report. Repeated-measures analyses were used to evaluate the neurocognitive development of these children between the ages of three and seven years. Children with HIV/no Class C conditions were more likely to experience exposure to hard drugs during pregnancy than were children without HIV. (Class C refers to the CDC categorization of clinical conditions or symptoms of HIV infection considered severe including recurrent serious bacterial infections and encephalopathy). Children with HIV infection and class C status scored significantly lower in all domains of cognitive development, across all time points, than did those who were HIV infected without an AIDS-defining illness and those who were HIV exposed but not infected adjusting for presence of hard and soft substance exposure and other maternal factors during pregnancy and delivery, social demographic variables, test administration variables, and maternal and child disease stages. There were no significant differences between the two latter groups in General Cognitive Index or specific domain scores. Rates of change in cognitive development were parallel among all three groups over a period of four years. Factors that were associated consistently and significantly with lower mean scores were HIV status, number of times an examination had been completed previously, primary language, maternal education, and gender. No factors were

related to rate of change of any mean domain score. An early AIDS-defining illness increased the risk of chronic static encephalopathy during the preschool and early school age years. Children with HIV infection but no class C event performed as well as non-infected children in measures of general cognitive ability. No significantly different profiles of strengths and weaknesses for verbal, perceptual-performance, quantitative, or memory functioning were observed among children with or without HIV infection. The authors recommend that future research include various environmental stressors in these children's lives including current parental drug use. Smith, R., Malee, K., Leighty, R., Brouwers, P., Mellins, C., Hittelman, J., Chase, C., Blasini, I., and the Women and Infants Transmission Study Group. Effects of Perinatal HIV Infection and Associated Risk Factors on Cognitive Development among Young Children. Pediatrics, 117(3), pp. 851-862, 2006.

Prenatal Exposure to Cocaine and Childhood Exposure to Violence: Association with Friends' and Own Substance Use

Children exposed to substances of abuse in utero may also be at risk for environmental stressors during childhood that can influence their neurodevelopmental trajectories and risk for substance use. This study examined the association between exposure to violence during childhood and own and friends' substance use in a sample of children from a prospective longitudinal study of in-utero cocaine exposure (IUCE). One hundred and four children were assessed at age 8.5, 9.5, and 11 years with the Violence Exposure Scale for Children-Revised (VEX-R) and the Substance Exposure Assessment, a child-report measure of their own and their friends' ATOD use. The sample consisted of 90% African-American/ Caribbean children (mean age 8.5 years, SD 3 years), 53% males, and 49% with IUCE. Twenty-eight percent of the sample reported own use of any ATOD by age 11. The percentage of children who reported having substance-using friends was 12% at 8.5 years, 25% by 9.5 years, and 45% by 11 years. In multivariate survival analyses controlling for caregiver type, in-utero cocaine exposure category (heavy, light, and none), and child gender, children in the upper quartile of violence exposure at age 8.5 years were at significantly greater risk of having reported friends' use of ATOD by age 11 compared to those in the first through third quartiles. Quartiles of the violence exposure score, however, were not significantly associated with children's acknowledgment of their own use. Findings suggest an association between exposure to violence in childhood and report of peer ATOD use at school age. Campaigns to prevent ATOD use should address the impact of childhood exposure to violence. Joseph, N.P., Augstyn, M., Cabral, H., and Frank, D.A. Preadolescents' Report of Exposure to Violence: Association with Friends' and Own Substance Use. Journal of Adolescent Health, 38(6), pp. 669-674, 2006.

Maternal Cocaine Use and Caregiving Status: Group Differences in Caregiver and Infant Risk Variables

This study examined differences between cocaine and non-cocaine-using mothers, and between parental and non-parental caregivers of cocaine-exposed infants on caregiver childhood trauma, psychiatric symptoms, demographic, and perinatal risks. Participants included 115 cocaine and 105 non-cocaine mother-infant dyads recruited at delivery. Approximately 19% of cocaine mothers lost custody of their infants by one month of infant age compared to 0.02% of non-cocaine mothers. Mothers who used cocaine during pregnancy had higher demographic and obstetric risks and their infants had higher perinatal risks. Birth mothers who retained custody of their infants had higher demographic risks and perinatal risks, higher childhood trauma, and higher psychiatric symptoms compared to birth mothers who did not use cocaine and non-parental caregivers of cocaine-exposed infants. Results highlight the importance of addressing childhood trauma issues and current

psychiatric symptoms in substance abuse treatment with women who engaged in substance use during pregnancy. Eiden, R.D., Foote, A., and Schuetze, P. Maternal Cocaine Use and Caregiving Status: Group Differences in Caregiver and Infant Risk Variables. Addictive Behaviors, July 10, 2006.

Gender, Substance Exposure, Lymphocyte Populations, Plasma HIV RNA Levels, and Disease Progression in a Cohort of HIV Exposed Children

Researchers from the Women and Infants Transmission study analyzed blood samples from antiretroviral therapy-treated, HIV-infected children (n = 158) and HIV-uninfected children (n = 1801) to examine gender and substance exposure differences in lymphocyte subsets and plasma RNA levels. In terms of immunologic parameters, for anti-retroviral therapy (ART) treated, HIV-infected children, maternal hard drug use during pregnancy showed a trend toward children having lower CD4+ cell counts (p= .06). Children whose mothers did not use hard drugs during pregnancy also had, on average, greater CD16+ CD56+ natural killer cell counts. In contrast, children exposed to hard drugs during pregnancy but not HIV infected had a higher CD4+ percentage. In terms of virologic parameters and mortality rates, ART-treated, HIV-infected children whose mothers used hard drugs during pregnancy had a higher mean log RNA level. Maternal alcohol use during pregnancy had no effect on CD4+ cell counts or percentages, however, ART-treated, HIV-infected children whose mothers did not use alcohol during pregnancy had on average higher absolute CD19+ cell counts and higher mean log RNA level. ART-treated, HIV-infected female children had lower plasma RNA levels than did their male counterparts, but lymphocyte differences were not noted. Despite their higher plasma RNA level, a greater proportion of male children survived through 8 years of age. There were no gender differences with respect to the age of diagnosis of HIV, time to antiretroviral therapy after diagnosis of HIV, or type of antiretroviral therapy. Lymphocyte differences were noted for uninfected children. Plasma RNA levels differed among antiretroviral therapy-treated, HIV-infected children according to gender, in a manner similar to that noted in previous pediatric and adult studies. Lymphocyte subsets varied according to gender in a cohort of HIV-exposed but uninfected children. Most importantly, overall mortality rates for this cohort differed according to gender. Foca, M., Moye, J., Chu, C., Matthews, Y., Rich, K., Handelsman, E., Luzuriaga, K., Paul, M., Diaz, C., and the Women and Infants Transmission Study. Gender Differences in Lympocyte Populations, Plasma HIV RNA Levels, and Disease Progression in a Cohort of Children Born to Women Infected with HIV. Pediatrics, 118(1) pp. 146-155, 2006.

Maternal Cocaine Use During Pregnancy and Caregiving Status: Group Differences in Caregiver and Infant Risk Variables

This study examined differences between caregiver childhood trauma, psychiatric symptoms, demographic variables, perinatal risks and infant birth outcomes between cocaine and non-cocaine-using mothers, and within the cocaine group, between parental and non-parental caregivers taking part in a longitudinal study on the long term effects of prenatal substance exposure. Two hundred and twenty mother-infant dyads including 115 cocaine exposed (93 parental care, 22 foster care) and 105 non-cocaine were recruited at delivery. Approximately 19% of cocaine mothers lost custody of their infants by 1 month of infant age compared to 0.02% of non-cocaine mothers. Mothers who used cocaine during pregnancy had higher demographic and obstetric risks and their infants had lower birth weights. Birth mothers who retained custody of their infants had higher demographic risks and perinatal risks, higher childhood trauma (childhood emotional abuse, sexual abuse, and emotional neglect), and higher psychiatric symptoms (PTSD, antisocial behavior, anger/hostility) compared to birth mothers who did not use cocaine and non-

parental caregivers of cocaine-exposed infants. Mothers in the cocaine group who retained custody of their children used more cigarettes and alcohol postnatally compared to non-cocaine users. The results highlight the importance of addressing childhood trauma issues and current psychiatric symptoms in substance abuse treatment and parenting interventions for mothers who used substances during pregnancy. Treatment planning should include treatment for other substances of abuse including cigarettes. Eiden, R.D., Foote, A., and Schuetze, P. Maternal Cocaine Use and Caregiving Status: Group Differences in Caregiver and Infant Risk Variables. Addictive Behaviors, July 10, 2006.

A Framework to Monitor Environment-induced Major Genes for Developmental Trajectories: Implications for a Prenatal Cocaine Exposure Study

Whether there are specific genes involved in response to different environmental agents and how such genes regulate developmental trajectories during lifetime are of fundamental importance in health, clinical and pharmaceutical research. Drs. Fonda Eyler, Marylou Behnke and colleagues at the University of Florida developed a novel statistical model for monitoring environment-induced genes of major effects on longitudinal outcomes of a trait. This model is derived within the maximum likelihood framework, incorporated by mathematical aspects of growth and developmental processes. A typical structural model is implemented to approximate time-dependent covariance matrices for the longitudinal trait. This model allows for a number of biologically meaningful hypothesis tests regarding the effects of major genes on overall growth trajectories or particular stages of development. It can be used to test whether and how major genetic effects are expressed differently under altered environmental agents. In a well-designed case-control study, the model has been employed to detect cocaine-dependent genes that affect growth trajectories for head circumference during childhood. The detected gene triggers significant effects on growth curves in both cocaine-exposed (case) and unexposed groups (control), but with different extents. Significant genotype-environment interactions due to this so-called environment-sensitive gene are promising for further studies toward its genomic mapping using polymorphic molecular markers. Hou, W., Garvan, C.W., Littell, R.C., Behnke, M., Eyler, F.D., and Wu, R. A Framework to Monitor Environment-Induced Major Genes for Developmental Trajectories: Implication for a Prenatal Cocaine Exposure Study. Statistics in Medicine, 25, pp. 4020-4035, 2006.

Bootstrapping Conceptual Deduction Using Physical Connection: Rethinking Frontal Cortex

Infants as young as 9 months of age have the ability to deduce abstract rules, but only if the items to be conceptually related are presented physically connected. Adele Diamond at the University of British Columbia hypothesizes that the periarcuate region of the frontal lobe (and its human homologue) is the crucial region responsible for learning abstract rules in the absence of physical connections. This region of the brain may be too immature in infants under the age of 21 months and thus the reason that a physical connection between items is necessary in order for infants to grasp the conceptual relationship. Many young children with developmental delays have difficulty learning abstract principles which could be due to a biological abnormality in the periarcuate. Dr. Diamond proposes that children with learning delays and especially those with autism should be able to perceive a conceptual connection if the items are presented physically connected. Diamond, A. Bootstrapping Conceptual Deduction Using Physical Connection: Rethinking Frontal Cortex, Trends in Cognitive Sciences, 10(5), pp. 212-218, 2006.

Development of Cognitive Control and Executive Functions from 4 to 13 Years: Evidence from Manipulations of Memory, Inhibition, and Task Switching

This study describes the developmental progression and interactions over development of working memory, inhibition and cognitive flexibility (switching between tasks or rules) abilities. A battery of interrelated tasks that could be used across a wide age range and that could be independently and systematically varied in order to manipulate memory and cognitive control skills were administered to 325 participants (approximately 30 per age from 4 to 13 years and young adults). The results indicated that as long as the rules remained constant, the youngest children could hold information in mind and could inhibit a dominant response and could also combine working memory and inhibition skills. Cognitive flexibility, even with memory demands kept to a minimum, showed a longer developmental progress with 13- year-olds still not reaching adult levels. Davidson, M., Amso, D., Anderson, L., and Diamond, A. Development of Cognitive Control and Executive Functions from 4 to 13 Years: Evidence from Manipulations of Memory, Inhibition and Task Switching, Neuropsychologia, 44, pp. 2037-2078, 2006.

Functional Correlates of Verbal Memory Deficits Emerging During Nicotine Withdrawal in Abstinent Adolescent Cannabis Users

Cannabis is the most commonly used illicit substance in the adolescent population. Among those teenagers who use cannabis, many of them also smoke tobacco. Dr. Leslie Jacobsen and her colleagues examined the interacting effects of these drugs on verbal learning and memory in twenty adolescent users of tobacco and cannabis users compared to 25 adolescent tobacco users with a minimal use of cannabis. Functional magnetic resonance (fMRI) was conducted to examine whether the modulation of regional activation and functional connectivity was different in cannabis users who continued to smoke versus those experiencing nicotine withdrawal. The results indicated that delayed recall of verbal stimuli was impaired in abstinent cannabis users, but only if they were also going through nicotine withdrawal. The fMRI data indicated a different pattern of activation in those subjects who were abstinent from both marijuana and nicotine with the withdrawal of nicotine selectively increasing task-related activation of posterior regions and disrupting frontoparietal connectivity relative to comparison subjects. Dr. Jacobsen proposes the hypothesis that adolescent cannabis users who also smoke tobacco may be inclined to increase their use of tobacco in order to prevent the attendant decline in cognitive function during nicotine withdrawal. Jacobsen, L., Pugh, K., Constable, R., Westerrveld, M., and Mencl, E. Functional Correlates of Verbal Memory Deficits Emerging During Nicotine Withdrawal in Abstinent Adolescent Cannabis Users. Biological Psychiatry, 59(8) Supplement, pp. 1-10, 2006.

μ Opioid receptor A118G Polymorphism in Association with Striatal Opioid Neuropeptide Gene Expression in Heroin Abusers

μ Opioid receptors are critical for heroin dependence, and A118G SNP of the _ opioid receptor gene (OPRM1) has been linked with heroin abuse. In a sample of European Caucasians, Dr. Yasmin Hurd and colleagues found that approximately 90% of the carriers of the118G allele were heroin users. Postmortem brain analyses showed that preproenkephalin and preprodynorphin genes were downregulated in all heroin users, but that these the effects were exaggerated in 118G subjects and were most prominent for preproenkephalin in the shell of the nucleus accumbens. Reduced opioid neuropeptide transcription was accompanied by increased dynorphin and enkephalin peptide concentrations exclusively in 118G heroin subjects, suggesting that the peptide

processing is associated with the OPRM1 genotype. Abnormal gene expression related to peptide convertase and ubiquitin/proteosome regulation was also evident in heroin users. Taken together, these data suggest that alterations in opioid neuropeptide systems might underlie the enhanced opiate abuse vulnerability apparent in 118G individuals. Drakenber, K., Nikjoshkov, A., Horvath, M.C., Fagergren, P., Gharibyan, A., Saarelainen, K., Rahman, S., Nylander, I., Bakalkin, G., Rajs, J., Keller, E., and Hurd, Y.L. μ Opioid receptor A118G Polymorphism in Association with Striatal Opioid Neuropeptide Gene Expression in Heroin Abusers. Proc Natl Acad Sci. 103(20), pp. 7883-7888, 2006.

C957T Polymorphism of the Dopamine D2 Receptor Gene Modulates the Effect of Nicotine on Working Memory Performance and Cortical Processing Efficiency

Nicotine has been shown to produce behavioral effects that vary across individuals in animals and humans, and recent work has shown that genetic variation at the dopamine D2 receptor (DRD2) predicts response to pharmacotherapy for tobacco dependence. To determine whether a polymorphism of the DRD2 gene, C957T, that alters DRD2 binding availability in humans modifies the effects of nicotine on verbal working memory performance and on processing efficiency of brain regions that support verbal working memory, Dr. Leslie Jacobsen and colleagues assessed working memory and brain function in 36 adult subjects, 15 of which carried the 957T allele while 21 were 957C homozygotes. Each participant was studied twice, once after placement of a placebo patch and once after placement of a nicotine patch. Brain function was assessed using functional magnetic resonance imaging while the subjects performed a verbal working memory task. They found that, in performing a task with high verbal working memory load, nicotine administration worsened the performance accuracy and reduced the processing efficiency of brain regions that support phonological rehearsal during verbal working memory in carriers of the 957T allele. These findings are consistent with the notion that genetic variation in the dopamine D2 receptor contributes to individual variation in a range of behavioral and brain responses to nicotine in humans. Jacobsen, L.K., Pugh, K.R., Menci, W.E., and Gelernter, J. C957T Polymorphism of the Dopamine D2 Receptor Gene Modulates the Effect of Nicotine on Working Memory Performance and Cortical Processing Efficiency, Psychopharmacology, 188(4), pp. 530-540, 2006.

Age of First Marijuana Use Associated with Marijuana Use Disorders in Southwest California Native Americans

In several national surveys a younger age of substance usage has been associated with a higher likelihood of the development of dependence. Some studies have suggested that age at first use is primarily an environmentally driven variable, whereas others suggest that it may be partially mediated by a general vulnerability to exhibit problem behaviors. Although Native Americans, overall, have the highest prevalence of substance dependence of any US ethnic group, the relationship of age of first marijuana use on the development of dependence in Native American populations is relatively unknown. In this study, Dr. Cindy Ehlers and her colleagues obtained demographic information and DSM-III-R diagnoses from 525 Southwest California Native American adults residing on contiguous reservations. Multinomial logistic regression was used to investigate the relationship between age of first use and marijuana use disorders. Early marijuana use was found to be strongly associated with abuse and dependence in this population, even in the presence of several other risk factors including externalizing diagnoses. These data suggest that effective environmental prevention efforts at reducing early marijuana use may be an important strategy to lower the prevalence of use disorders in this high risk population. Ehlers, C.L., Slutske, W.S., Gilder, D.A., and Lau, P. Age of First

Marijuana Use and the Occurrence of Marijuana Use Disorders in Southwest California Indians. Pharmacology, Biochemistry and Behavior, doi:10.1016/j.pbb.2006.07.024.

Electrophysiological Responses to Affective Stimuli in Native Americans Experiencing Trauma With and Without PTSD

Native Americans are at high risk for exposure to violence and other traumatic events, yet few studies have investigated posttraumatic stress disorder (PTSD) or its neurobiological consequences in Native American communities. In the present study data on traumatic life events and symptoms emerging following those events and electroencephalogram (EEG) spectra and visual event-related potentials (ERPs) to happy, sad, and neutral faces were recorded from 146 Native Americans participants recruited from eight geographically contiguous reservations. Trauma rates in the sample were high: 99% had experienced at least one category of trauma with the mean number being five, 27% had experienced at least eight categories, and 13% met DSM-IV criteria for PTSD. Sixty-three percent of the sample met criteria for a lifetime diagnosis of alcohol dependence, however, the PTSD group did not differ from the larger sample on rates of alcohol dependence or any other diagnostic or demographic variables. An electrophysiological signature for PTSD was found that included increases in high-frequency gamma activity (20-40 Hz) in frontal leads, higher N1 amplitudes to sad stimuli in frontotemporal leads, and longer latency P3 components to happy stimuli in midline, central, and right frontal leads. These findings were observed in participants with PTSD, but not in a group with equivalently high trauma counts. These findings suggest that PTSD is associated with EEG hyperarousal, higher attentional levels to sad stimuli, and slower processing of happy stimuli. They also partially confirm ERP data reported in combat victims with PTSD suggesting that PTSD may induce neurobiological consequences that transcend type of eliciting trauma as well as ethnic and cultural factors. Ehlers, C.L., Hurst, S., Phillips, E., Gilder, D.A., Dixon, M., Gross, A., Lau, P., and Yehuda, R. Electrophysiological Responses to Affective Stimuli in Native Americans Experiencing Trauma With and Without PTSD. Annals of NY Academy of Science, 1071, pp. 125-136, 2006.

First Injection of Ketamine Among Young Injection Drug Users

Ketamine, a dissociative anesthetic, has emerged as an increasingly common drug among subgroups of young injection drug users (IDUs) in cities across the United States. In-depth qualitative interviews were conducted with 213 young IDUs aged 16-28 years recruited in New York, New Orleans, and Los Angeles between 2004 and 2006. While some initiated injection drug use with ketamine, the drug was more frequently injected by IDUs with extensive polydrug using histories. IDUs initiating with ketamine commonly self-injected via an intramuscular mode of administration. The injection group provided crucial knowledge and material resources that enabled the injection event to occur, including ketamine, syringes, and injection skills. Injection paraphernalia was commonly shared during the first injection of ketamine, particularly vials of pharmaceutically-packaged liquid ketamine. Injection events infrequently occurred in a rave or club and more typically in a private home, which challenges ketamine's designation as a 'club' drug. The first injection of ketamine was a noteworthy event since it introduced a novel drug or new mode of administration to be further explored by some, or exposed others to a drug to be avoided in the future. Risk reduction messages directed towards young IDUs should be expanded to include ketamine. Lankenau, S.E., Sanders, B., Bloom, J.J., Hathazi, D., Alarcon, E., Tortu, S., and Clatts, M.C. First Injection of Ketamine among Young Injection Drug Users (IDUs) in Three U.S. Cities. Drug and Alcohol Dependence, doi 10.1016/j.drugalcdep.2006.08.015.

Prevalence of Primary HIV-1 Drug Resistance among Recently Infected Adolescents

Dr. Craig Wilson and his colleagues in the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) examined the prevalence of primary human immunodeficiency type 1 (HIV-1) drug resistance among recently infected youth in the United States. Previous studies on HIV drug resistance have been conducted primarily with adult, male, Caucasian samples. Fifty-five HIV+ youth were recruited from 15 clinical sites across the U.S. and Puerto Rico. Participants included male (65%) and female (35%), African American (47%), Hispanic (24%), Caucasian (22%) youth with an average age of 19.3 years (SD 1.9 yrs). Risk factors for HIV acquisition reported among the youth included having sex under the influence of drugs or alcohol (36% male, 21% female) and exchanging sex for money or drugs (14% male and 5% female). Major mutations conferring HIV drug resistance were present in 10 participants (18%). Eight (15%) had nonnucleoside reverse-transcriptase inhibitor (NNRTI) mutations, with the majority (6) having the K103N mutation; 2 (4%) had nucleoside reverse-transcriptase inhibitor (NRTI) mutations; and 2 (4%) had protease inhibitor (PI) mutations. Phenotypic drug resistance was present in 12 (22%) subjects: 10 (18%) for NNRTIs, 2 (4%) for NRTIs, and 3 (5.5%) for PIs. There was a high prevalence of primary HIV-1 drug resistance, particularly to NNRTIs, in this group of recently infected youth. Vivani, R.M., Peralta, L., Aldrovandi, G., Kapogiannis, B.G., Mitchell, R., Spector, S.A. Wilson, C.M. and the Adolescent Medicine Trials Network for HIV/AIDS Interventions. Prevalence of Primary HIV-1 Drug Resistance among Recently Infected Adolescents: A Multicenter Adolescent Medicine Trials Network for HIV/AIDS Interventions Study. Journal of Infectious Diseases, 194(11), pp. 1505-1509, 2006.

Director's Report to the National Advisory Council on Drug Abuse - February, 2007

Research Findings - Clinical Neuroscience Research

Damage to the Insula Disrupts Addiction to Cigarette Smoking

A number of brain systems have been implicated in addictive behavior, but none have yet been shown to be necessary for maintaining the addiction to cigarette smoking. Authors found that smokers with brain damage involving the insula, a region implicated in conscious urges, were more likely than smokers with brain damage not involving the insula to undergo a disruption of smoking addiction, characterized by the ability to quit smoking easily, immediately, without relapse, and without persistence of the urge to smoke. This result suggests that the insula is a critical neural substrate in the addiction to smoking. Naqvi, N.H., Rudrauf, D. Damasio, H. and Bechara, A. Science. 315(5811), pp. 531-534, January 26, 2007.

Cognitive Deficits and Degeneration of Interneurons in HIV+ Methamphetamine Users

Igor Grant and colleagues at the HIV Neurobehavioral Research Center, USCD explored the cellular basis for cognitive deficits in AIDS positive (HIV+) patients who either used or did not use methamphetamine (METH). The researchers found that HIV+ METH users had more severe loss of connecting neurons that was associated with cognitive impairment. Compared with other markers, loss of specific connecting neurons (i.e., calbindin and parvalbumin interneurons) in the frontal cortex. This loss was most related to memory problems, suggesting that HIV+ METH users were neurologically affected either by the disease, by the HIV+ virus or a combination of the two. Chana, G., Everall, I.P., Crews, L., Langford, D., Adame, A., Grant, I., Cherner, M., Lazzaretto, D., Heaton, R., Ellis, R., Masliah, E., and the HNRC Group*. Neurology, 67, pp, 1486 - 1489, 2006.

Young Adult Stimulant Users' Increased Striatal Activation during Uncertainty Is Related to Impulsivity

Dr. Martin Paulus and colleagues at the University of California, San Diego used fMRI to investigate whether young adults who had used stimulants have different neural responses to uncertainty during decision making than their stimulant-naive peers. Young adults who use stimulants (e.g., cocaine, amphetamines) are at particular risk of transitioning to dependence, and such subjects demonstrate increased risk-taking in laboratory decision-making tasks. Eleven young adults (age 18-25) who had used stimulants were compared with 11 age- and education-matched stimulant-naive controls. Subjects performed a card prediction task with relatively certain/uncertain outcome conditions during the fMRI scans. The caudate, an area involved in processing salient events, was among those regions more active in users than

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controls in response to uncertainty. Personality measures revealed that stimulant users were more impulsive than controls, and that neural response to uncertainty in a number of areas, including the thalamus/caudate, was positively correlated with impulsivity. These results are consistent with the idea that young adults who have used stimulants find uncertainty particularly salient, due in part to preexisting differences in impulsivity, and may be subject to more "action pressure" when making decisions under uncertainty. This neural and personality profile may constitute a marker for increased risk of stimulant use. Leland, D.S., Arce, E., Feinstein, J.S., and Paulus, M.P. Neuroimage, 33(2), pp. 725-731, 2006.

Cigarette Smoking Saturates Brain Alpha 4 Beta 2 Nicotinic Acetylcholine Receptors

Brody and colleagues at UCLA evaluated a recently developed radioligand (2-FA) that allows one to visualize specific nicotinic receptors (i.e., alpha 4 beta 2* nAChR) with positron emission tomography (PET) scanning in humans to determine the effect of cigarette smoking on the receptors occupancy in tobacco-dependent smokers. During the 2-FA PET scanning sessions, a total of 11 subjects smoked one of 5 amounts (none, 1 puff, 3 puffs, 1 full cigarette, or to satiety [2(1/2) to 3 cigarettes]. Dose-dependent effects of smoking on occupancy of the receptors as measured with 2-FA and PET in nicotine-rich brain regions showed that smoking 0.13 (1 to 2 puffs) of a cigarette resulted in 50% occupancy of the receptors for 3.1 hours after smoking. Smoking a full cigarette (or more) resulted in more than 88% receptor occupancy and was accompanied by a reduction in cigarette craving. Blood nicotine levels were 0.87 ng/mL (roughly 1/25th of the level achieved in typical daily smokers) and was associated with 50% occupancy of the receptors. The researchers concluded that cigarette smoking in the amounts used by typical daily smokers leads to nearly complete occupancy of the nicotine receptors indicating that tobacco-dependent smokers maintain receptor saturation throughout the day. Because prolonged binding of nicotine to these receptors is associated with desensitization of the receptors, the extent of receptor occupancy found in this study suggests that smoking may lead to withdrawal alleviation by maintaining receptors in a desensitized state. Brody, A.L., Mandelkern, M.A., London, E.D., Olmstead, R.E.O., Mukhin, A.G., Farahi, J., Scheibal, D., Jou, J., Allen, V., Tiongson, E., Chefer, S.I., Koren, A. Arch Gen Psychiatry, 63(8), pp. 907-915, 2006.

Human Tobacco Smokers in Early Abstinence Have Higher Levels of Beta2 Nicotinic Acetylcholine Receptors than Nonsmokers

Dr. Julie Staley and her colleagues at Yale School of Medicine used SPECT imaging to examine the effects of cigarette smoking cessation on a specific sub-type nicotine receptors, (beta2-nAChR). The Beta2-nAChRs are the most prevalent subtype of nicotine acetylcholine receptors in the brain and are thought to mediate the addictive chemical in tobacco smoke, nicotine. Thus it is possible that abnormal numbers of these receptors contribute to the continuation of the addiction to tobacco smoking during early abstinence. Initial studies in non-human primates chronically given 7 days of abstinence was required to avoid residual levels of nicotine interfering with radiotracer binding to the nicotine receptors. Therefore, human smokers were asked to abstain from smoking for approximately 7 days. Both urine and breath samples were taken to confirm that smoking had not occurred. Following an average of 7 days of abstinence, there were higher levels of receptors in recently abstinent smokers compared to non-smokers. Radiotracer uptake was highest in the abstinent smokers throughout the cerebral cortex and in the striatum in the smokers, and the elevated amount of ligand binding was related to the number of days since their last cigarette and their reported urge to smoke. These

results suggest that the number of nicotine receptors increases in smokers during abstinence and that the elevation in receptor levels may contribute to difficulties in maintaining abstinence. Staley, J.K., Krishnan-Sarin, S., Cosgrove, K.P., Krantzler, E., Frohlich, E., Perry, E., Dubin, J.A., Estok, K., Brenner, E., Baldwin, R.M., Tamagnan, G.D., Seibyl, J.P., Jatlow, P., Picciotto, M.R., London, E.D., O'Malley, S., and van Dyck, C.H. J Neurosci, 26(34), pp. 8707-14, 2006.

Automaticity and Reestablishment of Executive Control - An fMRI Study

Dr. Hugh Garavan and colleagues at Trinity College used fMRI to investigate brain systems involved in reestablishing executive control over previously automatized behavior. The ability to exert control over automatic behavior is of particular importance as it allows the interruption of behavior when the automatic response is no longer adequate or even dangerous. A visual search task was used that enabled participants to automatize according to defined criteria within about 3 hr of practice and then required them to reassert control without changing the stimulus set. Widespread cortical activation was observed early in practice. Activation in all frontal areas and in the inferior parietal lobule decreased significantly with practice. Only selected prefrontal (Brodmann's areas [BAs] 9/46/8) and parietal areas (BAs 39/40) were specifically reactivated when executive control was required, underlining the crucial role of the dorsolateral prefrontal cortex in executive control to guide our behavior. There is emerging evidence that addiction involves automatized substance use behavior (i.e., habits). The present study provides a framework for investigating deficits in executive control in substance abusers. Kubler, A., Dixon, V., and Garavan, H. Journal of Cognitive Neuroscience, 18(8), pp. 1331-1342, 2006.

Activation of Dorsal Nucleus Caudate and Putamen Was Positively Associated with Subjective Ratings of Pain

Dr. Jon-Kar Zubieta and colleagues at University of Michigan investigated the increasing evidence that the dopaminergic system in the basal ganglia are responsive to aversive stimuli as well as reward. This would implicate response relative to saliency rather than valence. Using their standard paradigm of inducing pain by injecting hypertonic saline into a jaw muscle and assessing DA receptor availability in PET with raclopride, results showed that gain in DA release was positively correlated with sensory and pain affect ratings and with the negative affect experienced by healthy volunteers. Nigrostriatal DA D2 system activation was associated exclusively with ratings of sensory and affective qualities of the pain, whereas mesolimbic DA D2/D3 activity was related to the increase in negative affective state and fear ratings. These data suggest that basal ganglia dopamine receptor-mediated neurotransmission is related to individual variation in the pain stress experience. Scott, D.J., Heitzeg, M.M., Koeppe, R.A., Stohler, C.S., Zubieta, J.K. J Neurosci, 26(42), pp. 10789-10795, 2006.

Sex Differences in Amphetamine-Induced Displacement of [F-18] Fallypride in Striatal and Extrastriatal Regions: A PET Study

Dr. David Zald and colleagues at Vanderbilt University used PET to examine gender differences in d- amphetamine-induced dopamine release striatal and extrastriatal brain regions. Dopamine release was indexed by displacements of [F-18]. In addition, these displacements were correlated with cognition and sensation seeking. Method: Six women and seven men underwent positron emission tomography (PET) with [F-18] fallypride before and after an oral dose of d-amphetamine. Percent displacements were calculated using regions of

interest and parametric images of dopamine 2 (D-2) receptor binding potential. The results demonstrated that female subjects had greater dopamine release than the male subjects in the right globus pallidus and right inferior frontal gyrus. Gender differences were observed in correlations of changes in cognition and sensation seeking with regional dopamine release. The finding that women exhibit greater dopamine release in response to amphetamine as well as gender differences in the relationship between regional dopamine release and sensation seeking and cognition may underlie gender differences in vulnerability for the abuse of psychostimulants. Schmidt, D., Baldwin, R., and Kessler, R. American Journal of Psychiatry, 163(9), pp. 1639-1641, 2006.

Sex Differences in Orbitofrontal Cortex (OFC) As Assessed by SPECT in Cocaine Dependent Subjects

Dr. Brian Adinoff and associates studied regional cerebral blood (rCBF) flow in treatment-seeking cocaine abusers after at least 11 days abstinence. This study reported relative rCBF between patients and healthy controls following saline infusion. The key finding was a decreased rCBF in the right and left lateral OFC in males but not female cocaine-dependent subjects in contrast with a decreased rCBF in the medial OFC in the female but not males. Additionally, it was found that increases in rCBF were found in diffuse regions in males with no significant increases in females. In other words, cerebral blood flow was disturbed to a greater extent in males and in different areas than in females. Post-hoc inferences based on other reported findings suggested sex differences in responsiveness or brain function during decision-making tasks or, possibly, assessment or suppression of reward saliency. In any case, it is concluded that these findings amplify the relevance of sex-specific differences in drug effects to the orbitofrontal cortex and the implications for clinical course and treatment. Adinoff, B., Williams, M.J., Best, S.E., Harris, T.S., Chandler, P., Devous, M.D. Gender Med, 3(3), pp. 206-222, 2006.

Apparent Transient Effects of Recent "Ecstasy" Use on Cognitive Performance and Extrapyramidal Signs in Human Subjects

Dr. David Beaversdorf and colleagues at Ohio State University investigated cognitive performance and extrapyramidal function early after Ecstasy (MDMA) use. Chronic Ecstasy use has been suggested to lead to cognitive deficits and Parkinsonian signs. Previous research has examined cognitive performance after a period of prolonged abstinence, but research assessing the early effects of ecstasy after recent use is limited. This study compared task performance between 13 ecstasy users (10 to 15 h postdrug use) and a control group on a battery of neuropsychological assessments while matching for education level, sleep deprivation, and premorbid IQ. The groups were also compared on measures relating to parkinsonian signs. The ecstasy subjects showed impairments on measures of executive function as evaluated by Raven's Standard Progressive Matrices (SPM) and the Wisconsin Card Sorting Task (WCST). Short-delay free recall memory was also impaired in ecstasy subjects on the California Verbal Learning Test (CVLT-II). No extrapyramidal motor impairments were detected. These deficits resemble deficits previously reported in chronic ecstasy use but also seem to reveal transient impairments in executive function. Riccardi, P., Zald, D., Li, R., Park, S., Ansari, M.S., Dawant, B., Anderson, S., Woodward, N., Smith, R.M., Tivarus, M., Campbell, H.L., Hillier, A., and Beversdorf, D.Q. Cognitive and Behavioral Neurology, 19(3), pp. 157-164, 2006.

PET Imaging of Norepinephrine Transporters

Dr. Yu-Shin Ding and colleagues at Yale School of Medicine and Brookhaven National Laboratory describe the design and biological evaluation of several

radioligands for imaging the brain NET system with PET. The involvement of the norepinephrine transporter (NET) in the pathophysiology and treatment of attention deficit hyperactivity disorder (ADHD), substance abuse, neurodegenerative disorders (e.g., Alzheimer's disease (AD) and Parkinson's disease (PD)) and depression has long been recognized. However, many of these important findings have resulted from studies in vitro using postmortem tissues; as of now, these results have never been verified via in vivo methods because brain imaging of NET in living systems has been hampered due to the lack of suitable radioligands. The fact that all three monoamine (dopamine, norepinephrine, and serotonin) transporters (DAT, NET and SERT) are involved in various neurological and psychiatric diseases further emphasizes the need to develop suitable NET ligands so that researchers will be able to probe the contributions of each monoamine transporter system to specific CNS disorders. In this review article, based on these characterization studies, including C-11 labeled desipramine (DMI), 2-hydroxydesipramine (HDMI), talopram, talsupram, nisoxetine (Nis), oxaprotiline (Oxap), lortalamine (Lort) and C-11 and F-18 derivatives of reboxetine (RB), methylreboxetine (MRB) and their individual (R, R) and (S, S) enantiomers, in conjunction with studies with radiolabeled 4-iodo-tomoxetine and 2-iodo-nisoxetine, we have identified the superiority of (S, S)-[C-11]MRB and the suitability of the MRB analogs as potential NET ligands for PET. In contrast, Nis, Oxap and Lort displayed high uptake in striatum (higher than thalamus). The use of these ligands is further limited by high non-specific binding and relatively low specific signal, as is characteristic of many earlier NET ligands. Thus, to our knowledge, (S, S)-[C-11]MRB remains by far the most promising NET ligand for PET studies. Ding, Y.S., Lin, K.S., and Logan, J. Current Pharmaceutical Design, 12(30), pp. 3831-3845, 2006.

The Effect of Graded Monetary Reward on Cognitive Event-Related Potentials and Behavior in Young Healthy Adults

Dr. Rita Goldstein and colleagues at Brookhaven National Laboratory investigated the temporal correlates of the brain circuits underlying reward processing in healthy adults. The current study investigated the P3 and contingent negative variation (CNV) as putative reward-related temporal markers. The effect of sustained monetary reward on these event-related potentials and on behavior was assessed using a warned reaction-time paradigm in 16 young healthy subjects. Monetary reward (0, 1 and 45 cents) varied across blocks of trials. While the CNV was unaffected by money, P3 amplitude was significantly larger for 45 than the 1 and 0 cent conditions. This effect corresponded to the monotonically positive subjective ratings of interest and excitement on the task (45 > 1 > 0). These findings suggest a difference between the P3 and CNV; the P3 is sensitive to the sustained effect of relative reward value, while the CNV does not vary with reward magnitude. Goldstein, R.Z., Cottone, L.A., Jia, Z.R., Maloney, T., Volkow, N.D., and Squires, N.K. International Journal of Psychophysiology, 62(2), pp. 272-279, 2006.

MDMA Use Is Associated with Increased Spatial BOLD fMRI Visual Cortex Activation in Human MDMA Users

Dr. Ron Cowan and colleagues at McLean Hospital used fMRI to investigate whether MDMA users have altered visual system function. Previous studies have found that human MDMA users have altered serotonergic function and reduced gray matter density in occipital cortex, consistent with animal studies demonstrating that 3,4-methylenedioxymethamphetamine (MDMA) exposure causes serotonin axotomy that is greatest in occipital cortex (including primary visual cortex). BOLD fMRI was used to probe visual cortical activation after photic stimulation in a group of adult MDMA users. Because MDMA users worldwide are polydrug users and therefore difficult to match to comparison groups in terms of polydrug exposure, primary within-group analysis was

conducted examining the correlation between lifetime episodes of MDMA exposure and measures of visual cortical activation. The within-group correlational analysis in the MDMA user group revealed that the degree of prior MDMA exposure was significantly positively correlated with the number of activated pixels for photic stimulation ($r=0.582$, $p=0.007$). A secondary between-group comparison of MDMA users with non-MDMA users found overall greater levels of polydrug exposure in the MDMA user cohort but no significant differences in visual cortical activation measures between the two groups. Cowan, R.L., Haga, E., Frederick, B.D., Dietrich, M.S., Vimal, R.L.P., Lukas, S.E., and Renshaw, R. Pharmacology Biochemistry and Behavior, 84(2), pp. 219-228, 2006.

Decision-Making and The Iowa Gambling Task: Ecological Validity in Individuals with Substance Dependence

Dr. Antoine Bechara and colleagues investigated whether real-life indices associated with escalation of addiction severity (as measured by the Addiction Severity Index -ASI-) are predictive of risky decisions, as revealed by impaired performance on different versions of the Iowa Gambling Task. Substance Dependent Individuals (SDIs) usually show deficits in real-life decision-making, as illustrated by their persistence in drug use despite a rise in undesirable consequences. Although most SDIs are impaired on the IGT there is a subgroup of them who perform normally on this task. One possible explanation for this differential performance is that impairment in decision-making is largely detected on the IGT when the use of drugs escalates in the face of rising adverse consequences. They administered the Addiction Severity Index (ASI) and different versions of the IGT (the main IGT version, a variant IGT version, and two parallel versions of each) to a large sample of SDI. Authors used regression models to examine the predictive effects of the seven real-life domains assessed by the ASI on decision-making performance as measured by the IGT We included in regression models both ASI-derived objective and subjective measures of each problem domain. Results showed (i) that several aspects of real-life functioning associated with addiction severity were moderate predictors of IGT decision-making performance; (ii) that the combined assessment of decision-making using different versions of the IGT yielded better predictive measures than assessment using isolated versions of the IGT; and (iii) that objective measures of real-life functioning were better predictors of decision-making performance on the IGT than subjective measures based on SDI's insight about their problems. These results support the notion that decision-making deficits as measured by the IGT are associated with a rise in real-life adverse consequences of addiction. Verdejo-Garcia, A., Bechara, A., Recknor, E.C., and Perez-Garcia, M. Psychologica Belgica, 46(1-2), pp. 55-78, 2006.

Blunted Prolactin Response Correlates with Severity of Cocaine Use

In a study to determine damage to serotonin function in cocaine dependent subjects, Dr. Ashwin Patkar and associates at Duke University used a mixed 5-HT agonist/antagonist to assess disturbance by measuring prolactin stimulation. A within-group correlation demonstrated a significant change in prolactin negatively correlated with the Addiction Severity Index--a lesser change corresponded to a high Index score. A between-group comparison with a control group of non-users showed lower levels at 2-3 hours even though cocaine patients had a higher baseline prolactin level. Furthermore, the change in prolactin in the patients seemed to be more related to the severity than to behavioral traits associated with cocaine use, suggesting the 5-HT system was modified by cocaine use. The conjecture for future research is to determine whether these modifications offer a pharmacological site for treatment. Patkar, A.A., Mannelli, P., Hill, K.P., Peindl, K., Pae, C-u, and Lee, T.H. Human

Psychopharmacology, Hum Psychopharmaco Clin Exp, 21, pp. 367-375, 2006.

Treatment of Schizophrenia and Comorbid Substance Abuse: Pharmacologic Approaches

Dr. Allen Green of Dartmouth School of Medicine reviewed theories of substance use disorders in schizophrenic patients. These theories include the notion that substance use could trigger psychotic symptoms in vulnerable individuals and the idea that the substances are used to self-medicate symptoms of schizophrenia. The author hypothesizes that a mesocorticolimbic brain reward circuit underlies the substance use disorder in patients with schizophrenia. Treatment of substance use disorder in these patients is best done with integrated treatment programs that combine psychosocial interventions with pharmacotherapy. Recent data suggest that the atypical antipsychotic clozapine and perhaps other atypical agents may lessen substance use in patients with schizophrenia. The author proposes that clozapine's effect in these patients may be related to its ability to decrease the brain reward circuit dysfunction. In addition, the adjunctive use of naltrexone or other agents also may be helpful. Nonetheless, further research on the optimal pharmacologic approach to patients with dual diagnosis is needed. Green, A.I. Journal of Clinical Psychiatry, 67, pp. 31-35 Suppl. 7, 2006.

Emotion-Based Decision-Making in Healthy Subjects: Short-Term Effects of Reducing Dopamine Levels

Dr. A. Bechara and colleagues investigated whether a decrease in dopaminergic activity impairs emotion-based decision-making. Dopamine depletion was induced in 11 healthy human subjects by administration of a mixture containing the branched-chain amino acids (BCAA) valine, isoleucine and leucine. A double-blind, placebo-controlled, within-subject design was used to examine the effect of dopamine depletion on prolactin, IGT performance, perceptual competency and visual aspects of visuospatial working memory, visual attention and working memory, and verbal memory. The expectancy-valence model was used to determine the relative contributions of distinct IGT components (attention to past outcomes, relative weight of wins and losses, and choice strategies) in the decision-making process. Compared to placebo, the BCAA mixture increased prolactin levels and impaired IGT performance. BCAA administration interfered with a particular component process of decision-making related to attention to more recent events as compared to more distant events. There were no differences between placebo and BCAA conditions for other aspects of cognition. These results suggest a direct link between a reduced dopaminergic activity and poor emotion-based decision-making and difficulties resisting short-term reward, despite long-term negative consequences. These findings have implications for behavioral and pharmacological interventions targeting impaired emotion-based decision-making in addictive disorders. Sevy, S., Hassoun, Y., Bechara, A., Yechiam, E., Napolitano, B., Burdick, K., Delman, H., Malhotra, A. Psychopharmacology, 188(2), pp. 228-235, 2006.

Amygdala Response to Facial Expressions Reflects Emotional Learning

Dr. Mark D'Esposito and colleagues at University of California, Berkeley used fMRI to investigate the role of the human amygdala in a fundamental aspect of social communication, the evaluation of emotional facial expressions. Previous animal and human research shows that the amygdala participates in processing positive and negative reinforcement as well as in learning predictive associations between stimuli and subsequent reinforcement. Thus, amygdala response to facial expressions could reflect the processing of primary

reinforcement or emotional learning. The results indicated that the amygdala is more responsive to learning object-emotion associations from happy and fearful facial expressions than it is to the presentation of happy and fearful facial expressions alone. The results provide evidence that the amygdala uses social signals to rapidly and flexibly learn threatening and rewarding associations. Since the amygdala is known to play a role in substance abuse, this study forms the foundation for the investigation of altered social interactions in substance abusers. Hooker, C.I., Germine, L.T., Knight, R.T., and D'Esposito, M. Journal of Neuroscience, 26(35), pp. 8915-8922, 2006.

A Low-Cost, MR-Compatible Olfactometer

Drs. Steven Lowen and Scott Lukas of McLean Hospital describe the design for an olfactometer, suitable for fMRI experiments, that can be constructed at extremely low cost. The olfactometer presents odors directly to the nose via a nasal cannula at unobtrusively low flow velocities, with no large assemblies required on or near the subject's face. The olfactometer can be controlled manually, or by computer via a serial interface. A validation study verified that the olfactometer reliably presents odors to test subjects. Errors and response latency times decreased with increased flow rate in an orderly manner, as expected. Since many drugs of abuse produce olfactory stimuli (e.g. nicotine, marijuana), this device will be useful in the study of brain processing of drug-related conditioned cues. Lowen, S.B., and Lukas, S.E. Behavior Research Methods, 38(2), pp. 307-313, 2006.

Topiramate Raises Anterior Cingulate Cortex Glutamine Levels in Healthy Men; A 4.0 T Magnetic Resonance Spectroscopy Study

Dr. Perry Renshaw and colleagues at McLean Hospital used MRS to investigate whether the mechanisms of action of topiramate include alterations of glutamatergic and GABAergic systems. In this study, the effect of acute oral topiramate on the GABA precursors glutamate and glutamine in the anterior cingulate cortex (ACC) and occipital lobe (OL) was measured using high-field (4.0 T) proton MRS (H-1 MRS). Proton MR spectra were acquired from healthy men at three times: at baseline and 2 and 6 h after ingesting 50 (N=5) or 100 mg (N=5) of topiramate. Blood samples were acquired prior to each scan for the purpose of obtaining serum topiramate levels. A 100-mg dose of topiramate significantly increased ACC glutamine levels within 2 h of ingestion and OL glutamine levels within 6 h of ingestion. There were no measured significant effects of topiramate on ACC or OL glutamate levels. Increased brain glutamine levels may be a consequence of topiramate positively modulating GABA(A) receptors. This result is of interest given the possible role for topiramate in the treatment of substance dependence. Moore, C.M., Wardrop, M., Frederick, B.D., and Renshaw, P.F. Psychopharmacology, 188(2), pp. 236-243, 2006.

Individual Differences in the Functional Neuroanatomy of Inhibitory Control

Dr. Hugh Garavan of Trinity University performed combined the data of five event-related fMRI studies of response inhibition. Functional differences were observed between the sexes with greater activity in females in many of these cortical regions. Despite the relatively narrow age range (18-46), cortical activity, on the whole, tended to increase with age, echoing a pattern of functional recruitment often observed in the elderly. More absentminded subjects showed greater activity in fronto-parietal areas, while speed of Go trial responses produced a varied pattern of activation differences in more posterior and subcortical areas. Although response inhibition produces robust activation in a discrete network of brain regions, these results reveal that individual

differences impact on the relative contribution made by the nodes of this network. These results provide a framework to interpret changes in brain activity during inhibitory control in substance abusers. Garavan, H., Hester, R., Murphy, K., Fassbender, C., and Kelly, C. Brain Research, 1105, pp. 130-142, 2006.

Behavioral, But Not Reward, Risk Modulates Activation of Prefrontal, Parietal, and Insular Cortices

Dr. Scott Huettel of Duke University used fMRI to determine whether different forms of risk have distinct neural correlates. Risky decisions may involve uncertainty about possible outcomes (i.e., reward risk) or uncertainty about which action should be taken (i.e., behavioral risk). In two functional magnetic resonance imaging experiments, normal subjects viewed shapes that had well-learned response-reward contingencies. Magnitude of a monetary reward was held constant within one experiment, whereas expected value was held constant within the other. Response selection, in the absence of behavioral risk evoked activation within a broad set of brain regions, as had been found in prior studies. However, behavioral risk additionally modulated activation in prefrontal, parietal, and insular regions, within which no effect of reward risk was observed. Reward delivery, in comparison with omission, evoked increased activity in the ventromedial. prefrontal cortex and the nucleus accumbens. Authors conclude that distinct brain systems are recruited for the resolution of different forms of risk. These results provide a foundation for investigating alterations in brain systems involved in the evaluation of risk in substance abusers. Huettel, S.A. Cognitive Affective & Behavioral Neuroscience, 6(2), pp. 141-151, 2006.

Mapping the Functional Anatomy of Task Preparation: Priming Task-Appropriate Brain Networks

Dr. Hugh Garavan of Trinity College used fMRI and a cued version of a flanker paradigm to elucidate the effects of task preparation on subsequent brain activation patterns in healthy subjects. A mixed block and event-related design was employed to examine activations associated with the cue periods themselves and the cued and un-cued correct responses to incongruent flankers. A number of areas were active during the cues, most notably left dorsolateral prefrontal cortex (DLPFC), which was interpreted as subserving a role in task-set maintenance. Widespread activity was noted for correct responses to incongruent flankers, including bilateral parietal and frontal regions, consistent with previous studies. Activation was increased in these regions for correct responses after cue periods. An overlapping network of regions was also noted for cues and correct responses, suggesting preparation of task-appropriate anatomical regions during the cue period. These results suggest that cue periods allow participants to prime task-relevant areas within the brain and highlight the importance of left DLPFC in top-down control. Similar processes may underlie brain activity during presentation of drug-related cues to substance abusers and in the subsequent generation of subjective craving experiences. Fassbender, C., Foxe, J.J., and Garavan, H. Human Brain Mapping, 27(10), pp. 819-827, 2006.

Advances in White Matter Imaging: A Review of In Vivo Magnetic Resonance Methodol-ogies and their Applicability to the Study of Development and Aging

Dr. Kelvin Lim of the University of Minnesota reviewed the magnetic resonance imaging (MRI) techniques that are increasingly being applied to the study of white matter development and pathology across the lifespan. These techniques go beyond traditional macrostructural volumetric methods and provide valuable

information about underlying tissue integrity and organization at the microstructural and biochemical levels. An overview of white matter development is first presented along with the role of white matter and myelin in cognitive function. Studies of development that have employed traditional volumetric measures are then reviewed. Finally, the contributions of four newer imaging paradigms to our understanding of brain development and aging are discussed. These paradigms are Diffusion Tensor Imaging (DTI), Magnetization Transfer Imaging (MTI), T2-Relaxography, and Magnetic Resonance Spectroscopy (MRS). Studies examining brain development, during childhood and adulthood as well as studies of the effects of aging are discussed. These new techniques have the potential of providing new information regarding the effects of substance abuse on brain structure. Wozniak, J.R., and Lim, K.O. Neuroscience and Biobehavioral Reviews, 30(6), pp. 762-774, 2006.

A Major Susceptibility Locus Found of Chromosome 10 for Nicotine Dependence in African Americans

Dr. Ming D. Li and associates report several susceptibility loci to one or more measures of nicotine dependence following a genome-wide scan; the strongest linkage was at 10q22 (LOD = 4.17). Suggestive linkages were also found on chromosomes 9, 11, and 13 and possibly 15, 17, and 18. Although chromosome 10 is novel for this population, other studies have also reported sites on chromosomes 9 and 11. Furthermore in a family-based study candidate genes (e.g., GABA-B2 and NTRK2) within the 9q22 region were found to be associated with nicotine dependence. Probands were required to be smoking 20 cigarettes/day for 5 years and have a smoking sibling. Other family members (regardless of smoking status) were recruited as best possible, yielding a final pool of 1261 subjects in 402 families. This study is believed to be the first large study focusing exclusively on African Americans. Li, M.D., Payne, T.J., Ma, J.Z., Lou, X-Y., Zhang, D., Dupont, R.T., Crews, K.M., Somes, G., Williams, N.J., and Elston, R.C., Amer. J. Hum Genet, 79, pp. 745-751, 2006.

Functional Imaging Studies in Cannabis Users

Dr. Linda Chang of the University of Hawaii reviewed neuroimaging studies in cannabis (marijuana) users. The majority of imaging studies examined the acute effects of delta-9-tetrahydrocannabinol (THC) administration, used PET methods and concluded that administration of THC leads to increased activation in specific brain regions (frontal and paralimbic) and the cerebellum. These increases in activation are broadly consistent with the behavioral effects of the drug. Although there is little evidence that chronic cannabis use might result in changing brain structures, specific imaging studies (i.e., BOLD fMRI) in chronic users do show consistent alterations in the activation of brain networks responsible for higher cognitive functions. It is not yet certain whether these changes are reversible with abstinence. Given the high prevalence of cannabis use among adolescents, studies are needed to evaluate whether cannabis use might affect the developing brain. Considerable further work, employing longitudinal designs, is also needed to determine whether cannabis use causes permanent functional alterations in the brains of adults. Chang, L., and Chronicle, E.P. Neuroscientist, 13(4), pp. 1-11, 2007.

Increased Risk for Bacterial Illness in Cocaine Dependent Persons

Dr. Irwin and colleagues found a decreased capacity of monocytes to express TNF-_ and IL-6 in non-treatment-seeking cocaine dependent men. In addition, these people had a further decline in the responsiveness to a bacterial ligand which persisted after cocaine had cleared from blood. These results and measures of heart rate variability suggested that cocaine alters autonomic

activity and induces protracted decreases in innate immune mechanisms. Among other implications, a suppressed immune system in these individuals may be responsible, in part, for the increased prevalence of hepatitis C seropositivity. Irwin, M.R., Olmos, L., Wang, M., Valladares, E.M., Motivala, S.J., Fong, T., Newton, T., Anthony, B., Olmstead, R., Cole, S.W. JPET Doi, pp. 10-1124, JPET, pp. 106-112797, 2006.

Director's Report to the National Advisory Council on Drug Abuse - February, 2007

Research Findings - Epidemiology and Etiology Research

Subtypes of Drug Users

This article applies methods of latent class analysis (LCA) to data on lifetime illicit drug use in order to determine whether qualitatively distinct classes of illicit drug users can be identified. Self-report data on lifetime illicit drug use (cannabis, stimulants, hallucinogens, sedatives, inhalants, cocaine, opioids and solvents) collected from a sample of 6265 Australian twins (ages 24-36) were analyzed using LCA. Rates of childhood sexual and physical abuse, lifetime alcohol and tobacco dependence, symptoms of illicit drug abuse/dependence and psychiatric comorbidity were compared across classes using multinomial logistic regression. LCA identified a 5-class model: Class 1 (68.5%) had low risks of the use of all drugs except cannabis; Class 2 (17.8%) had moderate risks of the use of all drugs; Class 3 (6.6%) had high rates of cocaine, other stimulant and hallucinogen use but lower risks for the use of sedatives or opioids. Conversely, Class 4 (3.0%) had relatively low risks of cocaine, other stimulant or hallucinogen use but high rates of sedative and opioid use. Finally, Class 5 (4.2%) had uniformly high probabilities for the use of all drugs. Rates of psychiatric comorbidity were highest in the polydrug class although the sedative/opioid class had elevated rates of depression/suicidal behaviors and exposure to childhood abuse. The authors conclude that aggregation of population-level data may obscure important subgroup differences in patterns of illicit drug use and psychiatric comorbidity, that LCS may help distinguish useful subtypes, and that further exploration of a "self-medicating" subgroup is needed. Lynskey, M., Agrawal, A., Bucholz, K., Nelson, E., Madden, P., Todorov, A., Grant, J., Martin, N., and Heath, A. Subtypes of Illicit Drug Users: A Latent Class Analysis of Data from an Australian Twin Sample. Twin Res Hum Genet, 9(4), pp. 523-530, 2006.

Drug Abuse Outcomes Associated with ADHD Subtypes in the Community

This study used data from a relatively large, community-identified longitudinal sample of children with attention-deficit/hyperactivity disorder (ADHD) to describe the late adolescent drug use outcomes associated with this disorder. Subjects have been assessed from childhood through late adolescence, and outcomes compared between ADHD-only (n = 27), ADHD-externalizing (mostly oppositional defiant disorder) (n = 82), and normal control (n = 91) groups. The ADHD-externalizing group revealed significantly worse drug use outcomes (drug use frequency and substance use disorders) compared to the other two groups, and the ADHD-only group showed outcomes comparable to the community control group. The authors conclude that ADHD without a comorbid externalizing disorder is not associated with an increased risk of drug abuse, while ADHD with a comorbid externalizing disorder, primarily oppositional

defiant disorder, is associated with an elevated risk of drug use, particularly with respect to marijuana and tobacco involvement. The use of a community-based sample augments the generalizability of these findings, which hold great potential to clarify which subgroups of children are at risk for later drug use disorders, and suggest that ADHD, when uncomplicated by another externalizing disorder, is not a risk factor for drug abuse. August, G., Winters, K., Realmuto, G., Fahnhorst, T., Botzet, A., and Lee, S. Prospective Study of Adolescent Drug Use Among Community Samples of ADHD and Non-ADHD Participants. J Am Acad Child Adolesc Psychiatry, 45(7), pp. 824-832, 2006.

Genetic and Environmental Vulnerabilities Underlying Adolescent Substance Use and Problem Use: General or Specific?

Are genetic and environmental risks for adolescent substance use specific to individual substances or general across substance classes? Researchers examined this question in 645 monozygotic twin pairs, 702 dizygotic twin pairs, 429 biological sibling pairs, and 96 adoptive (biologically unrelated) sibling pairs ascertained from community-based samples, and ranging in age from 12 to 18 years. Substance use patterns and symptoms were assessed using structured psychiatric interviews. Biometrical model fitting was carried out using age- and sex-specific thresholds for (a) repeated use and (b) problem use, defined as one or more DSM-IV symptoms of abuse or dependence. The researchers hypothesized that problem use would be more heritable than use in adolescence, and that both genetic and environmental risks underlying tobacco, alcohol, and marijuana use and problem use would be significantly correlated. Results of univariate analyses suggested significant heritable factors for use and problem use for all substances with the exception of alcohol use. Shared environmental factors were important in all cases and special twin environmental factors were significant for tobacco use, tobacco problem use, and alcohol use. Multivariate analyses yielded significant genetic correlations between each of the substances (for both levels studied), and significant shared environmental correlations among use variables only. These results suggest that tobacco, alcohol, and marijuana problem use are mediated by common genetic influences, but shared environmental influences may be more substance-specific for problem use. Young, S., Rhee, S., Stallings, M., Corley, R., and Hewitt, J. Genetic and Environmental Vulnerabilities Underlying Adolescent Substance Use and Problem Use: General or Specific? Behav Genet, 36(4), pp. 603-615, 2006.

Strong Evidence of Links Between Child Maltreatment and Adolescent Substance Abuse

The purpose of this study was to estimate the prevalence of child maltreatment in the United States and examine its relationship to sociodemographic factors and major adolescent health risks. The National Longitudinal Study of Adolescent Health is a prospective cohort study following a national sample of adolescents into adulthood. The wave III interview, completed by 15,197 young adults in 2001-2002 (77.4% response rate), included retrospective measures of child maltreatment. Authors used these measures to estimate the prevalence of self-reported supervision neglect, physical neglect, physical assault, and contact sexual abuse during childhood. Next, they investigated the relationship between sociodemographic characteristics and maltreatment. Finally, they examined the association between child maltreatment and adolescent self-rated health; overweight status; depression; cigarette, alcohol, marijuana, and inhalant use; and violent behavior. Having been left home alone as a child, indicating possible supervision neglect, was most prevalent (reported by 41.5% of respondents), followed by physical assault (28.4%), physical neglect (11.8%), and contact sexual abuse (4.5%). Each sociodemographic characteristic was associated with > or = 1 type of maltreatment, and race/ethnicity was associated with all 4. Each type of

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maltreatment was associated with no fewer than 8 of the 10 adolescent health risks examined. Self-reported childhood maltreatment was common. The likelihood of maltreatment varied across many sociodemographic characteristics. Each type of maltreatment was associated with multiple adolescent health risks. Hussey, J., Chang, J., and Kotch, J. Child Maltreatment in The United States: Prevalence, Risk Factors, and Adolescent Health Consequences. Pediatrics, 118(3), pp. 933-942, 2006.

Role of Poverty in Adolescents Weight

Prevalence of adolescent's weight issues in the United States has increased substantially during the past 3 decades. Whether socioeconomic disparities in adolescents increased, decreased, or remained constant during this period is not known. The objective of this study is to examine trends in weight issues among adolescents from 1971 to 2004 by family poverty status, as well as trends in potentially relevant eating and physical activity behaviors. Four cross-sectional, nationally representative surveys (US National Health and Nutrition Examination Surveys [NHANES] of 1971-1974, 1976-1980, 1988-1994, and 1999-2004) were examined for trends in the prevalence of weight among adolescents aged 12 to 17 years by family poverty status. Main outcome measures include prevalence of adolescent weight issues, defined as body mass index at or above the 95th percentile for age and sex in the 2000 Centers for Disease Control and Prevention growth charts; intermediate outcomes include physical inactivity in the past 30 days, proportion of caloric intake from sweetened beverages (24-hour recall), and whether respondent skipped breakfast (24-hour recall). Results suggest trends in the association of adolescent weight issues with family poverty differed by age stratum ($P = .01$). In 12- to 14-year-old adolescents, prevalence did not significantly differ by family poverty status in any of the surveys; however, among non-Hispanic black adolescents, overweight prevalence increased faster in nonpoor vs poor families. In contrast, a widening disparity that disfavored adolescents from poor families was present in the 15- to 17-year-old adolescents. This trend was similar among male, female, non-Hispanic white, and non-Hispanic black adolescents, resulting in an overall prevalence of overweight in 1999-2004 more than 50% higher among adolescents in poor vs nonpoor families (23.3% vs 14.4%, respectively; $P<.001$). Additional analyses suggest that physical inactivity, sweetened beverage consumption, and skipping breakfast may contribute to these disparities. Trends of increasing overweight showed a greater impact in families living below the poverty line vs not living below the poverty line among older (15-17 years) but not younger (12-14 years) adolescents. Furthermore, physical inactivity, high consumption of sweetened beverages, and breakfast skipping may be candidate targets for prevention programs aimed at reducing this recently emerged disparity. Miech, R., Kumanyika, S., Stettler, N., Link, B., Phelan, J., and Chang, V. Trends in The Association of Poverty with Overweight Among US Adolescents, 1971-2004. JAMA, 295(20), pp. 2385-2393, 2006.

Comorbidity Between Alcohol Dependence and Illicit Drug Dependence in Adolescents with Antisocial Behavior and Matched Controls

While comorbidity among substance use disorders is common, the causes have not been clear, and prior literature has been conflicting regarding the role of familial influences on common or substance-specific liability. This study addressed the issue using a clinical sample of 272 adolescents ages 13-20, treated for antisocial behavior and substance use disorders, and their siblings and a matched control sample. A model fitting approach was used to test 13 alternative hypotheses for the causes of comorbidity. The best supported hypothesis for the comorbidity between alcohol dependence and illicit drug dependence was a model hypothesizing that comorbid disorders are alternate

forms of a single underlying liability. The next best fitting models were two of the correlated liabilities models (correlated risk factors and reciprocal causation). These results suggest that the best hypotheses explaining the comorbidity between alcohol and illicit drug dependence in antisocial adolescents are that alcohol dependence and illicit drug dependence are manifestations of a single general liability to develop substance dependence or that there are separate liabilities that are highly correlated. Although these findings may not generalize to adults or to individuals without severe antisocial personality disorders, they may help point the way to approaches for searching for genes for this common liability. Rhee, S., Hewitt, J., Young, S., Corley, R., Crowley, T., Neale, M., and Stallings, M. Comorbidity Between Alcohol Dependence and Illicit Drug Dependence in Adolescents with Antisocial Behavior and Matched Controls. Drug Alcohol Depend, 84 (1), pp. 85-92, 2006.

Genetic and Cultural Transmission of Smoking Initiation

This study used an extended kinship design to examine the role of genetic and environmental factors for smoking initiation. The authors report that this design can take into account factors including assortative mating and parent-offspring transmission beyond what has been reported in traditional twin and adoption genetic epidemiologic studies. Data were collected by questionnaires from 14,763 twins and their parents, spouses, children, and siblings, for a total of 28,492 individuals from 8567 extended kinships. 58% of the sample was female and 50% were under the age of 50. Extensive modeling found that both genetic and environmental factors play a significant role in the liability to smoking initiation. This study showed significant heritability, partly due to assortment, and significant effects of primarily non-parental shared environment on smoking initiation. While confirming that genetic factors account for the majority of individual differences in liability to smoking initiation, the authors found that shared environmental factors do play a significant role, primarily due to within-generational influences, e.g. siblings and co-twins. The association between smoking behavior in parents and their children can be most likely accounted for by their genetic relatedness. The idea of social learning in smoking may apply to siblings or peers but does not appear to apply to children learning by modeling from their parents. Maes, H.H., Neale, M.C., Kendler, K.S., Martin, N.G., Heath, A.C., and Eaves, L.J. Genetic and Cultural Transmission of Smoking Initiation: An Extended Twin Kinship Model. Behav Genet, 36(6), pp. 795-808, 2006.

Reinterpreting Ethnic Patterns among White and African American Men Who Inject Heroin: A Social Science of Medicine Approach

Street-based heroin injectors represent an especially vulnerable population subject to negative health outcomes, including HIV/AIDS and other infectious diseases, and social stigma. Researchers used a multi-method approach to examine quantitative, clinical, and ethnographic data collected from 2 contemporaneous long-term studies in San Francisco, one epidemiological and one ethnographic. Both studies explored the impact of ethnicity on street-based heroin-injecting men (N=1,068), 45 years of age or older who were self-identified as either African American (n=453 or 42%) or White (n=614 or 57%). After stratifying 14 relevant epidemiological variables by median age and ethnicity, the researchers found significant differences in social practices between self-identified African Americans and Whites, particularly with respect to patterns of drug consumption; income generation; social and institutional relationships; and personal health and hygiene. African Americans and whites tended to experience different structural relationships to their shared condition of addiction and poverty. Specifically, African Americans had earlier and more negative contact with law enforcement but maintained long-term ties with their extended families. Most of the Whites, by contrast, were expelled from their families when they began engaging in drug-related crime. The authors argue

that historical-structural conditions generate distinct presentations of addiction, with Whites styling themselves as outcasts, defeated by addiction, and injecting to stave off ''dope sickness,'' and African Americans casting their addiction as an oppositional pursuit of autonomy and pleasure. The researchers discuss how bringing quantitative and qualitative methods and perspectives together in such an analysis yields insights and discoveries that would otherwise not be possible. Specifically, a clinical social science approach provides insights into how socio-cultural processes are mediated by historically rooted and institutionally enforced power relations. Bourgois, P., Martinez, A., Kral, A., Edlin, B., Schonberg, J., and Ciccarone, D. Reinterpreting Ethnic Patterns Among White and African American Men Who Inject Heroin: A Social Science of Medicine Approach. PLoS Medicine, 3(10), pp. 1805-1815, 2006.

Modeling Initation and Progression of Substance Use and Abuse

The authors note that twin data can provide valuable insight into the relationship between the stages of phenomena such as substance abuse, but existing models for the relationship between initiation and progression have been difficult to extend because they are usually expressed in terms of explicit integrals. In this paper, the problem is overcome by regarding the analysis of twin data on initiation and progression as a special case of missing data, in which individuals who do not initiate are regarded as having missing data on progression measures. Using the general framework for the analysis of ordinal data with missing values available in Mx makes extensions that include other variables much easier. The effects of continuous covariates such as age on initiation and progression becomes simple. Also facilitated are the examination of initiation and progression in two or more substances, and transition models with two or more steps. This paper describes and then applies these methods to twin data from 1942 adult female twins in the Virginia Twin Registry; models studied the effects of cohort on liability to cannabis use and abuse, bivariate analysis of tobacco use and dependence and cannabis use and abuse, and the relationships between initiation of smoking, regular smoking and nicotine dependence. In addition to the methodologic advances, this article offers substantive findings including a strong relationship between initiation of cannabis and smoking, and a stronger relationship between smoking initiation and regular smoking than either with nicotine dependence. These new methods hold much promise for making use of existing data and advancing our understanding of drug use progression and phenotypes. Neale, M., Harvey, E., Maes, H., Sullivan, P., and Kendler, K. Extensions To The Modeling of Initiation And Progression: Applications To Substance Use and Abuse. Behav Genet, 36(4), pp. 507-524, 2006.

Childhood Trauma Among Incarcerated Women in Substance Abuse Treatment

Authors sought to describe the prevalence of childhood traumatic events among incarcerated women in substance abuse treatment and to assess the relation between cumulative childhood traumatic events and adult physical and mental health problems. The study was modeled after the Adverse Childhood Events study's findings. In-depth baseline interview data for 500 women participating in the Female Offender Treatment and Employment Program evaluation were analyzed. Hypotheses were supported, and regression results showed that the impact of childhood traumatic events on health outcomes is strong and cumulative (greater exposure to childhood traumatic events increased the likelihood of 12 of 18 health-related outcomes, ranging from a 15% increase in the odds of reporting fair/poor health to a 40% increase in the odds of mental health treatment in adulthood). These findings suggest a need for early prevention and intervention, and appropriate trauma treatment, within correctional treatment settings. Messina, N., and Grella, C. Childhood Trauma and Women's Health Outcomes in a California Prison Population. Am J

Public Health, 96(10), pp. 1842-1848, 2006.

College Students' Illicit Use of Specific Prescription Stimulants

To explore the illicit use of specific prescription stimulants among college students and add to our understanding of reasons (motives) and routes of administration associated with illicit use of these drugs. A random sample of 4580 college students self-administered a Web-based survey. The survey contained a variety of items pertaining to the illicit use of prescription stimulants. An extensive list of prescription stimulants was provided, and students were asked to select all the specific prescription stimulants that they had used illicitly. Items were also included to assess the motives and routes of administration associated with illicit use of prescription stimulants. Lifetime and past-year prevalence rates for illicit use of prescription stimulants were 8.3% (382 students) and 5.9% (269 students), respectively. Approximately three fourths (75.8%) of the 269 past-year illicit users of prescription stimulants reported using an amphetamine-dextroamphetamine combination agent (e.g., Adderall) in the past year, and approximately one fourth (24.5%) reported using methylphenidate (e.g., Ritalin, Concerta, Metadate, Methylin). Past-year illicit use of prescription stimulants was more than 3 times more likely among Caucasians (odds ratio [OR] 3.1, 95% confidence interval [CI] 1.5-6.6) and Hispanics (OR 3.8, 95% CI 1.6-9.3) compared with African-Americans, and more than twice as likely among Caucasians (OR 2.1, 95% CI 1.3-3.4) and Hispanics (OR 2.6, 95% CI 1.4-5.1) compared with Asians. The most commonly reported motives for illicit use were to help with concentration (65.2%), help study (59.8%), and increase alertness (47.5%). Other motives included getting high (31.0%) and experimentation (29.9%). Nearly every illicit user (95.3%) reported oral administration, and 38.1% reported snorting prescription stimulants. Illicit use of amphetamine-dextroamphetamine is more prevalent than illicit use of methylphenidate formulations among college students. Teter, C., McCabe, S., Lagrange, K., Cranford, J., and Boyd, C. Illicit Use of Specific Prescription Stimulants Among College Students: Prevalence, Motives, and Routes of Administration. Pharmacotherapy, 26(10), pp. 1501-1510, 2006.

DAST Drug Abuse Screening of College Students

The present study assesses the prevalence of items from a modified version of the Drug Abuse Screening Test, Short Form (DAST-10) for substances other than alcohol among undergraduate students. More than 4,500 undergraduate students at a large Midwestern research university completed a web-based survey in 2005. Nearly 1 in every 10 undergraduate students experienced three or more DAST-10 items in the past 12 months. Although the prevalence of illicit drug use did not differ by gender, undergraduate men were significantly more likely than women to report DAST-10 items. Less than 6% of individuals who reported three or more drug DAST-10 items had ever used treatment services for substance use. As a brief screening instrument, the DAST-10 offers promise for detecting possible drug abuse among college students. Based on the prevalence of drug use, colleges and universities are encouraged to provide screening opportunities to identify and to provide services for students at high risk for drug abuse. McCabe, S., Boyd, C., Cranford, J., Morales, M., and Slayden, J. A Modified Version of The Drug Abuse Screening Test Among Undergraduate Students. J Subst Abuse Treat, 31(3), pp. 297-303, 2006.

Behavioral and Emotional Self-Control: Relations to Substance Use in Samples of Middle and High School Students

The authors tested how behavioral and emotional self-control are related to

adolescent substance (tobacco, alcohol, and marijuana) use. Data were obtained from 489 middle school students and 602 high school students. Multiple indicators were developed for each domain of self-control, and confirmatory analyses were used to test the measurement structure of latent constructs. Results showed that the domains of behavioral self-control and emotional self-control were statistically distinct, and both were related to adolescent substance use. Structural modeling analyses indicated indirect effects for self-control constructs primarily through pathways to competence and recent events. In addition, poor behavioral control had a direct effect to deviant peer affiliations, and poor emotional control had a direct effect to coping motives for substance use. The results indicate that both types of self-regulation are relevant for adolescent substance use. Implications for prevention and treatment research are discussed. Wills, T., Walker, C., Mendoza, D., and Ainette, M. Behavioral and Emotional Self-Control: Relations to Substance Use in Samples of Middle and High School Students. Psychol Addict Behav, 20(3), pp. 265-278, 2006.

Inhalant Use and Disorders among Adults in the US

This paper examines patterns of adult inhalant use and correlates of inhalant use disorder. Data were drawn from the 2002 and 2003 National Surveys on Drug Use and Health (NSDUH) and logistic regression was used to identify the characteristics associated both with inhalant use and inhalant use disorder. Study findings indicate that 1 in 10 of all adults had used an inhalant at least once in their lives, and 0.5% used one in the past year. Among all past year inhalant users, 8% met the criteria for an inhalant use disorder (i.e., 6.6% for abuse and 1.1% for dependence) within that period. There was an increased prevalence of past year inhalant use among young adults aged 18-25 years, Asians, past year alcohol abusers and dependents, lifetime drug users, white women, and men reporting symptoms of serious mental illness. Inhalant-using adults who met the criteria for an inhalant use disorder were predominantly adults aged 35-49 years and were less educated, had received recent professional treatment for emotional or psychological problems, used inhalants weekly, and had a coexisting alcohol use disorder. The authors conclude that the patterns and consequences of adult inhalant use differ from those of adolescents. Compared with adolescent inhalant users, adult users tend not to initiate inhalant use until adulthood, use inhalants less frequently, use fewer inhalants, and are less likely to engage in criminal activities. Wu, L. and Ringwalt, C. Inhalant Use and Disorders among Adults in the United States. Drug Alcohol Depend, 85(1), pp. 1-11, 2006.

Magazine Advertising and Adolescent Cigarette Smoking

The purpose of the present study is to examine the relation between magazine advertising for cigarettes and adolescent cigarette smoking. Participants (242 adolescents) reported their frequency of reading 46 magazines and their attention to cigarette ads. Recognition of cigarette ads, passive peer pressure (i.e., normative beliefs), and the smoker image also were assessed. Results indicate that exposure to cigarette advertising and recognition of ads augment the effect of passive peer pressure on smoking. In addition, a positive smoker image was associated with attention to advertising and mediated the relation between attention and smoking. It is suggested that the effect of magazine ads on adolescents should be considered in policymaking on cigarette advertising. Aloise-Young, P., Slater, M., and Cruickshank, C. Mediators and Moderators of Magazine Advertisement Effects on Adolescent Cigarette Smoking. J Health Commun, 11(3), pp. 281-300, 2006.

The Lifetime Cost of Current Human Immunodeficiency Virus Care in the United States

This collaborative effort, supported by NIDA, NIAID, and the AHRQ, sought to project the lifetime cost of medical care for HIV-infected adults using current antiretroviral therapy (ART) standards. Medical service utilization, including visits and hospitalizations for any reason, were estimated from cross-sectional data collected by the HIV Research Network, a consortium of high-volume HIV primary care sites. HIV treatment drug regimen efficacies were obtained from clinical guidelines and published sources. In a computer simulation model, researchers projected HIV medical care costs in 2004 U.S. dollars. They found that, from the time of entering HIV care, per person projected life expectancy is 24.2 years, discounted lifetime cost is $385,200, and undiscounted cost is $618,900 for adults who initiate ART with CD4 cell count <350/muL. An estimated 73% of the cost is on antiretroviral medications; 13% inpatient care; 9% outpatient care; and 5% other HIV-related medications and laboratory costs. For patients who initiate ART with CD4 cell count <200/muL, projected life expectancy is 22.5 years, discounted lifetime cost is $354,100 and undiscounted cost is $567,000. The results are sensitive to drug manufacturers' discounts, ART efficacy, and if the efficacy of ART regimens declines, whether the 4th line regimen includes enfuvirtide for salvage. If costs are discounted to the time of infection, the discounted lifetime cost is $303,100. These findings demonstrate the remarkable clinical benefit of ART in substantially improving survival. Not only is ART the most costly component of care, but individuals are incurring these costs over more years due to improved life expectancies. Schackman, B.R. , Gebo, K.A. , Walensky, R.P. , Losina, E. , Muccio, T. , Sax, P.E. , Weinstein, M.C. , Seage, G.R. 3rd , Moore, R.D., and Freedberg, K.A. The Lifetime Cost of Current Human Immunodeficiency Virus Care in the United States. Med Care, 44(11), pp. 990-997, 2006.

The Role of Parenting in Drug Use among Black, Latino, and White Adolescents

This study investigates the role of parenting in adolescent drug use for black, white and Latino adolescents. Parenting has been consistently identified as a crucial factor in drug use by adolescents. This study uses data from the National Longitudinal Study of Adolescent Health. Results show that parenting has a significant effect on drug use for these adolescents. The relationship between parenting and drug use is more strongly negative for the Latino adolescents, than for black and white adolescents. This indicates that greater parental warmth and family acceptance exert a stronger impact in reducing drug use for Latino adolescents than is the case for the black and white adolescents. Broman, C., Reckase, M., and Freedman-Doan, C. The Role of Parenting in Drug Use Among Black, Latino and White Adolescents. J Ethn Subst Abuse, 5(1), pp. 39-50, 2006.

Parent Psychopathology, Parenting and Internalizing Problems among Children of Substance Abusers

A structural model accounting for child internalizing problems in substance-abusing families was tested. Parents receiving substance abuse treatment (N = 242) completed forms about children between the ages of 6 and 18 who resided in their home. The effects of parent gender, child gender, and child age were controlled. Negative parenting was examined as a mediator between parent internalizing and externalizing problems and child anxiety and affective problems using path analysis. Negative parenting mediated relations only between parent internalizing problems and child affective problems. High-positive involvement moderated relations between parent externalizing problems and child internalizing problems. Relations between parent externalizing problems and child anxiety and affective problems were significant only among families in which high-positive involvement was present. Burstein, M., Stanger, C., Kamon, J., and Dumenci, L. Parent Psychopathology,

Parenting, and Child Internalizing Problems in Substance-Abusing Families. Psychol Addict Behav, 20(2), pp. 97-106, 2006.

Parents and Families as Contexts for the Development of Substance Use and Substance

Use Disorders Parenting and familial influences on substance use and substance use disorders (SUDs) are important areas of study both for theories of etiology and for the development of preventive and treatment interventions. The articles in this special section illustrate both the value and the challenges of studying parenting and familial influences. Noteworthy issues include the need for mediational and moderational models examining the processes by which familial influences operate in a longitudinal framework to consider outcomes in a developmental context. Future directions include a multidisciplinary expansion of these studies. Chassin, L., and Handley, E. Parents and Families as Contexts for the Development of Substance Use and Substance Use Disorders. Psychol Addict Behav, 20(2), pp. 135-137, 2006.

Substance Abusing Mothers and Disruptions in Child Custody

Using an attachment framework, authors examined (1) whether substance-abusing mothers' perceptions of how they were parented were related to the severity of their substance abuse and psychological maladjustment and (2) whether these two factors mediated the association between mothers' perceptions of how they were parented and their childrens' placement out of home. There were 108 mothers of 248 children who completed interviews upon admission to a methadone maintenance program for women. A multilevel modeling approach was used to model effects of the hierarchically organized data (e.g., children nested within families). Findings are consistent with an attachment perspective on parenting suggesting that the internal psychological processes of a parent play a critical role in the continuity of parenting. When multiple risk domains associated with children's out-of-home placement were examined together within the same statistical model, maternal substance abuse severity and psychological maladjustment were the strongest predictors of children's out of home placement. Furthermore, mothers who perceived their own mothers as uncaring and intrusive were more likely to have lost custody of a minor child. There was also evidence that this effect was partially mediated by maternal substance abuse severity and psychological maladjustment. Suchman, N., McMahon, T., Zhang, H., Mayes, L., and Luthar, S. Substance-Abusing Mothers and Disruptions in Child Custody: An Attachment Perspective. J Subst Abuse Treat, 30(3), pp. 197-204, 2006.

Parent-Child Attachment, Parenting, Family Ecology and Persistent Conduct Problems

A small proportion of children exhibit extreme and persistent conduct problems through childhood. The present study employed the multiple-domain model of Greenberg and colleagues as the framework for person-oriented analyses examining whether parent-child attachment combines with parenting, family ecology, and child characteristics in particular configurations of risk that are linked to this problematic developmental pathway. Using prospective data from a community sample of adolescent mothers and their children (n=255), latent variable growth mixture modeling identified a normative trajectory with declining problem behaviors during the preschool period. Consistent with research on early-starter pathways, a distinct group of children featured a higher intercept and a positive slope, indicating an escalation in disruptive behaviors. Attachment security played a role in defining specific risk profiles associated with the probability of exhibiting this problem trajectory. Given particular patterns of risk exposure, secure attachment served a protective

function. Avoidant, but not disorganized, attachment was associated with significantly higher likelihood of the disruptive problem trajectory. The results also indicated the general accumulation of risk was detrimental, but the particular configuration of risk made a difference. Overall, the findings suggest that early attachment operates in conjunction with personal and contextual risk to distinguish the development of later problem behaviors. Keller, T., Spieker, S., and Gilchrist, L. Patterns of Risk and Trajectories of Preschool Problem Behaviors: A Person-oriented Analysis of Attachment in Context. Dev Psychopathol, 17(2), pp. 349-384, 2005.

Early Risk Factors Predict Success in Transition to Adulthood Among Adolescent Mothers

This prospective longitudinal study is based on a diverse sample of adolescent mothers in the Northwest. Data have been collected from pregnancy through adulthood. Five risk factors were used (individually and in a cumulative risk index) to predict young mothers' life course pathways from age 17 through 23 years. A multinomial logistic regression indicated that, relative to the normative group, the problem-prone group had significantly greater odds of having a history of school problems, delinquency, and hard substance use. The psychologically vulnerable group had significantly greater odds of mental health problems, hard substance use, and marginally more delinquency. Importantly, the cumulative risk index (the sum of the five risk factors) predicted the patterns of transition into adulthood and demonstrated significant sensitivity and specificity in distinguishing those in the normative pathway from those in either the problem-prone or psychologically vulnerable pathway. Results suggest that specific risk factors assessed at pregnancy can differentiate among adolescent mothers who experience varying levels of success in their transition into early adulthood. The cumulative risk index demonstrates applied utility as a risk assessment tool capable of distinguishing among life-course pathways. Oxford, M., Gilchrist, L., Gillmore, M., and Lohr, M. Predicting Variation in the Life Course of Adolescent Mothers as they Enter Adulthood. J Adolesc Health, 39(1), pp. 20-26, 2006.

Associations Among Familial Alcoholism, Parent Socialization and Children's Adjustment, Coping Style and Coping Efficacy

The relations of children's coping strategies and coping efficacy to parent socialization and child adjustment were examined in a sample of school-age children that included families in which some of the grandparents and/or parents had an alcoholism diagnosis (n=300). Parents and older children reported on the children's coping strategies; parents reported on their parenting behavior; and teachers reported on children's externalizing and internalizing problems. Measures of parent socialization were associated with parents' and children's reports of active coping strategies and parents' reports of both support-seeking coping and coping efficacy. Some of these relations were moderated by familial alcohol status. Children higher in parent-reported active/support-seeking coping and coping efficacy were rated lower in teacher-reported externalizing and internalizing adjustment problems. The findings were consistent with the view that active/support-seeking coping and coping efficacy mediated the association of parent socialization to children's psychological adjustment and that this relation was sometimes moderated by parental alcohol status. Smith, C., Eisenberg, N., Spinrad, T., Chassin, L., Morris, A., Kupfer, A., Liew, J., Cumberland, A., Valiente, C., and Kwok, O. Children's Coping Strategies and Coping Efficacy: Relations to Parent Socialization, Child Adjustment, and Familial Alcoholism. Dev Psychopathol, 18(2), pp. 445-469, 2006.

Famililal Alcoholism, Family Harmony and Young Adults'

Substance Dependence Disorders

This study examined the prospective relations among family history density of alcoholism (FHD), adolescent family harmony, and young adults' (n=246) alcohol and drug dependence. Family harmony was rated by mothers and fathers in adolescence and young adults ' substance dependence diagnoses were obtained through structured interviews. Higher FHD predicted lower adolescent family harmony, which in turn increased young adults' odds of being diagnosed with drug dependence (with and without alcohol dependence) compared to no diagnoses or to alcohol dependence only. Family harmony also interacted with FHD such that the protective effect of family harmony on young adults' drug dependence with or without alcohol dependence decreased as FHD rose, and was nonsignificant at high levels of FHD. The findings suggest the importance of distinguishing among alcohol and drug dependence disorders and examining their differential etiological pathways, and also suggest that the protective effects of harmonious family environments on substance dependence may be limited at high levels of FHD. Zhou, Q., King, K., and Chassin, L. The Roles of Familial Alcoholism and Adolescent Family Harmony in Young Adults' Substance Dependence Disorders: Mediated and Moderated Relations. J Abnorm Psychol, 115(2), pp. 320-331, 2006.

Psychiatric Comorbidity and Progression in Drug Use in Adult Male Twins: Implications for the Design of Genetic Association Studies

Psychiatric comorbidity with drug dependence has been widely documented. In the present study, researchers used latent class methods to reanalyze DSM-III-R diagnostic data on 8,169 middle-aged male twins (3,372 complete twins and 1,425 singletons) from the Vietnam Era Twin Registry Study (VETS). They identified four subtypes based on 15 diagnostic categories, and showed that these subtypes are strongly associated with differential rates of transitions in drug use histories, with increased risks in relatives for depression, alcohol, drug and antisocial personality disorder as well as with a variety of non-normative and deviant behaviors in youth and in adulthood. They then use the result of these analyses to show how the use of a particular drug disorder phenotype for selecting cases could impact final sample composition. These findings suggest that, even though much of the liability to substance dependence may be shared, it appears that the choice of selection phenotype (e.g., opioid vs cannabis dependence) will affect the ultimate sample composition, not only in terms of the propensity to transition to dependence from experimental use, but also in terms of psychiatric comorbidity. Thus, analyses that focus on any substance dependence as the phenotypic endpoint may be introducing substantial heterogeneity into the data. These results indicate that a more controlled sampling scheme should ascertain samples for genetic association studies based on diagnostic profiles rather than on individual diagnoses. Todorov, A., Lynskey, M., Grant, J., Scherrer, J., Todd, R., and Bucholz, K. Psychiatric Comorbidity and Progression in Drug Use in Adult Male Twins: Implications for the Design of Genetic Association Studies. Addict Behav, 31(6), pp. 948-961, 2006.

Heritability of DSM-IV Nicotine Withdrawal

The authors determined the heritability of the eight symptoms of DSM-IV symptoms of nicotine withdrawal in adult twins in the Australian Twin Registry. They examined both the genetic influences on nicotine withdrawal as well as the genetic factors specific to nicotine withdrawal, after controlling for factors responsible for risk of progression beyond experimentation with cigarettes and for quantity smoked (average number of cigarettes per day at peak lifetime use). Epidemiologic and genetic analyses were conducted using telephone diagnostic interview data from young adult Australian twins reporting any

cigarette use (3026 women, 2553 men; mean age 30 years). Genetic analysis of the eight symptoms of DSM-IV nicotine withdrawal suggests heritability is intermediate for most symptoms (26-43%), and similar in men and women. The exceptions were depressed mood upon withdrawal, which had stronger additive genetic influences in men (53%) compared to women (29%), and decreased heart rate, which had low heritability (9%). Although prevalence rates were substantially lower for DSM-IV nicotine withdrawal syndrome (15.9%), which requires impairment, than for the DSM-IV nicotine dependence withdrawal criterion (43.6%), heritability was similar for both measures: as high as 47%. Genetic modeling of smoking more than 1 or 2 cigarettes lifetime (''progression ''), quantity smoked and nicotine withdrawal found significant genetic overlap across all three components of nicotine use/dependence (genetic correlations = 0.53-0.76). Controlling for factors associated with risk of cigarette smoking beyond experimentation and quantity smoked, evidence for genetic influences specific to nicotine withdrawal (up to 23% of total variance) remained. Their results suggest that at least some individuals become ''hooked '' or progress in the smoking habit, in part, because of a vulnerability to nicotine withdrawal. Pergadia, M., Heath, A., Martin, N., and Madden, P. Genetic Analyses of DSM-IV Nicotine Withdrawal in Adult Twins. Psychol Med, 36(7), pp. 963-972, 2006.

Examination of the Underlying Liability and Symptom Patterns among Syndromes of Substance Use Disorder for Illicit Drugs

The use of DSM criteria to evaluate liability to substance use disorders (SUDs) and to identify SUD phenotypes may not provide the sensitivity required to identify genes associated with vulnerability to SUDs. The authors of this study evaluated a number of basic aspects of substance use that may be more proximal than full SUDs to risk genes, some of which may thus have greater potential utility as phenotypes in subsequent molecular genetic analyses. In this paper they focused on how individual symptoms of abuse and dependence may be used to create alternate phenotypes for SUDs. Specifically, they used factor analysis and biometrical modeling on each symptom of illicit substance abuse and dependence within different types of substances, and compared and contrasted factor patterns and heritabilities across the different substances. These analyses were carried out using a population-based sample of 3372 male-male twin pairs from the Vietnam Era Twin Registry who participated in the Harvard Twin Study of Substance Abuse. Via telephone interview in 1992, they obtained extensive data on substance use and SUDs including opiates, cocaine, cannabis, sedatives, stimulants, and psychedelics. The results indicate that: A) although a one-factor model assuming a single underlying liability for abuse and dependence symptoms and behaviors can be rejected for most substances, there is no uniform support for a two-factor model differentiating between abuse versus dependence; B) patterns of symptoms or behaviors reported by substance users vary across substances; C) not all symptoms or behaviors contribute equally to the presentation of an SUD; and D) the heritability of symptoms or behaviors of substance users varies both within and between substances. These results represent important first steps in facilitating the search for SUD-risk genes in subsequent high-throughput molecular genetic analyses by providing alternate phenotypes that may have both optimal validity and increased heritability. Beseler, C., Jacobson, K., Kremen, W., Lyons, M., Glatt, S., Faraone, S., Gillespie, N., and Tsuang, M. Is there Heterogeneity Among Syndromes of Substance Use Disorder for Illicit Drugs? Addict Behav, 31(6), pp. 929-947, 2006.

Examination of Transitions from Initiation through Dependence in Adolescent Substance Involvement

The present study examined Lengths of Times for important transitions in substance involvement from Initiation to Regular use (LOTIR), first Problem

from drug use (LOTIP), and first experience of Dependence (LOTID) for alcohol, tobacco, cannabis, cocaine, and opiates. Data were from a longitudinal study of 590 children (22.2% female) at different levels of risk for substance use disorders based on their fathers' substance use-related diagnoses. Participants' substance involvement was assessed at four ages: 10-12, and follow-ups at two, five, and eight years later. Results suggested that faster transitions were more due to drug-related constructs (including possible social milieus of different drug classes and interactions between drug class and neurophysiology) than intrapersonal constructs. The shortest transition times (and greatest addictive liabilities) were for opiates followed respectively by cocaine, cannabis, tobacco, and alcohol. Females had shorter transition times, though gender differences were small. Some evidence was found for a familial influence on transition times above what was accounted for by differences between substances. Ridenour, T., Lanza, S., Donny, E., and Clark, D. Different Lengths of Times for Progressions in Adolescent Substance Involvement. Addict Behav, 31(6), pp. 962-983, 2006.

Duration of Cannabis Use as a Possible Phenotype

Although cannabis is the most commonly used illicit drug, duration of cannabis use is typically short, with many of those who initiate cannabis use ceasing use by their late twenties. This paper uses twin data to examine whether duration of cannabis use can be an informative phenotype for future genetic analyses. Data came from an Australian cohort of 2706 pairs of male and female twin's ages 24-36 (688 monozygotic female, 503 dizygotic female, 484 monozygotic male, 388 dizygotic male, 643 opposite sex) who were assessed for duration of cannabis use and dependence symptoms. Genetic modeling indicated moderate genetic influences on duration of cannabis use in both males (41%) and females (55%), and strong genetic influences on cannabis dependence in both males (72%) and females (62%). A substantial component of genetic influences on duration of cannabis use was shared with those influencing liability to cannabis dependence, but the overlap is not complete. The authors conclude that lifetime duration of cannabis use may constitute a novel phenotype that can be uniquely informative in assessing components of liability to cannabis use. Lynskey, M., Grant, J., Nelson, E., Bucholz, K., Madden, P., Statham, D., Martin, N., and Heath, A. Duration of Cannabis Use--A Novel Phenotype? Addict Behav, 31(6), pp. 984-994, 2006.

Cessation of Injection Drug Use and Change in Injection Frequency: the Chicago Needle Exchange Evaluation Study

Researchers examined the effect of a needle exchange program (NEP) on incidence of injection cessation and change in injection frequency; explored predictors for injection cessation and change in injection frequency; and assessed whether injection quitters transitioned to non-injected drug use. Between 1997-2002, 901 injection drug users (IDUs) were recruited from an NEP program or an area with no NEP in Chicago, Illinois, interviewed for drug use behaviors, tested for HIV, and followed for 3 annual visits. All participants were exposed to prevention services targeting HIV and drug abuse. Injection cessation was defined as no injection drug use since the last interview, and changes in the number of injections in a typical month were examined. The study found that 16% of study participants reported stopping injection, for a median duration of 16 months, and most of them also ceased rather than initiated the use of non-injected drugs. Those who continued injecting reduced their injection frequency by 12% per year, on average. Independent predictors of injection cessation were infrequent injection at baseline, younger age and injecting with others. NEP use was not associated with injection cessation and change in injection frequency. These results do not support the hypothesis that NEP use influences the frequency of injection over time. Rather, one-sixth of IDUs stopped injection for more than 1 year, providing a substantial window for

relapse prevention interventions. Huo, D., Bailey, S., and Ouellet, L. Cessation of Injection Drug Use and Change in Injection Frequency: The Chicago Needle Exchange Evaluation Study. Addiction, 101(11), pp. 1606-1613, 2006.

A Longitudinal Study of Syringe Acquisition by Puerto Rican Injection Drug Users in New York and Puerto Rico: Implications for Syringe Exchange and Distribution Programs

The purpose of this study is to examine changes during a 3-year period in syringe acquisition by street-recruited Puerto Rican IDUs characterized by frequent drug injection and high HIV seroprevalence. At baseline (1998-1999) and 36-month follow-up, 103 IDUs recruited in East Harlem, New York (NY), and 135 from Bayamon, Puerto Rico (PR) were surveyed about syringe sources and HIV risk behaviors in the prior 30 days. A majority of participants in both sites were male (NY 78.6%, PR 84.4%), were born in Puerto Rico (NY 59.2%, PR 87.4%), and had not completed high school (NY 56.3%, PR 51.9%). Compared to PR IDUs at follow-up, NY IDUs injected less (3.4 vs. 7.0 times/day, $p < .001$), and re-used syringes less (3.1 vs. 8.0 times, $p < .001$). Between baseline and follow-up, in NY the proportion of syringes from syringe exchange programs (SEPs) increased from 54.2% to 72.9% ($p = .001$); syringes from pharmacies did not increase significantly (0.2% to 2.5%, $p = .095$). In PR, the proportions of syringes from major sources did not change significantly: private sellers (50.9% to 50.9%, $p = .996$); pharmacies (18.6% to 19.0%, $p = .867$); SEP (12.8% to 14.4%, $p = .585$). The study indicates that NY SEPs became more dominant, while NY pharmacies remained a minor source even though a law enacted in 2001 legalized syringe purchases without prescription. Private sellers in PR remained the dominant and most expensive source. The only source of free syringes, the SEP, permitted more syringes to be exchanged but the increase was not statistically significant. Implications for syringe exchange and distribution programs are discussed. Finlinson, H., Oliver-Velez, D., Deren, S., Cant, J., Colon, H., Robles, R., Kang, S., and Andia, J. A Longitudinal Study of Syringe Acquisition by Puerto Rican Injection Drug Users in New York and Puerto Rico: Implications for Syringe Exchange and Distribution Programs. Subst Use Misuse, 41(9), pp. 1313-1336, 2006.

Antiretroviral Adherence and HIV Treatment Outcomes among HIV/HCV Co-infected Injection Drug Users: The Role of Methadone Maintenance Therapy

Researchers examined the association of methadone maintenance therapy (MMT) with highly active antiretroviral therapy (HAART) adherence and HIV treatment outcomes among a cohort of HIV/HCV co-infected injection drug users (IDUs). They obtained demographic, drug use, and addiction care history from the Vancouver Injection Drug User Study (VIDUS), which is an open cohort study of IDUs. The questionnaires were longitudinally linked to the British Columbia HIV/AIDS Drug Treatment Program to obtain HAART adherence and HIV treatment outcome data. There were 278 VIDUS participants who accessed HAART from August 1, 1996 to November 24, 2003. Longitudinal logistic models were constructed using generalized estimating equations to examine the independent associations between MMT and the following outcomes: HAART adherence; plasma HIV-1 RNA suppression; and CD4 cell rise of 100cells/mm (3). The study found that, among participants who reported at least weekly heroin use, MMT was independently associated with lower odds of subsequent weekly heroin use during the follow-up period (adjusted odds ratio; 95% confidence interval [AOR; 95% CI]: 0.24; 0.14-0.40). MMT was also positively associated with adherence (AOR 1.52; 95% CI 1.16-2.00), HIV-1 RNA suppression (AOR 1.34; 95% CI 1.00-1.79), and CD4 cell count rise (AOR 1.58; 95% CI 1.26-1.99). These findings indicate that, among HIV/HCV co-infected IDUs on HAART, enrollment in MMT was associated

with reduced heroin use, and improved adherence, HIV-1 RNA suppression and CD4 cell count response. Integrating opiate addiction care and HIV care are likely to improve health outcomes for this vulnerable population. Palepu, A., Tyndall, M., Joy, R., Kerr, T., Wood, E., Press, N., Hogg, R., and Montaner, J. Antiretroviral Adherence and HIV Treatment Outcomes among HIV/HCV Co-infected Injection Drug Users: The Role of Methadone Maintenance Therapy. Drug Alcohol Depend, 84(2), pp. 188-194, 2006.

Factors Asociated with Early Adolescent Initiation into Injection Drug Use: Implications for Intervention Programs

This study explores factors associated with early adolescent (aged < or = 16 years) initiation into injection drug use among young (< or = 29 years) injection drug users (IDUs). Data were collected through the Vancouver Injection Drug Users Study (VIDUS). Since 1996, 542 participants aged 29 years and younger have been enrolled and followed. In total, 205 (38%) young participants were initiated at age 16 years or younger. The proportion of young initiators was greater among: females, adjusted odds ratio [AOR]: 1.63 (95% confidence interval [CI]: 1.09-2.44); sex workers, AOR: 1.61 (CI: 1.11-2.31); binge drug users, AOR: 1.45 (CI: 1.01-2.08); and those who have been in juvenile detention or jail, AOR: 1.78 (CI: 1.16-2.66). Early initiates were more likely to be infected with HIV, OR: 2.6 (CI: 1.3-5.0) and hepatitis C virus (HCV), OR: 2.6 (CI: 1.3-5.0). These findings indicate that targeted early interventions are needed, specifically designed for and in collaboration with girls and young women. Miller, C., Strathdee, S., Kerr, T., Li, K., and Wood, E. Factors Associated with Early Adolescent Initiation into Injection Drug Use: Implications for Intervention Programs. J Adolesc Health, 38(4), pp. 462-464, 2006.

Transitions to Injecting Drug Use among Noninjecting Heroin Users: Social Network Influence and Individual Susceptibility

This study sought to determine the incidence/predictors of transitions to injecting among noninjecting heroin users (NIUs). Street-recruited NIUs (N=579) were recruited and interviewed in New York City, March/1996-March/2003, for a prospective cohort study about social network influence (communication promoting injecting; exposure to injectors) on transitions to injecting and on individual susceptibility. Of the 579, 369 (64%) were followed for a mean of 25 months (among 160 former injectors) to a mean of 31 months (among 209 never injectors). The mean number of months followed up was significantly shorter for former injectors compared to never injectors ($p<0.001$). The study spanned the time of the September 11, 2001 attacks, when it experienced delays and loss of data, records, and contact information; this may explain, in part, why some of the original cohort were lost to follow-up. However, the overall follow-up rate is comparable to that of several other studies of non-treatment recruited drug users in New York City. A transition to injecting was the first drug injection following baseline. Hazards ratios (HRs) ($P< 0.05$) were estimated by Cox proportional hazards regression, stratified by baseline injecting history. Former-injectors were more likely to transition to injecting (33% or 53/160 vs. 12% or 25/209; 16.0/100 person-years-at-risk [pyar] vs. 4.6/100 pyar; HR = 3.25). Independent predictors among never-injectors included using >or =2 bags of heroin daily (HR = 7.0); social network influence (communication) and homelessness (HR = 6.3); shorter-term heroin use (HR = 5.3); social network influence (exposure) and physically abused (HR = 4.7); friends approve/condone drug injecting (HR = 3.5); lower perceived social distance from injectors (HR = 2.9); and younger age at first heroin use (HR = 1.2). Independent predictors among former-injectors were social network influence (communication) and lower perceived social distance from injectors (HR = 3.4); white race/ethnicity (HR = 2.0); not very afraid of needles (HR = 1.8); and younger age (HR = 1.1). These findings indicate that

the risk of initiating injecting was lower than the risk of resuming injecting. Social network influence facilitates transitioning to injecting among those susceptible. Interventions to prevent injecting should address both social network influence and individual susceptibility. Neaigus, A., Gyarmathy, V., Miller, M., Frajzyngier, V., Friedman, S., and Des Jarlais, D. Transitions to Injecting Drug Use Among Noninjecting Heroin Users: Social Network Influence and Individual Susceptibility. J Acquir Immune Defic Syndr, 41(4), pp. 493-503, 2006.

Social Structural and Behavioral Underpinnings of Hyperendemic Hepatitis C Virus Transmission in Drug Injectors

Hepatitis C virus (HCV) is hyperendemic in drug injectors, yet social structural and behavioral factors underlying transmission are not well established. This case-control study of HCV seroconversion in drug injectors focused on transmission within networks. Incident case subjects (n=17) and seronegative control subjects (n=42) reported injection and sex partners and referred as many as 5 for interviewing and blood testing. Nucleotide sequencing was performed on HCV isolates from infected individuals. The study found that 78% of recent injection partnerships involved behavior that could transmit HCV. Case subjects and control subjects were similar demographically and behaviorally. Case subjects, however, had more HCV-infected partners and consequently engaged in injection risk behavior with more infected partners. The injection network was mostly connected, dense, and cyclic, but the sexual network was highly fragmented. Although participants generally injected with partners of similar age, most HCV-uninfected participants recently had injected with infected partners. In at least 1 of 4 pairs of genetically linked infections, transmission appeared to be due to sharing of injection equipment other than syringes. Except for transmission pairs, network distance between incident case subjects and genetic distance between their HCV variants were uncorrelated. These findings indicate that, without dramatic reductions in injection risk behaviors, shattering of cohesive injection networks, and/or broad coverage of an effective vaccine, HCV will likely remain hyperendemic in drug injectors. Brewer, D., Hagan, H., Sullivan, D., Muth, S., Hough, E., Feuerborn, N., and Gretch, D. Social Structural and Behavioral Underpinnings of Hyperendemic Hepatitis C Virus Transmission in Drug Injectors. J Infect Dis, 194(6), pp. 764-772, 2006.

Response to Overdose among Injection Drug Users

Drug overdose is a leading cause of mortality among illicit drug users. This study characterizes responses to overdose among injection drug users (IDUs) in Baltimore, Maryland, and identifies factors associated with medically inappropriate responses. A cross-sectional survey was administered to 924 IDUs in an ongoing cohort study between August 2003 and September 2004. Self-reported experiences of witnessing overdose were obtained by structured interview. Multiple logistic regression identified associations between overdose information sources and medically inappropriate responses. Most IDUs (69.7%) reported ever witnessing an overdose. The most common responses were walking the victim around (70.8%), shaking them (64.9%), and inflicting pain (62.6%). One in four (25.8%) injected the victim with salt water. Two thirds (63.4%) called 911, but more than half delayed the call by 5 or more minutes. The most common reason cited for delaying or foregoing the 911 call was the belief that they could revive the victim themselves, followed by fear of police involvement. Most IDUs had received information on how to prevent or respond to an overdose, but most (73.2%) received this information from friends or other drug users. IDUs who got overdose information solely from lay sources were less likely to call 911 (adjusted odds ratio [AOR] = 0.66, 95% confidence interval [CI] = 0.46-0.94) and more likely to inject the victim with salt water (AOR = 2.06, 95% CI = 1.36-3.13) than IDUs who received no information at

all. Injection drug users who received information from medical and social services providers only were less likely to delay the 911 call (AOR = 0.35, 95% CI = 0.22-0.72). These findings indicate that inappropriate overdose responses are widespread among IDUs in Baltimore. Interventions that provide overdose education and reduce police response to overdose events are likely to improve witness responses and reduce mortality associated with drug overdose. Pollini, R., McCall, L., Mehta, S., Celentano, D., Vlahov, D., and Strathdee, S. Response to Overdose Among Injection Drug Users. Am J Prev Med, 31(3), pp. 261-264, 2006.

Diversion of Ultram and Other Tramadol Products

Ultram (tramadol HCL) was approved by the Food and Drug Administration in 1994 as a non-scheduled drug under the Controlled Substance Act. The non-scheduled status was contingent on the development and implementation of a comprehensive post-marketing surveillance program by an Independent Steering Committee external to Ortho-McNeil Pharmaceutical charged with monitoring abuse and recommending scheduling if unexpectedly high abuse occurred. The program developed by this committee was composed of a variety of studies, and the results of the first three years of the surveillance efforts revealed that the rate of Ultram abuse was low. At a meeting of the FDA in 1998 to reexamine the scheduling status of Ultram, it was recommended that the scope of the postmarketing surveillance program be broadened to include data on diversion. After a 1-year pilot study, by January 2002, a nationwide diversion survey was fully operational. This brief communication describes the experiences of this diversion study, and compares the findings on the diversion of Ultram and other tramadol HCL products with that of more widely abused drugs. Survey data suggest that the diversion of Ultram and other tramadol products is low, and overall, diversion investigators did not consider tramadol to be a problem in their respective jurisdictions. Inciardi, J., Cicero, T., Munoz, A., Adams, E., Geller, A., Senay, E., and Woody, G. The Diversion of Ultram, Ultracet, and Generic Tramadol HCL. J Addict Dis, 25(2), pp. 53-58, 2006.

Polydrug Use among Ecstasy-Using Youth

In this study, the authors estimated the prevalence of ecstasy use within a large college student sample and investigated the polydrug-use history of those ecstasy users. They administered an anonymous questionnaire to college students (N = 1,206) in classrooms at a large university in the mid-Atlantic United States. The overall student response rate was 91%. Nine percent of the sample reported lifetime ecstasy use. Because 98% of ecstasy users had used marijuana, the authors compared polydrug use between ecstasy users and individuals who had used marijuana but not ecstasy. Ecstasy users, as compared with these marijuana users, were significantly more likely to have used inhalants (38% vs. 10%), LSD (38% vs. 5%), cocaine (46% vs 2%), and heroin (17% vs 1%) in the past year. Significant polydrug use among college student ecstasy users has important implications for their substance abuse treatment. Wish, E., Fitzelle, D., O 'Grady, K., Hsu, M., and Arria, A. Evidence for Significant Polydrug Use Among Ecstasy-Using College Students. J Am Coll Health, 55(2), pp. 99-104, 2006.

The Role of Internalizing and Externalizing Behavior Problems and Peer Selection in Adolescent Substance Use

To date, research examining the role of peers in the development of substance use has focused almost exclusively on externalizing behavior problems without considering internalizing behavior problems. This is a notable omission in the literature, because there is some evidence to suggest that internalizing behavior increases risk for substance use, and peers are considered to be

among the strongest proximal influences of substance use. The current study considered both internalizing and externalizing behavior problems and examined peer socialization and selection models of alcohol use using a 2-year longitudinal design. Authors examined potential reciprocal relations between internalizing and externalizing behavior and affiliations with delinquent peers, and how these variables predicted initiation of alcohol use. Participants were 86 children (71% male) ranging from 9-12 years of age (M=10.87). Results were consistent with socialization, whereby delinquent peer affiliations were associated with increases in externalizing behavior, and subsequently early initiation of alcohol use. There was also evidence to suggest that internalizing behavior served as a protective factor for delinquent peer affiliations and for early initiation of alcohol use. Implications of these findings for prevention and intervention efforts are discussed. Fite, P., Colder, C., and O 'Connor, R. Childhood Behavior Problems and Peer Selection and Socialization: Risk for Adolescent Alcohol Use. Addict Behav, 31(8), pp. 1454-1459, 2006.

Increased Access to Unrestricted Pharmacy Sales of Syringes in Seattle-King County, Washington: Structural and Individual-Level Changes, 1996 versus 2003

Researchers explored pharmacists' attitudes and practices related to syringe sales to injection drug users before and after legal reform and local programming in Seattle, Washington to enhance sterile syringe access. They replicated a 1996 study by conducting pharmacist phone surveys (with 227 of 269 eligible pharmacies, for a response rate of 85%) and syringe test-buys in 100 randomly selected pharmacies in the Seattle region and in the suburbs. Overall test-buy success increased from 48% in 1996 to 65% in 2003 (P=.04). Pharmacists agreeing that syringes should be available to injection drug users through pharmacy purchase increased over the study period from 49% to 71% (P<.01). These findings suggest that pharmacy policies and pharmacist attitudes were strongly associated with syringe access. Structural changes, including policy reform and pharmacy outreach, appear to increase syringe access. Interventions should address pharmacy policies and pharmacist attitudes and policies. Deibert, R., Goldbaum, G., Parker, T., Hagan, H., Marks, R., Hanrahan, M., and Thiede, H. Increased Access to Unrestricted Pharmacy Sales of Syringes in Seattle-King County, Washington: Structural and Individual-Level Changes, 1996 versus 2003. Am J Public Health, 96(8), pp. 1347-1353, 2006.

Changes in Canadian Heroin Supply Coinciding with the Australian Heroin Shortage

Prior research has largely attributed the Australian heroin shortage to increases in local law enforcement efforts. Because western Canada receives heroin from similar source nations, but has not measurably increased enforcement practices or funding levels, researchers in Vancouver sought to examine trends in Canadian heroin-related indices before and after the Australian heroin shortage, which began in approximately January 2001. During periods before and after January 2001, they examined the number of fatal overdoses and ambulance responses to heroin-related overdoses that required the use of naloxone in British Columbia, Canada. As an overall marker of Canadian supply reduction, they also examined the quantity of heroin seized during this period. Lastly, they examined trends in daily heroin use among IDUs enrolled in the Vancouver Injection Drug Users Study (VIDUS). They found a 35% reduction in overdose deaths, from an annual average of 297 deaths during the years 1998-2000 compared to an average of 192 deaths during 2001-03. Similarly, use of naloxone declined 45% in the period coinciding with the Australian heroin shortage. Interestingly, the weight of Canadian heroin seized declined 64% coincident to the Australian heroin shortage, from an average of 184 kg during 1998-2000 to 67 kg on average during 2001-03. Among 1587 VIDUS

participants, the period coinciding with the Australian heroin shortage was associated independently with reduced daily injection of heroin [adjusted odds ratio: 0.55 (95% CI: 0.50-0.61); P < 0.001]. These findings indicate that massive decreases in 3 independent markers of heroin use observed in western Canada coincided with the Australian heroin shortage, despite little if any budgetary changes for Canadian enforcement efforts. Markedly reduced Canadian seizure activity also coincided with the Australian heroin shortage. These findings underscore the importance and credence of external global heroin supply forces as a potential explanation for the Australian heroin shortage. Wood, E., Stoltz, J., Li, K., Montaner, J., and Kerr, T. Changes in Canadian Heroin Supply Coinciding with the Australian Heroin Shortage. Addiction, 101(5), pp. 689-695, 2006.

HTLV-2 Infection in Injection Drug Users in King County, Washington

Human T-cell lymphotropic virus type 2 (HTLV-2) is endemic in injection drug users (IDU), and Native American populations in the Americas. Transmission is associated with high-risk injection and sexual practices. A cohort of 2561 IDU in King County, Washington completed 2 study visits over 1 year. HTLV-2 infection was detected in 190 (7.4%) of 2,561 IDU, and 13 (7.8 cases per 1000 person-years) incident infections occurred during the study. Prevalent infection was associated with female gender, non-white race, longer duration as IDU, having a tattoo, combined injection of heroin and cocaine, and with serologic evidence of hepatitis B and C infection. Seroconversion was more common in women, and was associated with African American race, heterosexual identity and longer duration as IDU. Increased risk of HTLV-2 infection was associated with non-white race, and injection drug of choice, suggesting injection networks may play an important role in transmission of HTLV-2. The high correlation of HTLV-2 infection with HCV infection suggests the major route of transmission in IDU is via injection practices. This study points to the need for studies on the clinical manifestations of HTLV-2 infection, as well as the clinical and virological manifestations of HTLV-2/HCV coinfection. Zunt, J., Tapia, K., Thiede, H., Lee, R., and Hagan, H. HTLV-2 Infection in Injection Drug Users in King County, Washington. Scand J Infect Dis, 38(8), pp. 654-663, 2006.

Is the Quality of the Patient-Provider Relationship Associated with Better Adherence and Health Outcomes for Patients with HIV?

Patient-centeredness, originally defined as understanding each patient as a unique person, is widely considered the standard for high-quality interpersonal care. The purpose of this cross-sectional analysis was to examine the association between patient perception of being "known as a person" and receipt of highly active antiretroviral therapy (HAART), adherence to HAART, and health outcomes among patients with HIV. The analysis included 4,694 interviews with 1,743 (mean 2.69 interviews per patient) patients with HIV. The primary measures of interest were patient reports that their HIV provider "knows me as a person" and 3 outcomes: receipt of HAART, adherence to HAART, and undetectable serum HIV RNA. Findings indicated that patients who reported that their provider knows them "as a person" were more likely to receive HAART (60% vs 47%, P<.001), be adherent to HAART (76% vs 67%, P=.007), and have undetectable serum HIV RNA (49% vs 39%, P<.001). Patients who reported their provider knows them "as a person" were also older (mean 38.0 vs 36.6 years, P<.001), reported higher quality-of-life (mean LASA score 71.1 vs 64.8, P<.001), had been followed in clinic longer (mean 64.4 vs 61.7 months, P=.008), missed fewer appointments (mean proportion missed appointments 0.124 vs 0.144, P<.001), reported more positive beliefs about HAART therapy (39% vs 28% strongly believed HIV medications could help them live longer, P<.008), reported less social stress (50% vs 62% did not eat

regular meals, P<.001) and were less likely to use illicit drugs or alcohol (22% vs 33% used drugs, P<.001; 42% vs 53% used alcohol, P<.001). Controlling for patient age, sex, race/ethnicity, quality-of-life, length of time in clinic, missed appointments, health beliefs, social stress, and illicit drug and alcohol use, patients who reported their provider knows them "as a person" had higher odds of receiving HAART (odds ratio [OR] 1.41, 95% confidence interval [CI] 1.19 to 1.65), adhering to HAART (OR 1.33, 95% CI 1.02 to 1.72), and having undetectable serum HIV RNA (1.20, 95% CI 1.02 to 1.41). These findings indicate that a single item measuring the essence of patient-centeredness-i.e., the patients' perception of being "known as a person"- is significantly and independently associated with receiving HAART, adhering to HAART, and having undetectable serum HIV RNA. These results support the hypothesis that the quality of patient-physician relationship is directly related to the health of patients. Beach, M., Keruly, J., and Moore, R. Is the Quality of the Patient-Provider Relationship Associated with Better Adherence and Health Outcomes for Patients with HIV? J Gen Intern Med, 21(6), pp. 661-665, 2006.

Prevalence and Correlates of Suicidal Ideation among Young Injection vs. Noninjection Drug Users

The objective of this study was to identify correlates of suicidal ideation and to examine the hypothesis that injection drug users (IDUs) were more likely to report suicidal ideation than noninjection drug users (NIDUs). Participants included IDUs (n = 244) and NIDUs (n = 73) from Baltimore, Maryland, aged 15-30 who began snorting or smoking heroin or cocaine/crack (NIDUs) or injecting drugs (IDUs) within the past 5 years who were recruited between August 2000 and March 2002. Among the 317 participants, 42% were female, 59% were white, and median age was 24. The prevalence of suicidal ideation was 27%. IDUs were more likely to report suicidal ideation than NIDUs (31% vs. 14%, p = 0.003). Adjusting for age, gender, and race, IDUs were 2.4 times more likely than NIDUs to report suicidal ideation [95% Confidence Interval (CI): 1.1-5.2]. However, on further adjustment for homelessness, depressive symptoms, and gay/lesbian/bisexual identity, IDU status was no longer independently associated with suicidal ideation. These results suggest that factors associated with injection drug users' lifestyles and mental health status may account for the higher prevalence of suicidal ideation in IDUs vs. NIDUs. Further study into these associations is warranted in identifying avenues for suicide prevention among these populations. Havens, J., Sherman, S., Sapun, M., and Strathdee, S. Prevalence and Correlates of Suicidal Ideation among Young Injection vs. Noninjection Drug Users. Subst Use Misuse, 41(2), pp. 245-254, 2006.

Gender Differences in Sexual Behaviors, Sexual Partnerships, and HIV among Drug Users in New York City

Researchers sought to compare sexual behaviors/partnerships and sexual risk correlates associated with HIV by gender among sexually active, street-recruited drug users in New York City. The study sample included 818 men and women (average age 28 vs 30 years, p<.01). Men were more likely to be Latino (63% vs 41%, p<.01), recently homeless (61% vs 50%, p<.01) or previously incarcerated (90% vs 79%, p<.01) compared to women. More men than women reported being an IDU (29% vs 20%, p<.01). Among non-IDUs, men were less likely to report crack use, more likely to report marijuana use, and use of hallucinogens. Men reported higher risk sexual behaviors, yet fewer high-risk sexual partners than women. After adjustment, HIV seropositive men were more likely than seronegatives to be older, MSM, use condoms, and have an HIV-infected partner. HIV seropositive women were more likely to be older, have an HIV-infected partner, and not use non-injected heroin. IDU was not associated with HIV. These findings highlight the need to determine how gender-specific sexual behaviors/partnerships among drug users affect HIV

acquisition. Absalon, J., Fuller, C.M., Ompad, D.C., Blaney, S., Koblin, B., Galea, S., and Vlahov, D. Gender Differences in Sexual Behaviors, Sexual Partnerships, and HIV Among Drug Users in New York City. AIDS Behav, 10(6), pp. 707-715, 2006.

Service Uptake and Characteristics of Injection Drug Users Utilizing North America's First Medically Supervised Safer Injecting Facility

In 2003, the city of Vancouver, British Columbia, opened North America's first government-sanctioned safer injecting facility, where injection drug users (IDUs) can inject preobtained illicit drugs under the supervision of nurses between 10:00 AM to 4:00 AM. Of 713 IDUs who enrolled to use the facility, 308 (43.2%) reported using it daily at the first interview. The average number of daily visits in the first week of operation was 200; the average increased to 500 visits a day and has remained at that level since. Substances used include heroin (42%), cocaine (32%), and other substances (26%). Use of the service by IDUs was followed by measurable reductions in public drug use and syringe sharing. IDUs who are frequently using the program are significantly more likely to be high-intensity (daily) cocaine and heroin injectors, younger than non-daily users (38 yrs vs 40 yrs, $p<.001$), and homeless. Among the daily users, 88% tested HCV-positive and 16% tested HIV. The facility has provided high-risk IDUs a hygienic space where syringe sharing can be eliminated and the risk of fatal overdose reduced. Ongoing evaluation will be required to assess its impact on overdose rates and HIV infection levels, as well as its ability to improve IDU contact with medical care and addiction treatment. Wood, E., Tyndall, M., Qui, Z., Zhang, R., Montaner, J., and Kerr, T. Service Uptake and Characteristics of Injection Drug Users Utilizing North America 's First Medically Supervised Safer Injecting Facility. Am J Public Health, 96(5), pp. 770-773, 2006.

Nonadherence to Antiretroviral Therapy among a Community with Endemic Rates of Injection Drug Use

Highly active antiretroviral therapy (HAART) has resulted in major reductions in HIV-related morbidity and mortality. However, long-term use of HAART is challenging, and substantial numbers of patients discontinue their medications prematurely. The purpose of this analysis is to describe HAART adherence rates among a large urban cohort (N=2985) and examine factors associated with adherence (based on refill compliance). Of the 184 eligible participants on HAART, 129 (70%) were less than 95% adherent. Variables independently associated with nonadherence included frequent heroin injection (adjusted odds ratio [AOR] = 2.6, 95% confidence interval [CI], 1.6-4.0), baseline CD4 count less than 200 cells/mm (3) (AOR = 2.5; 95% CI, 1.9-3.2), and poor treatment by health care professionals (AOR = 1.7; 95% CI, 1.2-3.0). Variables inversely associated with HAART nonadherence included attaining viral load suppression (AOR = 0.3; 95% CI, 0.2-0.5) and methadone maintenance therapy (AOR = 0.5; 95% CI, 0.4-0.9). These findings suggest that innovative strategies that address the social barriers facing marginalized populations are needed to support the long-term continuation of HAART. Shannon, K., Kerr, T., Lai, C., Ishida, T., Wood, E., Montaner, J., Hogg, R., and Tyndall, M. Nonadherence to Antiretroviral Therapy Among a Community with Endemic Rates of Injection Drug Use. J Int Assoc Physicians AIDS Care (Chic Ill), 4(3), pp. 66-72, 2005.

Differences in Access to Care among Injection Drug Users Infected Either with HIV and Hepatitis C or Hepatitis C Alone

Access to HCV (Hepatitis C virus) care for HIV/HCV-co-infected patients is an

urgent public health concern. The objective of this study was to describe the self-reported health status of HIV/HCV-co-infected and HCV-mono-infected IDUs and to describe their access to HCV-related care. Beginning in May 1996, persons who had injected illicit drugs in the previous month were recruited into an open cohort study called the Vancouver Injection Drug User Study (VIDUS). At baseline and then semi-annually, participants complete an interviewer-administered questionnaire. Blood is drawn at each semi-annual interview and tested for HIV and Hepatitis C infection. Data for this descriptive, cross-sectional analysis were drawn from the most recent of either the July 2003 or December 2003 nurse-administered questionnaire. Statistics used were the chi-square, Wilcoxon Rank Sum and Student's t-test. Logistic regression was used to examine factors independently associated with accessing HCV care. There were 707 IDUs eligible for this analysis, including 240 HIV/HCV-co-infected and 467 HCV-mono-infected persons. Co-infected individuals were more likely to be female, younger, of Aboriginal ethnicity and less likely to use heroin daily. The HCV-mono-infected group tended to report higher rates of HCV-related symptoms, including fatigue, liver pain, nausea, night-sweats and stomach pain. However, it was the HIV/HCV-co-infected group who were more likely to report that they believed their HCV was affecting them. The HIV/HCV-co-infected group were also more likely to report having received any hepatitis-related follow-up care, including blood work, liver biopsies and referrals to specialists. In logistic regression analysis, factors independently associated with ever receiving any HCV-related follow-up were HIV/HCV-co-infection (AOR 3.1; 95% CI: 2-4.7), being older (AOR 1.04; 95% CI: 1.02-1.06 per year older), using heroin daily (AOR 0.54; 95% CI: 0.36-0.82) and believing that hepatitis C was affecting one's health (AOR 1.4; 95% CI: 1.0-2.1). These findings suggest that HCV healthcare utilization is greater among those who are HIV/HCV-co-infected, and that this group is experiencing more morbidity compared to the HCV mono-infected. Braitstein, P., Li, K., Kerr, T., Montaner, J., Hogg, R., and Wood, E. Differences in Access to Care among Injection Drug Users Infected Either with HIV and Hepatitis C or Hepatitis C Alone. AIDS Care, 18(7), pp. 690-693, 2006.

Needle Exchange Use, Sexual Risk Behaviour, and the Prevalence of HIV, Hepatitis B Virus, and Hepatitis C Virus Infections among Bulgarian Injection Drug Users

At a time when the rates of HIV, hepatitis C virus (HCV), and hepatitis B virus (HBV) infections have risen among injection drug users (IDUs) in other countries in the region, little is known about the prevalence of these infections among Bulgarian injectors, nor about their sexual risk behaviours. Geographically, Bulgaria is situated on the major trafficking routes of illegal drugs from the Middle East to Central and Western Europe. Large amounts of heroin enter Bulgaria through its border with Turkey; this, coupled with the fall of communism, has been linked to the country's first epidemic of heroin use in the early 1990s. This study supported by a NIDA international supplement, involved structured interviews with IDUs (n = 773) in a community-based needle exchange programme (NEP) and two major drug treatment facilities in Sofia, Bulgaria, as well as testing for HIV, HBV, and HCV antibodies. The mean age in the sample was 26 years, with 79% male, 84% Bulgarian, and 13% Roma. While HCV prevalence in the sample was 73.9%, HBV and HIV prevalence was low -6% and 0.5%, respectively. Having more than 10 sexual partners, having sex with someone with hepatitis C or another IDU, and never using a condom with another IDU were common among those who were recruited through the NEP. Given that 40% of the IDUs reported using the NEP, the study indicates that needle exchange provides an important opportunity to reach high-risk populations and prevent the drug use- and sexually-related transmission of HIV and other blood-borne pathogens. Vassilev, Z., Hagan, H., Lyubenova, A., Tomov, N., Vasilev, G., Krasteva, D., and Des Jarlais, D. Needle Exchange Use, Sexual Risk Behaviour, and the Prevalence of HIV, Hepatitis B

Virus, and Hepatitis C Virus Infections Among Bulgarian Injection Drug Users. Int J STD AIDS, 17(9), pp. 621-626, 2006.

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

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

A Comparison of Salivary Cotinine Concentrations with Self-Reported Cigarette Smoking in Adolescence

The authors examined the extent and sources of discrepancies between self-reported cigarette smoking and salivary cotinine concentration among adolescents. Household interviews with a cohort of 1,024 adolescents from an urban school system, histories of tobacco use in the last 7 days, and saliva samples were obtained. Logistic regressions identified correlates of three inconsistent patterns: (a) Pattern 1-self-reported nonsmoking among adolescents with high cotinine concentration, (b) Pattern 2-low cotinine concentration among adolescents reporting having smoked within the last 3 days, and (c) Pattern 3-high cotinine concentration among adolescents reporting not having smoked within the last 3 days. Rates of inconsistency were high among smokers defined by cotinine levels or self-reports (Pattern 1 = 49.1%; Pattern 2 = 42.0%). Controlling for other covariates, the authors found that reports of nonsmoking among those with high cotinine (Pattern 1) were associated with younger age, having few friends smoking, little recent exposure to smokers, and being interviewed by the same interviewer as the parent and on the same day. Low cotinine concentration among self-reported smokers (Pattern 2) was negatively associated with older age, being African American, number of cigarettes smoked, depth of inhalation, and exposure to passive smoke but positively associated with less recent smoking and depressive symptoms. High cotinine concentrations among self-reported nonsmokers was positively associated with exposure to passive smoke (Pattern

3). The authors report that the data are consonant with laboratory findings regarding ethnic differences in nicotine metabolism rate. The inverse relationship of cotinine concentration with depressive symptoms has not previously been reported. The authors suggest that depressed adolescent smokers may take in smaller doses of nicotine than nondepressed smokers; alternatively, depressed adolescents may metabolize nicotine more rapidly. Kandel, D., Schaffran, C., Griesler, P., Hu, M., Davies, M., and Benowitz, N. Salivary Cotinine Concentration Versus Self-Reported Cigarette Smoking: Three patterns of inconsistency in adolescence. Nicotine Tob Res, 8(4), pp. 525-537, 2006.

The Impact of Drug Use on Perceptions of Credibility in Indigenous Outreach Workers

This study examined perceptions of outreach worker credibility (i.e., expertise and trustworthiness) by the respective social network members (N = 20) of indigenous outreach workers in an HIV/AIDS prevention intervention. Most evaluations of outreach-based programs have focused on how and where a message is being conveyed rather than on the relationship between the speaker and listener, and have overlooked how a speaker's past or current drug use may affect his or her credibility as a messenger of behavioral change. The network members in this study participated in semistructured interviews following the program's completion. Outreach workers who were not actively using illicit drugs were more likely to be described as credible than were those who were using drugs. In general, drug use negatively affected perceptions of credibility via damaged trust in the outreach worker's relationship with his or her network member. These findings indicate the complexity of using indigenous drug users as outreach workers, the potential negative perceptions concerning hypocritical behavior, and the need to evaluate social interventions from the standpoint of indirect participants. Mitchell, S., Peterson, J., and Latkin, C. The Impact of Drug Use on Perceptions of Credibility in Indigenous Outreach Workers. Qual Health Res, 16(8), pp. 1108-1119, 2006.

Heritability of Drug Use and Dependence among Norwegian Twins

Prior population-based twin studies of drug abuse have taken place in two countries with similar cultures and high rates of drug abuse, namely the USA and Australia. In this study, the authors estimated genetic and environmental contributions to drug abuse in a sample from Norway, a Nordic country with a low prevalence of illicit drug use. Lifetime use, abuse and dependence of five illicit drug categories (cannabis, stimulants, opiates, cocaine and psychedelics) were assessed at personal interview in 1386 complete young adult twin pairs (ages 20-32) ascertained from the Norwegian Institute of Public Health Twin Panel. Twin model fitting was performed using the Mx statistical package on three phenotypes: any lifetime use, endorsement of at least one DSM-IV symptom of abuse or dependence, and meeting DSM-IV criteria for abuse or dependence. As expected, significant lifetime use of illicit substances (defined as use 10 or more times) was reported by only 6.4% of the sample. Meaningful analyses were possible for use of any substance and each of the five substances individually, but for symptoms or a diagnosis of abuse/dependence meaningful analyses were possible only for any substance and cannabis. Full twin models uniformly found twin resemblance to be due largely or entirely to genetic factors. Best-fit models for all analyses included only genetic and individual-specific environmental effects with heritability estimates ranging from 58% to 81%. In accord with prior results from the USA and Australia, genetic factors appear to play an important role in the etiology of use and abuse/dependence of illicit drugs in Norway. Thus, these findings suggest that heritabilty is not affected by drug availability; however, further work is needed. Kendler, K., Aggen, S., Tambs, K., and Reichborn-Kjennerud, T. Illicit Psychoactive Substance Use, Abuse and Dependence in a Population-based

Sample of Norwegian Twins. Psychol Med, 36(7), pp. 955-962, 2006.

Substance Abuse and Psychiatric Disorders in HIV-positive Patients: Epidemiology and Impact on Antiretroviral Therapy

There is a high prevalence of substance abuse and psychiatric disorders among HIV-infected individuals. Importantly, drug and alcohol-use disorders are frequently co-morbid with depression, anxiety, and severe mental illness. Not only do these disorders increase the risk of contracting HIV, they have also been associated with decreased highly active antiretroviral therapy (HAART) utilization, adherence and virological suppression. The literature evaluating the relationship between substance abuse and HIV outcomes has primarily focused on injection drug users, although there has been increasing interest in alcohol, cocaine and marijuana. Similarly, the mental health literature has focused largely on depression, with a lesser focus on severe mental illness or anxiety. To date, there is little literature evaluating the association between co-occurring HIV, substance abuse and mental illness on HAART uptake, adherence and virological suppression. Adherence interventions in these populations have demonstrated mixed efficacy. Both directly observed therapy and pharmacist-assisted interventions appear promising, as do integrated behavioural interventions. However, the current intervention literature has several limitations: few of these studies are randomized, controlled trials; the sample sizes have generally been small; and co-occurring substance abuse and mental illness has not specifically been targeted in these studies. Future studies examining individual substances of abuse, psychiatric disorders and co-occurring substance abuse and psychiatric disorders on HIV outcomes will inform targeted adherence interventions. Chander, G., Himelhoch, S., and Moore, R. Substance Abuse and Psychiatric Disorders in HIV-positive Patients: Epidemiology and Impact on Antiretroviral Therapy. Drugs, 66(6), pp. 769-789, 2006.

Substance Use and Problem Behavior across Three Generations

This study examined patterns of between-generation continuity in substance use from generation 1 (G1) parents to generation 2 (G2) adolescents and from G2 adult substance use and G1 substance use to generation 3 (G3) problem behavior in childhood. Structural equation modeling of prospective, longitudinal data from 808 participants, their parents, and their children showed low levels of G1 to G2 cross-generational continuity in the general tendency to use drugs. This effect was fully mediated by G2 early adolescent behavior problems. Drug-specific residual effects were observed across generations for cigarette smoking. Once established in adolescence, substance use in G2 showed stability over time. G2 substance use at age 27 significantly predicted G3 problem behavior. G1 substance use also was related to G3 problem behavior indirectly. These findings highlight the importance of interrupting intergenerational cycles of substance use and problem behavior. Bailey, J., Hill, K., Oesterle, S., and Hawkins, J. Linking Substance Use and Problem Behavior Across Three Generations. J Abnorm Child Psychol, 34(3), pp. 263-292, 2006.

Exposure to Family Violence and Childhood Bullying

The objectives of this study were to describe the prevalence of bullying involvement (ie, bullying and victimization) among children from a multigenerational study and to examine the relationship of these childhood behaviors and exposure to intimate partner violence. A community-based cohort of 112 children (aged 6 to 13 years) was asked to self-report on physical, verbal, and relational types of bullying and victimization experienced in the past year. Parents reported on their child's externalizing and internalizing behaviors during the previous 6 months using items from

Achenbach's Child Behavior Checklist. The frequency of parental experiences of intimate partner violence perpetration and victimization at 2 time points during the preceding 5 years was measured using Conflict Tactics Scale items. The association of intimate partner violence and parent-reported child behavioral problems was examined, followed by exposure to intimate partner violence and child-reported bullying or victimization. Parental risk factors (eg, race/ethnicity, education, problem drinking) that predispose to intimate partner violence were controlled for using propensity score statistical modeling. Eighty-two (73.2%) children reported being victimized by peers, and 38 (33.9%) children reported bullying behaviors in the past year. More reports came from girls than from boys (55% for victimization and 61% for bullying). Almost all (97%) child bullies were also victims themselves. Intimate partner violence was reported by parent respondents in 53 (50.5%) households at any or both of the 2 time points. Exposure to intimate partner violence was not associated with child-reported relational bullying behaviors or victimization by peers, however, intimate partner violence-exposed children were at increased risk for problematic levels of externalizing behavior/physical aggression and internalizing behaviors. In this sample, children who were 6 to 13 years of age reported a substantial amount of bullying and victimization; a large majority were bully-victims and female. Regression analyses did not show that children who were exposed to intimate partner violence were more likely to engage in relational bullying. However, children who are exposed to intimate partner violence have a higher likelihood of internalizing behaviors and physical aggression. Bauer, N., Herrenkohl, T., Lozano, P., Rivara, F., Hill, K., and Hawkins, J. Childhood Bullying Involvement and Exposure To Intimate Partner Violence. Pediatrics, 118(2), pp. e235-e242, 2006.

Neglect and Later Externalizing Problems in Children of Adolescent Mothers

The present study examines the role of neglect potential in adolescent mother-child dyads, both in terms of antecedents and its consequences for children's development. Participants were 100 adolescent mother-child dyads who were part of a larger, longitudinal study. Data were collected from the third trimester of pregnancy until the children's 10th year. Histories of maternal neglect and the quality of mother-child interactions during early childhood were found to predict neglect potential during middle childhood. Mothers with high neglect potential had children who exhibited more externalizing problems and fewer adaptive behaviors, with neglect potential mediating the effects of both early abuse potential and the quality of parenting on children's later externalizing behaviors. Results suggest that neglect potential may be a mechanism through which early potential for child abuse and insensitive maternal interactions affect later externalizing problems in children of adolescent mothers. Lounds, J., Borkowski, J., and Whitman, T. The Potential for Child Neglect: The Case of Adolescent Mothers and their Children. Child Maltreat, 11(3), pp. 281-294, 2006.

Aggressive Behaviors in Adolescents of HIV-positive and HIV-negative Drug Abusing Fathers

This study examined aggressive behaviors in the adolescent children of HIV-positive and HIV-negative drug-abusing fathers. Data were collected via individual structured interviews of low-income, predominantly African American and Hispanic, father-child dyads (N = 415). Structural Equation Modeling was used to assess the interrelationship of several latent constructs with respect to adolescent aggression. Results showed a mediational model linking paternal attributes (including HIV status) and ecological factors with the father-child relationship, which impacted peer influences and the adolescent's vulnerable personality, which was the most proximal construct to aggressive behaviors. Ecological factors were also mediated by peer influences and directly linked

with adolescent aggression. Brook, D., Brook, J., Rubenstone, E., and Zhang, C. Aggressive Behaviors in the Adolescent Children of HIV-positive and HIV-Negative Drug-Abusing Fathers. Am J Drug Alcohol Abuse, 32(3), pp. 399-413, 2006.

Barriers and Pathways to Diffusion of Methamphetamine Use Among African Americans in the Rural South: Preliminary Ethnographic Findings

There are no known studies of African American use of methamphetamine in the rural South, where it has been found to be widespread among whites. This qualitative ethnographic study was conducted to identify factors that may inhibit or facilitate the diffusion of methamphetamine use among African Americans living in rural Arkansas and Kentucky. Qualitative interviews were conducted with 86 stimulant users, 45 in rural Arkansas and 41in Kentucky. There were 51 whites, 34 African Americans, and one multiethnic participant. Among the 34 African Americans, 14 reported prior methamphetamine use, but only one reported being a current user. By contrast, 31 of the 51 whites or about 61% reported current methamphetamine use. These findings suggest that there is comparatively low prevalence of methamphetamine use among African Americans in the rural South. Interviewees cited several barriers to its diffusion, including the drug's ingredients, its psychoactive and physiological effects, and the difficulty of accessing distribution networks. They also described a preference among African-Americans for cocaine, attributed in part to its quicker onset of psychoactive effects. The authors caution that more research is needed to understand African American's low use of methamphetamine. They also note that multicultural connections among whites and African Americans are increasing and are likely to change barriers and pathways to diffusion of methamphetamine use among African Americans in years to come. Sexton, R., Carlson, R., Siegal, H., Falck, R., Leukefeld, C., and Booth, B. Barriers and Pathways to Diffusion of Methamphetamine Use Among African Americans in the Rural South: Preliminary Ethnographic Findings. J Ethn Subst Abuse, 4(1), pp. 77-103, 2005.

Sexual Identity Formation and AIDS Prevention: An Exploratory Study of Non-Gay-Identified Puerto Rican MSM from Working Class Neighborhood

As a subgroup of men who have sex with men (MSM), non-gay-identified (NGI) behaviorally bisexual Latino MSM are associated with heightened probabilities of HIV transmission, yet they have eluded HIV/AIDS interventionists. This exploratory study among 20 Puerto Rican MSM heroin-dependent injection drug users (average age 25 years) employed multi-session qualitative interviews to examine early life experiences related to gender identity and sexual orientation, and the place of risky drug and sexual behaviors in the process of sexual identity formation. NGI participants (n=8) experienced sexual debut between ages 13 and 20, and most were recruited to prostitution as young teens by NGI age mates who were also members of drug use networks. Participants emphasized their role as insertive sexual partners and that they maintained relationships with "pasivo" biological males. This exploratory study found that it is feasible to recruit NGI MSM through primary male sexual partners and drug use networks. HIV/AIDS prevention based on an awareness of developmental histories holds promise for intervening before NGI youth reach the point of engaging in male prostitution or injection drug use. Finlinson, H., Colon, H., Robles, R., and Soto, M. Sexual Identity Formation and AIDS Prevention: An Exploratory Study of Non-Gay-Identified Puerto Rican MSM from Working Class Neighborhoods. AIDS Behav, 10(5), pp. 531-539, 2006.

An Exploratory Qualitative Study of Polydrug Use Histories among Recently Initiated Injection Drug Users in San Juan, Puerto Rico

It has been shown that drug users often modulate the effects of their primary drugs of use (e.g., cocaine) by using other drugs (e.g., alcohol), yet the effect of modulating and primary drug interactions on transitions from one class of drugs to another and from noninjected drugs to injected drugs is not clear. This issue is critical for understanding polydrug abuse. Investigators conducted formative research based on in-depth qualitative interviews during 2003-2004 with 25 recently initiated drug injectors (ages 18 to 35; average 23.6 years; 84% male) residing in San Juan, Puerto Rico. Involvement in the criminal justice system was extensive (79%) and 71% currently lived with a parent or grandparent. Increased use of a primary drug (e.g., cocaine) was found to be influenced by a succession of enhancing or attenuating drugs, which participants viewed as progressively more dangerous. Use in a particular order (e.g., alcohol, heroin) seemed to reflect effectiveness in modulating primary drugs at different use intensities, as well as by the users' perceptions of the relative dangers of different drugs. Neither availability nor access appeared to affect the order in which participants used modulating drugs. Finlinson, H., Colon, H., Robles, R., and Soto-Lopez, M. An Exploratory Qualitative Study of Polydrug Use Histories among Recently Initiated Injection Drug Users in San Juan, Puerto Rico. Subst Use Misuse, 41(6-7), pp. 915-935, 2006.

Cross-National Differences in Drugs and Violence among Adolescents: Preliminary Findings of the DAVI Study

This study examined cross-national differences in drug use and violence among three sites that vary in social and political culture and drug use policies-Philadelphia, Toronto, and Amsterdam. The DAVI (Drugs, Alcohol and Violence International) study is based on personal interviews with 120 adolescents aged 14 to 17 years from three sites and two samples of 550 detainees and 570 dropouts, respectively. Seven drug use outcomes and three violence outcomes were compared across sites. The study found that site differences were dominant: only two of 10 outcomes (cannabis onset and relative drug-related violence) were not significantly related to site as a main effect or through an interaction. The most common site differences showed that the Toronto samples reported higher rates of drug use than Philadelphia and Amsterdam. The findings indicate that drug taking behavior transcends geopolitical boundaries. Moreover, rates of drug use among the disparate sites do not appear related to policy climate. Adlaf, E. M., Korf, D. J., Harrison, L., and Erickson, P. Cross-National Differences in Drugs and Violence among Adolescents: Preliminary Findings of the DAVI Study. J Drug Issues, 36(3), pp. 597-617, 2006.

Extracurricular Activities and Drug Use Among Affluent Youth

It has been suggested that over-scheduling of upper-class youth might underlie the high distress and substance use documented among them. This assumption was tested by considering suburban 8th graders' (n=314) involvement in different activities along with their perceptions of parental attitudes toward achievement. Results indicated negligible evidence for deleterious effects of high extracurricular involvement per se. Far more strongly implicated was perceived parent criticism for both girls and boys as well as the absence of after-school supervision. Low parent expectations connoted significant vulnerability especially for boys. The findings indicate that at least among early adolescents, converging scientific and media reports may have scapegoated extracurricular involvements, to some degree, as an index of ubiquitous achievement pressures in affluent communities. Luthar, S., Shoum, K., and Brown, P. Extracurricular Involvement Among Affluent Youth: A Scapegoat for

"Ubiquitous Achievement Pressures"? Dev Psychol, 42(3), pp. 583-597, 2006.

A Factor Analytic Approach to Measuring Dimensions of Proactive and Reactive Aggression

This study used a confirmatory factor model to distinguish pure and co-occurring dimensions of proactive and reactive aggression, and examined the relation between parenting variables and these dimensions of aggression in a sample of 100 children (9 to 12 years of age; 69 boys). Confirmatory factor analysis (CFA) supported 3 dimensions of proactive and reactive aggression: pure proactive, pure reactive, and their co-occurrence. Parenting variables differentially related to the pure and co-occurring dimensions of aggression. Findings indicate that CFA provides a promising approach for conceptualizing aggression on a continuum and allows researchers to distinguish pure and co-occurring dimensions of proactive and reactive aggression. Fite, P., Colder, C., and Pelham, W. A Factor Analytic Approach to Distinguish Pure and Co-occurring Dimensions of Proactive and Reactive Aggression. J Clin Child Adolesc Psychol, 35(4), pp. 578-582, 2006.

Director's Report to the National Advisory Council on Drug Abuse - February, 2007

Research Findings - Prevention Research

Universal Drug Prevention Programs Reduce Methamphetamine Use

This study examined the long-term effects of universal preventive interventions on methamphetamine use by adolescents in the general population during their late high school years, using data from two randomized, controlled prevention trials were. Participants attended public middle schools in the Midwest from 1993 to 2004. Study 1 began with 667 sixth grade students from 33 rural public schools, who were followed up 6 _ years later (grade 12); the follow-up included 457 students. Study 2 began with 679 seventh grade students from 36 rural public schools who were followed up 4 _ (grade 11) and 5 _ (grade 12) years later; the follow-up assessment included 597 students. Three interventions were used across the two RCTs. In study 1, schools were assigned to the Iowa Strengthening Families Program (ISFP), Preparing for the Drug Free Years, or a control condition. In study 2, schools were assigned to a revised ISFP (SFP 10- 14) plus Life Skills Training (SPF 10-14_LST), LST alone, or a control condition. Self-reports of lifetime and past-year methamphetamine use were collected at 6_ years past baseline (study 1) and at 4_ and 5_ years past baseline (study 2). In study 1, the ISFP past-year rate was 0.0% compared with 3.2% in the control condition (P=.04). In study 2, SFP 10-14_LST showed significant effects on lifetime and past-year use at the 4_year follow-up (eg, 0.5% lifetime use in the intervention condition vs 5.2% in the control condition, P=.006); both SFP 10-14_LST and LST alone had significant lifetime use effects at the 5_ year follow-up. Findings demonstrate that brief universal interventions have potential for public health impact by reducing methamphetamine use among adolescents. Spoth, R.L., Clair, S., Shin, C., and Redmond, C. Long-term Effects of Universal Preventive Interventions on Methamphetamine Use Among Adolescents. Arch Pediatr Adolesc Med, 160 pp. 876-882, 2006.

Raising Healthy Children Promotes Alcohol-free Driving

This study evaluated the impact of two targeted family sessions focused on driving issues delivered within the context of the Raising Healthy Children project. The Raising Healthy Children project began in the fall of 1993, drawing students in the 1st or 2nd grades from 10 schools. Schools were assigned to an intervention or control condition, and the school-wide, family- and student-focused preventive intervention to address developmentally salient risk and protective factors was delivered during elementary and middle school. The family driving sessions were administered to families in the intervention condition prior to and after teenagers received their driver's license. The first session consisted of a home visit with families designed to help parents and their children improve decision-making skills concerning driving and to develop

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clear standards and expectations regarding driving-related behavior. A second session, at the time of licensure, was designed to help parents and teens develop a written contract that stated family expectations, a plan for monitoring compliance with these expectations, and consequences for compliance or non-compliance. Consistent with the study's group-randomized design, intervention effects were assessed with multi-level logistic regression models in which students were grouped by their original school assignment. These models assessed specific effects of the driving sessions by adjusting for control variables measured when students were in 8th grade, prior to the driving sessions. Results indicated that students in the intervention group were more likely than students in the control group to report that they had a written driving contract ($p = .003$, OR = 4.98) and had participated in making the driving rules in the family ($p = .025$, OR = 1.70). Further, students in the intervention group reported significantly fewer risky behaviors including driving under the influence of alcohol ($p = .021$, OR = .45) and driving with someone who had been drinking ($p = .038$, OR = .56). Haggerty, K.P., Fleming, C.B., Catalano, R.F., Harachi, T.W., and Abbott, R.D. Raising Healthy Children: Examining the Impact of Promoting Healthy Driving Behavior within a Social Development Intervention. Prev Sci, 7 pp. 257-267, 2006.

Predictors of Intervention Adherence Among Young People Living With HIV

This study examined adherence to a 23-session intervention for young people living with HIV. Two hundred eight HIV-positive youth were assigned by small cohort to a behavioral intervention. Results showed that youth with more personal strengths were more likely to attend the intervention; those with more competing environmental demands (eg, employment, school) were less likely to attend the intervention. Using a social support, spiritual hope, or self-destructive and escape coping style was associated with attendance. Youth who reported many sexual partners attended fewer sessions. Adherence varied by cohort assignment. It was concluded that high attendance should be considered as a goal when designing future interventions. Song, J., Lee, M., Rotheram-Borus, M., and Swendeman, D. Predictors of Intervention Adherence Among Young People Living With HIV. Am J Health Behav, 30(2), pp. 136-146, 2006.

Family Focused Intervention Provides Similar Benefits for High and Low Risk Youth

This study extends earlier investigation of family risk-related moderation of two brief, family-focused preventive interventions. It examines effects on the trajectories of substance initiation over a period of six years after a pretest assessment, evaluating whether effects were comparable across higher- and lower-risk subgroups. The two interventions, designed for general-population families of adolescents, were the seven-session Iowa Strengthening Families Program (ISFP) and the five-session Preparing for the Drug Free Years program (PDFY). Thirty-three rural public schools were randomly assigned to either the ISFP, the PDFY, or a minimal contact control condition. Curvilinear growth curve analyses were used to evaluate the universality of intervention effectiveness by testing for risk moderation of intervention effects on school-level substance use trajectories of initiation of alcohol and illicit substance use. Results were most consistent with the interpretation that both interventions provided comparable benefits for both outcome measures, regardless of family risk status. Findings are discussed in terms of their implications for implementing universal preventive interventions in general populations. Spoth, R., Shin, C., Guyll, M., Redmond, C., and Azevedo, K. Universality of Effects: An Examination of the Comparability of Long-term Family Intervention Effects on Substance use Across Risk-related Subgroups. Prev Sci, 7(2), pp. 209-224, 2006.

Planned Meetings

Publications

Staff Highlights

Grantee Honors

Internet-Based Intervention for Mental Health and Substance Use Problems in Disaster-Affected Populations: A Pilot Feasibility Study

Early interventions that reduce the societal burden of mental health problems in the aftermath of disasters and mass violence have the potential to be enormously valuable. Internet-based interventions can be delivered widely, efficiently, and at low cost and as such are of particular interest. The development and feasibility analysis of an Internet-delivered intervention designed to address mental health and substance-related reactions in disaster-affected populations is described. Participants (n = 285) were recruited from a cohort of New York City-area residents that had been followed longitudinally in epidemiological research initiated 6 months after the terrorist attacks of September 11, 2001. The intervention consisted of 7 modules: posttraumatic stress/panic, depression, generalized anxiety, alcohol use, marijuana use, drug use, and cigarette use. Feasibility data were promising and suggest the need for further evaluation. Ruggiero, K., Resnick, H., Acierno, R., Coffey, S., Carpenter, M., Ruscio, A., Stephens, R., Kilpatrick, D., Stasiewicz, P., Roffman, R., Bucuvalas, M., and Galea, S. Internet-Based Intervention for Mental Health and Substance Use Problems in Disaster-Affected Populations: A Pilot Feasibility Study. Behav Ther, 37(2), pp. 190-205, 2006.

Providing Prevention Services for Conduct Problems to High Risk Children and Their Families

This study examined whether the link between risk factors for conduct problems and low rates of participation in mental health treatment could be decoupled through the provision of integrated prevention services in multiple easily-accessible contexts. It included 445 families of first-grade children (55% minority), living in four diverse communities, and selected for early signs of conduct problems. Children and families were participants in a larger study of a multi-component, multi-year Program, Fast Track, designed to prevent conduct problems among young children already exhibiting behavior problems. Results indicated that, under the right circumstances, these children and families could be enticed to participate at high rates in school-based services, therapeutic groups, and home visits. For example, 49% of the sample received a majority of the intervention services that were provided: 92% of school-based services, 88% of therapeutic groups, and 92% of home visits. Only 6% of the sample participated in a greater proportion of services. Because different sets of risk factors were related to different profiles of participation across the components of the prevention program, findings highlight the need to offer services in multiple contexts to reach all children and families who might benefit from them. Nix, R., Pinderhughes, E., Bierman, K., Maples, J., and Maples, J.T. Decoupling the Relation Between Risk Factors for Conduct Problems and the Receipt of Intervention Services: Participation Across Multiple Components of a Prevention Program. Am J Community Psychol, 36(3-4), pp. 307-325, 2005.

Prevention Program Format May Impact Participant Initiation and Exposure Rates

The primary aim of this study was to compare participation rates in two different formats of "Parents Who Care" a universal, family-based preventive intervention. Participants in the study were blocked on race and gender and randomized to three conditions: 1) a self administered format (SA) involving a video and workbook to be completed within 10 weeks 2) a parent adolescent group format (PAG) involving seven weekly meetings and 3) a no intervention control group. In this study, predictors of participation and exposure were compared across the two intervention formats. Families of 225 8th-grade

students were assigned to the (PAG) or the (SA) group. Logistic regression showed greater program initiation in SA than in PAG. Hierarchical regression showed only one variable (parent high-risk behavior) to be associated with lower program exposure in the self-administered format. In contrast, demographic variables (e.g., being African American) predicted lower exposure in PAG. Overall, the findings of this study were notable in that most of the variables that have been identified in past research as lowering participation rates were not related to program initiation or level of exposure to either format of "Parents Who Care". Further, the self-administered format may be particularly useful to increase program participation for families, even those who are traditionally difficult to reach. Haggerty, K., MacKenzie, E., Skinner, M., Harachi, T., and Catalano, R. Participation in "Parents Who Care": Predicting Program Initiation and Exposure in Two Different Program Formats. J Prim Prev, 27(1), pp. 47-65, 2006.

Peer Health Advocates are Trusted as Sources for HIV Prevention Material by Drug Using Peers

This article presents results from a process evaluation of a peer-led HIV prevention intervention. The Risk Avoidance Partnership, conducted from 2001 to 2005, trained active drug users to be peer health advocates (PHAs) to provide harm reduction materials and information to their peers. Results indicate that PHAs actively conducted harm reduction outreach both when partnered with staff and on their own time. Although PHAs conducted most of their outreach in public locations, they also provided drug users with harm reduction materials at critical moments in places where HIV risky behaviors were likely to occur. PHAs were credible and trusted sources of information to their drug-using peers who sought PHAs out for HIV prevention materials. Process evaluations of successful HIV prevention interventions are necessary to understand how and why such interventions work for further intervention refinement. Dickson-Gomez, J., Weeks, M., Martinez, M., and Convey, M. Times and Places: Process Evaluation of a Peer-led HIV Prevention Intervention. Subst Use Misuse, 41(5), pp. 669-690, 2006.

Tailoring Tobacco Counteradvertisements for Bicultural Mexican American Youth

The growing population of Mexican American youth and the increasing smoking rates in this population present a considerable public health challenge and little is known about the most effective ways to adapt messages aimed at this audience. To explore key variables that can affect success, a study was conducted with 249 Mexican American middle-school youth from a U.S./Mexico border community to examine the effectiveness of language (English, Spanish, or a combination of English and Spanish) and theme (secondhand smoke, anti-tobacco social norms, and tobacco industry manipulation) in print tobacco counteradvertisements. Measures included ad preferences, acculturation, and tobacco-related attitudes and behavior. Results showed that although a large percentage identified with the Mexican American rather than the Anglo American culture and spoke Spanish in selected contexts, readability was greater for ads in English, and participants rated the English ads as most effective. The social norms counteradvertisement was preferred overall. Kelly, K., Stanley, L., Comello, M., and Gonzalez, G. Tobacco Counteradvertisements Aimed at Bicultural Mexican American Youth: The Impact of Language and Theme. J Health Commun, 11(5), pp. 455-476, 2006.

Group Interventions May be Able to Minimize Peer Contagion

This study involving novel methodology applies a multi-player arms race model to peer contagion in the aggressive and delinquent behaviors of inner-city

elementary school students. Because this model of peer contagion differs from the usual model based on positive reinforcement of delinquent behavior, it raises the possibility that the persistent finding of iatrogenic effects of group treatment might not apply to group treatment of elementary school children if aggressive behavior in the group is limited. One way of limiting aggressive behavior is to include parents in the groups. To test this hypothesis, this study applies the model to groups of elementary school students assigned to Families and Schools Together (FAST), a group treatment that includes parental participation, or to an intervention focused on individual families. Data came from a longitudinal study of 403 children, their parents, and their teachers who participated in an evaluation of the FAST program. The model effectively describes the relationship between group averages of aggressive behavior in the classroom and aggressive and delinquent behavior outside the classroom for those students assigned to the individual intervention. The model fits those children assigned to FAST less well, suggesting that FAST may make it less likely that aggressive and delinquent behavior is generalized outside of aggressive classroom settings. Warren, K., Moberg, D., and McDonald, L. FAST and the Arms Race: The Interaction of Group Aggression and the Families and Schools Together Program in the Aggressive and Delinquent Behaviors of Inner-city Elementary School Students. J Prim Prev, 27(1), pp. 27-45, 2006.

Recommendations for the Prevention of HIV Transmission in Hispanic Adolescents

This article reviews the state of the science in HIV prevention for Hispanic adolescents. Literature is reviewed in three broad areas: (1) the prevalence rates of drug and alcohol misuse, sexual practices, and HIV infection; (2) risk and protective factors for drug and alcohol misuse and unprotected sex (in general and specifically for Hispanics); and (3) the state of HIV prevention intervention development and evaluation targeting Hispanic youth. Little basic and intervention research has been conducted on HIV prevention in Hispanic adolescents, with even less attention given to Hispanic young men who have sex with men (YMSM). There are a number of areas in which further knowledge development and scientific advancement are needed. The seven areas identified in this review were (a) the need for analyses of nationwide epidemiological data examining risk and protective factors for substance use and unsafe sexual behavior for heterosexual and homosexual youth; (b) explaining variations in drug/alcohol use, unsafe sexual behavior, and HIV infection among Hispanic subgroups; (c) need for adaptive preventive interventions for Hispanic subgroups with varying risk and protection profiles; (d) incorporation of ethnic, cultural, and sexual identity into prevention programs for Hispanic adolescents; (e) examination of the role of gender in preventive interventions for Hispanic adolescents; (f) research on the effects of psychiatric comorbidity on drug/alcohol use and unsafe sex and on the efficacy of prevention programs; and (g) increased focus on intravenous drug use as a mode of HIV infection among Hispanics, particularly Puerto Ricans. Research addressing these research needs has the potential to facilitate progress toward achieving the two primary objectives of Healthy People 2010--improving the quality of life for all Americans and reducing health disparities between and among segments of the U.S. population. Prado, G., Schwartz, S.J., Pattatucci-Aragon, A., Clatts, M., Pantin, H., Fernandez, M., Lopez, B., Briones, E., Amarof, H., and Szapocznik, J. The Prevention of HIV Transmission in Hispanic Adolescents. Drug Alcohol Depend, 84S pp. S43-S53, 2006.

Unprotected Sex Among Youth Living With HIV Before and After the Advent of Highly Active Antiretroviral Therapy

Since the advent of highly active antiretroviral therapy (HAART) in 1996, the incidence of HIV-especially among young men who have sex with men-and the prevalence of unprotected sex among HIV-positive persons have increased.

The characteristics associated with unprotected sex among youth living with HIV since the advent of HAART have not been explored. Samples of HIV-positive youth aged 13-24 were taken from two intervention studies that targeted the sexual behaviors of HIV-positive youth-one from 1994 to 1996 (pre-HAART) and the other from 1999 to 2000 (post-HAART). Generalized estimating equations were used to identify characteristics associated with unprotected sex in each sample. The prevalence of unprotected sex in the post-HAART sample was more than twice that in the pre-HAART sample (62% vs. 25%). Among the pre-HAART sample, being a man who has sex with men and having sex with a casual partner were negatively associated with the odds of unprotected intercourse (odds ratios, 0.5 and 0.2, respectively). Among the post-HAART sample, unprotected sex was negatively associated with knowing that a partner was HIV-negative (0.2) and positively associated with poorer mental health (1.02). In analyses among the post-HAART sample, poorer mental health was associated with increased odds of unprotected sex among youth living with HIV who were not receiving the treatment (1.02). It was concluded that interventions for HIV-positive youth must be designed to address the complex needs of those youth who simultaneously suffer from HIV and poor mental health. Rice, E., Batterham, P., and Rotheram-Borus, M. Unprotected Sex Among Youth Living With HIV Before and After the Advent of Highly Active Antiretroviral Therapy. Perspect Sex Reprod Health, 38(3), pp. 162-167, 2006.

Predictors of HIV-Related Stigma Among Young People Living with HIV

Enacted and perceived HIV stigma was examined among 147 substance-using young people living with HIV (YPLH) in Los Angeles, San Francisco, and New York City. Almost all YPLH (89%) reported perceived stigma, 31% reported enacted experiences in the past 3 months; and 64% reported experiences during their lifetime. The HIV stigma questions were characterized by factors of avoidance, social rejection, abuse, and shame. In multivariate models, enacted stigma was associated with gay or bisexual identity, symptomatic HIV or AIDS, and bartering sex. Perceived stigma was associated with female gender, symptomatic HIV or AIDS, bartering sex, lower injection drug use, and fewer friends and family knowing serostatus. Gay or bisexual YPLH who were also HIV symptomatic or AIDS diagnosed experienced more HIV stigma than their heterosexual peers. Swendeman, D., Rotheram-Borus, M., Comulada, S., Weiss, R., and Ramos, M. Predictors of HIV-Related Stigma Among Young People Living with HIV. Health Psychol, 25(4), pp. 501-509, 2006.

Prevalence and Correlates of Exchanging Sex for Drugs or Money Among Adolescents in the United States

This study examined the prevalence and correlates of exchanging sex for drugs or money among a nationally representative sample of 13,294 adolescents in the United States. Data are from the National Longitudinal Study of Adolescent Health, waves I and II. The lifetime prevalence of exchanging sex was estimated and a cross sectional analysis of sociodemographic and behavioral correlates was conducted. Unadjusted odds ratios were obtained. Results showed that 3.5% of adolescents had ever exchanged sex for drugs or money; two-thirds of these youths were boys. The odds of having exchanged sex were higher for youths who had used drugs, had run away from home, were depressed, and had engaged in various sexual risk behaviors. 15% of boys and 20% of girls who had exchanged sex reported they had ever been told they have HIV or another sexually transmitted infection (STI). It was concluded that adolescents with a history of exchanging sex have engaged in other high risk behaviors and may experience poor health outcomes, including depression and HIV/STIs. These findings should help inform strategies to prevent this high risk sexual behavior and its potential consequences. Edwards, J., Iritani, B., and

Hallfors, D. Prevalence and Correlates of Exchanging Sex for Drugs or Money Among Adolescents in the United States. Sex Transm Infect, 82(5), pp. 354-358, 2006.

Gender Differences in Associations Between Depressive Symptoms and Patterns of Substance Use and Risky Sexual Behavior Among a Nationally Representative Sample of U.S. Adolescents

This study uses a cluster analysis of adolescents, based on their substance use and sexual risk behaviors, to 1) examine associations between risk behavior patterns and depressive symptoms, stratified by gender, and 2) examine gender differences in risk for depression. Data are from a nationally representative survey of over 20,000 U.S. adolescents. Logistic regression was used to examine the associations between 16 risk behavior patterns and current depressive symptoms by gender. Compared to abstention, involvement in common adolescent risk behaviors (drinking, smoking, and sexual intercourse) was associated with increased odds of depressive symptoms in both sexes. However, sex differences in depressive symptoms vary by risk behavior pattern. There were no differences in odds for depressive symptoms between abstaining male and female adolescents (OR = 1.07, 95% CI 0.70-1.62). There were also few sex differences in odds of depressive symptoms within the highest-risk behavior profiles. Among adolescents showing light and moderate risk behavior patterns, females experienced significantly more depressive symptoms than males. It was concluded that adolescents who engage in risk behaviors are at increased risk for depressive symptoms. Girls engaging in low and moderate substance use and sexual activity experience more depressive symptoms than boys with similar behavior. Screening for depression is indicated for female adolescents engaging in even experimental risk behaviors. Waller, M., Hallfors, D., Halpern, C., Iritani, B., Ford, C., and Guo, G. Gender Differences in Associations Between Depressive Symptoms and Patterns of Substance use and Risky Sexual Behavior Among A Nationally Representative Sample of U.S. Adolescents. Arch Womens Ment Health, 9(3), pp. 139-150, 2006.

Genetic Contribution to Suicidal Behaviors and Associated Risk Factors Among Adolescents in the U.S.

This paper examines genetic contribution to suicidal behaviors and other risk factors associated with suicidal behavior among adolescents in the U.S. Using adolescent twin data in the National Longitudinal Study of Adolescent Health (N=1448), authors compared concordance in suicidal ideation and attempt among monozygotic (MZ) and dizygotic (DZ) twins. Heritability of risk factors for suicidal behaviors also was examined using Pearson correlation and mixed-model analyses. A trend of higher concordance in suicidal ideation and attempt was found among MZ than DZ twins but the difference was not statistically significant by the stringent test of bootstrapping analysis. Evidence of heritability was found for several suicide risk factors. The percentage of variance explained by heritability was larger among female twins for depression, aggression, and quantity of cigarettes smoked in comparison to heritability estimates for male twins. However, estimated heritability was larger among male than female twins for alcohol use and binge drinking. Heritability influence was negligible among both sexes for other drug use. Risk factors for suicidal behaviors among adolescents may be heritable. Gender differences found in the heritability of some suicide risk factors suggest these genetic contributions are gender specific. Future research examining potential interactions between expression of genetic influence and particular environmental contexts may enhance prevention and intervention efforts. Cho, H., Guo, G., Iritani, B.J., and Hallfors, D.D. Genetic Contribution to Suicidal

Behaviors and Associated Risk Factors Among Adolescents in the U.S. Prev Sci, 7(3), pp. 303-311, 2006.

In School Alcohol and Marijuana Use Among High School Students

The problem of adolescent substance use has been examined extensively. Beyond simple prevalence estimates, however, little research has been conducted on substance use in the school context. The present investigation was an in-depth study of students' attitudes and behaviors regarding alcohol and marijuana use during the school day. Based on a representative sample of 1123 high school students, 48% male, in grades 9-12 in western New York state, this study assessed the frequency of alcohol and marijuana use at school among demographic subgroups, the accessibility of drugs in school, and students' perceived consequences of being caught using drugs in school. Twelve percent of the sample reported using alcohol during school hours in the past 6 months while 16% reported using marijuana at school. Among students who used alcohol outside of school, 18% also used alcohol at school. For marijuana users, 47% used marijuana at school. There was evidence of some demographic differences in school drug use. Specifically, male and Hispanic students had slightly higher levels of drug use at school compared to female and white students, respectively, and in school drug use was more prevalent among older students. In terms of accessibility, students reported that alcohol and marijuana were easily obtained and used on school grounds. Many students (40%) were not aware of the specific actions taken in their schools to punish drug use. The need for additional research on school-related drug use is emphasized. Finn, K. V. Patterns of Alcohol and Marijuana Use at School. Journal of Research on Adolescence, 16(1), pp. 69-77, 2006.

Methodological Considerations for Testing Causal Effects in Drug Abuse Prevention Research

Observational data are often used to address prevention questions such as, "If alcohol initiation could be delayed, would that in turn cause a delay in marijuana initiation?" This question is concerned with the total causal effect of the timing of alcohol initiation on the timing of marijuana initiation. Unfortunately, when observational data are used to address a question such as the above, alternative explanations for the observed relationship between the predictor, here timing of alcohol initiation, and the response abound. These alternative explanations are due to the presence of confounders. Adjusting for confounders when using observational data is a particularly challenging problem when the predictor and confounders are time-varying. When time-varying confounders are present, the standard method of adjusting for confounders may fail to reduce bias and indeed can increase bias. In this paper, an intuitive and accessible graphical approach was used to illustrate how the standard method of controlling for confounders may result in biased total causal effect estimates. Based on the graphical approach, an alternative method proposed by James Robins was used to examine causal effect estimates. Implications for prevention researchers who wish to estimate total causal effects using longitudinal observational data are discussed. Bray, B., Almirall, D., Zimmerman, R., Lynam, D., and Murphy, S. Assessing the Total Effect of Time-varying Predictors in Prevention Research. Prev Sci, 7(1), pp. 1-17, 2006.

Rasch Analysis of Data From Prevention Study in South Africa Supports Jessors' Problem Behavior Theory

The goal of the study was to determine the presence of a syndrome of health risk behaviors in South African teenagers from Rasch modeling of items from self-report measures covering six conceptually distinct health risk domains

selected because they are among the most assessed health risk outcomes in prevention research and practice. A total of 2186 in-school adolescents participated in the study (males = 1077; females = 1119; age range = 12-16 years; median = 13 years). The data are baseline from a longitudinal study of a leisure-based drug abuse and HIV/AIDS prevention program at Mitchell's Plain in Cape Town, South Africa. The adolescents completed a self-report measure on various health risk vulnerabilities, including use of alcohol, tobacco and other drugs (ATOD), co-occurrence of penetrative sex with use of ATOD, health related self-efficacy, personal beliefs about health, peer perceptions, and use of contraceptives. The Rasch analysis calibrated data on 50 items from the conceptually distinct health risk domains. Infit and Outfit mean square statistics and principal components analysis of the standardized residuals suggested a fit of the data to the unidimensional Rasch measurement model. The findings support a syndrome view of health risk in teenagers as proposed by problem behavior theory. Mpofu, E., Caldwell, L., Smith, E., Flisher, A., Mathews, C., Wegner, L., and Vergnani, T. Rasch Modeling of the Structure of Health Risk Behavior in South African Adolescents. J Appl Meas, 7(3), pp. 323-334, 2006.

Parent Daily Report Checklist Can Be Used to Predict Foster Care Disruptions

The objective of this study was to identify reliable, inexpensive predictors of foster care placement disruption that could be used to assess risk of placement failure. Using the Parent Daily Report Checklist (PDR), foster or kinship parents of 246 children (5-12 years old; 131 boys, 115 girls) in California were interviewed three times about whether or not their foster child engaged in any of the 30 problem behaviors during the previous 24 hours. The PDR was conducted during telephone contacts (5-10 min each) that occurred from 1 to 3 days apart at baseline. Disruptions were tracked for the subsequent 12 months. Other potential predictors of disruption were examined, including the child's age, gender, and ethnicity, the foster parent's ethnicity, the number of other children in the foster home, and the type of placement (kin or non-kin). Foster/kin parents reported an average of 5.77 child problems per day on the PDR checklist. The number of problem behaviors was linearly related to the child's risk of placement disruption during the subsequent year. The threshold for the number of problem behaviors per day that foster and kinship parents tolerated without increased risk of placement disruption for these latency-aged children was 6 or fewer. Children in non-kin placements were more likely to disrupt than those in kinship placements. There was a trend for increased risk of disruption as the number of children in the home increased. The PDR Checklist may be useful in predicting which placements are at most risk of future disruption, allowing for targeted services and supports. Chamberlain, P., Price, J.M., Reid, J.B., Landsverk, J., Fisher, P.A., and Stoolmiller, M. Who Disrupts from Placement in Foster and Kinship Care? Child Abuse & Neglect, 30, pp. 409-424, 2006.

Predicting Reunification Failures in Foster Care

Previous studies have suggested that roughly 30% of all reunified foster children reenter foster care. Because reunification is one of the primary objectives of the child welfare system, it is imperative that correlates of reunification failure across parent, child, service, home and neighborhood domains be better understood. This study examined post-reunification variables regarding parent characteristics, child characteristics, parent service utilization, child service utilization, family environment, and neighborhood environment as they relate to reunification failure. The sample for the study included 16 foster children who, at reunification with their birth parents, ranged in age from 4-7 years. All participants were reunified with at least one parent. Among the variables found to significantly differentiate between failed and

successful reunifications were parental utilization of substance abuse treatment, child utilization of special educational services, child utilization of individual, family, or group therapy, overall parenting skill level, appropriate use of discipline, and quality of neighborhood. The article discusses the implications of these results for policies aimed at increasing the success rate of reunifications following foster care. Miller, K.A., Fisher, P.A., Fetrow, B., and Jordan, K. Trouble on the Journey Home: Reunification Failures in Foster Care. Children and Youth Services Review, 28, pp. 260-274, 2006.

Classroom Contextual Effects of Race on Children's Peer Nominations

Black children generally receive poorer sociometric nominations compared with Whites. This effect is not fully understood because Black children rarely hold a classroom majority and teachers' race is rarely investigated. Research from a person-environment perspective suggests that the effects of children's race depend on the racial composition of the classroom and society's racial attitudes. Sociometric nominations were obtained from 1,268 5th graders, between 9 and 11 years old (53% Black), across 57 classrooms (3-95% Black students). Half of the teachers were Black. The results indicated that ratings of Black children were more influenced by the racial context of classrooms than were ratings of White children. The implications of this study are discussed in relation to group dynamics and racial discrimination. Jackson, M., Barth, J., Powell, N., and Lochman, J. Classroom Contextual Effects of Race on Children's Peer Nominations. Child Dev, 77(5), pp. 1325-1337, 2006.

Improving Consent Return Rates Among Urban Elementary Students

This paper reports on consent form return rates for 3rd grade students attending schools in low-income, urban areas, where the researchers developed procedures to maximize their active parent consent efforts. The schools and participants were part of a larger study of a school-based prevention program. Research staff used a class incentive and class visits to retrieve consent forms from students. Of the 811 third-grade students, 98% returned a form and 79% (n = 627) of those students' parents provided an affirmative response. Return rates did not vary by students' ethnicity or by the schools' demographic variables. The authors conclude that incentives and class visits can yield a high return rate of active parent consent forms for third-grade minority, urban, low-income students. Ji, P., Flay, B., Dubois, D., Brechling, V., Day, J., and Cantillon, D. Consent Form Return Rates for Third-grade Urban Elementary Students. Am J Health Behav, 30(5), pp. 467-474, 2006.

The Relationship of Family Instability to Child Maladjustment

This study examines the relation between family instability and child maladjustment over a 6-year period in 369 children from four communities. The children and families were part of a larger study examining the impact of the multi-level, multi-year Fast Track preventive intervention on child conduct problems. Measures were collected annually from kindergarten through fifth grade. In associative growth curve models, family instability trajectories predicted children's externalizing and internalizing behavior trajectories during this time period. High levels of family instability also incrementally predicted the likelihood of meeting criteria for a DSM IV diagnosis during elementary school, above and beyond prediction from earlier measures of maladjustment. However, the timing of family instability had a different effect on externalizing versus internalizing disorders. In general, stronger relations were found between family instability and externalizing behaviors relative to internalizing behaviors, although children with comorbid disorders experienced the highest

levels of family instability. Future research that examines the underlying mechanisms that account for the influence of family instability on child maladjustment is discussed. Milan, S., Pinderhughes, E., and Pinderhughes, E.T. Family Instability and Child Maladjustment Trajectories During Elementary School. J Abnorm Child Psychol, 34(1), pp. 43-56, 2006.

Time Varying Family and Peer Influences on Adolescent Daily Mood

The time-varying influences of peer and family support on adolescent daily mood were explored among 268 youth transitioning from middle school to high school (8th to 9th grade) as compared to 240 youth transitioning from 10th to 11th grade. The participants were part of a larger study examining the natural history of smoking. Real-time ecological momentary assessments measures of daily positive and negative affect were collected via palmtop computers at baseline, 6 months, and 12 months. Participants rated 12 mood adjectives in response to 5 to 7 random prompts per day for 7 consecutive days. Perceived peer and family support were assessed via self-report. Mixed-effects regression analyses revealed significant grade by time by peer support interactions for positive and negative mood, with the younger cohort showing greater increases in the relation between peer support and affect over time than the older cohort. Family support did not interact with cohort or time. The authors summarize that peer influences may increase as adolescents develop, thus developmental influences should be included in examinations of dynamic relations between peers and adolescent mood. Also, these results may help elucidate transitions that may be optimal times for preventive interventions targeting emotional well-being of adolescents, specifically transition to high school. This transition point also coincides with a growth in mood disorders in adolescents, in particular girls. Girls were found to exhibit higher levels of negative moods at lower levels of peer support, relative to boys. The authors call for future research that captures the bidirectional nature of support--mood relations across adolescence. Weinstein, S., Mermelstein, R., Hedeker, D., Hankin, B., and Flay, B. The Time-varying Influences of Peer and Family Support on Adolescent Daily Positive and Negative Affect. J Clin Child Adolesc Psychol, 35(3), pp. 420-430, 2006.

Trajectories of Depression in Male and Female Children of Depressed Mothers

This study reports on relationships among gender, maternal depressed mood, and children's trajectories of depressive phenomena across middle childhood and early adolescence. It tested the hypothesis that, compared to boys, girls become increasingly vulnerable to maternal depression as they enter adolescence. The study sample consisted of 834 families from 10 Pacific Northwest schools that participated in the Raising Healthy Children project, a longitudinal study of the etiology of problem behaviors and test of a multicomponent, multiyear intervention targeting risk and protective factors within key child socializing domains of family, school, peer, group, and individual. Maternal depressed mood and children's depressive phenomena were assessed annually during an 8-year period that spanned Grade 3 through Grade 10 for the children. Mean scores for girls' depressive phenomena increased relative to those for boys as children matured. Maternal depressed mood was significantly and positively associated with children's level of depressive phenomena. An interaction effect of gender and maternal depressed mood on acceleration in children's depressive phenomena indicated that girls' trajectories of depressive phenomena were sustained in the presence of maternal depression while those of boys declined in the presence of maternal depression. Implications for the prevention and treatment of adolescent depression are discussed. Cortes, R.C., Fleming, C.B., Catalano, R.F., and Brown, E.C. Gender Differences in the Association Between Maternal Depressed

Mood and Child Depressive Phenomena from Grade 3 Through Grade 10. J Youth Adolescence, 35, pp. 815-826, 2006.

Tobacco Litigation In Argentina

This project evaluated the processes and outcomes of tobacco litigation in Argentina by analyzing the strategies and documents which the tobacco industry used to oppose litigation. A systematic search of tobacco industry documents on the internet dating from 1978 to 2002, and law library searches for Argentinean official and unofficial reports were combined with other online searches. This search pointed out that there have been at least 15 failed litigation cases in Argentina where the tobacco industry has been able to present a concerted defense in every claim regardless of cost. Industry strategies included hiring legal consultants from prestigious international and Argentinean law firms, monitoring of legal and academic meetings, controlling the development of new product liability legislation, obtaining favorable opinions from experts, and closely observing the development of litigation in Argentina. These strategies used by the industry have been successful in preventing recovery for tobacco injuries through litigation. The conclusion of this study is that Argentinean health advocates and lawyers need to be aware of the roles and strategies of the tobacco industry in order to develop effective litigation in Argentina. Flores, M., Barnoya, J., Mejia, R., Alderete, E., and Perez-Stable, E. Litigation in Argentina: Challenging the Tobacco Industry. Tob Control, 15(2), pp. 90-96, 2006.

Translation of Prevention Interventions From Research to Practice

This article summarizes research on Type II translation of prevention interventions aimed at enhancing the adoption of effective programs and practices in communities. The primary goal of Type II translation is to institutionalize evidence-based programs, products, and services. First, the authors describe theoretical frameworks that are useful to guide Type II translation research. Second, research on prevention program implementation, including fidelity of implementation and factors that are associated with successful program implementation, is summarized. The authors describe interventions designed to enhance the dissemination of preventive interventions in community and public health settings. Third, they describe strategies used by prevention program developers who have taken programs to scale. Fourth, they present a case example of Project Towards No Drug Abuse (TND), an empirically validated high school-based substance abuse prevention program. They describe ongoing research on the dissemination of Project TND. Finally, they provide suggestions for future Type II translation research. Rohrbach, L., Grana, R., Sussman, S., and Valente, T. Type II Translation: Transporting Prevention Interventions From Research to Real-world Settings. Eval Health Prof, 29(3), pp. 302-333, 2006.

Translation in the Health Professions: Converting Science into Action

The systematic translation of evidence-based research findings, tools, and information into practice is critical to improving the quality of our nation's health. However, despite several decades of advances in developing medical knowledge based on high-quality empirical evidence, widespread implementation of these findings into practice in diverse applied settings has not been achieved. This article reviews definitions and conceptual models that describe the translation of research from basic discovery to real-world applications, summarizes the various issues involved in the process of translation, discusses multiple barriers, and provides recommendations to surmount these hurdles. Areas of further research in this arena are suggested.

Finally, the article concludes that translational research is an important area to continue to pursue requiring long-term collaborative commitment among researchers and practitioners. Sussman, S., Valente, T., Rohrbach, L., Skara, S., and Pentz, M. Translation in the Health Professions: Converting Science into Action. Eval Health Prof, 29(1), pp. 7-32, 2006.

Universal Drug Prevention Programs Reduce Methamphetamine Use

This study examined the long-term effects of universal preventive interventions on methamphetamine use by adolescents in the general population during their late high school years, using data from two randomized, controlled prevention trials were. Participants attended public middle schools in the Midwest from 1993 to 2004. Study 1 began with 667 sixth grade students from 33 rural public schools, who were followed up 6 _ years later (grade 12); the follow-up included 457 students. Study 2 began with 679 seventh grade students from 36 rural public schools who were followed up 4 _ (grade 11) and 5 _ (grade 12) years later; the follow-up assessment included 597 students. Three interventions were used across the two RCTs. In study 1, schools were assigned to the Iowa Strengthening Families Program (ISFP), Preparing for the Drug Free Years, or a control condition. In study 2, schools were assigned to a revised ISFP (SFP 10- 14) plus Life Skills Training (SPF 10-14_LST), LST alone, or a control condition. Self-reports of lifetime and past-year methamphetamine use were collected at 6_ years past baseline (study 1) and at 4_ and 5_ years past baseline (study 2). In study 1, the ISFP past-year rate was 0.0% compared with 3.2% in the control condition (P=.04). In study 2, SFP 10-14_LST showed significant effects on lifetime and past-year use at the 4_year follow-up (eg, 0.5% lifetime use in the intervention condition vs 5.2% in the control condition, P=.006); both SFP 10-14_LST and LST alone had significant lifetime use effects at the 5_ year follow-up. Findings demonstrate that brief universal interventions have potential for public health impact by reducing methamphetamine use among adolescents. Spoth, R.L., Clair, S., Shin, C., and Redmond, C. Long-term Effects of Universal Preventive Interventions on Methamphetamine Use Among Adolescents. Arch Pediatr Adolesc Med, 160 pp. 876-882, 2006.

Raising Healthy Children Promotes Alcohol-free Driving

This study evaluated the impact of two targeted family sessions focused on driving issues delivered within the context of the Raising Healthy Children project. The Raising Healthy Children project began in the fall of 1993, drawing students in the 1st or 2nd grades from 10 schools. Schools were assigned to an intervention or control condition, and the school-wide, family- and student-focused preventive intervention to address developmentally salient risk and protective factors was delivered during elementary and middle school. The family driving sessions were administered to families in the intervention condition prior to and after teenagers received their driver's license. The first session consisted of a home visit with families designed to help parents and their children improve decision-making skills concerning driving and to develop clear standards and expectations regarding driving-related behavior. A second session, at the time of licensure, was designed to help parents and teens develop a written contract that stated family expectations, a plan for monitoring compliance with these expectations, and consequences for compliance or non-compliance. Consistent with the study's group-randomized design, intervention effects were assessed with multi-level logistic regression models in which students were grouped by their original school assignment. These models assessed specific effects of the driving sessions by adjusting for control variables measured when students were in 8th grade, prior to the driving sessions. Results indicated that students in the intervention group were more likely than students in the control group to report that they had a written

driving contract (p = .003, OR = 4.98) and had participated in making the driving rules in the family (p = .025, OR = 1.70). Further, students in the intervention group reported significantly fewer risky behaviors including driving under the influence of alcohol (p = .021, OR = .45) and driving with someone who had been drinking (p = .038, OR = .56). Haggerty, K.P., Fleming, C.B., Catalano, R.F., Harachi, T.W., and Abbott, R.D. Raising Healthy Children: Examining the Impact of Promoting Healthy Driving Behavior within a Social Development Intervention. Prev Sci, 7 pp. 257-267, 2006.

Predictors of Intervention Adherence Among Young People Living With HIV

This study examined adherence to a 23-session intervention for young people living with HIV. Two hundred eight HIV-positive youth were assigned by small cohort to a behavioral intervention. Results showed that youth with more personal strengths were more likely to attend the intervention; those with more competing environmental demands (eg, employment, school) were less likely to attend the intervention. Using a social support, spiritual hope, or self-destructive and escape coping style was associated with attendance. Youth who reported many sexual partners attended fewer sessions. Adherence varied by cohort assignment. It was concluded that high attendance should be considered as a goal when designing future interventions. Song, J., Lee, M., Rotheram-Borus, M., and Swendeman, D. Predictors of Intervention Adherence Among Young People Living With HIV. Am J Health Behav, 30(2), pp. 136-146, 2006.

Family Focused Intervention Provides Similar Benefits for High and Low Risk Youth

This study extends earlier investigation of family risk-related moderation of two brief, family-focused preventive interventions. It examines effects on the trajectories of substance initiation over a period of six years after a pretest assessment, evaluating whether effects were comparable across higher- and lower-risk subgroups. The two interventions, designed for general-population families of adolescents, were the seven-session Iowa Strengthening Families Program (ISFP) and the five-session Preparing for the Drug Free Years program (PDFY). Thirty-three rural public schools were randomly assigned to either the ISFP, the PDFY, or a minimal contact control condition. Curvilinear growth curve analyses were used to evaluate the universality of intervention effectiveness by testing for risk moderation of intervention effects on school-level substance use trajectories of initiation of alcohol and illicit substance use. Results were most consistent with the interpretation that both interventions provided comparable benefits for both outcome measures, regardless of family risk status. Findings are discussed in terms of their implications for implementing universal preventive interventions in general populations. Spoth, R., Shin, C., Guyll, M., Redmond, C., and Azevedo, K. Universality of Effects: An Examination of the Comparability of Long-term Family Intervention Effects on Substance use Across Risk-related Subgroups. Prev Sci, 7(2), pp. 209-224, 2006.

Internet-Based Intervention for Mental Health and Substance Use Problems in Disaster-Affected Populations: A Pilot Feasibility Study

Early interventions that reduce the societal burden of mental health problems in the aftermath of disasters and mass violence have the potential to be enormously valuable. Internet-based interventions can be delivered widely, efficiently, and at low cost and as such are of particular interest. The development and feasibility analysis of an Internet-delivered intervention

designed to address mental health and substance-related reactions in disaster-affected populations is described. Participants (n = 285) were recruited from a cohort of New York City-area residents that had been followed longitudinally in epidemiological research initiated 6 months after the terrorist attacks of September 11, 2001. The intervention consisted of 7 modules: posttraumatic stress/panic, depression, generalized anxiety, alcohol use, marijuana use, drug use, and cigarette use. Feasibility data were promising and suggest the need for further evaluation. Ruggiero, K., Resnick, H., Acierno, R., Coffey, S., Carpenter, M., Ruscio, A., Stephens, R., Kilpatrick, D., Stasiewicz, P., Roffman, R., Bucuvalas, M., and Galea, S. Internet-Based Intervention for Mental Health and Substance Use Problems in Disaster-Affected Populations: A Pilot Feasibility Study. Behav Ther, 37(2), pp. 190-205, 2006.

Providing Prevention Services for Conduct Problems to High Risk Children and Their Families

This study examined whether the link between risk factors for conduct problems and low rates of participation in mental health treatment could be decoupled through the provision of integrated prevention services in multiple easily-accessible contexts. It included 445 families of first-grade children (55% minority), living in four diverse communities, and selected for early signs of conduct problems. Children and families were participants in a larger study of a multi-component, multi-year Program, Fast Track, designed to prevent conduct problems among young children already exhibiting behavior problems. Results indicated that, under the right circumstances, these children and families could be enticed to participate at high rates in school-based services, therapeutic groups, and home visits. For example, 49% of the sample received a majority of the intervention services that were provided: 92% of school-based services, 88% of therapeutic groups, and 92% of home visits. Only 6% of the sample participated in a greater proportion of services. Because different sets of risk factors were related to different profiles of participation across the components of the prevention program, findings highlight the need to offer services in multiple contexts to reach all children and families who might benefit from them. Nix, R., Pinderhughes, E., Bierman, K., Maples, J., and Maples, J.T. Decoupling the Relation Between Risk Factors for Conduct Problems and the Receipt of Intervention Services: Participation Across Multiple Components of a Prevention Program. Am J Community Psychol, 36(3-4), pp. 307-325, 2005.

Prevention Program Format May Impact Participant Initiation and Exposure Rates

The primary aim of this study was to compare participation rates in two different formats of "Parents Who Care" a universal, family-based preventive intervention. Participants in the study were blocked on race and gender and randomized to three conditions: 1) a self administered format (SA) involving a video and workbook to be completed within 10 weeks 2) a parent adolescent group format (PAG) involving seven weekly meetings and 3) a no intervention control group. In this study, predictors of participation and exposure were compared across the two intervention formats. Families of 225 8th-grade students were assigned to the (PAG) or the (SA) group. Logistic regression showed greater program initiation in SA than in PAG. Hierarchical regression showed only one variable (parent high-risk behavior) to be associated with lower program exposure in the self-administered format. In contrast, demographic variables (e.g., being African American) predicted lower exposure in PAG. Overall, the findings of this study were notable in that most of the variables that have been identified in past research as lowering participation rates were not related to program initiation or level of exposure to either format of "Parents Who Care". Further, the self-administered format may be particularly useful to increase program participation for families, even those who are traditionally difficult to reach. Haggerty, K., MacKenzie, E., Skinner,

M., Harachi, T., and Catalano, R. Participation in "Parents Who Care": Predicting Program Initiation and Exposure in Two Different Program Formats. J Prim Prev, 27(1), pp. 47-65, 2006.

Peer Health Advocates are Trusted as Sources for HIV Prevention Material by Drug Using Peers

This article presents results from a process evaluation of a peer-led HIV prevention intervention. The Risk Avoidance Partnership, conducted from 2001 to 2005, trained active drug users to be peer health advocates (PHAs) to provide harm reduction materials and information to their peers. Results indicate that PHAs actively conducted harm reduction outreach both when partnered with staff and on their own time. Although PHAs conducted most of their outreach in public locations, they also provided drug users with harm reduction materials at critical moments in places where HIV risky behaviors were likely to occur. PHAs were credible and trusted sources of information to their drug-using peers who sought PHAs out for HIV prevention materials. Process evaluations of successful HIV prevention interventions are necessary to understand how and why such interventions work for further intervention refinement. Dickson-Gomez, J., Weeks, M., Martinez, M., and Convey, M. Times and Places: Process Evaluation of a Peer-led HIV Prevention Intervention. Subst Use Misuse, 41(5), pp. 669-690, 2006.

Tailoring Tobacco Counteradvertisements for Bicultural Mexican American Youth

The growing population of Mexican American youth and the increasing smoking rates in this population present a considerable public health challenge and little is known about the most effective ways to adapt messages aimed at this audience. To explore key variables that can affect success, a study was conducted with 249 Mexican American middle-school youth from a U.S./Mexico border community to examine the effectiveness of language (English, Spanish, or a combination of English and Spanish) and theme (secondhand smoke, anti-tobacco social norms, and tobacco industry manipulation) in print tobacco counteradvertisements. Measures included ad preferences, acculturation, and tobacco-related attitudes and behavior. Results showed that although a large percentage identified with the Mexican American rather than the Anglo American culture and spoke Spanish in selected contexts, readability was greater for ads in English, and participants rated the English ads as most effective. The social norms counteradvertisement was preferred overall. Kelly, K., Stanley, L., Comello, M., and Gonzalez, G. Tobacco Counteradvertisements Aimed at Bicultural Mexican American Youth: The Impact of Language and Theme. J Health Commun, 11(5), pp. 455-476, 2006.

Group Interventions May be Able to Minimize Peer Contagion

This study involving novel methodology applies a multi-player arms race model to peer contagion in the aggressive and delinquent behaviors of inner-city elementary school students. Because this model of peer contagion differs from the usual model based on positive reinforcement of delinquent behavior, it raises the possibility that the persistent finding of iatrogenic effects of group treatment might not apply to group treatment of elementary school children if aggressive behavior in the group is limited. One way of limiting aggressive behavior is to include parents in the groups. To test this hypothesis, this study applies the model to groups of elementary school students assigned to Families and Schools Together (FAST), a group treatment that includes parental participation, or to an intervention focused on individual families. Data came from a longitudinal study of 403 children, their parents, and their teachers who participated in an evaluation of the FAST program. The model effectively

describes the relationship between group averages of aggressive behavior in the classroom and aggressive and delinquent behavior outside the classroom for those students assigned to the individual intervention. The model fits those children assigned to FAST less well, suggesting that FAST may make it less likely that aggressive and delinquent behavior is generalized outside of aggressive classroom settings. Warren, K., Moberg, D., and McDonald, L. FAST and the Arms Race: The Interaction of Group Aggression and the Families and Schools Together Program in the Aggressive and Delinquent Behaviors of Inner-city Elementary School Students. J Prim Prev, 27(1), pp. 27-45, 2006.

Recommendations for the Prevention of HIV Transmission in Hispanic Adolescents

This article reviews the state of the science in HIV prevention for Hispanic adolescents. Literature is reviewed in three broad areas: (1) the prevalence rates of drug and alcohol misuse, sexual practices, and HIV infection; (2) risk and protective factors for drug and alcohol misuse and unprotected sex (in general and specifically for Hispanics); and (3) the state of HIV prevention intervention development and evaluation targeting Hispanic youth. Little basic and intervention research has been conducted on HIV prevention in Hispanic adolescents, with even less attention given to Hispanic young men who have sex with men (YMSM). There are a number of areas in which further knowledge development and scientific advancement are needed. The seven areas identified in this review were (a) the need for analyses of nationwide epidemiological data examining risk and protective factors for substance use and unsafe sexual behavior for heterosexual and homosexual youth; (b) explaining variations in drug/alcohol use, unsafe sexual behavior, and HIV infection among Hispanic subgroups; (c) need for adaptive preventive interventions for Hispanic subgroups with varying risk and protection profiles; (d) incorporation of ethnic, cultural, and sexual identity into prevention programs for Hispanic adolescents; (e) examination of the role of gender in preventive interventions for Hispanic adolescents; (f) research on the effects of psychiatric comorbidity on drug/alcohol use and unsafe sex and on the efficacy of prevention programs; and (g) increased focus on intravenous drug use as a mode of HIV infection among Hispanics, particularly Puerto Ricans. Research addressing these research needs has the potential to facilitate progress toward achieving the two primary objectives of Healthy People 2010--improving the quality of life for all Americans and reducing health disparities between and among segments of the U.S. population. Prado, G., Schwartz, S.J., Pattatucci-Aragon, A., Clatts, M., Pantin, H., Fernandez, M., Lopez, B., Briones, E., Amarof, H., and Szapocznik, J. The Prevention of HIV Transmission in Hispanic Adolescents. Drug Alcohol Depend, 84S pp. S43-S53, 2006.

Unprotected Sex Among Youth Living With HIV Before and After the Advent of Highly Active Antiretroviral Therapy

Since the advent of highly active antiretroviral therapy (HAART) in 1996, the incidence of HIV-especially among young men who have sex with men-and the prevalence of unprotected sex among HIV-positive persons have increased. The characteristics associated with unprotected sex among youth living with HIV since the advent of HAART have not been explored. Samples of HIV-positive youth aged 13-24 were taken from two intervention studies that targeted the sexual behaviors of HIV-positive youth-one from 1994 to 1996 (pre-HAART) and the other from 1999 to 2000 (post-HAART). Generalized estimating equations were used to identify characteristics associated with unprotected sex in each sample. The prevalence of unprotected sex in the post-HAART sample was more than twice that in the pre-HAART sample (62% vs. 25%). Among the pre-HAART sample, being a man who has sex with men and having sex with a casual partner were negatively associated with the odds of unprotected intercourse (odds ratios, 0.5 and 0.2, respectively). Among the

post-HAART sample, unprotected sex was negatively associated with knowing that a partner was HIV-negative (0.2) and positively associated with poorer mental health (1.02). In analyses among the post-HAART sample, poorer mental health was associated with increased odds of unprotected sex among youth living with HIV who were not receiving the treatment (1.02). It was concluded that interventions for HIV-positive youth must be designed to address the complex needs of those youth who simultaneously suffer from HIV and poor mental health. Rice, E., Batterham, P., and Rotheram-Borus, M. Unprotected Sex Among Youth Living With HIV Before and After the Advent of Highly Active Antiretroviral Therapy. Perspect Sex Reprod Health, 38(3), pp. 162-167, 2006.

Predictors of HIV-Related Stigma Among Young People Living with HIV

Enacted and perceived HIV stigma was examined among 147 substance-using young people living with HIV (YPLH) in Los Angeles, San Francisco, and New York City. Almost all YPLH (89%) reported perceived stigma, 31% reported enacted experiences in the past 3 months; and 64% reported experiences during their lifetime. The HIV stigma questions were characterized by factors of avoidance, social rejection, abuse, and shame. In multivariate models, enacted stigma was associated with gay or bisexual identity, symptomatic HIV or AIDS, and bartering sex. Perceived stigma was associated with female gender, symptomatic HIV or AIDS, bartering sex, lower injection drug use, and fewer friends and family knowing serostatus. Gay or bisexual YPLH who were also HIV symptomatic or AIDS diagnosed experienced more HIV stigma than their heterosexual peers. Swendeman, D., Rotheram-Borus, M., Comulada, S., Weiss, R., and Ramos, M. Predictors of HIV-Related Stigma Among Young People Living with HIV. Health Psychol, 25(4), pp. 501-509, 2006.

Prevalence and Correlates of Exchanging Sex for Drugs or Money Among Adolescents in the United States

This study examined the prevalence and correlates of exchanging sex for drugs or money among a nationally representative sample of 13,294 adolescents in the United States. Data are from the National Longitudinal Study of Adolescent Health, waves I and II. The lifetime prevalence of exchanging sex was estimated and a cross sectional analysis of sociodemographic and behavioral correlates was conducted. Unadjusted odds ratios were obtained. Results showed that 3.5% of adolescents had ever exchanged sex for drugs or money; two-thirds of these youths were boys. The odds of having exchanged sex were higher for youths who had used drugs, had run away from home, were depressed, and had engaged in various sexual risk behaviors. 15% of boys and 20% of girls who had exchanged sex reported they had ever been told they have HIV or another sexually transmitted infection (STI). It was concluded that adolescents with a history of exchanging sex have engaged in other high risk behaviors and may experience poor health outcomes, including depression and HIV/STIs. These findings should help inform strategies to prevent this high risk sexual behavior and its potential consequences. Edwards, J., Iritani, B., and Hallfors, D. Prevalence and Correlates of Exchanging Sex for Drugs or Money Among Adolescents in the United States. Sex Transm Infect, 82(5), pp. 354-358, 2006.

Gender Differences in Associations Between Depressive Symptoms and Patterns of Substance Use and Risky Sexual Behavior Among a Nationally Representative Sample of U.S. Adolescents

This study uses a cluster analysis of adolescents, based on their substance use

and sexual risk behaviors, to 1) examine associations between risk behavior patterns and depressive symptoms, stratified by gender, and 2) examine gender differences in risk for depression. Data are from a nationally representative survey of over 20,000 U.S. adolescents. Logistic regression was used to examine the associations between 16 risk behavior patterns and current depressive symptoms by gender. Compared to abstention, involvement in common adolescent risk behaviors (drinking, smoking, and sexual intercourse) was associated with increased odds of depressive symptoms in both sexes. However, sex differences in depressive symptoms vary by risk behavior pattern. There were no differences in odds for depressive symptoms between abstaining male and female adolescents (OR = 1.07, 95% CI 0.70-1.62). There were also few sex differences in odds of depressive symptoms within the highest-risk behavior profiles. Among adolescents showing light and moderate risk behavior patterns, females experienced significantly more depressive symptoms than males. It was concluded that adolescents who engage in risk behaviors are at increased risk for depressive symptoms. Girls engaging in low and moderate substance use and sexual activity experience more depressive symptoms than boys with similar behavior. Screening for depression is indicated for female adolescents engaging in even experimental risk behaviors. Waller, M., Hallfors, D., Halpern, C., Iritani, B., Ford, C., and Guo, G. Gender Differences in Associations Between Depressive Symptoms and Patterns of Substance use and Risky Sexual Behavior Among A Nationally Representative Sample of U.S. Adolescents. Arch Womens Ment Health, 9(3), pp. 139-150, 2006.

Genetic Contribution to Suicidal Behaviors and Associated Risk Factors Among Adolescents in the U.S.

This paper examines genetic contribution to suicidal behaviors and other risk factors associated with suicidal behavior among adolescents in the U.S. Using adolescent twin data in the National Longitudinal Study of Adolescent Health (N=1448), authors compared concordance in suicidal ideation and attempt among monozygotic (MZ) and dizygotic (DZ) twins. Heritability of risk factors for suicidal behaviors also was examined using Pearson correlation and mixed-model analyses. A trend of higher concordance in suicidal ideation and attempt was found among MZ than DZ twins but the difference was not statistically significant by the stringent test of bootstrapping analysis. Evidence of heritability was found for several suicide risk factors. The percentage of variance explained by heritability was larger among female twins for depression, aggression, and quantity of cigarettes smoked in comparison to heritability estimates for male twins. However, estimated heritability was larger among male than female twins for alcohol use and binge drinking. Heritability influence was negligible among both sexes for other drug use. Risk factors for suicidal behaviors among adolescents may be heritable. Gender differences found in the heritability of some suicide risk factors suggest these genetic contributions are gender specific. Future research examining potential interactions between expression of genetic influence and particular environmental contexts may enhance prevention and intervention efforts. Cho, H., Guo, G., Iritani, B.J., and Hallfors, D.D. Genetic Contribution to Suicidal Behaviors and Associated Risk Factors Among Adolescents in the U.S. Prev Sci, 7(3), pp. 303-311, 2006.

In School Alcohol and Marijuana Use Among High School Students

The problem of adolescent substance use has been examined extensively. Beyond simple prevalence estimates, however, little research has been conducted on substance use in the school context. The present investigation was an in-depth study of students' attitudes and behaviors regarding alcohol and marijuana use during the school day. Based on a representative sample of 1123 high school students, 48% male, in grades 9-12 in western New York

state, this study assessed the frequency of alcohol and marijuana use at school among demographic subgroups, the accessibility of drugs in school, and students' perceived consequences of being caught using drugs in school. Twelve percent of the sample reported using alcohol during school hours in the past 6 months while 16% reported using marijuana at school. Among students who used alcohol outside of school, 18% also used alcohol at school. For marijuana users, 47% used marijuana at school. There was evidence of some demographic differences in school drug use. Specifically, male and Hispanic students had slightly higher levels of drug use at school compared to female and white students, respectively, and in school drug use was more prevalent among older students. In terms of accessibility, students reported that alcohol and marijuana were easily obtained and used on school grounds. Many students (40%) were not aware of the specific actions taken in their schools to punish drug use. The need for additional research on school-related drug use is emphasized. Finn, K. V. Patterns of Alcohol and Marijuana Use at School. Journal of Research on Adolescence, 16(1), pp. 69-77, 2006.

Methodological Considerations for Testing Causal Effects in Drug Abuse Prevention Research

Observational data are often used to address prevention questions such as, "If alcohol initiation could be delayed, would that in turn cause a delay in marijuana initiation?" This question is concerned with the total causal effect of the timing of alcohol initiation on the timing of marijuana initiation. Unfortunately, when observational data are used to address a question such as the above, alternative explanations for the observed relationship between the predictor, here timing of alcohol initiation, and the response abound. These alternative explanations are due to the presence of confounders. Adjusting for confounders when using observational data is a particularly challenging problem when the predictor and confounders are time-varying. When time-varying confounders are present, the standard method of adjusting for confounders may fail to reduce bias and indeed can increase bias. In this paper, an intuitive and accessible graphical approach was used to illustrate how the standard method of controlling for confounders may result in biased total causal effect estimates. Based on the graphical approach, an alternative method proposed by James Robins was used to examine causal effect estimates. Implications for prevention researchers who wish to estimate total causal effects using longitudinal observational data are discussed. Bray, B., Almirall, D., Zimmerman, R., Lynam, D., and Murphy, S. Assessing the Total Effect of Time-varying Predictors in Prevention Research. Prev Sci, 7(1), pp. 1-17, 2006.

Rasch Analysis of Data From Prevention Study in South Africa Supports Jessors' Problem Behavior Theory

The goal of the study was to determine the presence of a syndrome of health risk behaviors in South African teenagers from Rasch modeling of items from self-report measures covering six conceptually distinct health risk domains selected because they are among the most assessed health risk outcomes in prevention research and practice. A total of 2186 in-school adolescents participated in the study (males = 1077; females = 1119; age range = 12-16 years; median = 13 years). The data are baseline from a longitudinal study of a leisure-based drug abuse and HIV/AIDS prevention program at Mitchell's Plain in Cape Town, South Africa. The adolescents completed a self-report measure on various health risk vulnerabilities, including use of alcohol, tobacco and other drugs (ATOD), co-occurrence of penetrative sex with use of ATOD, health related self-efficacy, personal beliefs about health, peer perceptions, and use of contraceptives. The Rasch analysis calibrated data on 50 items from the conceptually distinct health risk domains. Infit and Outfit mean square statistics and principal components analysis of the standardized residuals

suggested a fit of the data to the unidimensional Rasch measurement model. The findings support a syndrome view of health risk in teenagers as proposed by problem behavior theory. Mpofu, E., Caldwell, L., Smith, E., Flisher, A., Mathews, C., Wegner, L., and Vergnani, T. Rasch Modeling of the Structure of Health Risk Behavior in South African Adolescents. J Appl Meas, 7(3), pp. 323-334, 2006.

Parent Daily Report Checklist Can Be Used to Predict Foster Care Disruptions

The objective of this study was to identify reliable, inexpensive predictors of foster care placement disruption that could be used to assess risk of placement failure. Using the Parent Daily Report Checklist (PDR), foster or kinship parents of 246 children (5-12 years old; 131 boys, 115 girls) in California were interviewed three times about whether or not their foster child engaged in any of the 30 problem behaviors during the previous 24 hours. The PDR was conducted during telephone contacts (5-10 min each) that occurred from 1 to 3 days apart at baseline. Disruptions were tracked for the subsequent 12 months. Other potential predictors of disruption were examined, including the child's age, gender, and ethnicity, the foster parent's ethnicity, the number of other children in the foster home, and the type of placement (kin or non-kin). Foster/kin parents reported an average of 5.77 child problems per day on the PDR checklist. The number of problem behaviors was linearly related to the child's risk of placement disruption during the subsequent year. The threshold for the number of problem behaviors per day that foster and kinship parents tolerated without increased risk of placement disruption for these latency-aged children was 6 or fewer. Children in non-kin placements were more likely to disrupt than those in kinship placements. There was a trend for increased risk of disruption as the number of children in the home increased. The PDR Checklist may be useful in predicting which placements are at most risk of future disruption, allowing for targeted services and supports. Chamberlain, P., Price, J.M., Reid, J.B., Landsverk, J., Fisher, P.A., and Stoolmiller, M. Who Disrupts from Placement in Foster and Kinship Care? Child Abuse & Neglect, 30, pp. 409-424, 2006.

Predicting Reunification Failures in Foster Care

Previous studies have suggested that roughly 30% of all reunified foster children reenter foster care. Because reunification is one of the primary objectives of the child welfare system, it is imperative that correlates of reunification failure across parent, child, service, home and neighborhood domains be better understood. This study examined post-reunification variables regarding parent characteristics, child characteristics, parent service utilization, child service utilization, family environment, and neighborhood environment as they relate to reunification failure. The sample for the study included 16 foster children who, at reunification with their birth parents, ranged in age from 4-7 years. All participants were reunified with at least one parent. Among the variables found to significantly differentiate between failed and successful reunifications were parental utilization of substance abuse treatment, child utilization of special educational services, child utilization of individual, family, or group therapy, overall parenting skill level, appropriate use of discipline, and quality of neighborhood. The article discusses the implications of these results for policies aimed at increasing the success rate of reunifications following foster care. Miller, K.A., Fisher, P.A., Fetrow, B., and Jordan, K. Trouble on the Journey Home: Reunification Failures in Foster Care. Children and Youth Services Review, 28, pp. 260-274, 2006.

Classroom Contextual Effects of Race on Children's Peer Nominations

Black children generally receive poorer sociometric nominations compared with Whites. This effect is not fully understood because Black children rarely hold a classroom majority and teachers' race is rarely investigated. Research from a person-environment perspective suggests that the effects of children's race depend on the racial composition of the classroom and society's racial attitudes. Sociometric nominations were obtained from 1,268 5th graders, between 9 and 11 years old (53% Black), across 57 classrooms (3-95% Black students). Half of the teachers were Black. The results indicated that ratings of Black children were more influenced by the racial context of classrooms than were ratings of White children. The implications of this study are discussed in relation to group dynamics and racial discrimination. Jackson, M., Barth, J., Powell, N., and Lochman, J. Classroom Contextual Effects of Race on Children's Peer Nominations. Child Dev, 77(5), pp. 1325-1337, 2006.

Improving Consent Return Rates Among Urban Elementary Students

This paper reports on consent form return rates for 3rd grade students attending schools in low-income, urban areas, where the researchers developed procedures to maximize their active parent consent efforts. The schools and participants were part of a larger study of a school-based prevention program. Research staff used a class incentive and class visits to retrieve consent forms from students. Of the 811 third-grade students, 98% returned a form and 79% (n = 627) of those students' parents provided an affirmative response. Return rates did not vary by students' ethnicity or by the schools' demographic variables. The authors conclude that incentives and class visits can yield a high return rate of active parent consent forms for third-grade minority, urban, low-income students. Ji, P., Flay, B., Dubois, D., Brechling, V., Day, J., and Cantillon, D. Consent Form Return Rates for Third-grade Urban Elementary Students. Am J Health Behav, 30(5), pp. 467-474, 2006.

The Relationship of Family Instability to Child Maladjustment

This study examines the relation between family instability and child maladjustment over a 6-year period in 369 children from four communities. The children and families were part of a larger study examining the impact of the multi-level, multi-year Fast Track preventive intervention on child conduct problems. Measures were collected annually from kindergarten through fifth grade. In associative growth curve models, family instability trajectories predicted children's externalizing and internalizing behavior trajectories during this time period. High levels of family instability also incrementally predicted the likelihood of meeting criteria for a DSM IV diagnosis during elementary school, above and beyond prediction from earlier measures of maladjustment. However, the timing of family instability had a different effect on externalizing versus internalizing disorders. In general, stronger relations were found between family instability and externalizing behaviors relative to internalizing behaviors, although children with comorbid disorders experienced the highest levels of family instability. Future research that examines the underlying mechanisms that account for the influence of family instability on child maladjustment is discussed. Milan, S., Pinderhughes, E., and Pinderhughes, E.T. Family Instability and Child Maladjustment Trajectories During Elementary School. J Abnorm Child Psychol, 34(1), pp. 43-56, 2006.

Time Varying Family and Peer Influences on Adolescent Daily Mood

The time-varying influences of peer and family support on adolescent daily mood were explored among 268 youth transitioning from middle school to high school (8th to 9th grade) as compared to 240 youth transitioning from 10th to

11th grade. The participants were part of a larger study examining the natural history of smoking. Real-time ecological momentary assessments measures of daily positive and negative affect were collected via palmtop computers at baseline, 6 months, and 12 months. Participants rated 12 mood adjectives in response to 5 to 7 random prompts per day for 7 consecutive days. Perceived peer and family support were assessed via self-report. Mixed-effects regression analyses revealed significant grade by time by peer support interactions for positive and negative mood, with the younger cohort showing greater increases in the relation between peer support and affect over time than the older cohort. Family support did not interact with cohort or time. The authors summarize that peer influences may increase as adolescents develop, thus developmental influences should be included in examinations of dynamic relations between peers and adolescent mood. Also, these results may help elucidate transitions that may be optimal times for preventive interventions targeting emotional well-being of adolescents, specifically transition to high school. This transition point also coincides with a growth in mood disorders in adolescents, in particular girls. Girls were found to exhibit higher levels of negative moods at lower levels of peer support, relative to boys. The authors call for future research that captures the bidirectional nature of support--mood relations across adolescence. Weinstein, S., Mermelstein, R., Hedeker, D., Hankin, B., and Flay, B. The Time-varying Influences of Peer and Family Support on Adolescent Daily Positive and Negative Affect. J Clin Child Adolesc Psychol, 35(3), pp. 420-430, 2006.

Trajectories of Depression in Male and Female Children of Depressed Mothers

This study reports on relationships among gender, maternal depressed mood, and children's trajectories of depressive phenomena across middle childhood and early adolescence. It tested the hypothesis that, compared to boys, girls become increasingly vulnerable to maternal depression as they enter adolescence. The study sample consisted of 834 families from 10 Pacific Northwest schools that participated in the Raising Healthy Children project, a longitudinal study of the etiology of problem behaviors and test of a multicomponent, multiyear intervention targeting risk and protective factors within key child socializing domains of family, school, peer, group, and individual. Maternal depressed mood and children's depressive phenomena were assessed annually during an 8-year period that spanned Grade 3 through Grade 10 for the children. Mean scores for girls' depressive phenomena increased relative to those for boys as children matured. Maternal depressed mood was significantly and positively associated with children's level of depressive phenomena. An interaction effect of gender and maternal depressed mood on acceleration in children's depressive phenomena indicated that girls' trajectories of depressive phenomena were sustained in the presence of maternal depression while those of boys declined in the presence of maternal depression. Implications for the prevention and treatment of adolescent depression are discussed. Cortes, R.C., Fleming, C.B., Catalano, R.F., and Brown, E.C. Gender Differences in the Association Between Maternal Depressed Mood and Child Depressive Phenomena from Grade 3 Through Grade 10. J Youth Adolescence, 35, pp. 815-826, 2006.

Tobacco Litigation In Argentina

This project evaluated the processes and outcomes of tobacco litigation in Argentina by analyzing the strategies and documents which the tobacco industry used to oppose litigation. A systematic search of tobacco industry documents on the internet dating from 1978 to 2002, and law library searches for Argentinean official and unofficial reports were combined with other online searches. This search pointed out that there have been at least 15 failed litigation cases in Argentina where the tobacco industry has been able to

present a concerted defense in every claim regardless of cost. Industry strategies included hiring legal consultants from prestigious international and Argentinean law firms, monitoring of legal and academic meetings, controlling the development of new product liability legislation, obtaining favorable opinions from experts, and closely observing the development of litigation in Argentina. These strategies used by the industry have been successful in preventing recovery for tobacco injuries through litigation. The conclusion of this study is that Argentinean health advocates and lawyers need to be aware of the roles and strategies of the tobacco industry in order to develop effective litigation in Argentina. Flores, M., Barnoya, J., Mejia, R., Alderete, E., and Perez-Stable, E. Litigation in Argentina: Challenging the Tobacco Industry. Tob Control, 15(2), pp. 90-96, 2006.

Translation of Prevention Interventions From Research to Practice

This article summarizes research on Type II translation of prevention interventions aimed at enhancing the adoption of effective programs and practices in communities. The primary goal of Type II translation is to institutionalize evidence-based programs, products, and services. First, the authors describe theoretical frameworks that are useful to guide Type II translation research. Second, research on prevention program implementation, including fidelity of implementation and factors that are associated with successful program implementation, is summarized. The authors describe interventions designed to enhance the dissemination of preventive interventions in community and public health settings. Third, they describe strategies used by prevention program developers who have taken programs to scale. Fourth, they present a case example of Project Towards No Drug Abuse (TND), an empirically validated high school-based substance abuse prevention program. They describe ongoing research on the dissemination of Project TND. Finally, they provide suggestions for future Type II translation research. Rohrbach, L., Grana, R., Sussman, S., and Valente, T. Type II Translation: Transporting Prevention Interventions From Research to Real-world Settings. Eval Health Prof, 29(3), pp. 302-333, 2006.

Translation in the Health Professions: Converting Science into Action

The systematic translation of evidence-based research findings, tools, and information into practice is critical to improving the quality of our nation's health. However, despite several decades of advances in developing medical knowledge based on high-quality empirical evidence, widespread implementation of these findings into practice in diverse applied settings has not been achieved. This article reviews definitions and conceptual models that describe the translation of research from basic discovery to real-world applications, summarizes the various issues involved in the process of translation, discusses multiple barriers, and provides recommendations to surmount these hurdles. Areas of further research in this arena are suggested. Finally, the article concludes that translational research is an important area to continue to pursue requiring long-term collaborative commitment among researchers and practitioners. Sussman, S., Valente, T., Rohrbach, L., Skara, S., and Pentz, M. Translation in the Health Professions: Converting Science into Action. Eval Health Prof, 29(1), pp. 7-32, 2006.

Director's Report to the National Advisory Council on Drug Abuse - February, 2007

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

Prize-based Contingency Management Enhances Retention in People with High Psychiatric Symptom Severity

Dr. Nancy Petry and colleagues at University of Connecticut Health Center examined the impact of psychiatric symptom severity on treatment retention for 393 drug abusers enrolled in several clinical trials comparing either standard care or standard care plus a novel intervention, Prize-Based Contingency Management (PBCM). In PBMC participants are offered the opportunity to draw for prizes based when they either submit drug negative urine samples or complete treatment related goals. The researchers ranked participants into high, medium, and low psychiatric symptom severity based on their ASI Psychiatric Index score. Although researchers found a positive association between Psychiatric Index score severity and risk of drop out in people receiving the standard care condition, they did not observe such a relationship for participants assigned to standard care plus PBCM. These results indicate that the addition of PBCM to standard care may be especially useful for enhancing retention in people with dual psychiatric and substance use disorders, a group which is vulnerable to treatment dropout. Weinstock, J., Alessi, S.M., and Petry, N.M. Drug Alcohol Dependence, [epub ahead of print], September, 2006.

Contingency Management among More Effective Treatments Based on Meta-analysis

Dr. Michael Pendergast and colleagues at UCLA conducted a meta-analysis of 47 studies that used contingency management (CM) to treat addictions. Studies included in the meta-analysis most commonly used methadone take home doses, voucher based reinforcement, and cash as reinforcers, although all CM studies conducted since the 1970s were eligible for inclusion. The mean effect size on drug use outcomes at the end of treatment (d = .42) was stronger than what is often observed for behavioral interventions. Effect sizes for treatments targeting cocaine and opioids (d = .66) and (d = .65) respectively were higher than when tobacco (d =.31) or multiple drugs (d =.42) were targets. Results suggest that regardless of the method used, CM can provide a powerful incentive for abstinence during and at the end of treatment. Prendergast, M., Podus, D., Finney, J., Greenwell, L., and Roll, J. Addiction, pp. 1546-60, 2006.

Risky Behaviors and Mental Health in Homeless Men Who Have Sex with Men

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Cathy Reback and researchers at Friends Research Institute examined the psychiatric, demographic, drug use, and HIV risk characteristics of 20 men seeking services for homeless people in San Francisco who were not currently seeking drug abuse treatment. Most were Caucasian (65%) and self identified as gay or bisexual (95%). Self-reported seroprevalence of HIV was 21%. All met criteria for substance use diagnoses with alcohol and amphetamine being the most prevelant disorders. Additionally, 75% met criteria for Mood Disorder. Almost 50% had injected drugs during the previous month and most of those failed to clean needles with bleach. In terms of risky sexual behavior, individuals generally reported multiple risk behaviors, and rates of sex while high on drugs, exchanging sex for money or drugs, and unprotected sex including heterosexual vaginal intercourse was frequently reported. This study provides insights into the risk behavior of an infrequently studied population at extremely high risk for HIV transmission. Although none of these individuals were seeking treatment, they all accessed community AIDS services. Novel treatment and HIV prevention interventions may be developed that motivate treatment engagement in non-traditional settings such as the Community AIDS service centers frequented by these individuals. Reback, C.J., Kamien, J.B., and Amass, L. Addictive Behaviors. [epub ahead of print] July, 2006.

Contingency Management Efficacious for Methamphetamine Users

John Roll and researchers at Friends Research Institute and in the NIDA Clinical Trials Network evaluated the results of a trial in which people at several clinics in the western US were assigned to either treatment as usual available at that clinic (TAU) or TAU plus a novel contingency management intervention (CM). During the CM intervention, participants submitting drug negative urine samples could draw for prizes according to an escalating schedule, such that for each week they remained abstinent they received an additional opportunity to draw for a prize. In the prize drawing, fifty percent (250) of tokens were marked "good job" but had no prize value. Other prize tokens were distributed as follows; a single high value token (worth $80-$100), 8% medium value tokens (worth $20.00) and 41.8% small value tokens (worth $1-$5). Participants could turn in tokens for prizes such as toiletries, soft drinks, fast food coupons, electronic devices or television sets depending on the value. Participants in the TAU+CM group submitted significantly more drug negative urines and had longer mean period of abstinence than those in the TAU group. These results are significant because they are the first controlled trial of a CM intervention as an adjunct to TAU in Methamphetamine users. Even when TAU was the Matrix Model treatment, a comprehensive psychosocial intervention the CM still improved outcomes. Roll, J.M., Petry, N.M., Stitzer, M.L., Brecht, M.L., Peirce, J.M., McCann, M.J., Blaine, J., Macdonald, M., Dimaria, J., Lucero, L. and Kellogg, S. American Journal of Psychiatry, pp. 1993-1999, 2006.

Smoking Status in the Initial Weeks of Quitting as a Predictor of Smoking-Cessation Outcomes in Pregnant Women

In the general population of smokers, seminal findings of Kenford et al. (1994) suggest a robust relationship between early smoking during a quit attempt and later smoking. The findings indicate that any smoking during the initial 2 weeks of a quit attempt predicts poor longer-term outcomes. However, it is not known whether this same predictor rule applies under conditions where patients are quitting related to a medical condition for which smoking is contraindicated, like pregnancy. Investigators at the University of Vermont conducted this study to examine the association between smoking status during the initial 2 weeks of attempting to quit and smoking status at an end-of-pregnancy assessment among women enrolled in smoking cessation studies. Data were obtained from 129 women participating in clinical trials on smoking-cessation examining the efficacy of voucher-based incentives delivered contingent on biochemically-verified abstinence or a control conditions wherein incentives were given

independent of smoking status. Smoking status was assessed in weeks 1 and 2 of the cessation effort and again at an end-of-pregnancy. The findings show that women who smoked in the first 2 weeks of quitting had a greater than 80% chance of being classified as smokers at an end-of-pregnancy assessment and that relationship held across the two treatment conditions. These finding indicate that the predictor rule for the general population of smokers applies to pregnant women who are smokers. Thus, it is recommended that clinicians monitor smoking status during the initial weeks of a quit attempt and provide a change in treatment when smoking is detected. Higgins, S.T., Heil, S.H., Dumeer, A.M., Thomas, C.S., Solomon, L.J., and Bernstein, I.M. Drug and Alcohol Dependence, 85, pp. 138-141, 2006.

Treatment for Cigarette Smoking Among Depressed Mental Health Outpatients: A Randomized Clinical Trial

Dr. Hall and colleagues at the University of California, San Francisco conducted this study to test the efficacy of a Stage Care Intervention (SCI) for cigarette smoking in psychiatric patients in outpatient treatment for depression. Three-hundred and twenty-two participants were randomized to one of two conditions. The SCI operationalized the recommendations of the AHCPR and the APA practice guidelines. It integrated a computerized feedback system based on the Transtheoretical Model that provided feedback about smoking with provision of face-to-face psychological individual counseling and pharmacological treatment at the appropriate stage of readiness. The control (CON) participants received a self-help guide and referral list. The control condition was designed to model current practices in mental health clinics. Participants were assessed at baseline and at months 3, 6, 12, and 18. As hypothesized, abstinence rates in SCI (12 months=14.1%; 18 months=18.4%) exceeded those in CON (12 months=9.4%; 18 months=13.2%). Significant differences favoring SCI were also found in occurrence of a quit attempt and stringency of abstinence goal. The authors conclude that individuals in psychiatric treatment for depression can be aided in quitting smoking by staged care interventions, and that smoking cessation interventions used in the general population can be implemented in psychiatric outpatient settings. Hall, S.M., Tsoh, J.Y., Prochaska, J.J., Eisendrath, S., Rossi, J.S., Redding, C.A., Rosen, A.B., Meisner, M., Humfleet, G.L., and Gorecki, J.A. American Journal of Public Health, 96, pp. 1808-1814, 2006.

Weight Concerns Affect Motivation to Remain Abstinent From Smoking Postpartum

This study assessed motivation for postpartum abstinence among pregnant women who had quit smoking and examined the relationship of weight concerns and mood to abstinence motivation. Participants (N=119) completed assessments of smoking, weight concerns, depressive symptoms, and perceived stress. Sixty-five percent were highly motivated to remain abstinent postpartum. Women who were and were not motivated were similar in age, race, and nicotine dependence. Motivated women reported more stress, greater self-efficacy for weight management, less hunger and less smoking for weight control than less motivated women. After controlling for intention to breast-feed, nicotine dependence, years of smoking, partner smoking, and race, self-efficacy for weight control was related to motivation to maintain postpartum abstinence. This study suggests that weight concerns are linked with motivation for postpartum smoking abstinence, and interventions designed to prevent postpartum smoking may need to target eating, weight and shape concerns. Levine, M.D., Marcus, M.D., Kalarchian, M.A., Weissfeld, L., and Qin, L. Annals of Behavioral Medicine, 32, pp. 147-153, 2006.

Relationship of DSM-IV-Based Depressive Disorders to Smoking

Cessation and Smoking Reduction in Pregnant Smokers

Investigators at the University of Texas M.D. Anderson Cancer Center in Houston conducted this study to examine psychiatric disorders as predictors of smoking outcomes among pregnant smokers. Eighty-one pregnant women participating in a low-intensity smoking cessation trial were investigated. Thirty-two percent of the sample met criteria for current dysthymia, major depressive disorder in partial remission, or minor depression. The findings showed that no significant reduction in smoking among women with or without current depressive disorders was shown. Unexpectedly, compared to women without depressive disorders, women with dysthymia significantly increased the mean number of cigarettes smoked (from 8 to 23 cigarettes per day during the 2 to 30 days post-targeted quit date period) and were smoking significantly more at 30 days. A main effect approaching significance suggested that women with current depressive disorders were less likely to be abstinent than women without current depressive disorders. The current results add to previous findings indicating a correlation between depressive symptoms and continued smoking in pregnant women. These findings indicate that additional research is needed in evaluating the impact of depression on smoking outcomes in pregnant women and that investigation of mood-focused smoking cessation interventions may be warranted. Blalock, J.A., Robinson, J.D., Wetter, D.W., and Cinciripini, P.M. The American Journal on Addictions, 15, pp. 268-277, 2006.

Brief Motivational Interventions May Not Always Be Sufficient for Treating Teen Drug Abuse

Drs. Peggy Peterson, John Baer and colleagues at the University of Washington conducted a study of a brief motivational intervention for drug abusing, homeless teens. A sample of 285 teens was recruited via drop-in centers and street outreach, with high rates of self-reported and biologically-confirmed use of alcohol (87%), marijuana (94%), tobacco (93%), amphetamines (53%), hallucinogens (36%), heroin (27%), crack cocaine (28%), and other drugs in the past month. Guided interviews over 2 sessions assessed all teens' patterns of drug use and associated risk behaviors. Teens were randomly assigned to receive 1 session of personalized feedback in a motivational interviewing style, or to one of two assessment-only conditions (assessment at baseline and follow-up, or follow-up assessment only). Follow-up interviews were conducted at 1 month and 3 months after baseline. As a whole, there were no significant reductions in drug or alcohol use for any of the three conditions, and there were no significant differences in reductions in drug or alcohol use between any of the conditions. Looking separately at illicit drugs other than marijuana, the motivational intervention was associated with significantly larger reductions in use at 1-month follow-up than the assessment-only conditions, but this effect did not remain at the 3-month follow-up. Brief motivational-based interventions have been found to increase teen substance abuse treatment engagement and retention, and to reduce alcohol-related risk behaviors, but have not produced consistently positive results as stand-alone treatments. Future research may clarify for whom and for what purposes brief motivational-based interventions should be incorporated into a comprehensive treatment intervention. Peterson, P.L., Baer, J.S., Wells, E.A., Ginzler, J.A., and Garrett, S.B. Short-term Effects of a Brief Motivational Intervention to Reduce Alcohol and Drug Risk among Homeless Adolescents. Psychology of Addictive Behaviors, 20, pp. 254-264, 2006.

Twelve-Step Treatment for Drug Abuse Can Be Effective HIV Risk Reduction

Dr. Thomas Lyons and colleagues at the University of Illinois at Chicago

conducted a study of 64 cocaine- and methamphetamine-using MSM participating in Crystal Meth Anonymous meetings as part of drug abuse recovery. Participants were recruited at 12-step venues, HIV treatment clinics, and through advertisements. Data were collected at a number of Crystal Meth Anonymous (CMA) meetings designated as "open", and consisted of standardized questionnaires, interviews, and investigator observations. Self-reports indicated almost all participants were polydrug users, with 76% using methamphetamine (18% intravenously), and 52% using cocaine or crack cocaine (also 18% intravenously). Among the 15 participants reporting injection drug use, 13 were HIV positive. Overall, participants reported significant declines in sexual risk behavior after starting CMA meetings, with percent of participants engaging in unprotected anal intercourse dropping from 70% to 24%, and number of sexual partners dropping from 7 to 1 per month. Declines in risk behaviors were even larger for HIV positive participants. Participants' interview responses and comments in meetings highlighted the connection between use of methamphetamine in particular and sexual concerns. Participants frequently reported complications in sexual relations during recovery, and attributed reductions in sexual risk behaviors due to fear of relapse to drug use. This observational study adds to the growing body of literature indicating that drug abuse treatment is, in itself, HIV risk reduction. Lyons, T., Chandra, G., and Goldstein, J. Stimulant Use and HIV Risk Behavior: The Influence of Peer Support Group Participation. AIDS Education and Prevention, 18, pp. 461-473, 2006.

Contingency Management, Motivational/Skills-Building, and 12-Step Drug Counseling for Treating Young Adult Marijuana Abuse and Dependence

Dr. Kathleen Carroll and colleagues at the Yale University School of Medicine compared the efficacy of four treatments for marijuana-using, young adult probationers referred by the criminal justice system. Of the 136 participants, 90% were male, 60% were African-American, and all were between 18 - 25 years old. Participants were randomly assigned to one of four 8-week treatment conditions: 1) Motivational Enhancement Therapy and Cognitive Behavioral Therapy (MET/CBT); 2) MET/CBT with contingency management (MET/CBT + CM); 3) Twelve-step based individual Drug Counseling (DC); or 4) DC with contingency management (DC + CM). Assessments were conducted at baseline before treatment began, weekly during treatment, and at 3 and 6 months after treatment termination, and included self-reports and biological verification of marijuana use. Overall, treatments including contingency management (CM) produced better abstinence results than those without CM, including longer periods of continuous absence from marijuana use, and more total negative urine samples. Retention rates were 60% overall, and were significantly better for treatments with CM, and were significantly better for MET/CBT than for DC treatments. On the whole, participants maintained treatment gains through 6-month follow-ups, with those participating in either MET/CBT treatment showing even greater improvements than those in either DC treatment. These results confirm the potency of adjunctive CM in boosting treatment retention and effectiveness, and add confirm existing data suggesting that skills-based interventions can produce continued improvements, even after treatment ends. Carroll, K.M., Easton, C.J., Nich, C., Hunkele, K.A., Neavins, T.M., Sinha, R., Ford, H.L., Vitolo, S.A., Doebrick, C.A., and Rounsaville, B.J. The Use of Contingency Management and Motivational/Skills-Building Therapy to Treat Young Adults with Marijuana Dependence. Journal of Consulting and Clinical Psychology, 74, pp. 955-966, 2006.

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

Ninety cannabis-dependent adults seeking treatment were randomly assigned to receive cognitive-behavioral therapy, abstinence-based voucher incentives, or their combination. Treatment duration was 14 weeks, and outcomes were assessed for 12 months posttreatment. Findings suggest that (a) abstinence-based vouchers were effective for engendering extended periods of continuous marijuana abstinence during treatment, (b) cognitive-behavioral therapy did not add to this during-treatment effect, and (c) cognitive-behavioral therapy enhanced the post-treatment maintenance of the initial positive effect of vouchers on abstinence. This study extends the literature on cannabis dependence, indicating that a program of abstinence-based vouchers is a potent treatment option. Discussion focuses on the strengths of each intervention, the clinical significance of the findings, and the need to continue efforts toward development of effective interventions. Budney, A.J., Moore, B.A., Rocha, H.L., and Higgins, S.T. J Consult Clin Psychol. 74(2), pp. 307-316, April 2006.

Director's Report to the National Advisory Council on Drug Abuse - February, 2007

Research Findings - Research on Pharmacotherapies for Drug Abuse

Disulfiram Effects on Responses to Intravenous Cocaine Administration

Disulfiram has been studied as a treatment for cocaine dependence. Authors report results of a randomized, double-blind, placebo-controlled, within-subject study to examine the interaction of disulfiram with intravenous cocaine. Non-treatment-seeking, cocaine-dependent, volunteers participated in serial experiments in which they received disulfiram placebo, 62.5 or 250mg/day on days 1-6. On days 4-6, participants received a morning disulfiram dose 2h prior to a scheduled session in which they were administered intravenous cocaine placebo, 0.25mg/kg (n=9) or 0.5mg/kg (n=3) over 1 min. Blood, cardiovascular and subjective measures were collected. Seven days of washout occurred between disulfiram conditions. Following active disulfiram treatments and cocaine 0.25mg/kg administration, plasma cocaine AUC (0-480min) was increased (p=0.003 and 0.001) and cocaine clearance decreased (p<0.001). Disulfiram treatments also decreased cocaine clearance for the 0.5mg/kg cocaine dose (p=0.002 and<0.001). Neither disulfiram dose with cocaine altered cardiovascular responses relative to cocaine alone. Following cocaine 0.25mg/kg, 'any high' (p=0.021 and 0.019), 'cocaine high' (p=0.017 and 0.018) and 'rush' (p=0.013 and 0.047) significantly decreased with either disulfiram dose. Disulfiram decreased cocaine clearance without toxicity. Cocaine 'high' and 'rush' were diminished. Disulfiram may be a promising pharmacotherapy in selected cocaine dependent individuals. Baker, J.R., Jatlow, P., and McCance-Katz, E.F. Drug Alcohol Depend. September 15, 2006 [Epub ahead of print].

Marijuana Use and the Risk of Lung and Upper Aerodigestive Tract Cancers: Results of a Population-Based Case-Control Study

Despite several lines of evidence suggesting the biological plausibility of marijuana being carcinogenic, epidemiologic findings are inconsistent. Authors conducted a population-based case-control study of the association between marijuana use and the risk of lung and upper aerodigestive tract cancers in Los Angeles. This study included 1,212 incident cancer cases and 1,040 cancer-free controls matched to cases on age, gender, and neighborhood. Subjects were interviewed with a standardized questionnaire. The cumulative use of marijuana was expressed in joint-years, where 1 joint-year is equivalent to smoking one joint per day for 1 year. Although using marijuana for > or =30 joint-years was positively associated in the crude analyses with each cancer type (except pharyngeal cancer), no positive associations were observed when adjusting for several confounders including cigarette smoking. The adjusted odds ratio estimate (and 95% confidence limits) for > or =60 versus 0 joint-

years was 1.1 (0.56, 2.1) for oral cancer, 0.84 (0.28, 2.5) for laryngeal cancer, and 0.62 (0.32, 1.2) for lung cancer; the adjusted odds ratio estimate for > or =30 versus 0 joint-years was 0.57 (0.20, 1.6) for pharyngeal cancer, and 0.53 (0.22, 1.3) for esophageal cancer. No association was consistently monotonic across exposure categories, and restriction to subjects who never smoked cigarettes yielded similar findings. These results may have been affected by selection bias or error in measuring lifetime exposure and confounder histories; but they suggest that the association of these cancers with marijuana, even long-term or heavy use, is not strong and may be below practically detectable limits. Hashibe, M., Morgenstern, H., Cui, Y., Tashkin, D.P., Zhang, Z.F., Cozen, W., Mack, T.M., and Greenland, S. Cancer Epidemiol Biomarkers Prev. 15(10), pp. 1829-1834, 2006.

Oral Delta-9-Tetrahydrocannabinol Suppresses Cannabis Withdrawal Symptoms

This study assessed whether oral administration of delta-9-tetrahydrocannbinol (THC) effectively suppressed cannabis withdrawal in an outpatient environment. The primary aims were to establish the pharmacological specificity of the withdrawal syndrome and to obtain information relevant to determining the potential use of THC to assist in the treatment of cannabis dependence. Eight adult, daily cannabis users who were not seeking treatment participated in a 40-day, within-subject ABACAD study. Participants administered daily doses of placebo, 30mg (10mg/tid), or 90mg (30mg/tid) oral THC during three, 5-day periods of abstinence from cannabis use separated by 7-9 periods of smoking cannabis as usual. Comparison of withdrawal symptoms across conditions indicated that (1) the lower dose of THC reduced withdrawal discomfort, and (2) the higher dose produced additional suppression in withdrawal symptoms such that symptom ratings did not differ from the smoking-as-usual conditions. Minimal adverse effects were associated with either active dose of THC. This demonstration of dose-responsivity replicates and extends prior findings of the pharmacological specificity of the cannabis withdrawal syndrome. The efficacy of these doses for suppressing cannabis withdrawal suggests oral THC might be used as an intervention to aid cannabis cessation attempts. Budney, A.J., Vandrey, R.G., Hughes, J.R., Moore, B.A., and Bahrenburg, B. Drug Alcohol Depend. 86(1), pp. 22-29, 2007.

Substance Use and Psychosocial Outcomes Following Participation in Residential

Laboratory Studies of Marijuana, Methamphetamine and Zolpidem Non-therapeutic research with drugs of abuse in humans is important for a more comprehensive understanding of substance abuse and for the development of more effective treatments. However, the administration of substances from drug classes with abuse potential to human volunteers raises ethical questions regarding potential risk to study volunteers. The purpose of this study was to assess the psychosocial functioning and reported drug-taking behavior of volunteers before and after participating in a residential laboratory study, during which either marijuana, methamphetamine or zolpidem was administered. Twenty-two volunteers were administered Addiction Severity Index (ASI) interviews at intake and approximately six months following their study participation. No significant differences between intake and follow-up assessments were found on any ASI composite or drug/alcohol-taking variable. These preliminary data suggest that participation in residential laboratory studies involving the administration of drugs from classes with abuse potential does not alter subsequent psychosocial functioning or reported drug use. Vadhan, N.P., Hart, C.L., Roe, B., Colley, J., Haney, M., and Foltin, R.W. Am J Drug Alcohol Abuse. 32(4), pp. 589-597, 2006.

Planned Meetings

Publications

Staff Highlights

Grantee Honors

Opioid Antagonism of Cannabinoid Effects: Differences between Marijuana Smokers and Nonmarijuana Smokers

In non-human animals, opioid antagonists block the reinforcing and discriminative-stimulus effects of Delta(9)-tetrahydrocannabinol (THC), while in human marijuana smokers, naltrexone (50 mg) enhances the reinforcing and subjective effects of THC. The objective of this study was to test a lower, more opioid-selective dose of naltrexone (12 mg) in combination with THC. The influence of marijuana-use history and sex was also investigated. Naltrexone (0, 12 mg) was administered 30 min before oral THC (0-40 mg) or methadone (0-10 mg) capsules, and subjective effects, task performance, pupillary diameter, and cardiovascular parameters were assessed in marijuana smoking (Study 1; n=22) and in nonmarijuana smoking (Study 2; n=21) men and women. The results show that in marijuana smokers, low-dose naltrexone blunted the intoxicating effects of a low THC dose (20 mg), while increasing ratings of anxiety at a higher THC dose (40 mg). In nonmarijuana smokers, low-dose naltrexone shifted THC's effects in the opposite direction, enhancing the intoxicating effects of a low THC dose (2.5 mg) and decreasing anxiety ratings following a high dose of THC (10 mg). There were no sex differences in these interactions, although among nonmarijuana smokers, men were more sensitive to the effects of THC alone than women. To conclude, a low, opioid-selective dose of naltrexone blunted THC intoxication in marijuana smokers, while in nonmarijuana smokers, naltrexone enhanced THC intoxication. These data demonstrate that the interaction between opioid antagonists and cannabinoid agonists varies as a function of marijuana use history. Haney, M. Neuropsychopharmacology, advance online publication, 8 November 2006.

Cocaine Withdrawal Symptoms Predict Medication Response in Cocaine Users

The influence of cocaine withdrawal symptoms on addiction severity and treatment outcomes was evaluated in 85 methadone-stabilized cocaine users who participated in pharmacotherapy trials using GABA medications. Subjects who fulfilled DSM-IV cocaine withdrawal criteria (n=45) compared to those who did not (n=40) showed a greater increase in cocaine free urines in response to pharmacotherapy with GABA medications. The results support the clinical utility of cocaine withdrawal symptoms in predicting treatment response to medications. Sofuoglu, M., Poling, J., Gonzalez, G., Gonsai, K., and Kosten, T. Am. J. of Drug and Alcohol Abuse, 32, pp. 617-627, 2006.

Smoked Cocaine Self-Administration by Humans is Not Reduced by Large Gabapentin Maintenance Doses

This study follows a previous study reporting that gabapentin significantly reduced the 'positive' subjective effects of cocaine without reducing cocaine self-administration. This study examined the effects of larger gabapentin maintenance doses (0, 2400, and 3200 mg/day) on cocaine-related effects, including self-administration in six cocaine-dependent, non-treatment seeking, individuals. Gabapentin did not decrease cocaine self-administration, cardiovascular measures, or most subjective effects of cocaine. These findings suggest that gabapentin does not show promise as a treatment medication for cocaine dependence. Hart, C.L., Haney, M., Collins, E.D., Rubin, E. and Foltin, R.W. Drug and Alcohol Dep, 86, pp. 274-277, 2007.

Safety, Tolerability and Efficacy of Levodopa-Carbidopa Treatment for Cocaine Dependence: Two Double-blind, Randomized, Clinical Trials

Based on the fact that cocaine use can significantly alter dopaminergic

functioning through depletion of dopamine and changes in receptor functioning, two studies were designed to test the hypothesis that L-dopa pharmacotherapy may be helpful in reducing or abolishing cocaine use by evaluating the safety, tolerability and efficacy of L-dopa as a treatment for cocaine dependence. In Study 1, 67 cocaine-dependent subjects received either placebo or 400 mg L-dopa plus 100 mg carbidopa. In Study 2, 122 cocaine-dependent subjects received either placebo , 400mg/100mg L-dopa/carbidopa, or 800mg/200mg L-dopa/carbidopa. L-dopa was found to be well tolerated with similar retention and medication adherence rates compared to placebo, and had no effect on cocaine use, cocaine craving, or mood. Mooney, M.E., Schmitz, J.M., Moeller, F.G., and Grabowski, J. E-publication, Drug and Alcohol Dep., accepted 26 October, 2006.

A Double-Blind, Placebo-Controlled Trial of Amantadine, Propranolol, and Their Combination for the Treatment of Cocaine Dependence in Patients with Severe Cocaine Withdrawal Symptoms

This trial evaluated the effects of Amantadine, propranolol, and their combination in 199 cocaine dependent patients with severe cocaine withdrawal symptoms. The results of this study showed no significant differences between the four medication groups in treatment retention. In highly medication-adherent patients, treatment retention and rates of cocaine abstinence were significantly better in the propranolol group compared to the placebo group. None of the active treatments was significantly more effective than placebo in promoting cocaine abstinence in patients with more severe cocaine withdrawal symptoms. Kampman, K. M., Dackis, C., Lynch, K. G., Pettinati, H., Tirado, C., Gariti, P. et al. Drug Alcohol Depend. 85, pp. 129-137, 2006.

Six-Month Trial of Bupropion With Contingency Management for Cocaine Dependence in a Methadone-Maintained Population

This placebo-controlled, double-blind trial compared the efficacy of bupropion and contingency management (CM) for reducing cocaine use in 106 opiate-dependent, cocaine-abusing individuals. Participants were randomly assigned to one of four conditions: CM and placebo; CM and 300 mg/d bupropion (CMB); voucher control and placebo (VCP) or voucher control and bupropion (VCB). In this study, CMB was an effective treatment for cocaine abuse in the methadone-maintained population. CM alone was also effective in reducing cocaine use relative to VCP, but only during the last half of the study. Poling, J., Oliveto, A., Petry, N., Sofuoglu, M., Gonsai, K., Gonzalez, G., Martell, B., and Kosten, T. Arch Gen Psychiatry, 63, pp. 219-228, 2006.

Randomized, Placebo-Controlled Trial of Baclofen and Gabapentin for the Treatment of Methamphetamine Dependence

This trial evaluated the effects of two GABAergic medications, baclofen (20 mg tid) and gabapentin (800 mg tid) for the treatment of methamphetamine dependence in 88 methamphetamine-dependent patients. The results of this study showed no statistically significant effects for either baclofen or gabapentin in reducing methamphetamine use. Heinzerling, K.G., Shoptaw, S., Peck, J.A., Yang, X., Liu, J., Roll, J., and Ling, W. Drug and Alcohol Dependence 85, pp. 177-184, 2006.

Randomized, Placebo-Controlled Trial of Sertraline and Contingency Management for the Treatment of Methamphetamine Dependence

This study evaluated the effects of sertraline, sertraline plus contingency

management (CM), placebo plus CM, or placebo only, in 229 methamphetamine-dependent patients. The study results did not show any efficacy for sertraline or CM in reducing methamphetamine use. Sertraline conditions produced significantly more adverse events than placebo conditions. Shoptaw, S., Huber, A., Peck, J.A., Yang, X., Liu, J., Dang, J., Roll, J., Shapiro, B., Rotherham-Fuller, E., and Ling, W. Drug and Alcohol Dependence 85, pp. 12-18, 2006.

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

A previous study carried out by this group found that 20 mg aripiprazole attenuated many of the behavioral effects of d-amphetamine, but also impaired performance on a computerized version of the DSST when administered alone, indicating that the attenuation observed might be due to functional, rather than receptor mediated, effects. The present study in 6 healthy adults examined the effects of a lower dose of aripiprazole (10 mg) on the discriminative-stimulus, subject-rated, and physiological effects of d-amphetamine without impairing performance. The results of this study indicate that 10 mg aripiprazole attenuated some abuse-related behavioral effects of d-amphetamine and showed no significant performance impairment. These findings suggest that 10 mg aripiprazole would be a reasonable starting dose for the treatment of stimulant abuse and dependence. Stoops. W.W., Lile, J.A., Glaser, P.E.A., and Rush, C. Drug and Alcohol Dependence 84, pp. 206-209, 2006.

Injectable, Sustained-Release Naltrexone for the Treatment of Opioid Dependence

Oral naltrexone can completely antagonize the effects produced by opioid agonists, but poor compliance with this medication has been an obstacle to its use in the treatment of opioid dependency. This study evaluated the safety and efficacy of a sustained-release depot formulation of naltrexone in treating opioid dependence in a randomized, double-blind, placebo-controlled trial in 60 patients at 2 medical centers. The main outcome measures were treatment retention and percentage of opioid-negative urines. In this study, the injectable, sustained-release depot formulation of naltrexone was well tolerated and produced a robust, dose-related increase in treatment retention. Comer, S., Sullivan, M.A., Yu, E., Rothenberg, J.L., Kleber, H.D., Kampman, K., Dackis, C., and O'Brien, C. Archives of General Psychiatry 63, pp. 210-218, 2006.

Director's Report to the National Advisory Council on Drug Abuse - February, 2007

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

Micronutrient Levels and HIV Disease Status in HIV-Infected Patients on Highly Active Antiretroviral Therapy in the Nutrition for Healthy Living Cohort

Low serum micronutrient levels were common before widespread use of highly active antiretroviral therapy (HAART) and were associated with adverse outcomes. Few data are available on micronutrient levels in subjects taking HAART. This cross-sectional study was conducted to determine the prevalence of low serum retinol, alpha-tocopherol, zinc, and selenium in HIV-infected subjects taking HAART and to assess the association of micronutrient levels with HIV disease status. Participants were HIV-infected subjects on HAART in an ongoing Nutrition for Healthy Living (NFHL) study at Tufts. Retinol, alpha-tocopherol, zinc, and selenium were determined in frozen serum samples from 171 men and 117 women. Low serum levels were defined as retinol <30 mug/dL, selenium <85 mug/L, alpha-tocopherol <500 mug/dL, and zinc <670 mug/L. Association of micronutrient quartiles with CD4 cell count, CD4 count <200 cells/mm, HIV viral load (VL), and undetectable VL was assessed using adjusted multivariate regression. Results indicated that 5% of men and 14% of women had low retinol, 8% of men and 3% of women had low selenium, and 7% of men and no women had low alpha-tocopherol. Forty percent of men and 36% of women had low zinc, however. Subjects in the upper quartiles of zinc had lower log VL levels than those in the lowest quartile (significant for women). Subjects in the upper quartiles of selenium also tended to have lower VL levels compared with those in the lowest quartile. Surprisingly, women in the upper quartiles of retinol had higher log VLs than those in the lowest quartile. There was no significant association of any micronutrient with CD4 cell count or likelihood of CD4 count <200 cells/mm. The level of CD4 cell count influenced the association of retinol with log VL in men, however. In men with CD4 counts >350 cells/mm, those with higher retinol had higher log VLs compared with the lowest quartile, whereas in men with CD4 counts <350, those with higher retinol levels had lower log VLs compared with the lowest quartile. The authors concluded that low retinol, alpha-tocopherol, and selenium are uncommon in HIV-infected subjects on HAART. Zinc deficiency remains common, however. Jones, C.Y., Tang, A.M., Forrester, J.E., Huang, J., Hendricks, K.M., Knox, T.A., Spiegelman, D., Semba, R.D., and Woods, M.N. J Acquir Immune Defic Syndr. 43(4), pp. 475-482, December 1, 2006.

Increased Serum Lipids are Associated with Higher CD4 Lymphocyte Count in HIV-Infected Women

Highly active antiretroviral therapy (HAART) has been associated with dyslipidaemia; however, the roles of immune status and non-HIV-disease risk

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factors remain unclear. A cross-sectional analysis of fasting lipids was carried out for 231 women, of whom 132 were HIV-infected and 99 were uninfected. The concentrations of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, and apolipoprotein B (apo B) were measured. CD4 lymphocyte count, hepatitis C status, demographics, diet, and anthropometrics were also assessed. A total of 132 women were HIV-infected [30 were antiretroviral-naive, 68 were on protease inhibitors (PIs), and 34 were on non-PI HAART]. HIV infection was associated with higher triglycerides, lower HDL-C, and, among obese women, higher total cholesterol and LDL-C. Non-PI and PI HAART were each independently associated with higher total cholesterol, LDL-C, and apo B, compared with being ART-naive. Among HIV-infected women, after adjustment for HAART use, women with a CD4 lymphocyte count > or =500 cells/microL had total cholesterol 41.8 mg/dL (P = 0.002) and LDL-C 28.8 mg/dL (P = 0.01) higher, on average, than women with a CD4 count <200 cells/microL. Women with a CD4 count of 200-499 cells/microL had total cholesterol 26.31 mg/dL higher, on average, than those with a CD4 count <200 cells/microL (P = 0.04), although differences in LDL-C did not reach significance (15.51 mg/dL; P = 0.12). A higher CD4 count was also associated with higher apo B (P < 0.001). Active hepatitis C infection was associated with lower total cholesterol, LDL-C, triglycerides, and apo B. The authors concluded that higher CD4 ymphocyte counts were associated with higher lipid levels, suggesting that immune competence may independently affect the dyslipidaemia seen in the HAART era. In addition, it is important that hepatitis C status be assessed in studies of dyslipidaemia in the HIV-infected population. Floris-Moore, M., Howard, A.A., Lo, Y., Arnsten, J.H., Santoro, N., and Schoenbaum, E.E. Increased Serum Lipids are Associated with Higher CD4 Lymphocyte Count in HIV-infected Women. HIV Med. 7(7), pp. 421-430, 2006.

Abnormal Glucose Metabolism among Older Men with or at Risk of HIV Infection

The objective of this study was to determine factors associated with diabetes, insulin resistance, and abnormal glucose tolerance in older men with or at risk of HIV infection. Diabetes was assessed by self-report in 643 men >or=49 years old with or at risk of HIV infection. In a subset of 216 men without previously diagnosed diabetes [including 90 HIV-uninfected men, 28 HIV-infected, antiretroviral-naive men, 28 HIV-infected men taking non-protease inhibitor (PI)-containing highly active antiretroviral therapy (HAART), and 70 HIV-infected men taking PI-containing HAART], an oral glucose tolerance test with insulin levels was performed. HIV serology, CD4 cell count, weight, height and waist circumference were measured. Antiretroviral use, drug use, family history of diabetes, physical activity and sociodemographic data were obtained using standardized interviews. Of 643 participants, 116 (18%) had previously diagnosed diabetes. With the oral glucose tolerance test, 15 of 216 men (7%) were found to have undiagnosed diabetes and 40 (18%) impaired glucose tolerance. Factors independently associated with previously diagnosed diabetes included use of non-PI-containing HAART, methadone treatment, positive CAGE test for alcoholism, obesity and family history of diabetes. Factors independently associated with greater insulin resistance included waist circumference and heroin use. Factors independently associated with abnormal glucose tolerance (impaired glucose tolerance or diabetes) included age >or=55 years and Hispanic ethnicity. HIV-infected men with diabetes risk factors should undergo screening for diabetes regardless of HAART use. Interventions targeting modifiable risk factors, including overweight and physical inactivity, are warranted. The potential impact of opiate and alcohol abuse on glucose metabolism should be recognized in clinical care, and addressed in future research studies of HIV-infected persons. Howard, A.A., Floris-Moore, M., Lo, Y., Arnsten, J.H., Fleischer, N., and Klein, R.S. HIV Med. 7(6), pp. 389-396, 2006.

Planned Meetings

Publications

Staff Highlights

Grantee Honors

CCR5 Expression and Duration of High Risk Sexual Activity among HIV-Seronegative Men Who have Sex with Men

The objectives of this study were to test the hypothesis that in comparison with those with shorter risk duration, individuals with longer HIV risk duration would have reduced susceptibility to HIV-1 infection as measured by CCR5 expression, and to evaluate whether variation in CCR5 expression could be explained by known genetic polymorphisms. Methodology involved a cross-sectional study of HIV-1 exposed but uninfected men who have sex with men. The risk duration was estimated from self-reported years since first receptive anal intercourse. CCR5 expression on peripheral blood CD4+ monocytes and T cells was determined by flow cytometry. The CCR5-Delta32 mutation and polymorphisms in the CCR5 promoter and CCR2 as well as the copy number of CCL3L1 were analyzed by polymerase chain reaction. Plasma levels of MIP-1alpha (CCL3), MIP-1beta (CCL4) and RANTES (CCL5) were also measured. As risk duration varied with age, analyses were restricted to 67 individuals aged 30-49 years. Multiple linear regression analyses, adjusted for age and race, showed a significant negative association between HIV risk duration and CCR5 expression on monocytes (P = 0.01), and in a separate model, a similar negative association with CCR5 expression on T cells (P = 0.03). Low CCR5 expression was attributable mainly to CCR5-Delta32 heterozygosity and the CCR5-59029G allele. Authors confirmed a role for reduced CCR5 expression in HIV-1 resistance. CCR5-Delta32 heterozygosity and the CCR5-59029G allele were significant predictors of low CCR5 expression. Individuals with high CCR5 expression who resisted infection despite long HIV risk duration form an interesting group within which to search for additional mechanisms of resistance to HIV infection. Thomas, S.M., Tse, D.B., Ketner, D.S., Rochford, G., Meyer, D.A., Zade, D.D., Halkitis, P.N., Nadas, A., Borkowsky, W., and Marmor, M. AIDS. 20(14), pp. 1879-1883, 2006.

Pharmacokinetic Interactions between Buprenorphine and Antiretroviral Medications

Buprenorphine is used for the treatment of opioid dependence. As the number of persons receiving buprenorphine treatment and antiretroviral therapy continues to grow, so too does the existence and clinical impact of drug interactions between buprenorphine and medications for treating human immunodeficiency virus (HIV) infection. Awareness that such interactions exist may deter some patients and physicians from initiating potentially lifesaving therapy or lead to complications among patients whose treatment is already under way. Complications include nonadherence to antiretroviral therapy and the development of viral resistance. Illicit drug use is a frequent consequence of adverse drug effects experienced by injection drug users. The occurrence of unrecognized drug interactions can lead to unsuccessful therapy for HIV infection and the treatment of substance dependence. The present review is organized to provide a working background of buprenorphine pharmacology. Review of the current state of knowledge regarding specific interactions between buprenorphine and antiretrovirals is followed by a review of the clinical applicability of these interactions. Bruce, R.D., McCance-Katz, E., Kharasch, E.D., Moody, D.E., and Morse, G.D. Clin Infect Dis. 43 Suppl 4, pp. S216-223, 2006.

Interactions between Buprenorphine and Antiretrovirals. II. The Protease Inhibitors Nelfinavir, Lopinavir/Ritonavir, and Ritonavir

Authors examined drug interactions between buprenorphine, an opioid partial agonist available by prescription for treatment of opioid dependence, and the protease inhibitors (PIs) nelfinavir (NFV), ritonavir (RTV), and lopinavir/ritonavir (LPV/R). Opioid-dependent, buprenorphine/naloxone-

maintained, human immunodeficiency virus (HIV)-negative volunteers (n=10 per PI) participated in 24-h pharmacokinetic studies, before and after administration of each PI. Symptoms of opiate withdrawal and excess were determined before and after PI administration. PI pharmacokinetics were determined and compared between opiate-dependent participants and healthy control participants (n=15 per PI). Administration of RTV, but not of NFV or LPV/R, resulted in a significant increase in the buprenorphine area under the concentration-time curve (AUC). Symptoms of opiate excess, however, were not observed. Buprenorphine had no significant effects on PI AUC. Adjustments of doses of either buprenorphine or NFV, LPV/R, or RTV are not likely to be necessary when these drugs are administered for the treatment of opioid dependence and HIV disease. McCance-Katz, E.F., Moody, D.E., Smith, P.F., Morse, G.D., Friedland, G., Pade, P., Baker, J., Alvanzo, A., Jatlow, P., and Rainey, P.M. Clin Infect Dis. 43 Suppl 4. pp. S235-246, 2006.

Interactions between Buprenorphine and Antiretrovirals. I. The Nonnucleoside Reverse-Transcriptase Inhibitors Efavirenz and Delavirdine

This study examined drug interactions between buprenorphine, an opioid partial agonist medication used in the treatment of opioid dependence, and the nonnucleoside reverse-transcriptase inhibitors (NNRTIs) efavirenz (EFV) and delavirdine (DLV). Opioid-dependent, buprenorphine/naloxone-maintained, human immunodeficiency virus (HIV)-negative volunteers (n=10 per NNRTI) participated in 24-h sessions to determine pharmacokinetics of buprenorphine and of buprenorphine with either EFV or DLV after administration of standard doses of either antiretroviral for 15 or 7 days, respectively. Opiate withdrawal symptoms, cognitive effects, and adverse events were determined before and after antiretroviral administration in opioid-dependent participants. The pharmacokinetics of NNRTIs in healthy control participants were used to determine the effect of buprenorphine on NNRTIs. EFV decreased the buprenorphine area under the concentration-time curve (P<.001). DLV increased buprenorphine concentrations (P<.001). Clinically significant consequences of these interactions were not observed. Buprenorphine did not alter antiretroviral pharmacokinetics. Adjustments of doses of either buprenorphine or EFV or DLV are not likely to be necessary when these drugs are administered for the treatment of opiate dependence and HIV disease. McCance-Katz, E.F., Moody, D.E., Morse, G.D., Friedland, G., Pade, P., Baker, J., Alvanzo, A., Smith, P., Ogundele, A., Jatlow, P., and Rainey, P.M. Clin Infect Dis. 43 Suppl 4, pp. S224-234, 2006.

Methamphetamine Modulates Gene Expression Patterns in Monocyte Derived Mature Dendritic Cells: Implications for HIV-1 Pathogenesis

The US is currently experiencing a grave epidemic of methamphetamine use as a recreational drug, and the risk for HIV-1 infection attributable to methamphetamine use continues to increase. Recent studies show a high prevalence of HIV infection among methamphetamine users. Dendritic cells (DCs) are potent antigen presenting cells that are the initial line of defense against HIV-1 infection. In addition, DCs also serve as reservoirs for HIV-1 and function at the interface between the adaptive and the innate immune systems, which recognize and internalize pathogens and subsequently activate T cells. Exposure to methamphetamine results in modulation of immune functional parameters that are necessary for host defense. Chronic methamphetamine use can cause psychiatric co-morbidity, neurological complications, and can alter normal biological processes and immune functions. Limited information is available on the mechanisms by which methamphetamine may influence immune function. This study explores the effect of methamphetamine on a

specific array of genes that may modulate immune function. The authors hypothesize that methamphetamine treatment results in the immunomodulation of DC functions, leading to dysregulation of the immune system of the infected host. This suggests that methamphetamine has a role as a cofactor in the pathogenesis of HIV-1. Authors used the high-throughput technology of gene microarray analysis to understand the molecular mechanisms underlying the genomic changes that alter normal biological processes when DCs are treated with methamphetamine. Additionally, they validated the results obtained from microarray experiments using a combination of quantitative real-time PCR and Western blot analysis. These data are the first evidence that methamphetamine modulates DC expression of several genes. Methamphetamine treatment alters categories of genes that are associated with chemokine regulation, cytokinesis, signal transduction mechanisms, apoptosis, and cell cycle regulation. This report focuses on a selected group of genes that are significantly modulated by methamphetamine treatment and that have been associated with HIV-1 pathogenesis. The purpose of this study was to identify genes that are unique and/or specific to the complex immunomodulatory mechanisms that are altered as a result of methamphetamine abuse in HIV-1-infected patients. These studies will help to identify the molecular mechanisms that underlie methamphetamine toxicity, and several functionally important classes of genes have emerged as targets in methamphetamine-mediated immunopathogenesis of HIV-1. Identification of novel DC-specific and methamphetamine-responsive genes that modulate several biological, molecular, and signal transduction functions may serve as methamphetamine- and/or HIV-1-specific drug targets. Mahajan, S.D., Hu, Z., Reynolds, J.L., Aalinkeel, R., Schwartz, S.A., and Nair, M.P. Mol Diagn Ther. 10(4), pp. 257-269, 2006.

Functional Studies of an HIV-1 Encoded Glutathione Peroxidase

In an alternate reading frame overlapping the viral envelope gene, HIV-1 has been shown to encoded a truncated glutathione peroxidase (GPx) module. Essential active site residues of the catalytic core regions of mammalian GPx sequences are conserved in the putative viral GPx (vGPx, encoded by the env-fs gene). Cells transfected with an HIV-1 env-fs construct show up to a 100% increase in GPx enzyme activity, and are protected against the loss of mitochondrial transmembrane potential and subsequent cell death induced by exogenous oxidants or mitochondrial reactive oxygen species. An intact vGPx gene was observed to be more common in HIV-1-infected long-term non-progressors, as compared to HIV-1 isolates from patients developing AIDS. An antioxidant/ antiapoptotic protective role of the vGPx is also consistent with the observation that -1 frameshifting induced by the HIV-1 env-fs sequence AAAAAGA (which contains a potential "hungry" arginine codon, AGA) increases during arginine deficiency, which has been associated with increased oxidative stress. Under arginine-limited conditions, nitric oxide synthase generates superoxide, which rapidly combines with NO to form peroxynitrite, which can cause activated T-cells to undergo apoptosis. Thus, biosynthesis of the HIV-1 GPx as an adaptive response to low arginine conditions might delay oxidant-induced apoptotic cell death, providing an enhanced opportunity for viral replication. Zhao, L., Olubajo, B., and Taylor, E.W. Biofactors. 27(1-4), pp. 93-107, 2006.

Limited Effectiveness of Antiviral Treatment for Hepatitis C in an Urban HIV Clinic

The objective of this study was to evaluate predictors and trends of referral for hepatitis C virus (HCV) care, clinic attendance and treatment in an urban HIV clinic. Methodology for this study comprised a retrospective cohort analysis in which 845 of 1318 co-infected adults who attended the Johns Hopkins HIV clinic between 1998 and 2003 after an on-site viral hepatitis clinic was opened,

attended regularly (>/= 1 visit/year for >/= 2 years). Logistic regression was used to examine predictors of referral. A total of 277 (33%) of 845 were referred for HCV care. Independent predictors of referral included percentage elevated alanine aminotransferase levels [adjusted odds ratio (AOR) for 10% increase,1.16; 95% confidence interval (CI), 1.10-1.22] and CD4 cell count > 350 cells/mul (AOR, 3.20; 95% CI, 2.10-4.90), while injection drug use was a barrier to referral (AOR, 0.26; 95% CI, 0.11-0.64). Overall referral rate increased from < 1% in 1998 to 28% in 2003; however, even in 2003, 65% of those with CD4 cell count > 200 cells/mul were not referred. One hundred and eighty-five (67%) of 277 referred kept their appointment, of whom 32% failed to complete a pre-treatment evaluation. Of the remaining 125, only 69 (55%) were medically eligible for treatment, and 29 (42%) underwent HCV treatment. Ninety percent of 29 were infected with genotype 1 and 70% were African American; six (21%) achieved sustained virologic response (SVR). Only 0.7% of the full cohort achieved SVR. Authors concluded that although the potential for SVR and the recent marked increase in access to HCV care are encouraging, overall effectiveness of anti-HCV treatment in this urban, chiefly African American, HCV genotype 1 HIV clinic is extremely low. New therapies and treatment strategies are an urgent medical need. Mehta, S.H., Lucas, G.M., Mirel, L.B., Torbenson, M., Higgins, Y., Moore, R.D., Thomas, D.L., and Sulkowski, M.S. AIDS. 20(18), pp. 2361-2369, 2006.

A Success Story: HIV Prevention for Injection Drug Users in Rhode Island

New HIV diagnoses related to injection drug use (IDU) have declined in the United States. Decreasing HIV transmission among IDUs and clean syringe access have been HIV prevention priorities of the Rhode Island (RI) HIV community. To examine trends in IDU-related new HIV diagnoses in RI, a retrospective analysis of new HIV diagnoses according to HIV risk factors from 1990-2003 was performed. An 80% absolute reduction in IDU-related new HIV diagnoses was found in RI coincident with IDU-specific prevention efforts. A greater decline was found in IDU-related new HIV diagnoses in Rhode Island compared to reported national data from the Centers for Disease Control and Prevention. The dramatic decline in Rhode Island is hypothesized to be related to extensive HIV prevention efforts targeting IDUs. Further research is needed to examine the impact of specific HIV prevention interventions for IDUs. Beckwith, C.G., Moreira, C.C., Aboshady, H.M., Zaller, N., Rich, J.D., and Flanigan, T.P. Subst Abuse Treat Prev Policy. 1(1):34 [Epub ahead of print], 2006.

Director's Report to the National Advisory Council on Drug Abuse - February, 2007

Research Findings - Services Research

Optimal Amounts of Counseling Plus Buprenorphine-Naloxone Maintenance Therapy for Opioid Dependence

In this study published in the New England Journal of Medicine, the authors determined the optimal level of counseling and frequency of clinic attendance for medication distribution in primary care practices engaged in office-based buprenorphine-naloxone treatment of opioid dependence. The study was conducted as a 24-week randomized, controlled clinical trial with 166 patients assigned to one of three treatments: standard medical management and either once-weekly or thrice-weekly medication dispensing or enhanced medical management and thrice-weekly medication dispensing. Standard medical management was brief, manual-guided, medically focused counseling; enhanced management was similar, but each session was extended. The primary outcomes were the self-reported frequency of illicit opioid use, the percentage of opioid-negative urine specimens, and the maximum number of consecutive weeks of abstinence from illicit opioids. It was found that the three treatments had similar efficacies with respect to the mean percentage of opioid-negative urine specimens (standard medical management and once-weekly medication dispensing, 44 percent; standard medical management and thrice-weekly medication dispensing, 40 percent; and enhanced medical management and thrice-weekly medication dispensing, 40 percent; P=0.82) and the maximum number of consecutive weeks during which patients were abstinent from illicit opioids. All three treatments were associated with significant reductions from baseline in the frequency of illicit opioid use, but there were no significant differences among the treatments. The proportion of patients remaining in the study at 24 weeks did not differ significantly among the patients receiving standard medical management and once-weekly medication dispensing (48 percent) or thrice-weekly medication dispensing (43 percent) or enhanced medical management and thrice-weekly medication dispensing (39 percent) (P=0.64). Adherence to buprenorphine-naloxone treatment varied; increased adherence was associated with improved treatment outcomes. Therefore, among patients receiving buprenorphine-naloxone in primary care for opioid dependence, the efficacy of brief weekly counseling and once-weekly medication dispensing did not differ significantly from that of extended weekly counseling and thrice-weekly dispensing. This study also has implications for clinical care and research. The fact that many patients can receive efficacious care in a primary care, office-based setting with weekly brief counseling and medication dispensing is important. The recent finding that the availability of buprenorphine-naloxone attracts new patients to treatment for addiction provides support for federal efforts to expand access to the treatment. The findings also show that supervised nurses can provide appropriate counseling. The finding of ongoing cocaine use among patients treated for opioid dependence is consistent with findings among patients

receiving methadone maintenance and supports efforts to monitor and address this coexisting disorder. Finally, the variability in buprenorphine-naloxone adherence highlights the need both to measure adherence in future research and to monitor and encourage adherence in practice in order to reduce the potential misuse of the medication and to improve the treatment outcomes. Strategies to improve buprenorphine-naloxone adherence are needed. Fiellin, D., Pantalon, M., Chawarski, M., Moore, B., Sullivan, L., O 'Connor, P., and Schottenfeld, R. Counseling Plus Buprenorphine-Naloxone Maintenance Therapy for Opioid Dependence. N Engl J Med, 355(4), pp. 365-374, 2006.

Training Primary Care Clinicians in Maintenance Care for Moderated Alcohol Use

Despite belief in a responsibility to help their patients with alcohol problems, primary care physicians are often hesitant to accept responsibility for the management of these disorders. The authors goal in this study was to evaluate whether training primary care clinicians in maintenance care for patients who have changed (reduced) their drinking, will influence the provider behavior in the medical practice. The study randomized 15 physicians and 3 mid-level clinicians in 2 primary care offices in a 2:1 design. The 12 intervention clinicians received a total of 2 (1/4) hours of training in the maintenance care of alcohol problems in remission, a booster session, study materials and chart-based prompts at eligible patients' visits. Six controls provided usual care. Screening forms in the waiting rooms identified eligible patients, defined as those who endorsed: 1 or more items on the CAGE questionnaire or that they had an alcohol problem in the past; that they have "made a change in their drinking and are trying to keep it that way"; and that they drank <15 (men) or <10 (women) drinks per week in the past month. Exit interviews with patients evaluated the clinician's actions during the visit. Of the 164 patients, 62% saw intervention clinicians. Compared with patients of control clinicians, intervention patients were more likely to report that their clinician asked about their alcohol history (odds ratio, 2.8; 95% confidence interval, 1.3, 5.8). Intervention clinicians who asked about the alcohol history were more likely to assess prior and planned alcohol treatment, assist through offers for prescriptions and treatment referral, and receive higher satisfaction ratings for the visit. This pilot study suggests that training, and chart based prompting, can increase by nearly 3-fold the likelihood that clinicians will inquire about the alcohol history with patients who have changed their drinking behavior. The magnitude of these findings is similar to that of a primary care study of brief counseling for patients with current hazardous drinking. Systemic prompts and training in the maintenance care of alcohol use disorders in remission might increase primary care clinicians' inquiries about the alcohol history as well as appropriate assessment and intervention after an initial inquiry. Friedmann, P., Rose, J., Hayaki, J., Ramsey, S., Charuvastra, A., Dube, C., Herman, D., and Stein, M. Training Primary Care Clinicians in Maintenance Care for Moderated Alcohol Use. J Gen Intern Med, 21, pp. 1-7, 2006.

Welfare Reform, Employment, and Alcohol and Drug Use among Low-Income Women

In 1996 welfare reform legislation transformed income assistance for needy families by imposing work requirements, time-limited benefits, and explicit provisions allowing states to sanction recipients who fail to meet program requirements. Though they represent a minority of the welfare population, women with substance use disorders (SUDs) experience multiple, and more severe, employment barriers than other Temporary Assistance to Needy Families (TANF) recipients. This review of welfare reform, substance abuse, and employment documents the evidence to date regarding the employment patterns of women with SUDs before and after welfare reform, and proposes several topics for further research. Based on higher rates of unemployment,

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less work experience, and lower earnings when working, women with SUDs have worse employment records than other TANF recipients. Despite elevated employment barriers, women with SUDs left TANF after 1996 as fast as, or faster than, other women. Since the 1996 welfare reform, women with SUDs have increased their employment and earnings, but by less than similar women without SUDs. Future research should describe how specific state welfare policies relate to employment of low-income women with SUDs, how the well-being of these women and their children changes with employment, and how welfare and employment interact to affect access to health insurance among this population. Meara, E. Welfare Reform, Employment, and Drug and Alcohol Use Among Low-Income Women. Harv Rev Psychiatry, 14(4), pp. 223-232, 2006.

Negative Reinforcement: A Behavioral Paradigm to Inform Services Research in the Criminal Justice System

This article is part of a series of conceptual papers examining a proposal to offer depot naltrexone to certain nonviolent opiate-addicted criminal offenders in exchange for release from incarceration or diversion from prosecution. Operant conditioning paradigms of behavioral change suggest the application of negative-reinforcement has a better chance of impacting offender drug use and associated criminal activity than what has heretofore been attempted with drug-abusing offenders. Traditional correctional efforts have been largely unsuccessful due to the complexities of implementation and the side effects of punishment. Although positive reinforcement can be more efficacious, it has often been strenuously resisted on the ground that it is inequitable to reward antisocial individuals for doing what is minimally expected of most citizens. Negative reinforcement steers between these hurdles by avoiding the iatrogenic effects of punishment, while also being palatable to stakeholders. More research is needed to identify the effects, costs, and side effects of negative-reinforcement arrangements for drug offenders. The current proposal provides an excellent platform for conducting this research because the target intervention (depot naltrexone) is demonstrably efficacious, nonpsychoactive, and has few, if any, side effects. Therefore, use of this medication would be unlikely to invoke the same types of legal and ethical objections that have traditionally been levied against the use of psychoactive medications with vulnerable populations of institutionalized offenders. Specific recommendations are offered for questions that must be addressed in future research studies. Marlowe, D. Depot Naltrexone in Lieu of Incarceration: a Behavioral Analysis of Coerced Treatment for Addicted Offenders. J Subst Abuse Treat, 31(2), pp. 131-139, 2006.

Private As Opposed to Public Sector Providers Differ in Ways that Affect Types of Patients Treated, As Well As Therapeutic and Business Practices

As an organizational field, substance abuse treatment clearly includes a remarkable range of organizations. This study summarizes findings from an ongoing research program by examining the organizational structure, service delivery, and patterns of innovation adoption in two large samples of substance abuse treatment programs in the United States (N= 403 private- and 363 publicly-funded). Among highlighted findings, there are notable differences between the public and private sectors in structural and staffing characteristics, as well as in the characteristics of clients receiving substance abuse treatment. With regard to the use of evidence-based practices, findings suggest that pharmacotherapies are more likely to be adopted in private centers, whereas notably effective voucher approaches are more common in public centers. Also found was that private treatment centers had stronger financial performance when they were embedded within larger organizations yet maintained decentralization with regard to their staff; private centers were more likely to

treat co-morbid patients (65% vs 50%) and patients with other addictions (eating & gambling); whereas public centers more often helped patients with transportation to care (71% vs 53%). Roman, P.M., Ducharme, L.J., and Knudsen, H.K. Patterns of Organization and Management in Private and Public Substance Abuse Treatment Programs. J Subst Abuse Treat, 31(3), pp. 235-243, 2006.

Health Literacy: Depression, Mental Health, Quality Adjusted Life Years and Addictions

The researchers hypothesized that low literacy would be associated with higher addiction severity, higher levels of depressive symptoms, and worse mental health functioning compared with those with higher literacy in adults with alcohol and drug dependence. The association of literacy with multiple mental health outcomes was assessed using multivariable analyses. Measurement instruments included the Rapid Estimate of Adult Literacy in Medicine (REALM), the Center for Epidemiologic Studies-Depression (CES-D) scale, the Mental Component Summary scale of the Short Form Health Survey, and the Addiction Severity Index for drug and alcohol addiction. Subjects included 380 adults recruited during detoxification treatment and followed prospectively at 6-month intervals for 2 years. Based on the REALM, subjects were classified as having either low (< or = 8th grade) or higher (> or = 9th grade) literacy levels. In longitudinal analyses, low literacy was associated with more depressive symptoms. The adjusted mean difference in CES-D scores between low and high literacy levels was 4 ($P<.01$). Literacy was not significantly associated with mental health-related quality of life or addiction severity. In people with alcohol and drug dependence, low literacy is associated with worse depressive symptoms. The mechanisms underlying the relationship between literacy and mental health outcomes should be explored to inform future intervention efforts. Lincoln, A., Paasche-Orlow, M., Cheng, D., Lloyd-Travaglini, C., Caruso, C., Saitz, R., and Samet, J. Impact of Health Literacy on Depressive Symptoms and Mental Health-Related: Quality of Life Among Adults with Addiction. J Gen Intern Med, 21(8), pp. 818-822, 2006.

Adoption of Buprenorphine for Addiction Treatment is More Common Among Accredited Service Providers that Include Physician Services and Detoxification

The recent approval of buprenorphine for the treatment of opiate dependence offers an opportunity to analyze innovation adoption in community-based treatment. Using data collected from national samples of 299 privately funded and 277 publicly funded treatment centers, research examined buprenorphine adoption using baseline data collected between 2002 and 2004 as well as follow-up data collected 12 months later. Private centers were significantly more likely than public centers to report current use of buprenorphine. The baseline data indicated that early adoption was positively associated with center accreditation, physician services, availability of detoxification services, current use of naltrexone, and the percentage of opiate-dependent clients. Multivariate analyses of follow-up data suggest that adoption was greater in accredited centers, for-profit facilities, organizations offering detoxification services, and naltrexone-using centers. Future research should continue to monitor the extent to which buprenorphine is adopted in these settings. Knudsen, H.K., Ducharme, L.J., and Roman, P.M. Early Adoption of Buprenorphine in Substance Abuse Treatment Centers: Data from the Private and Public Sectors. J Subst Abuse Treat, 30, pp. 363-373, 2006.

Retention in Methadone Treatment is Highest for Patients Receiving Both Case Management and Voucher Reinforcement

A clinical trial contrasted two interventions designed to link opioid-dependent hospital patients to drug abuse treatment. The 126 out-of-treatment participants were randomly assigned to (a) case management, (b) voucher for free methadone maintenance treatment (MMT), (c) case management plus voucher, or (d) usual care. Participants were heroin dependent, 75% male, between 18 and 65 years of age, were receiving medical treatment at San Francisco General Hospital (inpatient or outpatient), were eligible fore methadone treatment under California law, and had at least two prior treatment failures. Services were provided for 6 months. MMT enrollment at 3 months was 47% (case management), 89% (voucher), 93% (case management plus voucher), and 11% (usual care); at 6 months enrollment was 48%, 68%, 79%, and 21%, respectively. Case management and vouchers can be valuable in health settings to link substance abusers with medical problems to drug abuse treatment. Sorensen, J.M., Barnett, P.G., Mitsuishi, F., Lin, C., Song, Y., Chen, T., Hall, S.M., and Mason, C.L. Randomized Trial of Drug Abuse Treatment-Linkage Strategies. J Consult Clin Psychol, 73(6), pp. 1026-1035, 2006.

Attitudes Towards Spending for Drug Rehabilitation

Although a large body of literature clearly demonstrates the clinical and economic benefits of addiction treatment for many clients and in most settings, the general public has a somewhat ambivalent attitude toward treatment expansion and taxpayer financing. This study uses data from the General Social Survey (GSS), a nationally representative repeated cross-section survey of the English-speaking U.S. adult population (aged 18 years and older) living in noninstitutionalized settings, to examine trends in attitudes towards spending on drug rehabilitation between 1984 and 2004. Analyses were conducted on N=11,094, respondents which represents 84.9% of all those eligible. Respondents were asked whether they believed the country spent too little, about the right amount, or too much on drug rehabilitation. Averaging across the years, 57.6 % of respondents said the country spent too little 32.1% said about right, and 10.3% too much on drug rehabilitation, although public support for more spending has been declining in recent years. Age, gender, marital status, education, religion, and political affiliation all were associated with attitudes. The authors describe a comprehensive social strategy to translate public opinion and the knowledge base on substance abuse treatment into political will and policy. French, M., Homer, J., and Nielsen, A. Does America Spend Enough on Addiction Treatment? Results From Public Opinion Surveys. J Subst Abuse Treat, 31(3), pp. 245-254, 2006.

High-Cost Health Services Utilization Among Drug Using Prisoners Re-entering Community

The use of health services by prisoners during their incarceration and after their return to the community impacts the U.S. health care system and health care costs associated with this system. These health care costs are expected to increase over the next decade as more prisoners return to their communities. The current study prospectively examined the use of high-cost health care services-emergency room visits and hospitalizations-among 565 male drug-abusing prisoners one year after prison release. A series of structural equation models were used to examine predisposing factors, including health status and drug use, and to estimate the frequency of high-cost health service utilization. As expected, health status was the most robust predictor of high-cost health services. However, the finding that drug abuse had nonsignificant relationships with high-cost health services utilization was not expected. Leukefeld, C., Hiller, M., Webster, J., Tindall, M., Martin, S., Duvall, J., Tolbert, V., and Garrity, T. A Prospective Examination of High-Cost Health Services Utilization Among Drug Using Prisoners Reentering the Community. J Behav Health Serv Res, 33(1), pp. 73-85, 2006.

Few Racial Differences Were Found on Most Health Indicators for Cocaine-abusing Veterans

Racial minorities generally exhibit worse health status than do whites. To assess the presence of similar phenomena among long-term cocaine-using veterans, this study examined racial variations in mortality and health status among cocaine-dependent men who were originally recruited at their admissions to cocaine treatment in 1988-1989 and were interviewed approximately 12 years later in 2002-2003. Mortality was higher among whites (15%) than blacks (6%), particularly due to drug overdose. Controlling for socioeconomic factors, cocaine severity, and depression, the racial difference was still significant in the survival analysis. Racial differences were examined in the health status of those interviewed in the 12-year follow-up study (178 blacks and 65 whites), after confirmation of their comparable socioeconomic backgrounds and levels of healthcare access and utilization. Contrary to expectations, few racial differences were found on most health indicators, although the level of cocaine use was higher among blacks. Furthermore, fewer blacks reported having hepatitis or sexually transmitted diseases than did whites. The study results suggest that black cocaine-dependent veterans do not have worse health status when compared with white veterans on most health indicators. Yang, J. C., Huang, D., and Hser, Y. Long-Term Morbidity and Mortality among a Sample of Cocaine-Dependent Black and White Veterans . J Urban Health, 83(5), pp. 926-940, 2006.

Organizational and Management Factors Influence Use of EBPs

This study overviews data from several national longitudinal studies (N > 1000 clinics) of substance abuse treatment practices conducted by the University of Chicago and the University of Michigan via the National Drug Abuse Treatment System Survey to develop an understanding as to why there exists a seemingly wide gap between research and practice in the field of substance abuse treatment. Data collected in the 1980s reported marked reductions in the nature and number of primary health care, mental health care, and social services provided within substance abuse treatment. Data colleted in the 1990s indicate that reductions have stopped, yet 2005 data show services remain below 1980-s levels. Several organizational characteristics are related to the availability of health care, mental health, and social services. For example, clinics affiliated with hospitals and mental health centers are significantly more likely to have medical care (physical exams and routine primary care) and mental health services available for clients. Organizational characteristics also affect therapeutic practices. Clinics that treat higher percentages of African American clients are more likely to provide methadone doses that are too low tobe effective. Clinics with JCAHO accreditation were more likely to provide higher methadone doses. The 2005 NDATSS sample showed that clinics whose directors held a strong 12-step orientation but weak support for HIV prevention practice were more likely to give low doses. Finally, methadone clinics with managed care arrangements requiring prior authorization for treatment also provided lower doses. D'Aunno, T. The Role of Organization and Management in Substance Abuse Treatment: Review and Roadmap. J Subst Abuse Treat, 31(3), pp. 221-233, 2006.

ED and Hopsital Utilization Among Alcohol and Drug Dependent Detox

Utilization of emergency department (ED) services and hospitalization among a cohort of substance abusers are described based on structured research interviews with 470 adults without primary care admitted to an urban residential detoxification program. Cross-sectional analysis of baseline data of

subjects found nearly 19% of subjects went to an ED on 2 or more occasions in the 6 months prior to detoxification and 14% were admitted for an overnight hospitalization. Upon further analysis of past 6-month ED utilization, the following factors were independently associated with increased odds of ED use: White race; at least one month homeless in the past 5 years; chronic health condition; injury in past 6 months; and subject perception that their substance abuse interfered with seeking care from a regular doctor. Subjects with cocaine as a primary problem had lower odds of ED utilization than a reference group with alcohol as a primary problem. Access to primary care is apparently needed to lower ED and hospital utilization episodes. Larson, M., Saitz, R., Horton, N., Lloyd-Travaglini, C., and Samet, J. Emergency Department and Hospital Utilization Among Alcohol and Drug-Dependent Detoxification Patients Without Primary Medical Care. Am J Drug Alcohol Abuse, 32(3), pp. 435-452, 2006.

HIV-specific Health Maintenance in Middle Aged and Older Patients

Given the increased prevalence of HIV infection in older individuals, the investigators evaluated the adequacy of HIV-specific health maintenance, age-appropriate cancer screening, and diabetes management in an urban HIV clinic. They randomly selected 222 HIV-positive patients 40 years or older followed at the Johns Hopkins University Moore Clinic between 1999 and 2002. Demographic, clinical, and pharmaceutical data were abstracted from clinic charts. Outcomes of interest were vaccinations, annual rapid plasmin reagin (RPR) testing, and Papanicoloau smears and mammography in women. Logistic regression analyses were performed to identify variables significantly associated with being up to date on vaccinations. The sample was 56% female and 82% African American with a mean age of 50.9 years. Sixty-five percent used tobacco, 10% used alcohol, and 13% used illicit drugs daily. At the time of evaluation, 87% had received the pneumococcal vaccine. Of nonimmune patients, 66% were vaccinated for hepatitis B and 28% for hepatitis A. Eighty-two percent of women were referred for Papanicoloau smears and 56% for mammography. Only 59% completed the Papanicoloau smear, and 31% had mammography. Forty-two percent of patients with diabetes underwent quarterly foot examinations, and 33% had microalbuminuria screening. Risk factors for missed vaccinations include prior AIDS diagnosis (odds ratio [OR] 1.82, 95% confidence interval [CI] 1.55, 3.13), CD4+ cell count less than 50 cells/mm(3) at the time of visit (OR 6.31, 95% CI 1.74, 22.9), and a history of chronic obstructive pulmonary disease (COPD) or asthma (OR 2.54, 95% CI 1.03, 6.28). In summary, HIV-positive patients are more likely to receive HIV-specific primary care interventions, especially vaccinations that can be given in clinic, than routine health maintenance screening that required referral and evaluation elsewhere. This suggests that if health maintenance screening can be delivered in the same clinic, usage rates are likely to increase. Sheth, A., Moore, R., and Gebo, K.. Provision of General and HIV-Specific Health Maintenance in Middle Aged and Older Patients in an Urban HIV Clinic. AIDS Patient Care STDS, 20(5), pp. 318-325, 2006.

Mental Health Problems and Criminal Justice Involvement Among Female Street-Based Sex Workers

This paper examines the connections of mental health, victimization, and criminal justice involvement among a sample of 343 street-based female sex workers in Miami, Florida. Using targeted sampling strategies, drug-using sex workers were recruited into an HIV prevention intervention and research program. Data were collected by trained interviewers using standardized questionnaires that focused on drug use, childhood abuse, recent victimization, mental health, and criminal justice involvement. More than half of the participants reported histories of physical (54.5%) or sexual (54.2%) abuse as children, and more than one-third reported violent victimization in the past

year. Nearly 32% were classified with moderate or severe anxiety symptoms, 46.2% had symptoms of moderate or severe depression, and 64.6% had symptoms of acute traumatic stress. In addition, 81.9% had prior arrest histories. The intersection of these factors suggests that police and law enforcement agencies must play a substantial role in managing an offender population with impaired mental health functioning. The policy implications of these findings are discussed. Surratt, H. Mental Health Problems and Criminal Justice Involvement Among Female Street-Based Sex Workers. Law Enforcement Executive Forum, 6, pp. 121-134, 2006.

Validation of a New Screener for Pain Patients at Risk of Opioid Addiction

The Screener and Opioid Assessment for Patients with Pain (SOAPP) is a brief, self-administered screening instrument used to assess suitability of long-term opioid therapy for chronic pain patients. This study examined the reliability and validity of the SOAPP as a measure of risk of opioid abuse for patients on opioid medication. Patients taking opioids for noncancer pain (N=396) from two pain centers completed the SOAPP prior to being placed on opioids for pain. Demographic data, SOAPP scores, and results of urine toxicology screens from the patients' medical records were examined. Patients were divided into two groups of high and low risk of opioid abuse potential based on cutoff scores of 8 and higher on the SOAPP. Results showed that patients in the high-risk group were younger, more likely to be asked to give a urine screen, and had more abnormal urine screens compared with those in the low-risk group ($P < 0.05$). A combined factor analysis of the SOAPP revealed five factors labeled 1) history of substance abuse, 2) legal problems, 3) craving medication, 4) heavy smoking, and 5) mood swings. Preliminary support was found for the internal reliability and predictive validity of the SOAPP. Akbik, H., Butler, S.F., Budman, S.H., Fernandez, K., Katz, N.P., and Jamison, R.N. Validation and Clinical Application of the Screener and Opioid Assessment for Patients with Pain (SOAPP). Journal of Pain & Symptom Management, 32(3), pp. 287-293, 2006.

Validation of the ASI to Screen for Mental Disorders Among Drug Abusers

This study, used data from the Drug Evaluation Network System and a study conducted through the Center for Studies on Addiction of the University of Pennsylvania/Philadelphia Veterans Administration Medical Center (N=2,813) to determine the potential of the Addiction Severity Index (ASI) to serve as a screening instrument for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) substance dependence. A significant positive correlation was found between ASI composite scores (CSs) and DSM-IV diagnoses of dependence in both the alcohol ($r = .7$) and drug ($r = .5$) domains ($p < .01$). Receiver operating characteristic analyses were run to predict DSM-IV alcohol and drug dependence diagnoses from the respective ASI CSs. Results showed good to strong prediction; ASI CSs identified dependent clients with approximately 85% sensitivity and 80% specificity. Rikoon, S.H., Cacciola, J.S., Carise, D., Alterman, A.I., and McLellan, A.T. Predicting DSM-IV Dependence Diagnoses from Addiction Severity Index Composite Scores. J Subst Abuse Treat, 31(1), pp. 17-24, 2006.

Racial Differences in Marijuana-users Risk of Arrest in the United States

A recent study of arrest data shows that African Americans are 2.5 times more likely to be arrested for marijuana possession offences than Whites, even though general prevalence estimates show that they are no more likely to be using. The current study investigates the purchase patterns of marijuana users

from the 2002 National Survey on Drug Use and Health (NSDUH) to evaluate whether differences in purchasing behaviors exist across racial groups. Although in general people who purchase marijuana are more likely to buy in private settings and from someone they know, this analysis shows that African Americans are statistically more likely to engage in risky purchasing behaviors that increase their likelihood of arrest. Using trivariate probit regression with demographic, drug use, and drug market covariates, analyses reveal that African Americans are nearly twice as likely to buy outdoors (0.31 versus 0.14), three times more likely to buy from a stranger (0.30 versus 0.09), and significantly more likely to buy away from their homes (0.61 versus 0.48). These results provide an additional explanation for the differential in arrest rates between African Americans and Whites. Ramchand, R., Pacula, R., and Iguchi, M. Racial Differences in Marijuana-Users ' Risk of Arrest in the United States. Drug Alcohol Depend, 84(3), pp. 264-272, 2006.

Factor Structure of the Comprehensive Severity Inventory (CASI)

This article describes the results of psychometric work conducted on the Comprehensive Adolescent Severity Inventory (CASI) among 205 in-treatment substance-abusing adolescents. Four dimensions, each composed of component subscales, resulted from standard psychometric analyses: Chemical Dependency, Psychosocial Functioning, Delinquency, and Risk Behavior. Each dimension had high internal consistency (alpha coefficients for the component subscales comprising each clinical dimension range from .78 to .96) and test-retest reliability (intraclass correlation coefficients range from .88 to .96 and all are significant at $p < .0001$.). Concurrent validity and specificity of the CASI dimensions also were found: significant and substantial variance in NIMH Diagnostic Interview Schedule for Children-Revised (DISC-IV) and Brief Symptom Inventory (BSI) scores was associated with relevant CASI dimensions; CASI dimensions that theoretically should show no significant relationship with divergent pathology were not associated. The dimensions forecasted substantial variance in adolescent functioning post treatment discharge, supporting predictive validity. Finally, the dimensional clinical structure was found to be generalizable over male and female adolescents, younger and older adolescents, and adolescents from different ethnic groups. These results provide further evidence for the CASI's promise in research and practice as an adolescent-specific assessment instrument that comprehensively assesses multidimensional areas of functioning within a developmental context of measurement. Meyers, K., Hagan, T., McDermott, P., Webb, A., Randall, M., and Frantz, J. Factor Structure of the Comprehensive Adolescent Severity Inventory (CASI): Results of Reliability, Validity, and Generalizability Analyses. Am J Drug Alcohol Abuse, 32(3), pp. 287-310, 2006.

Co-morbid "Spill Over" Among Cocaine-dependent Homeless Persons

Data from an addiction treatment trial for 95 cocaine-dependent homeless persons (1996-1998) were used to profile psychiatric diagnoses at baseline and 6 months, including mood-related disorders (e.g. depression) and anxiety-related disorders (e.g. post-traumatic stress disorder). Treatment interventions, including systematic reinforcement for goal attainment, were behavioral in orientation. There was a 32% reduction in the prevalence of comorbid nonaddiction psychiatric disorder from baseline to 6 months, with similar reductions in the prevalence of mood (-32%) and anxiety-related disorders (-20%) ($p=0.12$). Among cocaine-dependent homeless persons with psychiatric comorbidity undergoing behavioral addiction treatment, a reduction in comorbid psychiatric disorder prevalence was observed over 6 months. Not all participants improved, suggesting that even evidence-based behavioral addiction treatment will prove insufficient for a meaningful proportion of the dually diagnosed homeless population. Kertesz, S. G., Madan, A., Wallace, D.,

Schumacher, J.E., and Milby, J.B. Substance Abuse Treatment and Psychiatric Comorbidity: Do Benefits Spill Over? Analysis of Data from a Prospective Trial Among Cocaine-Dependent Homeless Persons. Subst Abuse Treat Prev Policy, 1(1), pp. 27-27, 2006.

Biometric Measures were Frequently Less Sensitive to the Severity of Other Problems

This study examined the need, feasibility, and validity of combining two biometric (urine and saliva) and three self-report (recency, peak quantity, and frequency) measures of substance use for marijuana, cocaine, opioids, and other substances (including alcohol and other drugs). Using data from 337 adults with substance dependence, the investigators used structural equation modeling to demonstrate that these multiple measures are driven by the same underlying factor (substance use) and that no single measure is without error. Individual measures and several possible combinations of them (including one based on the latent factors and another based on the Global Appraisal of Individual Needs (GAIN) Substance Frequency Scale) were compared to examine how well each predicted a wide range of substance-related problems. The measure with the highest construct validity in these analyses varied by drug and problem. Despite their advantages for detection, biometric measures were frequently less sensitive to the severity of other problems. Composite measures based on the substance-specific latent factors performed better than simple combinations of the biometric and psychometric measures. The Substance Frequency Scale from the GAIN performed as well as or better than all measures across problem areas, including the latent factor for any use. While the research was limited in some ways, it has important implications for the ongoing debate about the proper way to combine biometric and psychometric data. Lennox, R., Dennis, M.L., Scott, C.K., and Funk, R. Combining Psychometric and Biometric Measures of Substance Use. Drug Alcohol Depend, 83, pp. 95-108, 2006.

Organizational Characteristics are Associated with Providing Psychiatric Care for Co-morbid Substance Abuse Patients

This study examines the prevalence and key correlates of the availability of integrated care for co-occurring conditions within public and private-sector addiction treatment programs (N>400 private and >360 public). Overall, 57.5% of centers offered concurrent or co-located care for co-occurring psychiatric disorders. These tend to be larger, accredited, hospital affiliated, high percentages of adolescent patients, and which offer psychiatric services to non substance abusing patients. Private/public support did not distinguish centers that provided care for co-occurring disorders in this study. Ducharme, L.J., Knudsen, H.K., and Roman, P.M. Availability of Integrated Care for Co-occurring Substance Abuse and Psychiatric Conditions. Community Ment Health J, 42(4), pp. 363-375, 2006.

Patterns of Hepatitis-C Service Provision in Drug-Free Treatment Programs

Hepatitis C virus (HCV) infection is a global health problem, and in many countries (including the U.S.), illicit drug users constitute the group at greatest risk for contracting and transmitting HCV. Drug treatment programs are therefore unique sites of opportunity for providing medical care and support for many HCV infected individuals. This paper determines subtypes of a large sample of U.S. drug-free treatment programs (N=333) according to services they provide to patients with HCV infection, and examines the organizational and aggregate patient characteristics of programs in these subtypes. A latent class analysis identified four subtypes of HCV service provision: a "Most

Comprehensive Services" class (13% of the sample), a "Comprehensive Off-Site Medical Services" class (54%), a "Medical Monitoring Services" class (8%) and a "Minimal Services" class (25%). "Comprehensive" services class programs were less likely to be outpatient and private for profit than those in the other two classes. It is of concern that so many programs belong to the "Minimal Services" class, especially because some of these programs serve many injection drug users. "Minimal Services" class programs in the U.S. need to innovate services so that their HCV infected patients can get the medical and support care they need. Similar analyses in other countries can inform their policy makers about the capacity of their drug treatment programs to provide support to their HCV infected patients. Strauss, S., Rindskopf, D., Astone-Twerell, J., Des Jarlais, D., and Hagan, H. Using Latent Class Analysis to Identify Patterns of Hepatitis C Service Provision in Drug-Free Treatment Programs in the U.S. Drug Alcohol Depend, 83(1), pp. 15-24, 2006.

Nicotine Replacement Therapy: Patterns of Use After a Quit Attempt Among Methadone-Maintained Smokers

This is the first study offering a detailed description of the use of transdermal nicotine replacement and its relationship with daily cigarette smoking in a population of heavy smokers. The authors also determined predictors of greater NRT use among methadone-maintained smokers. Three hundred and eighty three methadone-maintained smokers from 5 methadone maintenance centers enrolled in this 2 arm RCT, where assignment was either to a group given free nicotine patches (8 to 12 weeks) plus either (1) a baseline-tailored brief motivational intervention, a quit date behavioral skills counseling session, and a relapse prevention follow-up session (max), or (2) brief advice using NCI's 4 A's model (min). Of the study participants; 309 (80.6%) set a specific quit date (received NRT) and were located for assessments. Participants were 51.8% male, 78.6% Caucasian, and smoked 26.6 (SD=12.2) cigarettes/day. The outcome measured was the use of NRT and smoking behaviors during the 180-day follow-up period assessed by the Timeline follow-back method. On the day following their quit day, 86.4% of participants used NRT. The percentage of participants using NRT was 52.3%, 27.1%, and 10.4% on day 30, day 60, and day 90, respectively. Participants used NRT on 44.1% of the days through the 90 days of the treatment protocol. The estimated odds of smoking abstinence was 7.1 ($P<.001$) times higher on days when NRT was used than on days when NRT was not used, and cigarettes/day was also significantly lower on NRT days (14.93 vs. 4.65; $P<.001$). Despite being given free NRT and counseling, participants who set quit dates used NRT on only 44% of treatment period days. It is therefore apparent that nicotine replacement therapy use was inconsistent following an initial quit attempt among methadone-maintained smokers. However, on days when NRT was used, individuals were likely to smoke at reduced levels or not at all. Reasons for inconsistent patch use were postulated by the authors; and a greater understanding of expectancies and the reasons for nonadherence with NRT use is felt to be necessary to promote optimal pharmacological care and improve smoking cessation outcomes. Stein, M., Anderson, B., and Niaura, R. Nicotine Replacement Therapy: Patterns of Use After a Quit Attempt Among Methadone-Maintained Smokers. J Gen Intern Med, 21(7), pp. 753-757, 2006.

Blood Pressure Levels May Vary in Population because of Genetic, Ethnic and Body Size Factors

Blood pressure data of 2278 Indian boys and 2930 Indian girls in the age group of 3-18 years were analyzed to study the distribution pattern of systolic blood pressure and diastolic blood pressure and to develop reference values to define hypertension. Blood pressure was measured using standardized techniques in all. The first and fifth phases of Korotkoff sounds were taken as indicative of systolic blood pressure and diastolic blood pressure respectively. Height

percentiles were computed for each one-year age group. According to percentiles of height 50th, 90th, 95th and 99th percentiles of systolic blood pressure and diastolic blood pressure were estimated for every one-year age. Results indicated that the blood pressure (both systolic and diastolic) tends to increase with age. The stepwise regression analysis revealed that the age and height but not gender, are important determinants of blood pressure. Age and height specific, 50th, 90th and 95th and 99th percentiles of systolic and diastolic blood pressure were derived and are presented in tabular form. Authors concluded that the blood pressure of children and adolescents can be evaluated using the reference table according to body size. The table provided helps to classify blood pressure as 'normal' or 'pre hypertension' and to define different stages of 'hypertension'. Pushpa, K., KumanPrasanna, K.M., Nagaraj, D., and Thennarasu, K. Blood Pressure Reference Tables for Children and Adolescents of Karnataka. Indian Pediatrics, 43 (June), pp. 491-501, 2006.

New Challenges and Opportunities in Managing Substance Abuse in Malaysia

Prior to mid-year 2005, the portfolio for drug addiction treatment was under the Ministry of Internal Security, which emphasized long-term incarceration and drug-free after-care as the primary approach. This approach has been viewed a failure, and Malaysia has lagged behind in the treatment of drug addiction and related disorders, despite experiencing severe drug problems. For example, by the end of 2004, 234,000 heroin users or heroin-dependent individuals had been registered in the official government registry out of 24 million persons. However, other estimates exceed 500,000 for heroin abusers in this population. Because of this situation, the Prime Minister instructed the national narcotic agency to review its existing policy on treatment of drug addiction, and as a result, the Ministry of Health now has authority for providing medical treatment for heroin dependence. This shift signals a remarkable change in Malaysian policies and approaches to addiction and an important opportunity to develop, implement and disseminate effective treatments. Amphetamine-type stimulant abuse is also increasing and of considerable public and government concern. Among the population of drug users, HIV and other infectious diseases rates are very high. In the Western Pacific regions, Malaysia has the second highest HIV prevalence (after Vietnam) among adult populations (0.62%) and the highest proportion of HIV cases resulting from injection drug use (76.3%). Drug use and related disorders exert a heavy burden on the country's health care and legal systems. Naltrexone was introduced in 1999; buprenorphine was introduced in 2001 and methadone in 2003. Agonist maintenance programs were embraced rapidly by the medical community in Malaysia. Currently, over 30,000 opiate-dependent patients are treated with agonist maintenance treatments by more than 500 medical practitioners in Malaysia. Despite these recent advances, treatments for amphetamine-type stimulant abuse or dependence are underdeveloped, and diversion of agonist medications is an emerging concern. Malaysia is addressing these problems, continues to improve treatment for heroin dependence, and act as a model for other countries in the region. Mazlan, M., Schottenfeld, R., and Chawarski, M. New Challenges and Opportunities in Managing Substance Abuse in Malaysia. Drug Alcohol Rev, 25(5), pp. 473-478, 2006.

Organizational Characteristics of Italian Substance Abuse Clinics Found to be Similar to Those in the USA

The Texas Christian University (TCU) organizational functioning and readiness for change instrument (ORC) was translated into Italian and administered to 405 substance abuse treatment program directors and staff from both public and private sectors in the Veneto Region of Northern Italy. Results indicated that the psychometric properties of the ORC in the USA and Italy are

consistent. Some general differences in staff attributes were found between USA and Italian programs with US staff having more training but fewer resources such as internet and email access than Italian staff. However, organizational climates were found to be remarkably similar. Rampazzo, L., De Angeli, M., Serpelloni, G., Simpson, D.D., and Flynn, P. M. Italian Survey of Organizational Functioning and Readiness for Change: A Cross-Cultural Transfer of Treatment Assessment Strategies. European Addiction Research, 12, pp. 176-181, 2006.

Director's Report to the National Advisory Council on Drug Abuse - February, 2007

Clinical Trials Network Research

Contingency Management for the Treatment of Methamphetamine Use Disorders

This article was featured on the In This Issue page of the American Journal of Psychiatry and a news release was issued by NIDA. Theory and some preliminary evidence suggest that contingency management may be an effective treatment strategy or adjunct to psychosocial treatment for methamphetamine use disorders. An experimentally rigorous investigation on the topic was provided by a large multisite trial conducted under the auspices of the Clinical Trials Network of the National Institute on Drug Abuse. The authors report data on 113 participants who were diagnosed with methamphetamine abuse or dependence. They were randomly assigned to receive 12 weeks of either treatment as usual or treatment as usual plus contingency management. Urine samples were tested for illicit drugs, and breath samples were tested for alcohol. The reinforcers for drug-negative samples were plastic chips, some of which could be exchanged for prizes. The number of plastic chips drawn increased with each week of negative samples but was reset to one after a missed or positive sample. The participants in both groups remained in treatment for equivalent times, but those receiving contingency management in addition to usual treatment submitted significantly more negative samples, and they were abstinent for a longer period of time (5 versus 3 weeks). These results suggest that contingency management has promise as a component in treatment strategies for methamphetamine use disorder. Roll, J.M., Petry, N.M., Stitzer, M.L., Brecht, M.L., Peirce, J.M., McCann, M.J., Blaine, J., Macdonald, M., Dimaria, J., Lucero, L., and Kellogg, S. Contingency Management for the Treatment of Methamphetamine Use Disorders. Am J Psychiatry 163(11), pp. 1993-1999, November 2006.

Director's Report to the National Advisory Council on Drug Abuse - February, 2007

Research Findings - International Research

NIDA-Supported Researchers Identify New Injection Practice Among Tanzanian Women

Dr. Mark Williams, University of Texas at Houston and colleagues (Dr. Sheryl McCurdy, University of Texas at Houston; Dr. Gad P. Kilonzo and Dr. M. T. Lesheaberi, University of Muhumbili, Dar Es Salaam, Tanzania) presented their recent epidemiological findings on Tanzanian IDUs and HIV at a conference December 1, 2006 - World AIDS Day - at the University of Muhumbili. The research was supported by a NIDA International Program collaborative research supplement (NOT-02-003) and a subsequent R21 (DA19394). The binational research team reports that heroin injection and risky injection practices are continuing to increase in Dar Es Salaam and spreading outward to neighboring communities. Using modified snowball sampling and outreach, the team recruited 537 heroin IDUs in Dar Es Salaam (318 male, 219 female); 42% of whom tested HIV positive (27% among males, 64% among females). The team observed a new and unusual practice among women IDUs - termed "flashblood" - where IDUs share blood-filled syringes after one has injected heroin. The research has been published in AIDS Care, June 2005; 17(Supplement 1): S65-S76; BMJ 2005; 331: 778-781; Drug and Alcohol Dependence 82 Supplement 1(2006): S23-S27; and AIDS Behavior DOI 10.1007/s10461-006-9102-x. Participants at the conference included representatives from the University of Muhumbili medical faculty; the Tanzanian Ministry of Labor, Employment, and Youth; the Tanzanian Ministry of Health; other Tanzanian officials; and invited media. The binational research team also met with Tanzanian Deputy Minister of Labor, Employment, and Youth Dr. Emmanuel Nchimbi on October 18, 2006.

DISCA-Supported Research Suggests Fluoxetine May Be an Effective Methamphetamine Pharmacotherapy

In research published by the *Annals of the New York Academy of Science* (2006 Aug;1074:295-302), a binational research team supported in part by a 2004 NIDA Distinguished International Scientist Collaboration Award (DISCA) concludes that fluoxetine may be a useful tool for treating methamphetamine (METH) dependence. The DISCA Scientist, Dr. Kazutaka Ikeda, Tokyo Institute of Psychiatry, Japan, his research partner, Dr. Athina Markou, The Scripps Research Institute, and their colleagues investigated the effects of intraperitoneal (i.p.) injections of 20 mg/kg fluoxetine, a selective serotonin reuptake inhibitor (SSRI), on 2 mg/kg METH (i.p.) conditioned place preference (CPP) and locomotor sensitization to 1 mg/kg METH (i.p.) in C57BL/6J mice. Fluoxetine treatment before both the conditioning and preference tests abolished METH CPP. A two-way analysis of variance (ANOVA) revealed that METH CPP tended to be lower in mice pretreated with fluoxetine before the

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preference test than in control mice pretreated with saline before the preference test. Furthermore, pretreatment with fluoxetine had inhibitory effects on METH-induced locomotor sensitization. Following Dr. Ikeda's DISCA research exchange visit with Dr. Markou, the team received a 3-year grant from the U.S. - Japan Brain Research Cooperation Program as well as additional support from the Tokyo Institute of Psychiatry and the Japanese Society of Pharmacopoeia.

Research Publications by International Program Alumni

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

Former NIDA INVEST Drug Abuse Research Fellows

Variations of Alcohol Impairment in Different Types, Causes and Contexts of Injuries: Results of Emergency Room Studies from 16 Countries
Macdonald, S., Cherpitel, C.J., Desouza, A., Stockwell, T., Borges, G., and Giesbrecht, N. Accid Anal Prev. July 5, 2006 [Epub ahead of print]
INVEST Fellow: Guilherme Borges, Mexico, 1997-1998
The purpose of this paper is to document alcohol impairment (based on a blood alcohol content (BAC) of at least 80mg%) for different types, causes and location contexts of injuries. Data from 45 studies with 11,536 injury patients were merged to determine variations in the percent of alcohol impairment among injury patients. In each study, emergency room (ER) injury patients were given a short interview on the circumstances of their injury and BAC was measured. Injury severity, measured by number of body regions injured was significantly associated with BACs over 80mg%. The highest percentage of injury type to involve alcohol was head injury/concussion. In terms of causes of injuries, patients with alcohol impairment were significantly more likely to be involved in violence than any other cause (i.e., vehicle, falling, poisoning or burns). Finally, injuries occurring at a bar or restaurant were significantly more likely to involve alcohol impairment than any other setting. The results demonstrate considerable variation in the circumstances where alcohol is involved in injuries. These results may be useful for the development of prevention initiatives.

Treatment and Adequacy of Treatment of Mental Disorders among Respondents to the Mexico National Comorbidity Survey
Borges, G., Medina-Mora, M.E., Wang, P.S., Lara, C., Berglund, P., and Walters, E. Am J Psychiatry. 163(8), pp. 1371-1378, August 2006.
INVEST Fellow: Guilherme Borges, Mexico, 1997-1998
This study described the rate and adequacy of mental health service use among participants in the Mexico National Comorbidity Survey and the correlates of any 12-month treatment and of adequate treatment. The authors conducted face-to-face household surveys of a probability sample of individuals ages 18 to 65 years in the noninstitutionalized population living in urban areas of Mexico from 2001 to 2002. The use of mental health services and 12-month DSM-IV disorders was assessed with the World Mental Health version of the World Health Organization Composite International Diagnostic Interview. The rates and correlates of any service use and the adequacy of treatment were identified in logistic regression analyses, taking into account the complex sample design and weighting process. The data reported here were based on 2,362 interviews. Fewer than one in five respondents with any psychiatric disorder during the last 12 months used any service during the prior year. The rates of service use by those with mood disorders were somewhat higher. About one in every two respondents who used services received minimally adequate care. The authors found large unmet needs for mental health services among those with psychiatric disorders. Those with mental illness and those

who deliver or seek to improve mental health care in Mexico face enormous challenges.

Influence of Blood Loss on the Pharmacokinetics of Citalopram
Kugelberg, F.C., Alkass, K., Kingback, M., Carlsson, B., and Druid, H. Forensic Sci Int. July 11, 2006 [Epub ahead of print]
INVEST Fellow: Henrik Druid, Sweden, 2001-2002
Extended blood loss results in several compensatory physiological mechanisms, including transfer of extravascular fluid into the blood circulation. If drugs are present in the body, this fluid exchange may imply that blood drug concentrations found in a trauma victim may differ from the concentrations present at the time of the trauma. To address this issue, an animal model was used to investigate the influence of blood loss on pre-existing levels of the antidepressant drug citalopram and its demethylated metabolites. Rats were administered citalopram either acutely (40mg/kg, orally) or chronically (20mg/kg daily, subcutaneously) for 6 days using osmotic pumps. In the experimental rats, blood loss was accomplished by withdrawing 0.8mL blood at 10min intervals during 70min. In the control rats, blood was withdrawn at 0 and 70min only. Blood, brain and lung drug concentrations were analyzed with an enantioselective HPLC method. In the chronically treated rats, the ratios between final and initial citalopram concentrations were 1.08+/-0.15 and 1.01+/-0.09 in the experimental rats and controls, respectively, indicating no major effect of blood loss. In contrast, acute oral administration resulted in increased ratios in the exsanguinated rats as compared to controls (1.84+/-0.50 versus 0.73+/-0.07; p=0.0495). In conclusion, the observation of increased blood drug levels in the acute oral rats indicates that absorption of fluid from the gastrointestinal tract may be important in the intravascular refill. Further, in the interpretation of post-mortem blood levels of drugs, these physiological mechanisms should be taken into account.

The u-opioid Receptor Gene and Smoking Initiation and Nicotine Dependence
Zhang, L., Kendler, K.S., and Chen, X. Behav Brain Funct. 2(1):28, August 4, 2006 [Epub ahead of print]
INVEST Fellow: Lan Zhang, China, 2004-2005
The gene encoding the mu-opioid receptor (OPRM1) is reported to be associated with a range of substance dependence. Experiments in knockout mice indicate that the mu-opioid receptor may mediate reinforcing effects of nicotine. In humans, opioid antagonist naltrexone may reduce the reinforcing effects of tobacco smoking. Additionally, the OPRM1 gene is located in a region showing linkage to nicotine dependence. The OPRM1 is thus a plausible candidate gene for smoking behavior. To investigate whether OPRM1 contributes to the susceptibility of smoking initiation and nicotine dependence, the authors genotyped 11 SNPs in the gene for 688 Caucasian subjects of lifetime smokers and nonsmokers. Three SNPs showed nominal significance for smoking initiation and one reached significance for nicotine dependence. The global test for three-marker (rs9479757-rs2075572-rs10485057) haplotypes was significant for smoking initiation (p = 0.0022). The same three-marker haplotype test was marginal (p = 0.0514) for nicotine dependence. These results suggest that OPRM1 may be involved in smoking initiation and nicotine dependence.

Effects of NAAG Peptidase Inhibitor 2-PMPA in Model Chronic Pain - Relation to Brain Concentration
Nagel, J., Belozertseva, I., Greco, S., Kashkin, V., Malyshkin, A., Jirgensons, A., Shekunova, E., Eilbacher, B., Bespalov, A., and Danysz, W. Neuropharmacology. August 18, 2006 [Epub ahead of print].
INVEST Fellow: Anton Bespalov, Russia, 1994-1995.
N-acetylated-alpha-linked-acidic peptidase (NAAG peptidase) converts N-acetyl-aspartyl-glutamate (NAAG, mGluR3 agonist) into N-acetyl-aspartate and glutamate. The NAAG peptidase inhibitor 2-PMPA (2-

(phosphonomethyl)pentanedioic acid) had neuroprotective activity in an animal model of stroke and anti-allodynic activity in CCI model despite its uncertain ability to penetrate the blood-brain barrier. The NAAG concentration in brain ECF under basal conditions and its alteration in relation to the brain ECF concentration of 2-PMPA is unclear. Authors therefore assessed those brain concentrations after i.p. administration of 2-PMPA, using in vivo microdialysis combined with LC/MS/MS analysis. Administration of 2-PMPA (50mg/kg) produced a mean peak concentration of 2-PMPA of 29.66+/-8.1muM. This concentration is about 100,000 fold more than is needed for inhibition of NAAG peptidase, and indicates very good penetration to the brain. Application of 2-PMPA was followed by a linear increase of NAAG-concentration reaching a maximum of 2.89+/-0.42muM at the end of microdialysis. However, during the time the anti-allodynic effects of 2-PMPA were observed, the NAAG concentration in the ECF did not reach levels which are likely to have an impact on any known target. It appears therefore that the observed behavioral effects of 2-PMPA may not be mediated by NAAG nor, in turn, by mGluR3 receptors.

Lowered Brain Stimulation Reward Thresholds in Rats Treated with a Combination of Caffeine and N-methyl-D-aspartate but not Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate or Metabotropic Glutamate Receptor-5 Receptor Antagonists
Bespalov, A., Dravolina, O., Belozertseva, I., Adamcio, B., and Zvartau, E. Behav Pharmacol. 17(4), pp. 295-302, 2006.
INVEST Fellow: Anton Bespalov, Russia, 1994-1995.
Previous studies suggested that adenosine A1 and A2A receptor agonists counteract behavioral effects of N-methyl-D-aspartate (NMDA) receptor antagonists while adenosine receptor antagonists may produce opposite effects enhancing the actions of NMDA receptor antagonists. To further evaluate the effects of combined administration of adenosine receptor antagonist caffeine and various NMDA and non-NMDA glutamate receptor antagonists on brain stimulation reward (discrete-trial threshold current intensity titration procedure), rats with electrodes implanted into the ventral tegmental area were tested after pretreatment with NMDA receptor channel blocker MK-801 (0.01-0.3 mg/kg), competitive antagonist D-CPPene (0.3-5.6 mg/kg), glycine site antagonist L-701,324 (1.25-5 mg/kg), alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor antagonist GYKI-53655 (1-10 mg/kg), metabotropic glutamate receptor 5 (mGluR5) antagonist MPEP (1-10 mg/kg) alone and in combination with caffeine (1-30 mg/kg). MK-801 (0.056 and 0.1 mg/kg) was the only tested glutamate antagonist that lowered self-stimulation thresholds, while D-CPPene (5.6 mg/kg) and MPEP (5.6 and 10 mg/kg) had the opposite effects. Threshold-increasing effects of D-CPPene, but not of MPEP, however, were associated with marked impairment of operant performance, reflected by longer latencies to respond and higher rates of responding during the inter-trial intervals. Operant performance was also disrupted by the highest dose of MK-801 (0.3 mg/kg). For subsequent experiments, caffeine (1-30 mg/kg) was combined with the highest doses of NMDA receptor antagonists that did not lower the brain stimulation reward thresholds and did not impair operant performance. Caffeine had no appreciable effects on self-stimulation behavior when given alone. A low dose of caffeine (3 mg/kg) significantly lowered self-stimulation thresholds only when given together with MK-801 (0.03 mg/kg) or D-CPPene (3 mg/kg). Combined with the same antagonist drugs, higher doses of caffeine (10 and 30 mg/kg) facilitated time-out responding. These results indicate that, within a limited dose range, caffeine in combination with an NMDA receptor channel blocker and a competitive antagonist significantly lowers brain stimulation reward thresholds in rats.

Effects of Group I Metabotropic Glutamate Receptor Antagonists on the Behavioral Sensitization to Motor Effects of Cocaine in Rats
Dravolina, O.A., Danysz. W., and Bespalov, A.Y. Psychopharmacology (Berl).187(4), pp. 397-404, 2006. Epub June 20, 2006.
INVEST Fellow: Anton Bespalov, Russia, 1994-1995.

Metabotropic glutamate receptors (mGluRs) were reported to regulate various behavioral effects of addictive drugs. The present study evaluated the role of group I mGluRs in the progressive augmentation ("sensitization") of the behavioral effects observed after repeated, intermittent cocaine exposure. After habituation to handling and baseline activity measurement (days 1-2), rats received eight injections of cocaine (10 mg/kg) or saline on days 3-6, 8-11, and then, were tested twice with acute saline and cocaine given in a counterbalanced manner on days 13 and 15. Before the test sessions, subjects were pretreated with mGluR1 antagonist EMQMCM (JNJ16567083, (3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methanesulfonate) and mGluR5 antagonist MTEP ([(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine). Pretreatment with EMQMCM (2.5-10 mg/kg) but not MTEP (2.5-10 mg/kg) significantly reduced expression of the sensitized ambulatory motor activity of the cocaine-experienced animals acutely challenged with cocaine. Both EMQMCM and MTEP significantly reduced vertical motor activity across all cocaine/saline treatment conditions. These findings indicate that the expression of behavioral sensitization to cocaine-induced stimulation of locomotor activity may be modulated by group I mGluR antagonists (mGluR1 rather than mGluR5), but these effects occur at the dose levels that attenuate vertical activity.

A Risk Index for 12-month Suicide Attempts in the National Comorbidity Survey Replication (NCS-R)

Borges, G., Angst, J., Nock, M.K., Ruscio, A.M., Walters, E.E., and Kessler, R.C. Psychol Med. August 29, 2006, pp. 1-11 [Epub ahead of print].
INVEST Fellow: Guilherme Borges, Mexico, 1997-1998

Clinical judgments about the likelihood of suicide attempt would be aided by an index of risk factors that could be quickly assessed in diverse settings. The authors sought to develop such a risk index for 12-month suicide attempts among suicide ideators. The National Comorbidity Survey Replication (NCS-R), a household survey of adults aged 18+, assessed the 12-month occurrence of suicide ideation, plans and attempts in a subsample of 5692 respondents. Retrospectively assessed correlates include history of prior suicidality, sociodemographics, parental psychopathology and 12-month DSM-IV disorders. Twelve-month prevalence estimates of suicide ideation, plans and attempts are 2.6, 0.7 and 0.4% respectively. Although ideators with a plan are more likely to make an attempt (31.9%) than those without a plan (9.6%), 43% of attempts were described as unplanned. History of prior attempts is the strongest correlate of 12-month attempts. Other significant correlates include shorter duration of ideation, presence of a suicide plan, and several sociodemographic and parental psychopathology variables. Twelve-month disorders are not powerful correlates. A four-category summary index of correlates is strongly related to attempts among ideators [area under the receiver operator characteristic curve (AUC)=0.88]. The distribution (conditional probability of attempt) of the risk index is: 19.0% very low (0.0%), 51.1% low (3.5%), 16.2% intermediate (21.3%), and 13.7% high (78.1%). Two-thirds (67.1%) of attempts were made by ideators in the high-risk category. A short, preliminary risk index based on retrospectively reported responses to fully structured questions is strongly correlated with 12-month suicide attempts among ideators, with a high concentration of attempts among high-risk ideators.

Endogenous Opioids are Involved in Morphine and Dipyrone Analgesic Potentiation in the Tail Flick Test in Rats

Hernandez-Delgadillo, G.P., and Cruz, S.L.. Eur J Pharmacol. Sepember 28, 2006, 546(1-3) pp. 54-59. Epub 2006 Jul 22.
INVEST Fellow: Silvia Cruz, Mexico, 1996-1997.

The combined administration of low doses of opiates with non-steroidal anti-inflammatory drugs can produce additive or supra-additive analgesic effects while reducing unwanted side effects. We have recently reported that co-administration of morphine with dipyrone (metamizol) produces analgesic

potentiation both in naive and in morphine-tolerant rats. The purpose of this work was to determine the role of opioids on the acute potentiation observed between morphine and dipyrone i.v. in the rat tail flick test. To do this, two experiments were done. In the first one, naloxone was administered 10 min before morphine (3.1 mg/kg), dipyrone (600 mg/kg) or their combination at the same doses. Control animals received saline instead of naloxone. In the second experiment, naloxone (or saline) was given 2 min after reaching the maximal peak effect with each individual analgesic treatment. When naloxone was i.v. administered prior to analgesics, it completely blocked morphine effects, partially prevented morphine/dipyrone antinociception and delayed dipyrone-induced nociception. At 3.1 mg/kg, naloxone produced an increased nociception. When naloxone was given after analgesics, it dose-dependently blocked the effects of morphine alone and in combination with dipyrone but with different potency in each case. As to dipyrone, naloxone delayed the time to antinociceptive peak effect. Taken together, these results support the notion that endogenous opioids are involved in the analgesic potentiation observed with the combination of morphine plus dipyrone.

Neocortical Neurogenesis in Humans is Restricted to Development
Bhardwaj, R.D., Curtis, M.A., Spalding, K.L., Buchholz, B.A., Fink, D., Bjork-Eriksson, T., Nordborg, C., Gage, F.H., Druid, H., Eriksson, P.S., and Frisen, J. Proc Natl Acad Sci U S A. August 15, 2006, 103(33):12564-125688. Epub 2006 Aug 10.
INVEST Fellow: Henrik Druid, Sweden, 2000-2001.
Stem cells generate neurons in discrete regions in the postnatal mammalian brain. However, the extent of neurogenesis in the adult human brain has been difficult to establish. We have taken advantage of the integration of (14)C, generated by nuclear bomb tests during the Cold War, in DNA to establish the age of neurons in the major areas of the human cerebral neocortex. Together with the analysis of the neocortex from patients who received BrdU, which integrates in the DNA of dividing cells, our results demonstrate that, whereas nonneuronal cells turn over, neurons in the human cerebral neocortex are not generated in adulthood at detectable levels but are generated perinatally.

The Selective Dopamine D3 Receptor Antagonist SB-277011A Reduces
Nicotine-enhanced Brain Reward and Nicotine-paired Environmental Cue Functions Pak, A.C., Ashby, C.R., Heidbreder, C.A., Pilla, M., Gilbert, J., Xi, Z.X., and Gardner, E.L. Int J Neuropsychopharmacol. August 31, 2006, pp. 1-18 [Epub ahead of print].
INVEST Fellow: Zhengxiong Xi, China, 1995-1996.
Increasing evidence suggests that enhanced dopamine (DA) neurotransmission in the nucleus accumbens (NAc) may play a role in mediating the reward and reinforcement produced by addictive drugs and in the attentional processing of drug-associated environmental cues. The meso-accumbens DA system is selectively enriched with DA D3 receptors, a DA receptor subtype increasingly implicated in reward-related brain and behavioral processes. From a variety of evidence, it has been suggested that selective DA D3 receptor antagonism may be a useful pharmacotherapeutic approach for treating addiction. The present experiments tested the efficacy of SB-277011A, a selective DA D3 receptor antagonist, in rat models of nicotine-enhanced electrical brain-stimulation reward (BSR), nicotine-induced conditioned locomotor activity (LMA), and nicotine-induced conditioned place preference (CPP). Nicotine was given subcutaneously within the dose range of 0.25-0.6 mg/kg (nicotine-free base). SB-277011A, given intraperitoneally within the dose range of 1-12 mg/kg, dose-dependently reduced nicotine-enhanced BSR, nicotine-induced conditioned LMA, and nicotine-induced CPP. The results suggest that selective D3 receptor antagonism constitutes a new and promising pharmacotherapeutic approach to the treatment of nicotine dependence.

Cannabinoid CB1 Receptor Antagonist AM251 Inhibits Cocaine-primed Relapse in Rats: Role of Glutamate in the Nucleus Accumbens

Xi, Z.X., Gilbert, J.G., Peng, X.Q., Pak, A.C., Li, X., and Gardner, E.L. J Neurosci. August 16, 2006, 26(33) pp. 8531-8536. INVEST Fellow: Zhengxiong Xi, China, 1995-1996.

Blockade of cannabinoid CB1 receptors has been reported to inhibit cocaine- or cocaine cue-induced reinstatement of drug seeking. However, the mechanisms underlying this action are poorly understood. Given the importance of dopamine, glutamate, and GABA in cocaine reward and relapse, the authors studied the effects of AM251 [N-(piperidin-1-yl)-5-(4-iodophonyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide], a novel highly selective CB1 receptor antagonist, on cocaine-primed reinstatement of drug-seeking behavior and on cocaine-induced changes in extracellular DA, glutamate, and GABA in the nucleus accumbens (NAc) under reinstatement conditions. The authors found that systemic administration of AM251 selectively inhibited cocaine-induced, but not sucrose plus sucrose cue-induced, reinstatement of reward-seeking behavior. AM251 alone did not trigger reinstatement. Local perfusion of AM251 into the NAc or the dorsal striatum also inhibited cocaine-triggered reinstatement. AM251 alone dose dependently elevated NAc glutamate in a voltage-dependent Na+ channel-dependent manner. AM251 did not affect NAc DA or GABA. Pretreatment with AM251 dose dependently inhibited cocaine-induced increases in NAc glutamate but not in DA. Blockade of NAc metabotropic glutamate mGluR2/3 receptors by LY341495 [(2S)-2-amino-2-[(1S,2S)-2-carboxycycloprop-1-yl]-3-(xanth-9-yl) propanoic acid] slightly facilitated cocaine-enhanced glutamate release but blocked the antagonism of cocaine-induced reinstatement by AM251. These data suggest the following: (1) CB1 receptors exert tonic inhibition over NAc glutamate release under cocaine-extinction conditions; (2) blockade of CB1 receptors by AM251 inhibits cocaine-enhanced NAc glutamate release and cocaine-triggered reinstatement; and (3) these effects appear to be mediated by activation of presynaptic mGluR2/3 autoreceptors secondary to AM251-induced increase (disinhibition) of NAc glutamate release.

Methadone Doses upon Multiple Readmissions to Inpatient Detoxification: Clinical Evidence for Very Moderate Opioid Tolerance

Madlung, E., Haring, C., Crespo, J.A., Saria, A., Grubinger, P., and Zernig, G. Pharmacology. 78(1) pp. 38-43, 2006. Epub 2006 August 15.
INVEST Fellow: Gerald Zernig, Austria, 1993-1994.

Escalation of drug use by addicts has traditionally been interpreted as tolerance to the drug's effects. On the basis of animal behavioral data, several groups have recently proposed alternative explanations, i.e., that such an escalation of drug dose might not be based on tolerance but rather be indicative of (i) sensitization to the reinforcing effect or the incentive salience of the drug of abuse or (ii) shifts in baseline mood, i.e., allostasis. In the present study, the emergence of opioid tolerance or sensitization during the progression of opioid dependence was assessed by comparing the methadone doses that were initially required to alleviate the opioid withdrawal symptoms of intravenous opioid users who presented for detoxification upon 3-7 consecutive admissions over the course of up to 84 months. Upon the second admission, the 48 surveyed male patients needed 115 +/- 6% ($p = 0.012$) and the 32 female patients needed 121 +/- 12% ($p = 0.01$) of the methadone dose required upon the first admission. Upon the third admission, the respective values were 121 +/- 8% (males; $p = 0.013$) and 111 +/- 12% (females; n.s.), and upon the fourth admission, 125 +/- 14% (males; $p = 0.026$) and 131 +/- 14 (females; $p = 0.01$). Inter-admission intervals averaged 14 +/- 1 months ($n = 135$) for males and 13 +/- 1 months ($n = 91$) for females and were not significantly different across consecutive admissions, suggesting that tolerance did not develop faster upon repetition of abuse-withdrawal cycles. In conclusion, the intravenous opioid users surveyed in the present study developed only very moderate tolerance during the repeated abuse-detoxification cycles that were typical for their disease progression. The present data do not support the notion that sensitization to the opioids' reinforcing effects occurred in this naturalistic clinical sample.

mGlu1 Receptor Blockade Attenuates Cue- and Nicotine-Induced Reinstatement of Extinguished Nicotine Self-administration Behavior in Rats

Dravolina, O.A., Zakharova, E.S., Shekunova, E.V., Zvartau, E.E., Danysz, W., and Bespalov, A.Y. Neuropharmacology. September 7, 2006; [Epub ahead of print]

INVEST Fellow: Anton Bespalov, Russia, 1994-1995.

Glutamatergic neurotransmission is believed to be critically involved in the acquisition and maintenance of drug addiction. The present study evaluated the role of metabotropic glutamate (mGlu) 1 receptors in the reinstatement of nicotine-seeking behavior. Rats were trained to nose-poke to receive response-contingent intravenous infusions of nicotine (0.01mg/kg/infusion, free base). Following the subsequent extinction phase, reinstatement tests were conducted in animals that were exposed either to response-contingent presentations of the nicotine-associated discrete light cues or to non-contingent nicotine priming injection (0.3mg/kg, s.c., salt) just prior to the test session. In a separate experiment, rats were subjected to the nearly identical response-reinstatement procedure but operant responding was established using food pellets instead of nicotine infusions. Pretreatment with the mGlu1 receptor antagonist EMQMCM (JNJ16567083, (3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methanesulfonate) significantly inhibited cue-induced reinstatement of nicotine-seeking behavior (5 and 10, but not 2.5mg/kg). EMQMCM (5mg/kg) also prevented nicotine priming-induced reinstatement of nicotine-seeking behavior. At the highest tested dose only (10mg/kg), EMQMCM attenuated cue-induced reinstatement of food-seeking behavior. Taken together with the previous reports, the present findings further suggest that blockade of mGlu1 receptors may be beneficial for preventing relapse to tobacco smoking in nicotine-dependent individuals.

Cause of Death and Drug Use Pattern in Deceased Drug Addicts in Sweden, 2002-2003

Jonsson, A.K., Holmgren, P., Druid, H., and Ahlner, J. Forensic Sci Int. Sepember 9, 2006; [Epub ahead of print].

INVEST Fellow: Henrik Druid, Sweden, 2001-2002.

Compared with their contemporaries, individuals abusing illicit drugs suffer a higher risk of premature death. In Sweden, a simple protocol for registration of fatalities among abusers of alcohol, pharmaceuticals, illicit drugs, or other substances, has been used by the forensic pathologists since 2001. This routine was introduced to allow for an evaluation of the cause and manner of death, and patterns of abuse among different groups of abusers. The authors explored the data on drug abusers (i.e. abusers of illicit drugs) subjected to a forensic autopsy 2002-2003. The Swedish forensic pathologists examined 10,273 dead victims during the study period and 7% (743/10,273) of the cases were classified as drug abusers. Toxicological analyses were carried out in 99% (736/743) and illicit drugs were detected in 70% (514/736) of these. On average, 3.8 substances (legal or illegal) were found per case. The most common substances were ethanol and morphine, detected in 43 and 35% of the cases, respectively. When exploring the importance of the different substances for the cause of death, the authors found that the detection of some substances, such as fentanyl and morphine, strongly indicated a poisoning, whereas certain other substances, such as benzodiazepines more often were incidental findings. In total, 50% (372/743) died of poisoning, whereas only 22% (161/743) died of natural causes. Death was considered to be directly or indirectly due to drug abuse in 47% (346/743), whereas evidence of drug abuse was an incidental finding in 21% (153/743) or based on case history alone in 33% (244/743). The authors believe that this strategy to prospectively categorize deaths among drug addicts constitutes a simple means of standardizing the surveillance of the death toll among drug addicts that could allow for comparisons over time and between countries.

Pharmacological MRI in Awake Rats Reveals Neural Activity in Area Postrema and Nucleus Tractus Solitarius: Relevance as a Potential Biomarker for Detecting Drug-induced Emesis

Chin, C.L., Fox, G.B., Hradil, V.P., Osinski, M.A., McGaraughty, S.P., Skoubis, P.D., Cox, B.F., and Luo, Y. Neuroimage. October 3, 2006; [Epub ahead of print]

INVEST Fellow: Steven P. McGaraughty, Canada, 1995-1996.

Drug-induced vomiting (emesis) is a major concern in patient care and a significant hurdle in the development of novel therapeutics. With respect to the latter, rodents, such as the rat and mouse, are typically used in efficacy and safety studies; however, drug-induced emesis cannot be readily observed in these species due to the lack of an emetic reflex. It is known that emesis can be triggered by neural activity in brain regions including area postrema (AP) and nucleus tractus solitarius (NTS). In this study, using pharmacological magnetic resonance imaging (phMRI) and a blood-pool contrast agent, authors imaged the hemodynamic consequences of brain activity in awake rats initiated by the administration of compounds (apomorphine 0.1, 0.3 micromol/kg i.v. and ABT-594 0.03, 0.1, 0.3 micromol/kg i.v.) that elicit emesis in other species. Regional drug-induced relative cerebral blood volume (rCBV) changes and percent activated area within the AP and NTS were calculated, in which a dose-dependent relationship was evident for both apomorphine and ABT-594. Additionally, to correlate with behavioral readouts, it was found that the activation of AP and NTS was observed at plasma concentrations consistent with those that induced emesis in ferrets for both drugs. These data thus suggest that phMRI in awake rats may be a useful tool for predicting emetic liability of CNS-acting drugs and may provide insights into depicting the underlying emetic neural pathways in vivo.

Blockade of mGluR1 Receptor Results in Analgesia and Disruption of Motor and Cognitive Performances: Effects of A-841720, A Novel Non-competitive mGluR1 Receptor Antagonist

El-Kouhen, O., Lehto, S.G., Pan, J.B., Chang, R., Baker, S.J., Zhong, C., Hollingsworth, P.R., Mikusa, J.P., Cronin, E.A., Chu, K.L., McGaraughty, S.P., Uchic, M.E., Miller, L.N., Rodell, N.M., Patel, M., Bhatia, P., Mezler, M., Kolasa, T., Zheng, G.Z., Fox, G.B., Stewart, A.O., Decker, M.W., Moreland, R.B., Brioni, J.D., and Honore, P. Br J Pharmacol. October 3, 2006; [Epub ahead of print]. INVEST Fellow: Steven P. McGaraughty, Canada, 1995-1996.

The purpose of this study was to further assess the clinical potential of the blockade of metabotropic glutamate receptors (mGluR1) for the treatment of pain. Authors characterized the effects of A-841720, a novel, potent and non-competitive mGluR1 antagonist in models of pain and of motor and cognitive function. At recombinant human and native rat mGluR1 receptors, A-841720 inhibited agonist-induced calcium mobilization, with IC(50) values of 10.7+/-3.9 and 1.0+/-0.2 nM, respectively, while showing selectivity over other mGluR receptors, in addition to other neurotransmitter receptors, ion channels, and transporters. Intraperitoneal injection of A-841720 potently reduced complete Freund's adjuvant-induced inflammatory pain (ED(50)=23 mumol kg(-1)) and monoiodoacetate-induced joint pain (ED(50)=43 mumol kg(-1)). A-841720 also decreased mechanical allodynia observed in both the sciatic nerve chronic constriction injury and L5-L6 spinal nerve ligation (SNL) models of neuropathic pain (ED(50)=28 and 27 mumol kg(-1), respectively). Electrophysiological studies demonstrated that systemic administration of A-841720 in SNL animals significantly reduced evoked firing in spinal wide dynamic range neurons. Significant motor side effects were observed at analgesic doses and A-841720 also impaired cognitive function in the Y-maze and the Water Maze tests. The analgesic effects of a selective mGluR1 receptor antagonist are associated with motor and cognitive side effects. The lack of separation between efficacy and side effects in pre-clinical models indicates that mGluR1 antagonism may not provide an adequate therapeutic window for the development of such antagonists as novel analgesic agents in humans. British Journal of Pharmacology advance online publication, 3 October 2006;

doi:10.1038/sj.bjp.0706877.

PMA and Doxorubicin Decrease Viability, MTT Activity and Expression of CD10 Marker on NALM-1 Leukemic Cells
Martin-Kleiner, I,., Svoboda-Beusan, I. and Gabrilovac, J. Immunopharmacol Immunotoxicol. 28(3), pp. 411-420, 2006.
INVEST Fellow: Irena Martin-Kleiner, Croatia, 1995-1996.
PMA (10, 20 ng/ml) and doxorubicin (5-20 ng/ml) decreased the viability and MTT-activity of NALM-1 pre-B leukemic cells (3 days' treatment). Further, CD10 was downregulated, suggesting that PMA and doxorubicin induced differentiation of NALM-1 cells. However, PMA did not alter expression of B cell markers CD20 and of mIgM. In contrast to PMA, another differentiation agent ATRA did not alter CD10 expression on NALM-1 cells but affected viability after 6 days (5, 10 ng/ml). The data in this study are the first evidence that PMA and doxorubicin inhibited viability and MTT activity and induced partial differentiation, by decreasing CD10 on NALM-1 cells.

Peripheral Formalin Injection Induces Long-Lasting Increases in Cyclooxygenase 1 Expression by Microglia in the Spinal Cord
Zhang, F., Wan, Y., Zhang, Z.K., Light, A.R., and Fu, K.Y. J Pain. Sepember 1, 2006; [Epub ahead of print].
INVEST Fellow: You Wan, China, 1998-1999.
Activated glia are a source of substances known to enhance pain, including centrally synthesized prostaglandins. The authors have previously shown that microglia are activated in the spinal cord following peripheral formalin injection. In the present study, they investigated cyclooxygenase (COX-1 and COX-2) expression in the spinal cord using immunohistochemistry and Western blots in the formalin pain model, to further understand how spinal glia modulate pain processing. The authors show that both COX-1 and COX-2 are constitutively expressed in the spinal cord. Hind paw formalin injection increased COX-1 expression, beginning at 1 day after injection and lasting at least 2 weeks, the duration of experiments. The COX-2 expression changed considerably less, with a significant increase of COX-2 protein level only observed at 2 h after injection. Double labeling studies showed that COX-1 was expressed in microglia and COX-2 was expressed in neurons. These data indicate that both COX-1 and COX-2 are increased in the spinal cord following formalin injection, but the time course and cellular sources are different, suggesting that both COX-1 (longer time points) and COX-2 (very short time points) may be involved in spinal modulation in the formalin pain model. Our study also suggests that spinal microglial activation may play a role in long-term hyperalgesia through the increased expression of COX-1. This article reports that COX-1 expression by microglia is increased in the spinal cord after peripheral formalin injection into the rat hind paw. This result could potentially help clinicians understand how COX-1 may be involved in pain processing and the role microglial activation plays in pain mechanisms.

Highly Variable mRNA Expression and Splicing of L-type Voltage-dependent Calcium Channel Alpha Subunit 1C in Human Heart Tissues
Wang, D., Papp, A.C., Binkley, P.F., Johnson, J.A., and Sadee, W. Pharmacogenet Genomics. 16(10), pp. 735-745, October 2007.
INVEST Fellow: Danxin Wang, China, 1996-1997.
The voltage-dependent L-type calcium channel alpha-subunit 1c (Cav1.2, CACNA1C) undergoes extensive mRNA splicing, leading to numerous isoforms with different functions. L-type calcium channel blockers are used in the treatment of hypertension and arrhythmias, but response varies between individuals. Authors have studied the interindividual variability in mRNA expression and splicing of CACNA1C, in 65 heart tissue samples, taken from heart transplant recipients. Splice variants were measured quantitatively by polymerase chain reaction in 12 splicing loci of CACNA1C mRNA. To search for functional cis-acting polymorphisms, we determined allelic expression ratios for total CACNA1C mRNA and several splice variants using marker single

nucleotide polymorphisms in exon 4 and exon 30. Total CACNA1C mRNA levels varied approximately 50-fold. Substantial splicing occurred in six loci generating two or more splice variants, some with known functional differences. Splice patterns varied broadly between individuals. Two heart tissues expressed predominantly the dihydropyridine-sensitive smooth muscle isoform of CACNA1C (containing exon 8), rather than the cardiac isoform (containing exon 8a). Lack of significant allelic expression imbalance, observed with total mRNA and several splice variants, argued against CACNA1C polymorphisms as a cause of variability. Taken together, highly variable splicing can cause profound phenotypic variations of CACNA1C function, potentially associated with disease susceptibility and response to L-type calcium channel blockers.

The Reovirus {micro}1 Structural Rearrangements that Mediate Membrane Penetration

Zhang, L., Chandran, K., Nibert, M.L., and Harrison, S.C. J Virol. Sepember 27, 2006; [Epub ahead of print].

INVEST Fellow: Lan Zhang, China, 2004-2005.

Membrane penetration by nonenveloped reoviruses is mediated by the outer-capsid protein, micro 1 (76 kDa). Previous evidence has suggested that an autolytic cleavage in micro 1 allows release of its N-terminally myristoylated peptide, micro 1N (4 kDa), which probably then interacts with the target-cell membrane. A substantial rearrangement of the remaining portion of micro 1, micro 1C (72 kDa), must also have occurred for micro 1N to be released, and some regions in micro 1C may make additional contacts with the membrane. Authors describe here a particle-free system to study conformational rearrangements of micro 1. The authors show that removal of the protector protein sigma3 is not sufficient to trigger rearrangement of free micro 1 trimer and that free micro 1 trimer undergoes conformational changes similar to those of particle-associated micro 1 when induced by similar conditions. The micro 1 rearrangements require separation of the micro 1 trimer head domains, but not the micro 1N/C autocleavage. The authors have also obtained a relatively homogeneous form of the structurally rearranged micro 1 (micro 1*) in solution. It is an elongated monomer and retains substantial alpha-helix content. The authors have identified a protease-resistant, approximately 23-kDa fragment of micro 1*, which contains the largely alpha-helical regions designated as domains I and II in the conformation of micro 1 prior to rearrangement. The authors propose that the micro 1 conformational changes preceding membrane penetration or disruption during cell entry involve: (i) separation of the beta-barrel head domains in the micro 1 trimer; (ii) autolytic cleavage at the micro 1N/C junction, associated with partial unfolding of micro 1C and release of micro 1N; and (iii) refolding of the N-terminal helical domains of micro 1C, with which micro 1N was previously complexed, accompanied by dissociation of the micro 1 trimer.

The Last Decade of Solvent Research in Animal Models of Abuse: Mechanistic and Behavioral Studies

Bowen, S.E., Batis, J.C., Paez-Martinez, N., and Cruz, S.L. Neurotoxicol Teratol. Sepember 20, 2006; [Epub ahead of print]

INVEST Fellow: Silvia Cruz, Mexico, 1996-1997.

The abuse of volatile organic solvents (inhalants) leads to diverse sequelae at levels ranging from the cell to the whole organism. This paper reviews findings from the last 10 years of animal models investigating the behavioral and mechanistic effects of solvent abuse. In research with animal models of inhalant abuse, NMDA, GABA(A), glycine, nicotine, and 5HT(3) receptors appear to be important targets of action for several abused solvents with emerging evidence suggesting that other receptor subtypes and nerve membrane ion channels may be involved as well. The behavioral effects vary in magnitude and duration among the solvents investigated. The behavioral effects of acute and chronic inhalant abuse include motor impairment, alterations in spontaneous motor activity, anticonvulsant effects, anxiolytic

effects, sensory effects, and effects on learning, memory and operant behavior (e.g., response rates and discriminative stimulus effects). In addition, repeated exposure to these solvents may produce tolerance, dependence and/or sensitization to these effects.

Measuring Air Quality to Protect Children from Secondhand Smoke in Cars

Rees, V.W., and Connolly, G.N. Am J Prev Med. 31(5), pp. 363-368, November 2006.

INVEST Fellow: Vaughan W. Rees, Australia, 1999-2000

Secondhand tobacco smoke (SHS) is a major, preventable contributor to acute and chronic adverse health outcomes that affect children disproportionately. The predominant source of SHS among children is domestic exposure, and while up to two thirds of U.S. households have car smoking bans, an unacceptable number of children remain vulnerable. To help promote more effective protection through legislation, health communication strategies, or behavioral interventions, data demonstrating the adverse effect of SHS on air quality in cars are needed. Secondhand tobacco smoke in a motor vehicle under actual driving conditions was monitored by measuring respirable suspended particles (RSPs) of less than 2.5 microns in diameter, and carbon monoxide. Forty-five driving trials were conducted, using teams of volunteer drivers and smokers recruited from the general community. Three smoking conditions (nonsmoking baseline, active smoking, and immediate post-smoking period, each 5 minutes) were crossed with two ventilation conditions (windows open, closed) in a 3 x 2 within-sessions factorial design. The highest mean observed RSP level was 271 mug/m(3), which is unsafe, particularly for children. Peak RSP levels were considerably higher. RSPs and carbon monoxide increased significantly from baseline after smoking, and these increases were greatest during the closed ventilation condition, compared with open ventilation. Authors concluded that private passenger cars are a domestic environment with the potential to yield unsafe levels of SHS contaminants. These data may assist policymakers and health advocates to promote protective strategies to ensure smoke-free domestic environments for children.

Searching for Polymorphisms that Affect Gene Expression and mRNA Processing: Example ABCB1 (MDR1)

Wang, D., and Sadee, W. AAPS J. 8(3), pp. E515-520, August 2006. Review.

INVEST Fellow: Danxin Wang, China, 1996-1997.

Cis-acting genetic variations can affect the amount and structure of mRNA/protein. Genomic surveys indicate that polymorphisms affecting transcription and mRNA processing, including splicing and turnover, may account for the main share of genetic factors in human phenotypic variability; however, most of these polymorphisms remain yet to be discovered. The authors use allelic expression imbalance (AEI) as a quantitative phenotype in the search for functional cis-acting polymorphisms in many genes, including ABCB1 (multidrug resistance 1 gene, MDR1, Pgp). Previous studies have shown that ABCB1 activity correlates with a synonymous polymorphism, C3435T; however, the functional polymorphism and molecular mechanism underlying this clinical association remained unknown. Analysis of allele-specific expression in liver autopsy samples and in vitro expression experiments showed that C3435T represents a main functional polymorphism, accounting for 1.5- to 2-fold changes in mRNA levels. The mechanism appears to involve increased mRNA turnover, probably as a result of different folding structures calculated for mRNA with the Mfold program. Other examples of the successful application of AEI analysis for studying functional polymorphism include 5-HTT (serotonin transporter, SLC6A4) and OPRM1 (mu opioid receptor). AEI is therefore a powerful approach for detecting cis-acting polymorphisms affecting gene expression and mRNA processing.

Former Hubert H. Humphrey Drug Abuse Research Fellows

Marked Ethnic Differences in HIV Prevalence and Risk Behaviors among Injection Drug Users in Dushanbe, Tajikistan, 2004
Stachowiak, J.A., Tishkova, F.K., Strathdee, S.A., Stibich, M.A., Latypov, A., Mogilnii, V., and Beyrer, C. Drug Alcohol Depend. 82 Suppl 1:S7-14, April 2006.
HHH Fellow: Alisher Latypov, Tajikistan, 2002-2003
The purpose of this study was to examine differences by ethnicity of HIV prevalence and correlates among injection drug users (IDUs) in Dushanbe, Tajikistan. The researchers enrolled 489 active adult IDUs in a cross-sectional risk factor study of HIV infection. Participants were provided HIV pre-and posttest counseling and risk reduction counseling and answered an interviewer-administered questionnaire. HIV-1 status was determined with rapid tests and confirmed with ELISA. Participants included four ethnicities: 204 Tajiks (49.1%), 145 Russians (29.7%), 58 Uzbeks (11.9%), and 46 participants of other nationalities (9.4%). Overall prevalence of HIV-1 infection was 12% and varied significantly by ethnicity: it was highest among ethnic Tajiks, at 19.2%; lowest among Russians and Uzbeks, at 3.4%; and 13% among other nationalities. Ethnic groups differed significantly in years injecting, receiving a needle from a needle exchange program (NEP), injecting in groups, having undergone drug treatment, reported condom use, and arrest history. Among Tajiks, HIV infection was significantly associated with daily injecting (OR 2.16); reporting that narcotics were very easy to obtain (OR 2.46); having undergone drug treatment (OR 2.75), and injecting "alone" (OR 3.12). The authors concluded that ethnic differences were strongly associated with HIV prevalence and risk behaviors in this multiethnic study, and prevention efforts might need to be targeted by ethnicity.

Hepatitis C Virus Infection among Injecting Drug Users in the Czech Republic -- Prevalence and Associated Factors
Zabransky, T., Mravcik, V., Korcisova, B., and Rehak, V. Czech National Focal Point for Drugs and Drug Addiction, Praha-Mala Strana, Czech Republic. Eur Addict Res. 12(3), pp. 151-160, 2006.
HHH Fellow: Tomas Zabransky, Czech Republic, 2003-2004
The aim of this study was to determine the prevalence of, and factors associated with, hepatitis C virus (HCV) infection in the population of Czech injecting drug users (IDUs) in a multicentric cross-sectional study. A convenience sample of injecting drug users was recruited using the snowball sampling method. Participants comprised a sample of 760 IDUs from 9 different Czech regions. Authors used one-drop instant blood tests to determine the anti-HCV antibodies status; a structured questionnaire was completed during the interview with the researcher. They calculated the ratio of positive findings and performed univariate analyses of correlations between predictors and independent variables. Finally, they created a logistic regression model that controlled for age, region of residence, reported sharing of injection paraphernalia, and length of injection drug use and for the interaction between length of injection use and imprisonment in order to assess the predictive value of imprisonment in an individual's history. 226 participants (29.74% of the tested sample) were found to be anti-HCV positive. After adjusting for the sensitivity of the test, the 'true proportion' was 34.97% (95% CI: 31.56-38.35). Many correlated independent variables were found in the univariate analyses. In this logistic regression model, the authors have found that imprisonment increases the odds of being anti-HCV positive by a factor of 4.3. The authors concluded that anti-HCV seroprevalence remains relatively low in the Czech IDUs population compared to similar populations in the developed countries. Regional differences exist in anti-HCV prevalence within the Czech Republic. The strong association of anti-HCV prevalence with imprisonment history when controlled for other potentially clinically important factors suggests the need for more effective preventive measures in Czech prisons.

Director's Report to the National Advisory Council on Drug Abuse - February, 2007

Research Findings - Intramural Research

Development and Plasticity Section, Cellular Neurobiology Research Branch

An In Vitro Model of Human Dopaminergic Neurons Derived from Embryonic Stem Cells: MPP(+) Toxicity and GDNF Neuroprotection Human embryonic stem cells (hESCs) can proliferate indefinitely yet also differentiate in vitro, allowing normal human neurons to be generated in unlimited numbers. Here, IRP investigators describe the development of an in vitro neurotoxicity assay using human dopaminergic neurons derived from hESCs. The authors showed that the dopaminergic neurotoxin 1-methyl-4-phenylpyridinium (MPP(+)), which produces features of Parkinson's disease in humans, was toxic for hESC-derived dopaminergic neurons. Treatment with glial cell line-derived neurotrophic factor protected tyrosine hydroxylase-positive neurons against MPP(+)-induced apoptotic cell death and loss of neuronal processes as well as against the formation of intracellular reactive oxygen species. The availability of human dopaminergic neurons, derived from hESCs, therefore allows for the possibility of directly examining the unique features of human dopaminergic neurons with respect to their responses to pharmacological agents as well as environmental and chemical toxins. Zeng, X., Chen, J., Deng, X., Liu., Y., Rao, M., Cadet, J.L., and Freed, W.J. Neuropsychopharmacology, 31(12), pp. 2708-2715, 2006.

GABAergic Lineage Differentiation of AF5 Neural Progenitor Cells In Vitro AF5 neural cells derived from fetal rat mesencephalic tissue were immortalized with a truncated SV40 LT vector lacking the p53-inactivating domain to maintain long-term cultures with a p53-responsive phenotype. This study examined p53 function in producing programmed cell death in propagating AF5 neural cells after exposure to hydrogen peroxide (H2O2) and the kinase inhibitor staurosporine (STSP). Concentration-dependent exposure of AF5 cells to 0-800 mM H2O2 and STSP at 0-1000 nM revealed increasing cytotoxicity from MTS cell viability assays. Apoptosis occurred at 400 mM H2O2 as evidenced by subG1 DNA and Annexin V flow cytometry analyses and cellular immunofluorescence staining with propidium iodide, anti-Annexin V and DAPI. DNA fragmentation, caspase-3/7 activity and cytochrome c release into cytosol also confirmed H2O2-mediated apoptotic events. p53 protein levels were increased over 24 h by H2O2 in a coordinated fashion with mdm2 expression. p53 activation by H2O2 was evidenced by elevated Ser15 phosphorylation, increased luciferase p53 reporter activity and upregulation of the downstream p53 targets p21(waf1) and apoptotic proteins, bax, Noxa and PUMA. STSP exposure produced apoptosis demonstrated by DNA fragmentation, caspase-3/7 activity, cytochrome c release and over 24 h was accompanied by sustained increase in p53 and Ser15 phosphorylation, rise in p21(waf1) and bax and a transient increase in p53 reporter activity but without

Annexin V binding. These findings demonstrate that AF5 cells undergo apoptosis in response to H2O2-mediated oxidative stress and signal pathway disruption by STSP that therefore would be useful in studies related to p53-dependent neuronal cell death and neurodegeneration. McNeill-Blue, C., Wetmore, B.A., Sanchez, J.F., Freed, W.J., and Merrick, B.A. Brain Res, 1112(1), pp. 1-15, 2006.

Cellular Pathobiology Unit, Development and Plasticity Section, Cellular Neurobiology Research Branch

Chronic Antidepressants Potentiate via Sigma-1 Receptors the Brain-Derived Neurotrophic Factor-Induced Signaling for Glutamate Release Up-regulation of BDNF (brain-derived neurotrophic factor) has been suggested to contribute to the action of antidepressants. However, it is unclear whether chronic treatment with antidepressants may influence acute BDNF signaling in central nervous system neurons. Because BDNF has been shown by us to reinforce excitatory glutamatergic transmission in cultured cortical neurons via the phospholipase-gamma (PLC-gamma)/inositol 1,4,5-trisphosphate (IP3)/Ca2+ pathway (Numakawa, T., Yamagishi, S., Adachi, N., Matsumoto, T., Yokomaku, D., Yamada, M., and Hatanaka, H. J. Biol. Chem. 277, pp. 6520-6529, 2002), IRP investigators examined in this study the possible effects of pretreatment with antidepressants on the BDNF signaling through the PLC-gamma)/IP3/Ca2+ pathway. Furthermore, because the PLC-gamma/IP3/Ca2+ pathway is regulated by sigma-1 receptors (Hayashi, T., and Su, T.P. Proc. Natl. Acad. Sci. U. S. A. 98, pp. 491-496, 2001), authors examined whether the BDNF signaling is modulated by sigma-1 receptors (Sig-1R). Authors found that the BDNF-stimulated PLC-gamma activation and the ensued increase in intracellular Ca2+ ([Ca2+]i) were potentiated by pretreatment with imipramine or fluvoxamine, so was the BDNF-induced glutamate release. Furthermore, enhancement of the interaction between PLC-gamma and TrkB (receptor for BDNF) after imipramine pretreatment was observed. Interestingly, BD1047, a potent Sig-1R antagonist, blocked the imipramine-dependent potentiation on the BDNF-induced PLC-gamma activation and glutamate release. In contrast, overexpression of Sig-1R per se, without antidepressant pretreatment, enhances BDNF-induced PLC-gamma activation and glutamate release. These results suggest that antidepressant pretreatment selectively enhance the BDNF signaling on the PLC-gamma/IP3/Ca2+ pathway via Sig-1R, and that Sig-1R plays an important role in BDNF signaling leading to glutamate release. Yagasaki, Y., Numakawa, T., Kumamaru, E., Hayashi, T., Su, T.P., and Kunugi, H. Journal of Biological Chemistry, 281(18), pp. 12941-12949, 2006.

Proteomics Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Allosteric Modulation of Dopamine D2 Receptors by Homocysteine It has been suggested that L-DOPA-induced hyperhomocysteinemia can increase the risk of stroke, heart disease, and dementia and is an additional pathogenetic factor involved in the progression of Parkinson's disease. In Chinese hamster ovary (CHO) cells stably cotransfected with adenosine A(2A) and dopamine D2 receptors, homocysteine selectively decreased the ability of D2 receptor stimulation to internalize adenosine A(2A)-dopamine D2 receptor complexes. Radioligand-binding experiments in the same cell line demonstrated that homocysteine acts as an allosteric D2 receptor antagonist, by selectively reducing the affinity of D2 receptors for agonists but not for antagonists. Mass spectrometric analysis showed that, by means of an arginine (Arg)-thiol electrostatic interaction, homocysteine forms noncovalent complexes with the two Arg-rich epitopes of the third intracellular loop of the D2 receptor, one of them involved in A(2A)-D2 receptor heteromerization. However, homocysteine was unable to prevent or disrupt A(2A)-D2 receptor

Planned Meetings

Publications

Staff Highlights

Grantee Honors

heteromerization, as demonstrated with Fluorescence Resonance Energy Transfer (FRET) experiments in stably cotransfected HEK cells. The present results could have implications for Parkinson's disease. Agnati, L.F., Ferre, S., Genedani, S., Leo, G., Guidolin, D., Filaferro, M., Carriba, P., Casado, V., Lluis, C., Franco, R., Woods, A.S., and Fuxe, K. Journal of Proteome Research, 5(11), pp. 3077-3083, 2006.

Molecular Neurobiology Research Branch

Whole Genome Association Studies of Human Addiction Vulnerability Addictions are substantially-heritable complex disorders. This work reports whole genome association studies that identify 88 genes likely to contain variants that contribute to vulnerability to addictions. Each of these genes contains clustered SNPs that display significant allele frequency differences between abusers and controls in each of two samples studied with 639,401 SNP arrays and confirmatory SNPs from each of two other abuser/control samples studied with 100k arrays. These genes are implicated in interesting functions that include "cell adhesion" processes that are important for establishing and maintaining neuronal connections of special relevance to addiction's memory-like features. Liu, Q.R., Drgon, T., Johnson, C., Walther, D., Hess, J., and Uhl, G.R. Am J Med Genet B Neuropsychiatr Genet. 2006 Nov 10; [Epub ahead of print].

Fine Mapping of Human Addiction Vulnerability Loci: Chromosome 4 GABA A Receptor Gene Cluster Strong genetic contributions to individual differences in vulnerability to addictions are well supported by classical genetic studies. Linkage and association genome scans for addiction vulnerability have provided converging evidence for several chromosomal regions which are likely to harbor allelic variants that contribute to such vulnerability. IRP scientists and others have delineated a candidate addiction-associated chromosome 4p12 "rSA3" region based on convergent data from association genome scanning studies in polysubstance abusers (Uhl and others 2001), linkage based studies in alcoholism (Long and others 1998; Reich and others 1998) and association-based studies for alcoholism and association-based studies for individual differences in electroencephalographic (EEG) spectral power phenotypes (Edenberg and others 2004; Porjesz and others 2002). The rSA3 region contains interesting candidate genes that encode the alpha2, alpha4, beta1 and gamma1 receptor subunits for the principal brain inhibitory neuron-transmitter, GABA (Covault and others 2004; Edenberg and others 2004; Lappalainen and others 2005). The authors now report assessment of single nucleotide polymorphism (SNP) genotypes in this region in three samples of substance abusers and controls. These results delineate the haplotypes and patterns of linkage disequilibrium in this region, focus attention of the GABRA2 gene and identify modest associations between GABRA2 genotypes and addiction phenotypes. These results are consistent with modest roles for GABRA2 variants in addiction vulnerabilities. Drgon, T., D'Addario, C., and Uhl, G.R. Am J Med Genet B Neuropsych Genet., 2006.

CB2 Receptors in Brain Brain expression of CB2 cannabanoid receptors has been much less well established and characterized in comparison to the expression of brain CB1 receptors. Since CB2 receptors are intensely expressed in peripheral and immune tissues, expression in brain microglia has been anticipated. This work describes expression of CB2 receptor like immunoreactivity in brain in neuronal patterns that support broader CNS roles for this receptor. These studies, and initial RT-PCR and in situ hybridization analyses of brain CB1 and CB2 mRNAs, also supported brain CB2 expression at levels much lower than those of CB1 receptors. Immunohistochemical analyses revealed abundant CB2 immunostaining in apparent neuronal and glial processes in a number of brain areas. Cerebellar Purkinje cells and hippocampal pyramidal cells revealed substantial immunoreactivity that was absent when sections were stained with preadsorbed sera. CB2

immunoreactivity was also observed in olfactory tubercle, islands of Calleja, cerebral cortex, striatum, thalamic nuclei, hippocampus, amygdale, substantia nigra, periaqueductal gray, paratrochlear nucleus, paralemniscal nucleus, red nucleus, pontine nuclei, inferior colliculus and the parvicellular portion of the medial vestibular nucleus. CB2 immunoreactivity was also present in cells of primary hippocampal cultures. Two anti-CB2 affinity purified polyclonal antibodies were raised in rabbits immunized with peptide conjugates that corresponded to amino acids 1-33 and 20-33. Western blot analyses revealed specific bands that were identified using these sera and were absent when the sera were preadsorbed with 8.3 The multifocal expression of CB2 immunoreactivity in neuronal and glial patterns in a number of brain regions suggests reevaluation of the possible roles that CB2 receptors may play in the brain. Onaivi, E.S., Ishiguro, H., Gong, J.P,, Patel, S., Perchuk, A., Meozzi, P.A., Myers, L., Mora, Z., Tagliaferro, P., Gardner, E., Brusco, A., Akinshola, B.E., Liu, Q.R., Hope, B., Iwasaki, S., Arinami, T., Teasenfitz, L., and Uhl, G.R. Ann N Y Acad Sci. 1074, pp. 514-553, August 2006.

Psychobiology Section, Medications Discovery Research Branch

The Effects of Dopamine Receptor Agonists on Food-maintained Operant Behavior Dopamine D1-like agonists have been proposed as potential treatments for cocaine abuse, however, the pharmacology of these drugs is complex and poorly understood. IRP investigators compared the effects on behavior of several D1 dopamine receptor agonists (SKF 38393, SKF 77434 and SKF 82958), both alone and in combination with the D1-receptor antagonist, SCH 23390. Each drug produced dose related reductions in the rate of a learned behavior, in order of potency: SKF 82958 > SKF 77434 > SKF 38393. Antagonism of these behavioral effects by SCH 23390 was only significant for SKF 82958; surprisingly, SCH 23390 enhanced the effects of SKF 38393. For SKF 82958, the antagonism was receptor subtype-specific, since the D2-receptor antagonist spiperone was ineffective. The non-selective serotonergic antagonist metergoline produced a significant rightward shift of the SKF 38393 dose-response function, indicating effective antagonism. Because the behavioral effects of D1-receptor agonists differed in their susceptibility to antagonism by D1-receptor antagonists, the results support the view of substantial mechanistic differences among drugs suggested to act through D1 dopamine receptors, and that the manner in which they produce their behavioral effects needs to be carefully studied with their evaluation as potential treatments for cocaine abuse. Katz, J.L., Kopajtic, T.A. and Terry, P. Behavioural Pharmacology, 17, pp. 303-309, 2006.

Medicinal Chemistry Section, Medications Discovery Research Branch

Structure-Activity Relationship Studies on a Novel Series of Benztropine Analogs for In Vivo Investigation IRP scientists have discovered that in general, benztropine-based dopamine uptake inhibitors do not demonstrate cocaine-like pharmacological activity in animal models of psychostimulant abuse and have been proposed as potential medications for the treatment of cocaine addiction. However, several (S)-2-carboalkoxy-substituted-analogues were discovered to stimulate locomotor activity and substitute in subjects trained to discriminate cocaine, suggesting a role of the 2-position substituent in mediating these cocaine-like actions. Hence, a novel a series of N- and 2-substituted-benztropine analogs were designed and synthesized to further explore the pharmacological profiles of this class of compounds. Most of these analogues demonstrated high binding affinities to the dopamine transporter (DAT; Ki=1.8-40 nM), and were selective over the other monoamine transporters and muscarinic M1 receptors. For example, when the (S)-2-carboalkoxy substituent was replaced with (S)-2-ethenyl, the resulting analogue demonstrated the highest DAT binding affinity in the series

(Ki=1.81 nM) with DAT selectivity over serotonin transporters (SERT; 989-fold), norepinephrine transporters (NET; 261-fold) and muscarinic receptors (90-fold). The behavioral profiles of several analogues were evaluated and it was discovered that manipulation of the 2-, N- and 3-position substituents in the benztropine class of dopamine uptake inhibitors can result in ligands with high affinity and selectivity for the DAT, but distinctive in vivo pharmacological profiles that cannot be predicted by their effects in vitro. Zou, M.-F., Cao, J., Kopajtic, T., Desai, R. I., Katz, J. L., Newman, A. H. Journal of Medicinal Chemistry 49, pp. 6391-6399, 2006.

Design and Synthesis of a Novel Photoaffinity Ligand for the Dopamine and Serotonin Transporters Tropane-based photoaffinity ligands covalently bind to discrete points of attachment on the dopamine transporter (DAT). To further explore structure-activity relationships, a ligand in which the photoactivatable azido-group was extended from the 3-position of the tropane ring was synthesized from cocaine via a Stille or Suzuki coupling strategy. The resulting ligand, JHC 2-48, demonstrated high binding affinity for the DAT (Ki=15.1+/-2.2 nM). Moreover, this compound showed moderate binding affinity for the serotonin transporter (SERT, Ki=109+/-14 nM) suggesting the potential utility of the radioligand [125I]JHC 2-48 in both DAT and SERT protein structure studies. Newman, A.H., Cha, J.H., Cao, J., Kopajtic, T., Katz, J.L., Parnas, M.L., Vaughan, R., and Lever, R., Journal of Medicinal Chemistry, published online October 5, 2006.

Novel Analogues of the Dopamine D2 Receptor Antagonist L741,626 A series of analogues of the dopamine D2 receptor antagonist L741,626 were synthesized and evaluated for binding and function at D2 family receptor subtypes. Several analogues showed comparable binding profiles to the parent ligand, however, in general, chemical modification served to reduce D2 binding affinity and selectivity. Nevertheless, one analogue demonstrated a comparable binding profile to the parent ligand and may have utility in in vivo studies of drug addiction. Grundt, P., Husbands, S.L.J., Luedtke, R.R., Taylor, M., and Newman, A.H., Bioorganic Medicinal Chemistry Letters, published online October 29, 2006.

Clinical Psychopharmacology Section, Chemical Biology Research Branch

Amphetamine Analogs Increase Plasma Serotonin: Implications for Cardiac and Pulmonary Disease Elevations in plasma serotonin (5-HT) have been implicated in the pathogenesis of cardiac and pulmonary disease. Normally, plasma 5-HT concentrations are kept low by transporter-mediated uptake of 5-HT into platelets and by metabolism to 5-hydroxyindoleacetic acid (5-HIAA). Many abused drugs (e.g., substituted amphetamines) and prescribed medications (e.g., fluoxetine) target 5-HT transporters and could thereby influence circulating 5-HT. IRP scientists evaluated the effects of amphetamines analogs [(+/-)-fenfluramine, (+/-)-3,4-methylenedioxymethamphetamine, (+)-methamphetamine, (+)-amphetamine, phentermine] on extracellular levels (i.e., plasma levels) of 5-HT and 5-HIAA in blood from catheterized rats. Effects of the 5-HT uptake blocker fluoxetine were examined for comparison. Drugs were tested in vivo and in vitro; plasma indoles were measured using a novel microdialysis method in whole blood. Authors found that baseline dialysate levels of 5-HT are approximately 0.22 nM, and amphetamine analogs evoke large dose-dependent increases in plasma 5-HT ranging from 4 to 20 nM. The ability of drugs to elevate plasma 5-HT is positively correlated with their potency as 5-HT transporter substrates. Fluoxetine produced small, but significant, increases in plasma 5-HT. Although the drug-evoked 5-HT concentrations are below the micromolar levels required for contraction of pulmonary arteries, they approach concentrations reported to stimulate mitogenesis in pulmonary artery smooth muscle cells. Additional studies are

needed to determine the effects of chronic administration of amphetamines on circulating 5-HT. Zolkowska, D., Rothman, R.B., and Baumann, M.H. J Pharmacol Exp Ther. 318, pp. 604-610, 2006.

Neuropsychopharmacology Section, Chemical Biology Research Branch

Slow-Onset Long-Duration Methylphenidate Analogs with Increased Selectivity for the Dopamine Transporter IRP scientists have previously synthesized indanamine-structure molecules that produce exceedingly slow-onset long-duration inhibition of presynaptic dopamine reuptake in the addiction-related synapses of the nucleus accumbens of the forebrain. Now, these scientists have synthesized slow-onset long-duration dopamine reuptake inhibitors of the methylphenidate chemical class. Based on a molecular modeling/superimposition model of methylphenidate with tropane-containing compounds, they hypothesized that methylphenidate analogs with the ester moiety replaced by an alkyl group should be active and have longer durations of action - potentially useful as anti-addiction medications. Many analogs were synthesized and tested using transfected human monoamine transporters. Many of the RR/SS diastereomers proved to have low nanomolar potencies in the transporter assays, and compounds with a para-Cl group had good selectivity for the dopamine transporter. In the 3,4-diCl series, RS/SR diastereomers showed significant, low nanomolar activity. In a rodent locomotor assay, one of the 4-Cl compounds (CTDP-32,476) showed a slow-onset long-duration profile that may be predictive of clinical utility as an anti-addiction medication. This same compound also showed a slow-onset, long-duration profile as assessed by in vivo brain microdialysis and by electrical brain-stimulation reward in laboratory animals - profiles that have in the past been predictive of potential clinical utility. One 4-Cl compound in the series (CTDP-32,648) met the dopamine selectivity criteria of the NIDA Cocaine Treatment Discovery Program and is being advanced by them as a possible treatment for cocaine abuse. Froimowitz, M., Gu, Y., Dakin, L.A., Kelley, C.J., Parrish, D., Deschamps, J.R., Pak, A.C., Gilbert, J.G., Peng, X.-Q., Xi, Z.-X. and Gardner, E.L., Poster, 2006. College on Problems of Drug Dependence Annual Meeting, Scottsdale, AZ, June 17-22, 2006.

Methadone Pretreatment Attenuates Heroin's Rewarding Effects and Heroin-Induced Dopamine Release in the Nucleus Accumbens: Comparison to the Effects of CTDP-31,345, a Long-Acting Dopamine Transporter Inhibitor IRP scientists have been investigating the possible utility of slow-onset long-duration monoamine transporter inhibitors as potential pharmacotherapies for psychostimulant addiction. In a conceptually analogous vein, methadone and l-_-acetyl-methadol (long-acting opiate receptor agonists), have proven to be successful treatments for opiate addiction. The long-acting dopamine transporter (DAT) inhibitors CTDP-31,345 or CTDP-32,476 have additive effects with cocaine in preclinical animal test systems. To further evaluate the potential utility of these DAT inhibitors for the treatment of psychostimulant addiction, these scientists observed the effects of methadone pretreatment on heroin self-administration and heroin-induced dopamine release in the nucleus accumbens. They found that methadone inhibited heroin self-administration in rats. In vivo microdialysis demonstrated that methadone significantly elevated extracellular dopamine, lasting for about 4 hours. However, pretreatment with methadone significantly attenuated acute heroin-induced increases in extracellular dopamine in the nucleus accumbens. Thus, methadone pretreatment appears to attenuate heroin-induced DA release, contrary to the effects of DAT inhibitors on cocaine-induced increases in nucleus accumbens dopamine. These data suggest that the analogy between methadone for opiate addiction and slow-onset long-duration DAT inhibitors for psychostimulant addiction may be more analogy than homology. Although more studies will be required to further determine the mechanisms of actions

produced by methadone and DAT inhibitors, respectively, the present data raise serious conceptual concerns about the utility of slow-onset long-acting DAT inhibitors for the pharmacotherapeutic treatment of psychostimulant addiction. Peng, X.-Q., Xi, Z.-X., Li, X., Gilbert, J.G., Pak, A.C., Froimowitz, M. and Gardner, E.L., Poster, 2006. Society for Neuroscience Annual Meeting, Atlanta, GA, October 14-18, 2006.

Gamma-Vinyl GABA Inhibits Cocaine-Primed Relapse to Drug-Seeking Behavior by a Dopamine-Independent Mechanism IRP scientists have previously shown that gamma-vinyl GABA (GVG), a suicide inhibitor of GABA transaminase in the brain, shows a promising anti-addiction profile in preclinical animal models related to addiction. In the present research, these same scientists investigated whether and how GVG inhibits cocaine-triggered relapse to drug-seeking behavior in laboratory rats. Systemic administration of GVG (25-300 mg/kg i.p.) dose-dependently inhibited cocaine-triggered relapse. However, the mechanism appears to be DA-independent, because GVG pretreatment failed to block cocaine-induced increases in extracellular dopamine (DA) in the reward- and relapse-related nucleus accumbens. GVG alone also failed to alter extraellular DA. In contrast, GVG pretreatment produced an additive or synergistic increase with cocaine on extracellular glutamate, and dose-dependently elevated extracellular GABA levels. Finally, GVG-induced increase in glutamate is tetrodotoxin-dependent, while GVG-induced increases in GABA were partially blocked by blockade of type 1 GABA transporters. Together, the present data, for the first time, demonstrate that GVG inhibits cocaine-triggered relapse by a mechanism correlated to GVG-induced increases in GABA and/or glutamate, but not to a decrease in cocaine-induced increases in nucleus accumbens DA. Gardner, E.L., and Xi, Z.-X. Acta Pharmacologica Sinica, 51[suppl.1], p. 96, 2006.

S-(+)-Gamma Vinyl GABA (S-GVG) Blocks the Response to Methamphetamine in Adolescent and Adult Animals Treated with Methamphetamine and S-GVG During Adolescence IRP scientists have previously shown that gamma-vinyl GABA, a suicide inhibitor of GABA transaminase in the brain, shows a promising anti-addiction profile in preclinical animal models related to addiction. In the present research, these same scientists used small animal neuroimaging with [11C]-raclopride and [18F]-fluorodeoxyglucose positron emission tomography (PET) to examine the effects of S-GVG on methamphetamine-induced increases in brain dopamine and metabolism, respectively. Adolescent rats received baseline PET scans, then received a methamphetamine challenge followed by more PET scans. Methamphetamine significantly reduced the striatal binding of [11C]-raclopride (i.e., caused an increase in extracellular dopamine) and increased [18F]-fluorodeoxyglucose cortically, subcortically, and in the cerebellum. There were no effects of methamphetamine on [18F]-fluorodeoxyglucose uptake. However, an acute dose of S-GVG (150 mg/kg; 2.5 h prior to the methamphetamine challenge) completely abolished these increases, as it blocked the expression of methamphetamine-induced conditioned place preference. These adolescent animals were then placed on subchronic S-GVG (150 mg/kg/day) for 5 days. This subchronic S-GVG treatment blocked methamphetamine-triggered reactivation of this expression of conditioned place preference. As adults (> 90 days old), these animals received another methamphetamine-challenge during [18F]-fluorodeoxyglucose uptake. Adolescent exposure to S-GVG attenuated methamphetamine-induced changes in [18F]-fluorodeoxyglucose uptake in the adult animals. In sum, these data suggest that S-GVG may constitute an effective strategy for blocking the biochemical and behavioral effects associated with methamphetamine abuse. Dewey, S.L., Schiffer, W.K., Lee, D., Aquilina, S., Kothari, S., Mullapudi, U., Patel, V., Fowler, J., Gardner, E., Ashby, C.R. Jr., and Brodie, J.D., Poster, 2006. College on Problems of Drug Dependence Annual Meeting, Scottsdale, AZ, June 17-22, 2006.

Gabapentin has no Effect on Cocaine-Triggered Relapse to Drug-

Seeking Behavior or on Cocaine-Induced Dopamine Increases in the Nucleus Accumbens of the Brain IRP scientists have previously shown that gamma-vinyl GABA shows a promising anti-addiction profile in preclinical animal models related to addiction. Since gamma-vinyl GABA is a GABAmimetic (i.e., enhances brain levels of the neurotransmitter GABA), these same scientists have now extended these studies to another GABAmimetic - gabapentin. Gabapentin's actions in the brain may involve increases in synthesis and nonvesicular release of GABA, as well as prevention of GABA catabolism. Gabapentin reportedly inhibits the subjective effects (the "high") of smoked cocaine. In the present research, IRP scientists investigated whether gabapentin attenuates intravenous cocaine self-administration, cocaine-triggered relapse to cocaine-seeking behavior, and cocaine-induced increases in the neurotransmitter dopamine in the addiction-related brain locus - the nucleus accumbens. Gabapentin failed to alter cocaine-induced reinstatement (relapse) of cocaine-seeking behavior in laboratory rats previously experienced at intravenous cocaine self-administration. In vivo brain microdialysis studies demonstrated that acute cocaine administration significantly increased extracellular dopamine in the nucleus accumbens, but that this was not altered by pretreatment with gabapentin. These findings are in stark contrast to previous findings by these same investigators that gamma-vinyl GABA significantly inhibits cocaine-triggered relapse to cocaine-seeking behavior in the laboratory rat reinstatement model. These findings strongly suggest that gamma-vinyl GABA's anti-addiction properties in preclinical animal models do not necessarily generalize to other putative GABAmimetic drugs. Li, X., Peng, X.-Q., Gilbert, J., Xi, Z.-X., and Gardner, E.L., Poster, 2006. College on Problems of Drug Dependence Annual Meeting, Scottsdale, AZ, June 17-22, 2006.

Activation of the Metabotropic Glutamate Receptor 7 (mGluR7) by AMN082 Attenuates the Rewarding Effects of Cocaine by a Dopamine-Independent Mechanism in Rats IRP scientists have begun to explore the role played by brain metabotropic glutamate receptors in the rewarding effects (the "high") produced by cocaine. In the present study, IRP scientists studied the role of the metabotropic glutamate receptor 7 (mGluR7) in drug reward and its related neurochemistry using the selective mGluR7 agonist AMN082. These scientists observed that AMN082 dose-dependently inhibited cocaine self-administration behavior under both fixed ratio and progressive-ratio reinforcement schedules, and inhibited cocaine-induced increases in locomotion. These behavioral effects appear to be DA-independent, because the same doses of AMN082 had no effect on cocaine-induced increases in extracellular dopamine in the nucleus accumbens. AMN082 alone, when administered systemically or locally into the nucleus accumbens, dose-dependently decreased extracellular GABA levels, increased extracellular glutamate levels, but had no effect on extracellular dopamine levels in the nucleus accumbens, as measured from the same in vivo brain microdialysis samples. Such agonist-induced increases in glutamate appears to be mediated by reduction in extracellular GABA levels because blockade of nucleus accumbens GABAB receptors with 2-hydroxysaclofen completely blocked AMN082-induced increases in glutamate. Further, AMN082 lowered extracellular glutamate after GABAB receptor blockade. These data, for the first time, demonstrate that activation of mGluR7 inhibits cocaine=s rewarding effects and cocaine-induced hyperactivity by a dopamine-independent mechanism. Presynaptic inhibition mediated by mGluR7 activation on the release of other neurotransmitters, such as GABA or glutamate, may underlie these effects. These findings suggest that the glutamatergic circuitry of the limbic forebrain may constitute a useful target for the development of anti-addiction medications. Li, X., Peng, X.-Q., Gilbert, J.G., Pak, A.C., Xi, Z.-X., and Gardner, E.L., Poster, 2006. Society for Neuroscience Annual Meeting, Atlanta, GA, October 14-18, 2006.

Δ9-Tetrahydrocannabinol (Δ9-THC) Inhibits Glutamate Release in the

Nucleus Accumbens via a non-CB1 Receptor-Mediated Mechanism IRP scientists were the first to establish that Δ9-Tetrahydrocannabinol (Δ9-THC), the addictive constituent of marijuana, acts on the reward circuits of the brain in a manner similar to other addictive drugs. From that prior work, it is widely believed that cannabinoid addictive action is mediated by brain cannabinoid CB1 receptors and by the brain's dopamine system. In contrast, little is known about cannabinoid effects on the glutamate system, which is also proposed to be involved in drug reward and addiction. Now, IRP scientists have used in vivo microdialysis to measure brain extracellular glutamate in freely moving animals. They found that systemic or local Δ9-THC administration lowered extracellular glutamate levels in the nucleus accumbens. This reduction in glutamate appears to be CB1 receptor-independent because: 1) co-administration of Δ9-THC with SR141716A, a CB1 receptor antagonist, failed to reverse local Δ9-THC-induced inhibition of glutamate; and 2) Δ9-THC inhibited glutamate release in the nucleus accumbens in both CB1-knockout mice and littermate wild-type mice. It has been proposed that drug reward and addictive effects are mediated by dopamine-induced inhibition of nucleus accumbens medium spiny GABAergic neurons. If this is true, the presently-observed reduction in glutamatergic input to the nucleus accumbens after Δ9-THC administration might well potentiate such inhibition of the nucleus accumbens medium spiny GABAergic neurons, thus contributing to the rewarding and addictive effects of cannabinoids and Δ9-THC. Xi, Z.-X., Peng, X.-Q., Li, X., Gilbert, J., Pak, A.C., and Gardner, E.L., Poster, 2006. Society for Neuroscience Annual Meeting, Atlanta, GA, October 14-18, 2006.

Behavioral Neuroscience Section, Behavioral Neuroscience Research Branch

Role of Brain Dopamine in Food Reward and Reinforcement The ability of food to establish and maintain response habits and conditioned preferences depends largely on the function of brain dopamine systems. While dopaminergic transmission in the nucleus accumbens appears sufficient for some forms of reward, the role of dopamine in food reward does not appear to be restricted to this region. Dopamine plays an important role in both the ability to energize feeding and to reinforce food-seeking behaviour; the role in energizing feeding is secondary to the prerequisite role in reinforcement. Dopaminergic activation is triggered by the auditory and visual as well as the tactile, olfactory, and gustatory stimuli of foods. While dopamine plays a central role in the feeding and food-seeking of normal animals, some food rewarded learning can be seen in genetically engineered dopamine-deficient mice. Wise, R.A. Philosophical Transactions of the Royal Society B-Biological Sciences, 361(1471), pp. 1149-1158, 2006.

Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch

Blockade of Adenosine A2A Receptors Prevents Protein Phosphorylation in the Striatum Induced by Cortical Stimulation Previous studies have shown that cortical stimulation selectively activates extracellular signal-regulated kinase 1/2 (ERK1/2) phosphorylation and immediate early gene expression in striatal GABAergic enkephalinergic neurons. In the present study, the authors demonstrate that blockade of adenosine A2A receptors with caffeine or a selective A2A receptor antagonist counteracts the striatal activation of cAMP-protein kinase A cascade (phosphorylation of the Ser845 residue of the glutamate receptor 1 subunit of the AMPA receptor) and mitogen-activated protein kinase (ERK1/2 phosphorylation) induced by the in vivo stimulation of corticostriatal afferents. The results indicate that A2A receptors strongly modulate the efficacy of glutamatergic synapses on striatal enkephalinergic neurons. Quiroz, C., Gomes, C., Pak, A. C., Riberiro, J. A., Goldberg, S. R. and Hope, B.T. Journal of

Neuroscience, 26, pp. 10808-10812, 2006.

Anandamide Administration Alone and After Inhibition of Fatty Acid Amide Hydrolase (FAAH) Increases Dopamine Levels in the Nucleus Accumbens Shell Although endogenous cannabinoid systems have been implicated in the modulation of the rewarding effects of abused drugs and food, little is known about the direct effects of endogenous ligands for cannabinoid receptors on brain reward processes. Here IRP scientists show for the first time that the intravenous administration of anandamide, an endogenous ligand for cannabinoid receptors, and its longer-lasting synthetic analog methanandamide, increase the extracellular dopamine levels in the nucleus accumbens shell of awake, freely moving rats, an effect characteristic of most drugs abused by humans. Anandamide produced two distinctly different effects on dopamine levels: (1) a rapid, transient increase that was blocked by the cannabinoid CB1 receptor antagonist rimonabant, but not by the vanilloid VR1 receptor antagonist capsazepine, and was magnified and prolonged by the fatty acid amide hydrolase (FAAH) enzyme inhibitor, URB597; (2) a smaller delayed and long-lasting increase, not sensitive to CB1, VR1 or FAAH blockade. Both effects were blocked by infusing either tetrodotoxin (TTX, 1 microm) or calcium-free Ringer's solution through the microdialysis probe, demonstrating that they were dependent on the physiologic activation of dopaminergic neurotransmission. Thus, these results indicate that anandamide, through the activation of the mesolimbic dopaminergic system, participates in the signaling of brain reward processes. Solinas, M., Justinova, Z., Goldberg, S.R. and Tanda, G. Journal of Neurochemistry, 98, pp. 408-419, 2006.

Intramembrane Receptor-receptor Interactions: A Novel Principle in Molecular Medicine In 1980/81 Agnati and Fuxe introduced the concept of intramembrane receptor-receptor interactions and presented the first experimental observations for their existence in crude membrane preparations. The second step was their introduction of the receptor mosaic hypothesis of the engram in 1982. The third step was their proposal that the existence of intramembrane receptor-receptor interactions made possible the integration of synaptic (WT) and extrasynaptic (VT) signals. With the discovery of the intramembrane receptor-receptor interactions with the likely formation of receptor aggregates of multiple receptors, so called receptor mosaics, the entire decoding process becomes a branched process already at the receptor level in the surface membrane. Recent developments indicate the relevance of cooperativity in intramembrane receptor-receptor interactions namely the presence of regulated cooperativity via receptor-receptor interactions in receptor mosaics (RM) built up of the same type of receptor (homo-oligomers) or of subtypes of the same receptor (RM type1). The receptor-receptor interactions will to a large extent determine the various conformational states of the receptors and their operation will be dependent on the receptor composition (stoichiometry), the spatial organization (topography) and order of receptor activation in the RM. The biochemical and functional integrative implications of the receptor-receptor interactions are outlined and long-lived heteromeric receptor complexes with frozen RM in various nerve cell systems may play an essential role in learning, memory and retrieval processes. Intramembrane receptor-receptor interactions in the brain have given rise to novel strategies for treatment of Parkinson's disease (A2A and mGluR5 receptor antagonists), schizophrenia (A2A and mGluR5 agonists) and depression (galanin receptor antagonists). The A2A/D2, A2A/D3 and A2A/mGluR5 heteromers and heteromeric complexes with their possible participation in different types of RM are described in detail, especially in the cortico-striatal glutamate synapse and its extrasynaptic components, together with a postulated existence of A2A/D4 heteromers. Finally, the impact of intramembrane receptor-receptor interactions in molecular medicine is discussed outside the brain with focus on the endocrine, the cardiovascular and the immune systems. Ciruela, F., Ferre, S., Casado, V., Cortes, A., Cunha, R. A., Lluis, C. and Franco, R. Cellular Molecular Life Sciences, October 19, 2006,

Epubmed ahead of print, PMID 17058035.

Receptor-receptor Interactions Involving Adenosine A(1) or Dopamine D (1) Receptors and Accessory Proteins The molecular basis for the known intramembrane receptor-receptor interactions among heptahelical receptors (G protein coupled receptors, GPCR) was postulated to be heteromerization based on receptor subtype specific interactions between different types of homomers of GPCR. Adenosine and dopamine receptors in the basal ganglia have been fundamental to demonstrate the existence of receptor heteromers and the functional consequences of such molecular interactions. The heterodimer is only one type of heteromeric complex and the evidence is equally compatible with the existence of higher order heteromeric complexes, where also adapter proteins such as homer proteins and scaffolding proteins can exist, assisting in the process of linking the GPCR and ion channel receptors together in a receptor mosaic that may have special integrative value and may constitute the molecular basis for learning and memory. Heteromerization of D(2) dopamine and A(2A) adenosine receptors is reviewed by Fuxe in another article in this special issue. Here, heteromerization between D(1) dopamine and A(1) adenosine receptors is reviewed. Heteromers formed by dopamine D(1) and D(2) receptors and by adenosine A(1) and A(2A) receptors also occur in striatal cells and open new perspectives to understand why two receptors with apparently opposite effects are expressed in the same neuron and in the nerve terminals. The role of accessory proteins also capable of interacting with receptor-receptor heteromers in regulating the traffic and the molecular physiology of these receptors is also discussed. Overall, the knowledge of the reason why such complex networks of receptor-receptor and receptor-protein interactions occur in striatal cells is crucial to develop new strategies to combat neurological and neuropsychiatric diseases. Franco, R., Lluis, C., Canela, E. I., Mallol, J., Agnati, L., Casado, V., Ciruela, F., Ferre, S. and Fuxe, K. Journal of Neural Transmission, October 6, 2006, Epubmed ahead of print, PMID 17024327.

Working Memory Deficits in Transgenic Rats Overexpressing Human Adenosine A(2A) Receptors in the Brain Adenosine receptors in the central nervous system have been implicated in the modulation of different behavioural patterns and cognitive functions although the specific role of A(2A) receptor (A(2A)R) subtype in learning and memory is still unclear. In the present work IRP investigators establish a novel transgenic rat strain, TGR(NSEhA2A), overexpressing adenosine A(2A)Rs mainly in the cerebral cortex, the hippocampal formation, and the cerebellum. Thereafter, the authors explore the relevance of this A(2A)Rs overexpression for learning and memory function. Animals were behaviourally assessed in several learning and memory tasks (6-arms radial tunnel maze, T-maze, object recognition, and several Morris water maze paradigms) and other tests for spontaneous motor activity (open field, hexagonal tunnel maze) and anxiety (plus maze) as modification of these behaviours may interfere with the assessment of cognitive function. Neither motor performance and emotional/anxious-like behaviours were altered by overexpression of A(2A)Rs. TGR(NSEhA2A) showed normal hippocampal-dependent learning of spatial reference memory. However, they presented working memory deficits as detected by performance of constant errors in the blind arms of the 6 arm radial tunnel maze, reduced recognition of a novel object and a lack of learning improvement over four trials on the same day which was not observed over consecutive days in a repeated acquisition paradigm in the Morris water maze. Given the interdependence between adenosinic and dopaminergic function, the present results render the novel TGR(NSEhA2A) as a putative animal model for the working memory deficits and cognitive disruptions related to overstimulation of cortical A(2A)Rs or to dopaminergic prefrontal dysfunction as seen in schizophrenic or Parkinson's disease patients. Gimenez-Llort, L., Schiffmann, S. N., Shmidt, T., Canela, L., Camon, L., Wassholm, M., Canals, M. Terasmaa, A., Fernandez-Teruel, A., Tobena, A., Popova, E., Ferre, S., Agnati, L., Ciruela, F., Martinez, E., Scheel-

Kruger, J., Lluis, C., Franco, R., Fuxe, K. and Bader, M.. Neurobiology Learning Memory, July 4, 2006, Epubmed ahead of print, PMID 16824773.

Effects of Stress Modulation on Morphine-induced Conditioned Place Preferences and Plasma Corticosterone Levels in Fischer, Lewis, and Sprague-Dawley Rat Strains There is a direct relationship between hypothalamic-pituitary-adrenal axis (HPA) reactivity and susceptibility to drug use in outbred rats. Specifically, manipulations that increase or decrease HPA activity also increase or decrease drug intake, respectively. Interestingly, this relationship has not been established in the inbred Fischer (F344) and Lewis (LEW) rat strains that are often used as animal models of susceptibility to drug use. The present study investigated the effects of manipulations known to affect HPA activity on morphine-induced conditioned place preference (CPP) in male LEW, F344, and Sprague-Dawley (SD) rats. In experiment 1, animals were exposed to an injection of methyl-6,7-dimethoxy-4-ethyl-beta-carboline-3-carboxylate (DMCM) and 2-h restraint stress prior to the conditioning of a morphine-induced place preference (1, 4, or 10 mg/kg subcutaneous). In experiment 2, animals were chronically exposed to corticotropin-releasing hormone type 1 receptor antagonist, antalarmin, prior to CPP training. The effects of DMCM/restraint and antalarmin on corticosterone levels were examined in experiments 3 and 4. In outbred rats, DMCM/restraint increased both HPA activity and morphine-induced CPP, while antalarmin decreased CPP and produced a slight, but nonsignificant, decrease in corticosterone levels. In the inbred rats, however, DMCM/restraint increased plasma corticosterone yet decreased place preferences in the LEW strain, and antalarmin treatment decreased plasma corticosterone but increased place preferences in the F344 strain. These data suggest that the relationship between stress and drug use may be nonmonotonic. The use of these inbred strains in genetic analysis of drug addiction may require reexamination. Grakalic, I., Schindler, C.W., Baumann, M.H., Rice, K.C. and Riley, A.L. Psychopharmacology (Berlin), October 3, 2006, Epubmed ahead of print, PMID 17016707.

Cocaine Self-administration Under Variable-dose Schedules in Squirrel Monkeys Squirrel monkeys self-administered cocaine under a variable-dose schedule, with the dose varied from injection to injection. As in earlier studies with rats, post-injection pauses varied as a monotonic function of dose, allowing a cocaine dose-effect curve to be obtained during each session. These curves were shifted by pretreatment with dopamine antagonists, demonstrating that this procedure may provide an efficient means of evaluating treatments that affect drug self-administration. However, drug intake eventually became "dysregulated" after extensive training (100-300 sessions), with relatively short pauses following all doses. Dose-sensitivity was restored by adding a 60-s timeout period after each injection, suggesting that dysregulation occurred because the monkeys developed a tendency to self-administer another injection before the previous injection had been adequately distributed. Finally, when the response requirement under the variable-dose schedule was increased from 1 to 10, both the post-injection pause and the rate of responding following the pause ("run rates") were found to vary with dose. The dose-dependency of run rates suggests that post-injection pauses reflect not only motivational factors, such as satiety, but also the direct effects of cocaine on lever pressing. Panlilio, L.V., Thorndike, E.B. and Schindler, C.W. Pharmacology Biochemistry and Behavior, 84, pp. 235-243, 2006.

Dopamine D(3) Receptor Ligands for the Treatment of Tobacco Dependence Among the 5 dopamine receptors identified, the DRD3 is located in the nucleus accumbens, ventral tegmental area and amygdala: 3 brain structures that are implicated in the motivational control of drug-seeking behaviour and drug-conditioning processes. Although it has been proposed that modulating dopamine transmission would be effective in the treatment of drug dependence, no validation has been provided in humans so far. Several highly selective DRD3 ligands have recently been evaluated in preclinical models of

drug dependence. These ligands act as DRD3 antagonists in vivo and are able to decrease the motivation to take various drugs of abuse and reduce the influence of associated drug-conditioned behaviour. Of note is that these effects have been found with nicotine-seeking behaviour and nicotine relapse in rodents, suggesting a potential use of these ligands for the treatment of tobacco smokers. In contrast to nicotine replacement therapy, varenicline and bupropion (which are currently used for the treatment of smokers), DRD3 antagonists do not seem to produce nicotine-like effects in experimental animals and, therefore, may not substitute for nicotine or alleviate nicotine withdrawal symptoms in human smokers. This behavioural profile, which was also reported recently with cannabinoid CB(1) receptor antagonists, may result from effects on specific brain pathways that express DRD3 receptors and are involved in relapse and conditioning processes. These preclinical studies suggest that the clinical evaluation of DRD3 ligands should be performed with clinical trials designed specifically to evaluate the relapse phenomena. LeFoll, B., Goldberg, S.R. and Sokoloff, P. Expert Opin Investig Drugs, 16, pp. 45-57, 2007.

Neurobiology of Relapse Section, Behavioral Neuroscience Research Branch

The Anxiogenic Drug Yohimbine Reinstates Palatable Food-seeking in a Rat Relapse Model: A Role of CRF1 Receptors The major problem in treating excessive eating is high rates of relapse to maladaptive eating habits during diet treatments; this relapse is often induced by stress or anxiety states. Preclinical studies have not explored this clinical problem. Here, IRP researchers adapted a reinstatement model (commonly used to study relapse to abused drugs) to examine the role of stress and anxiety in relapse to palatable food seeking during dieting. Rats were placed on restricted diet (75-80% of daily standard food) and for 12 intermittent training days (9 h/d, every other day) lever-pressed for palatable food pellets (25% fat, 48% carbohydrate) under a fixed-ratio 1 (20-sec timeout) reinforcement schedule. Subsequently, the rats were given 10 daily extinction sessions during which lever-presses were not reinforced, and were then injected with yohimbine (an alpha-2 adrenoceptor antagonist that induces stress and anxiety in humans and nonhumans) or given a single food pellet to assess reinstatement of food seeking. The rats rapidly learned to lever-press for the palatable pellets and across the training days the ratio of timeout non-reinforced lever-presses to reinforced lever-presses progressively increased more than 3-fold, suggesting the development of compulsive eating-behavior. After extinction, yohimbine injections and pellet priming reliably reinstated food seeking. The corticotropin-releasing factor1 (CRF1) receptor antagonist antalarmin attenuated the reinstatement induced by yohimbine, but not pellet priming. Antalarmin also reversed yohimbine's anxiogenic effects in the social interaction test. These data suggest that CRF is involved in stress-induced relapse to palatable food seeking and that CRF1 antagonists should be considered for the treatment of maladaptive eating habits. Ghitza, U.E., Gray, S.M., Rice, K.C., Epstein, D.E. and Shaham, Y. Neuropsychopharmacology, 31, pp. 2188-2196, 2006.

Activation of Group II Metabotropic Glutamate Receptors in the Nucleus Accumbens Shell Attenuates Context-induced Relapse to Heroin Seeking Using a rat relapse model, IRP scientists previously reported that re-exposing rats to a drug-associated context, following extinction of operant responding in a different context, reinstates heroin seeking. In an initial pharmacological characterization, the authors found that the mGluR2/3 agonist LY379268, which acts centrally to reduce evoked glutamate release, attenuates context-induced reinstatement of heroin seeking when injected systemically or into the ventral tegmental area, the cell body region of the mesolimbic dopamine system. Here, the authors tested whether injections of LY379268 into the nucleus accumbens (NAc), a terminal region of the

mesolimbic dopamine system, would also attenuate context-induced reinstatement of heroin seeking. Rats were trained to self-administer heroin; drug infusions were paired with a discrete tone-light cue. Subsequently, lever pressing was extinguished in the presence of the discrete cue in a context that differed from the drug self-administration context in terms of visual, auditory, tactile, and circadian cues. After extinction of responding, LY379268 was injected to different groups of rats into the NAc core or shell or into the caudate-putamen, a terminal region of the nigrastriatal dopamine system. Injections of LY379268 into the NAc shell (0.3 or 1.0 ug) dose-dependently attenuated context-induced reinstatement of heroin seeking. Injections of 1.0 ug of LY379268 into the NAc core had no effect, while a higher dose (3.0 ug) decreased this reinstatement. Injections of LY379268 (3.0 ug) 1.5 mm dorsal from the NAc core into the caudate-putamen were ineffective. Results suggest an important role of glutamate transmission in the NAc shell in context-induced reinstatement of heroin seeking. Bossert, J.M., Gray, S., Lu, L. and Shaham, Y. Neuropsychopharmacology, 31, pp. 2197-3109, 2006.

Director's Report to the National Advisory Council on Drug Abuse - February, 2007

Program Activities

New NIDA PAs and RFAs

On August 3, 2006, NIDA/CCTN released RFA-DA-07-001, **Announcement of a Limited Competition of THE NATIONAL DRUG ABUSE TREATMENT CLINICAL TRIALS NETWORK (U10)**. This RFA announced a limited competition for competitive renewal applications from established clinical investigators to participate in the National Drug Abuse Treatment Clinical Trials Network (CTN). The competition was restricted to only those institutions that currently house an existing, active Node in the CTN. Six applications were received by the November 28, 2006 receipt date. Initial peer review is planned for February/March 2007.

On September 18, 2006, NIDA issued a Program Announcement (PA) entitled **NIDA Research Education Grants in Drug Abuse and Addiction (R25) (PAR-06-550)**. The NIDA Research Education grant is a flexible and specialized mechanism designed to foster the development of drug addiction researchers through creative and innovative educational programs. Programs that focus on preparing researchers in cross-disciplinary integration and/or translational research of neuroscience, basic behavioral, prevention, clinical, treatment, and services research are particularly encouraged.

On December 6, 2006, NIDA issued a PA entitled **Drug Abuse Prevention Intervention Research (R01) (PA-07-110)**. The goals of this Funding Opportunity Announcement (FOA) are to encourage investigstions of cognitive, behavioral, and social processes as they relate to: 1) the development of novel drug abuse prevention approaches; 2) the efficacy and effectiveness of newly developed and/or modified prevention programs; and 3) the processes associated with the selection, adoption, adaptation, implementation, sustainability and financing of empirically validated intervention; and 4) methodologies appropriate for studying complex aspects of prevention science.

On December 7, 2006, NIDA issued a PA entitled **MDMA: Research Areas Needing More Emphasis (R01) (PA-07-112)**. Through this FOA, NIDA solicits grant applications from institutions/organizations that propose to focus on specific areas of MDMA research, across all research disciplines urgently needing attention.

On December 7, NIDA issued a PA entitled **Health Services Research on Practice Improvement Utilizing Community Treatment Programs within the National Drug Abuse Clinical Trials Network (CTN) (R01) (PA-07-1143)**. This FOA solicits health services research in conjunction with NIDA's Clinical Trials Network (CTN). The CTN is a research partnership between more than 150 community treatment programs (CTPs) and drug abuse researchers in multiple sites across the country. With its extensive network of providers

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servicing diverse populations of drug users, the CTN provides an infrastructure for the investigation of (a) systems-level factors that facilitate practice improvement in community treatment programs and (b) new research tools to facilitate higher quality health services research on practice improvement in drug abuse treatment.

On December 7, 2006, NIDA issued a PA entitled **Drug Abuse as a Cause, Correlate or Consequence of Criminal Justice Related Health Disparities Among African Americans (R01) (PA-007-114)**. This FOA solicits Research Project Grants (R01) applications from institutions/organizations that propose to conduct epidemiologic, prevention, treatment and services research on criminal justice related health disparities among African Americans as it relates to drug abuse and addiction.

On December 8, 2006, NIDA issued a PA entitled Inhalant Abuse: Supporting Broad-Based Research Approaches (R01) (PA-07-117). The goal of this PA is to encourage research on all aspects of inhalant abuse (i.e., epidemiology; prevention, treatment and service delivery; antecedents, consequesnces and neurobiological mechanisms).

On December 8, 2006, NIDA issued a PA entitled **Prescription Drug Abuse (R01) (PA-07-123)**. The purpose of this FOA is to encourage research aimed at reducing prescription drug abuse while supporting appropriate medical use of therapeutic agents with abuse liability. A range of research is needed to combat prescription drug abuse--from specifying the extent and nature of the problem (including health and social consequences) and identifying their determinants, to discovering effective clinical practices that identify those at risk and designing and disseminating prevention and treatment interventions.

On December 8, 2006, NIDA issued a PA entitled **Epidemiology of Drug Abuse (R01) (PA-07-118)**. This FOA is intended to support research projects that address (1) drug use patterns and trends within and across populations; (2) interplay of social interactions, social environment, structural context with individual behavioral characteristics and genetic vulnerability; (3) the phenotypic heterogeneity of drug abuse; (4) causal mechanisms leading to onset, maintenance, and remittance of drug abuse as well as protective mechanisms that reduce the risk of drug abuse; and (5) drug abuse over the life course, including developmental processes that influence drug use trajectories and behavioral, health and social consequences of drug abuse.

On December 14, 2006, NIDA issued a PA entitled **Functional Genetics and Genomics of Drug Addiction (R01) (PA-07-166)**. This FOA encourages basic functional genomic research in two areas: 1) functional validation to determine which candidate genes/variants have an authentic role in addictive processes, and 2) detailed elucidation of the molecular pathways and processes modulated by candidate genes/variants, particularly for those genes with an unanticipated role in addiction. This FOA will utilize the R01 grant mechanism.

On December 14, 2006, NIDA issued a PA entitled **Functional Genetics and Genomics of Drug Addiction (R03) (PA-07-168)**. This FOA encourages basic functional genomic research in two areas: 1) functional validation to determine which candidate genes/variants have an authentic role in addictive processes, and 2) detailed elucidation of the molecular pathways and processes modulated by candidate genes/variants, particularly for those genes with an unanticipated role in addiction. This FOA will utilize the R03 grant mechanism.

On December 14, 2006, NIDA issued a PA entitled **Functional Genetics and Genomics of Drug Addiction (R21) (PA-07-167)**. This FOA encourages basic functional genomic research in two areas: 1) functional validation to determine which candidate genes/variants have an authentic role in addictive processes, and 2) detailed elucidation of the molecular pathways and processes modulated by candidate genes/variants, particularly for those genes with an

Planned Meetings

Publications

Staff Highlights

Grantee Honors

unanticipated role in addiction. This FOA will utilize the R21 grant mechanism.

On December 21, 2006, NIDA issued a PA entitled **Non-Injection Drug Abuse and HIV/AIDS (R21) (PAS-07-262)**. This FOA seeks to understand the contribution of non-injection drug abuse to the acquisition and/or transmission and/or disease progression of HIV/AIDS through use of the R21 mechanism to support new exploratory and developmental research projects.

On December 21, 2006, NIDA issued a PA entitled **Non-Injection Drug Abuse and HIV/AIDS (R03) (PAS-07-261)**. This FOA seeks to understand the contribution of non-injection drug abuse to the acquisition and/or transmission and/or disease progression of HIV/AIDS through use of the NIH Small Research Grant (R03) award mechanism.

On January 5, 2007, NIDA issued a PA entitled **International Research Collaboration on Drug Addiction (R01) (PA-07-275)**. This PA solicits collaborative research proposals on drug abuse and addiction that take advantage of special opportunities that exist outside the United States. Special opportunities include access to unusual talent, resources, populations, or environmental conditions in other countries that will speed scientific discovery. Projects must have relevance to the mission of NIDA and where feasible should address NIDA's scientific priority areas.

On January 9, 2007, NIDA issued a PA entitled **Collaborative Multi-Site Research in Addiction (COMRAD) (R01) (PA-07-286)**. Through this PA, NIDA seeks to increase the collaboration of investigators at two or more sites in order to address critical issues in the epidemiology, services, and prevention of substance abuse and related disorders that require sample sizes or sample diversity greater than a single site can reasonably attain.

On October 17, 2006, NIDA issued an RFA entitled **Development of Immunotherapeutic Products for the Treatment of Methamphetamine Addiction (U01) (RFA-DA-07-004)**. The objective of this solicitation is to support research in the design, synthesis, and pre-clinical evaluation of vaccines developed from methamphetamine-protein conjugates for the active immunotherapeutic treatment of methamphetamine addiction.

On October 17, 2006, NIDA issued an RFA entitled **Design, Synthesis, and Preclinical Testing of Potential Treatment Agents for Drug Addiction (R01) (RFA-DA-07-006)**. This FOA solicits research applications from institutions/organizations that propose design, synthesis, and preclinical testing of potential treatment agents for drug addiction and/or relapse prevention.

On November 16, 2006, NIDA issued an RFA entitled **Brain Imaging Drug Use Prevention Messages (R21) (RFA-DA-07-007)**. The purpose of this FOA is to stimulate exploratory, i.e., descriptive, hypothesis-generating, research on neurobiological responses to substance abuse prevention media messages in humans using established brain imaging methods. There is particular interest in studies across developmental stages and age groups.

On November 3, 2006, NIDA issued an RFA entitled **Extinction and Pharmacotherapies for Drug Addiction (R03) (RFA-DA-07-011)**. The purpose of this FOA is to stimulate research on the mechanisms underlying extinction in order to guide the development of interventions for enhancing extinction of drug-seeking behavior. This FOA will utilize the R03 grant mechanism.

On November 21, 2006, NIDA issued an RFA entitled **Extinction and Pharmacotherapies for Drug Addiction (R01) (RFA-DA-07-010)**. The purpose of this FOA is to stimulate research on the mechanisms underlying extinction in order to guide the development of interventions for enhancing extinction of drug-seeking behavior. This FOA will utilize the R01 grant mechanism.

On October 12, 2006, NIDA issued a Request for Applications entitled **Mechanisms of Drug Abuse Interactions with HIV Neuropathogenesis (R21) RFA-DA-07-003 as well as a Notice of Intent to Publish an R01 Request for Applications to Accompany the Published R01 (NOT-DA-07-001)**. The receipt date for these applications is March 21, 2007. There is evidence that drug exposure increases the rate and/or severity of HIV-associated neurologic complications. Whether these interactions are mediated by effects on viral entry into the CNS, changes in the neural environment that affect viral replication, chronic processes that contribute to disease progression in the brain, or altered susceptibility of neural cells to damage is unknown. In order to broaden the AIDS research portfolio in both basic and clinical neuroscience, this RFA will encourage a broad range of interdisciplinary basic and/or clinical research approaches to define the basis of interaction between substances of abuse and HIV infection of the brain, including effects on neuropathogenesis and neuropathology.

On November 20, 2006, NIDA issued an RFA entitled **Mechanisms of Drug Abuse Interactions with HIV Neuropathogenesis (R01) (RFA-DA-07-002)**. This FOA solicits research grant applications to examine the mechanisms of interaction between licit or illicit substance abuse, or medications to treat substance abuse, and events related to the etiology and pathogenesis of HIV-associated neurologic complications.

NIDA is the lead institute for a Roadmap Initiative (RFA-RM-07-004) that was released recently entitled, **Facilitating Interdisciplinary Research via Methodological and Technological Innovation in the Behavioral and Social Sciences (R21)**. Dr. Lisa Onken is the NIDA contact for this RFA.

PAs and RFAs with Other NIH Components/Agencies

Bioengineering Research Grants (BRG) (R01) (PA-07-279)

Mechanisms, Models, Measurement and Management in Pain Research (R01) (PA-07-282)

Health Disparities in HIV/AIDS: Focus on African Americans (R21) (PA-07-289)

Health Disparities in HIV/AIDS: Focus on African Americans (R03) (PA-07-290)

Research on Social Work Practice and Concepts in Health (R01) (PA-07-292)

NIH Pathway to Independence (PI) Award (K99/R00) (PA-07-297)

Community Participation in Research (R01) (PAR-07-283)

Research on Ethical Issues in Human Subjects Research (R01) (PA-07-277)

Nanoscience and Nanotechnology in Biology and Medicine (R01) (PAR-07-270)

Nanoscience and Nanotechnology in Biology and Medicine (R21) (PAR-07-271)

Characterization, Behavior and Plasticity of Pluripotent Stem Cells (R01) (PA-07-201)

Decision Making in Health: Behavior Maintenance (R01) (PA-07-204)

Networks and Pathways Collaborative Research Projects (R01) (PA-07-266)

Collaborations with National Centers for Biomedical Computing (R01) (PAR-07-249)

Exploratory Collaborations with National Centers for Biomedical Computing (R21) (PAR-07-250)

Brain Disorders in the Developing World: Research Across the Lifespan (R01) (PAR-07-268)

Interactions Between Stem and Progenitor Cells and the Microenvironment in Vivo (R01) (PAS-07-189)

Non-Human Lentiviral Models of the Neurological Complications of AIDS (R01) (PAS-07-191)

Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral Fellowships (F31) to Promote Diversity in Health-Related Research (PA-07-106)

Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral Fellows (F31) (PA-07-002)

Ruth L. Kirschstein National Research Service Awards (NRSA) for Individual Postdoctoral Fellows (F32) (PA-07-107)

Research on Sleep and Sleep Disorders (PA-07-140)

Understanding Mechanisms of Health Risk Behavior Change in Children and Adolescents (R01) (PA-07-148)

The Science and Ecology of Early Development (SEED) (R01) (PA-07-149)

Health Disparities Among Minority and Underserved Women (R01) (PA-07-154)

The Effect of Racial and Ethnic/Discrimination /Bias on Healthcare Delivery (R01) (PA-07-206)

Research on Pathways Linking Environments, Behaviors and HIV/AIDS (R01) (PAR-07-143)

Tools for Zebrafish Research (R01) (PAR-07-145)

Building Translational Research in Integrative Behavioral Science (R01) (PAR-07-155)

National Cooperative Drug Discovery Groups for the Treatment of Mental Disorders, Drug or Alcohol Addiction (U10) (PAR-07-159)

Innovations in Biomedical Computational Science and Technology Initiative (SBIR [R43/R44]) (PAR-07-160)

Innovations in Biomedical Computational Science and Technology Initiative (STTR [R41/R42]) (PAR-07-161)

Research on Rural Mental Health and Drug Abuse Disorders (R01) (PA-07-103)

Co-Occurring Mental Illness, Alcohol and/or Drug Abuse & Medical Conditions (R01) (PA-07-104)

Psychopharmacology of Widely Available Psychoactive Natural Products (R01) (PA-07-108)

Cross-Disciplinary Translational Research at NIH (R01) (PA-07-109)

Behavioral & Integrative Treatment Development Program (R01) (PA-07-111)

Health Disparities in HIV/AIDS: Focus on African Americans (R01) (PA-07-116)

Health Services Research on the Prevention and Treatment of Drug and Alcohol Abuse (R01) (PA-07-119)

Complementary and Alternative Medicine for Substance Abuse and Alcohol Related Disorders (R01) (PA-07-120)

The Development of Frontal Cortex and Limbic System and Their Roles in Drug Abuse or Mental Health (R01) (PA-07-121)

Economics and Prevention and Treatment Services for Drug and Alcohol Abuse (R01) (PA-07-122)

Non-Injection Drug Abuse and HIV/AIDS (R01) (PAS-07-115)

HIV/AIDS, Severe Mental Illness and Homelessness (R01) (PA-07-090)

Social and Cultural Dimensions of Health (R01) (PA-07-045)

Research on Mind-Body Interactions and Health (R01) (PA-07-046)

Methodology and Measurement in the Behavioral and Social Sciences (R01) (PA-07-060)

Parenting Capacities and Health Outcomes in Youths and Adolescents (R01) (PA-07-061)

Mechanisms of Alcohol and Drug Induced Pancreatitis (R01) (PA-07-067)

Research Project Grant (Parent R01) (PA-07-070)

Molecular Genetics of Drug Addiction and Related Co-Morbidities (R01) (PA-07-073)

Research on the Reduction and Prevention of Suicidality (R01) (PA-07-079)

Women's Mental Health in Pregnancy and the Postpartum Period (R01) (PA-07-081)

Risk Factors for Psychopathology Using Existing Data Sets (R01) (PA-07-082)

Basic and Translational Research in Emotion (R01) (PA-07-083)

Developmental Psychopharmacology (R01) (PA-07-084)

Recent HIV Infection: New Prevention Challenges and Opportunities (R01) (PA-07-087)

Functional Links Between the Immune System, Brain Function and Behavior (R01) (PA-07-088)

HIV Infection of the Central Nervous System (R01) (PA-07-089)

Drug Discovery for Nervous System Disorders (R01) (PA-07-048)

Drug Discovery for Nervous System Disorders (R21) (PA-07-049)

Dissemination and Implementation Research in Health (R01) (PA-07-086)

Senior Scientist Research and Mentorship Award (K05) (PA-06-555)

Women's Interagency HIV Study (WIHS) IV, Limited Competition (U01) (RFA-AI-07-004)

Neuroimaging Informatics Software Enhancement for Improved Interoperability and Dissemination (R03) (RFA-EB-07-002)

The Genes, Environment and Development Initiative (U01) (RFA-DA-07-012)

Joint NIDA-NIJ Initiative for Research on Retail Drug Markets (R21) (RFA-DA-07-013)

Ruth L. Kirschstein National Research Service Awards for Interdisciplinary Individual Postdoctoral Fellows for Training in Neurodegeneration Research

(F32) (RFA-AG-07-004)

Short-term Interdisciplinary Career Enhancement Awards for Neurodegeneration Research (K18) (RFA-DC-07-005)

Therapeutics Delivery for Neurodegenerative Diseases (R21) (RFA-EY-07-001)
Biomarkers for Neurodegeneration (R21) (RFA-NS-07-004)

In November 2006, NIDA and the Dutch Addiction Program (DAP) announced the availability of administrative supplements in FY07 to support binational collaborative research projects. This program is a continuation of the U.S.-Netherlands Collaborative Research Program on Drug Abuse, using the uniquely successful model of joint funding for binational collaborative research. The joint scientific reviews conducted by the separate U.S. and Dutch funding agencies ensure that each binational research project meets the individual nations' research criteria and priorities; the joint funding permits NIDA and DAP to expand the impact of their scarce financial resources. NIDA provides support to the U.S. researcher and DAP provides support to the Dutch scientist. Letters of intent were due December 15, 2006; applications are due March 26, 2007; and funding will be approved no later than July 2007. The supplement announcement is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-DA-07-003.html.

Other Program Activities

CTN Update

The CCTN received proposals in response to an NIH SBIR Contract Solicitation for the following titles. A review meeting is planned for February or March.

> **Topic 088**, Automation of the Development of Electronic Data Capture System for Clinical Trials Data Collection and Management
> **Topic 089**, Development of Practical Training Materials for Evidence-Based Treatment

A total of 25 protocols have been initiated since 2001. A total of 7,451 participants enrolled in studies as of October 31, 2006. Of these studies, 16 have completed enrollment and locked the data; four completed enrollment and are in the follow-up phase; and five are currently enrolling. Two new protocols are in the development phase.

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

> **Protocol CTN 0001**, Buprenorphine/Naloxone versus Clonidine for Inpatient Opiate Detoxification
> **Protocol CTN 0002**, Buprenorphine/Naloxone versus Clonidine for Outpatient Opiate Detoxification
> **Protocol CTN 0005**, MI (Motivational Interviewing) To Improve Treatment Engagement and Outcome in Subjects Seeking Treatment for Substance Abuse
> **Protocol CTN 0006**, Motivational Incentives for Enhanced Drug Abuse Recovery: Drug Free Clinics
> **Protocol CTN 0007**, Motivational Incentives for Enhanced Drug Abuse Recovery: Methadone Clinics

Eleven other protocols have locked the data:

> **Protocol CTN 0003**, Bup/Nx: Comparison of Two Taper Schedules
> **Protocol CTN 0004**, MET (Motivational Enhancement Treatment) To Improve Treatment Engagement and Outcome in Subjects

Seeking Treatment for Substance Abuse
Protocol CTN 0008, A Baseline for Investigating Diffusion of Innovation
Protocol CTN 0009, Smoking Cessation Treatment with Transdermal Nicotine Replacement Therapy in Substance Abuse Rehabilitation Programs
Protocol CTN 0011, A Feasibility Study of a Telephone Enhancement Procedure (TELE) to Improve Participation in Continuing Care Activities
Protocol CTN 0012, Characteristics of Screening, Evaluation, and Treatment of HIV/AIDS, Hepatitis C Viral Infection, and Sexually Transmitted Infections in Substance Abuse Treatment Programs
Protocol CTN 0016, Patient Feedback: A Performance Improvement Study in Outpatient Addiction Treatment
Protocol CTN 0017, (HIV and HCV Intervention in Drug Treatment Settings).
Protocol CTN 0018, (Reducing HIV/STD Risk Behaviors: A Research Study for Men in Drug Abuse Treatment)
Protocol CTN 0019, (Reducing HIV/STD Risk Behaviors: A Research Study for Women in Drug Abuse Treatment)
Protocol CTN 0021, (Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome for Spanish-Speaking Individuals Seeking Treatment for Substance Abuse). This is the first Spanish-only protocol in the CTN.

Four protocols have ended new enrollment and are in either follow-up or data-lock phase:

Protocol CTN 0010, (Buprenorphine/Naloxone Facilitated Rehabilitation for Opioid Dependent Adolescents/Young Adults) began enrollment in July 2003. Recruitment ended in January 2006.
Protocol CTN 0013, (Motivational Enhancement Therapy to Improve Treatment Utilization and Outcome In Pregnant Substance Abusers) began enrollment in November 2003 and completed recruitment in May 2006 and follow-up in September 2006.
Protocol CTN 0015, (Women's Treatment for Trauma and Substance Use Disorder: A Randomized Clinical Trial) began in March 2004. The study reached its enrollment target in October 2005, and follow-up continues until early 2007.
Protocol CTN 0020, (Job Seekers Training for Substance Abusers). The protocol began enrollment in October 2004 and reached its enrollment target in February 2006. This study is also being conducted in a Navajo American Indian site, the Na'nizhoozhi Center, Inc. in Gallup, New Mexico, the first CTN study to be conducted there. Follow-up is complete at all sites as of December 2006.

Five protocols are currently enrolling:

Protocol CTN 0014, Brief Strategic Family Therapy for Adolescent Drug Abusers (BSFT), has been implemented at eight sites. The study has reached 96% enrollment. There currently are a total of 460 randomized participants.
Protocol CTN 0027, Starting Treatment with Agonist Replacement Therapies (START) is a randomized, open-label, multi-center study that was developed in collaboration with the Division of Pharmacotherapies & Medical Consequences of Drug Abuse (DPMCDA). Enrollment began in April 2006 and includes eight sites. Seven of the sites are actively recruiting. As of October 31, 2006, there were 107 randomized participants.

Protocol CTN 0028, Randomized Controlled Trial of Osmotic-Release Methylphenidate (OROS MPH) for Attention Deficit Hyperactivity Disorder (ADHD) in Adolescents with Substance Use Disorders (SUD). Enrollment is now open at 10 sites. Thirty-six participants have been randomized.
Protocol CTN 0029, A Pilot Study of Osmotic-Release Methylphenidate (OROS MPH) in Initiating and Maintaining Abstinence in Smokers with Attention Deficit Hyperactivity Disorder (ADHD). This study is being carried out at six community treatment sites across five Nodes. There are a total of 116 randomized participants.
Protocol CTN 0030, Prescription Opioid Addiction Treatment Study (POATS) is a randomized 2-phase, open-label, multi-center study in outpatient treatment settings. Pre-screening began in May 2006. The study will be carried out in 11 sites. Forty-three participants have been randomized.

Two protocols are in the development phase:

Protocol CTN 0031, Twelve-Step Facilitation: Evaluation of an Intervention to Improve Substance Abuse Treatment Outcomes by Increasing 12-Step Involvement. This protocol has been presented to the DSMB/Protocol Review Board.
Protocol CTN 0032, HIV Rapid Testing. This protocol is in the early planning stages; the concept was recently approved by the CTN Steering Committee and NIDA and the investigators will begin to develop the protocol.

In addition to the primary CTN trials, there are currently 27 funded studies supported by independent grants that use CTN studies as a platform.

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

Anastasio, Noelle C. -- University of Texas Medical Branch Galveston
Role of NMDAR Regulation in Phencyclidine-Induced Neurotoxicity

Anderson, Karen G. *-- West Virginia University*
Effects of Abused Drugs and Genetics on Impulsive Choice

Ang, Rosalind L. *-- Mount Sinai School of Medicine of New York University*
Mechanisms of Hallucinogen Specific Neuronal Response

Angstman, Sarah E. *-- University of Montana*
Tobacco Use Among Alaska Native College Students

Anthony, James C. *-- Michigan State University*
NIDA Epidemiology Training Program: ICOHRTA

Atkinson, Nigel S. *-- University of Texas Austin*
Chromatin Remodeling as a Mechanism to Produce Drug Tolerance

Bai, Guang *-- University of Maryland Baltimore Professional School*
Epigenetic Developmental Effects of Paternal Cocaine Exposure

Baicy, Kate *-- University of California Los Angeles*
Methamphetamine Dependence and Emotion Regulation

Baldwin, Gayle C. *-- University of California Los Angeles*
In Vivo Modeling of Methamphetamine and HIV Interactions

Barbarich-Marsteller, Nicole C. *-- Associated University-Brookhaven National Laboratory*

Neurochemical and Behavioral Alterations in Reward

Barr, Gordon A. *-- Hunter College*
MIDARP at Hunter College

Belenko, Steven R. *-- Treatment Research Institute, Inc. (TRI)*
Implementing Evidence-Based Drug Treatment in Criminal Justice Settings

Berg, Karina M. *-- Yeshiva University*
Improving Measurement of Antiretroviral Adherence in Current and Former Drug User

Bhide, Pradeep G. *-- Massachusetts General Hospital*
Cocaine and Brain Development

Blackard, Jason T. *-- University of Cincinnati*
Extrahepatic Replication and Viral Evolution of HCV During HCV/HIV Co-Infection

Blanco, Carlos *-- New York State Psychiatric Institute*
Substance Abuse In US Hispanics: A National Study

Booth, Brenda M. *-- University of Arkansas Medical Sciences Little Rock*
The 2006 Addiction Health Services Research Conference

Bornovalova, Marina A. *-- University of Maryland College Park Campus*
Distress Tolerance Treatment For Inner-City Drug Users

Boyer, Edward W. *-- University of Massachusetts Medical School Worcester*
Opioids, Internet Pharmacies, Self-Treated Chronic Pain, and HIV/AIDS

Brenner, Sharon L. *-- University of Washington*
Temperamental and Social Risk For Youth Substance Use

Brisson, Anne E. *-- Columbia University Health Sciences*
HIV Prevention With Heroin Using Women Sex Workers In Tajikistan

Brody, Gene H. *-- University of Georgia*
Preventing Substance Use and Risky Behavior Among Rural African American Youth

Bromberg, Jonas *-- Inflexxion, Inc.*
Improving Pain Management In Cancer Care In Latinos

Brookmeyer, Kathryn A. *-- Georgia State University*
Disentangling Pathways of Adolescent Sexual Risk from Problem Behavior Syndrome

Brown, Lawrence S. *-- Addiction Research and Treatment Corp.*
Electronic Information System To Enhance Practice At An Opioid Treatment Program

Brown, Russell W. *-- East Tennessee State University*
Amphetamine Sensitization In a Model of Schizophrenia

Burdon, William M. *-- University of California Los Angeles*
Residential Vs. Intensive Outpatient Prison-Based Treatment

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

Cain, Mary E. *-- Kansas State University*
The Amygdala, Individual Differences, and Conditioned Hyperactivity

Caron, Marc G. *-- Duke University*
Drug Abuse: Discovering Ligands for Pertinent Gpcrs

Carroll, Kathleen M. *-- Yale University*
Computer-Based Training in Cognitve Behavioral Therapy

Carroll, Marilyn E. *-- University of Minnesota Twin Cities*
Vulnerability to Drug Abuse and Treatment Efficacy: Animal Models

Catalano, Richard F. *-- University of Washington*
Reducing Risk & Enhancing Protective Factors In Children

Chandra, Siddharth *-- University of Pittsburgh at Pittsburgh*
Population-Level Analyses of Multi-Drug Comsumption

Chao, Michael Y. *-- California State University San Bernardino*
Serotonin and Dopamine Regulation of Behavioral Plasticity In C. Elegans

Chartoff, Elena H. *-- McLean Hospital, Belmont, MA*
Consequences of Repeated Kappa Receptor Activation on Brain Stimulation Reward

Chavkin, Charles *-- University of Washington*
Dynorphins and Kappa Opioid Receptors in the Stress Response

Chen, Xiangning *-- Virginia Commonwealth University*
Genetics of Nicotine and Other Abused Substances

Cherek, Don R. *-- University of Texas Health Sciences Center Houston*
Drugs of Abuse and Human Aggressive Behavior

Chung, Hwan *-- Michigan State University*
Model Assessment and Selection for Latent Transition Models

Cochran, Susan D. *-- University of California Los Angeles*
Drug Use, HIV, and Other Comorbidities In A Vulnerable Population

Cohen, Mark S. *-- University of California Los Angeles*
Comprehensive Training In Neuroimaging Fundamentals and Applications

Cohen, Mark S. *-- University of California Los Angeles*
Comprehensive Training in Neuroimaging Fundamentals and Applications

Colder, Craig R. *-- State University of New York at Buffalo*
Problem Behavior, Peers, and Motivational Aspects of Temperament In Substance Use

Coles, Lisa D. *-- University of Maryland Baltimore Professional School*
Changes in Brain and Placental Distribution During Pregnancy

Colfax, Grant N. *-- Public Health Foundation Enterprises*
Aripiprazole Treatment for Methamphetamine Dependence among High-Risk MSM

Comer, Sandra D. *-- New York State Psychiatric Institute*
Sustained-Release Naltrexone for Opioid Dependence: Longitudinal Study In Humans

Conrad, Kelly L. *-- Rosalind Franklin University of Medicine & Science*
Cocaine Craving and Receptor Trafficking

Copenhaver, Michael M. *-- University of Connecticut Storrs*
A Healthy Transition for Newly Released HIV-Infected Prisoners

Copenhaver, Michael M. *-- University of Connecticut Storrs*

Testing A Community-Friendly Risk Reduction Intervention For Injection Drug Users

Cottler, Linda B. *-- Washington University*
Indo-US Fogarty Training Program In Behavioral Disorders

Cottler, Linda B. *-- Washington University*
Prescription Drug Misuse, Abuse and Dependence

Courser, Matthew *-- Pacific Institute for Research and Evaluation*
The Impact of Active Consent On Student Survey Data

Coviello, Donna M. *-- University of Pennsylvania*
Employment Intervention For Offenders

Crowley, Thomas J. *-- University of Colorado Denver/Health Science Center Aurora*
Substance Dependent Adolescents: Imaging Risk-Taking

Damaj, Mohamad Imad *-- Virginia Commonwealth University*
Role of Calcium-Dependent Mechanisms In Nicotine's Tolerance and Effects

D'aquila, Richard T. *-- Vanderbilt University*
Vanderbilt Meharry Center for AIDS Research

Dawidowicz, Eliezar A. *-- Marine Biological Laboratory*
Neural Development and Genetics of Zebrafish

Day, Jeremy J. *-- University of North Carolina Chapel Hill*
Neural Regulation of Effort In Goal-Directed Behaviors

De Lecea, Luis *-- Stanford University*
Hypocretin and Drug Addiction

Delbello, Melissa P. *-- University of Cincinnati*
Topiramate For Co-Occurring Cannabis Use and Bipolar Disorders In Adolescents

Dembo, Richard *-- University of South Florida*
Brief Intervention for Drug Use and HIV/STD Risk Prevention Among Non-Delinquent Truants

Dewey, William L. *-- Virginia Commonwealth University*
Training In the Pharmacology of Abused Drugs

Dichter, Marc A. *-- University of Pennsylvania*
Postdoc Training In Translational Research In Neural Injury and Neurodegeneration

Dickinson, Michael H. *-- California Institute of Technology*
Crcns: Automated Behavior Analysis for Model Genetic Organism

Dickson-Gomez, Julia B. *-- Institute for Community Research*
High Risk Crack Use Settings and HIV In El Salvador

Domino, Edward F. *-- University of Michigan at Ann Arbor*
Effects of Nicotine On Human Cerebral Transmitters

Dracheva, Stella *-- Mount Sinai School of Medicine of New York University*
Vulnerability to Addiction: A Role For 5-Ht2c Receptor Editing and Expression

Drenan, Ryan M. *-- California Institute of Technology*
Nicotinic ACh Receptors and Noradrenergic Neurotransmission In Nicotine Addiction

Eby, Lillian T. *-- University of Georgia*
Clinical Supervision and Turnover In Substance Abuse Treatment

Edwards, Robert H. *-- University of California San Francisco*
Presynaptic Mechanisms of Neural Plasticity

Eitan, Shoshana *-- Texas A&M University System*
Functionality of the Opioid System During Adolescent Development Across Genders

Eliassen, James C. *-- University of Cincinnati*
Linking Serotonin and Memory Functions In MDMA Users By Concurrent EEG and fMRI

Elmer, Gregory I. *-- University of Maryland Baltimore Professional School*
Algorithm for Drug Discovery

Engle, Bretton C. *-- Florida International University*
Commitment Language In Adolescent AOD Treatment Groups

Eshleman, Susan H. *-- Johns Hopkins University*
HIV Prevention Trials Network: Network Laboratory

Evins, A. Eden *-- Massachusetts General Hospital*
Glycine Transport Inhibition for Nicotine Dependence In Schizophrenia

Fellows, Lesley K. *-- McGill University*
Orbitofrontal and Striatal Mechanisms In Stress and Addiction

Finkel, Leif H. *-- University of Pennsylvania*
Integrated Interdisciplinary Training In Computational Neuroscience

Fleming, Thomas R. *-- Fred Hutchinson Cancer Research Center*
Leadership for HIV/AIDS Clinical Trials Networks: HIV Prevention Trials Network

Fortuna, Lisa R. *-- Cambridge Health Alliance*
CBT Treatment For PTSD and SUDs In Minority Youth

Fricker, Lloyd D. *-- Yeshiva University*
Neuropeptides, Processing Enzymes, and Drug Abuse

Furneaux, Henry M. *-- University of Connecticut School of Medicine and Dentistry*
Cannabinoid Receptor (CNR1) MicroRNAs and Addictive Disease

Garavan, Hugh P. *-- Nathan S. Kline Institute for Psychiatric Research*
The Role of Executive Functions In Cocaine Abuse

Garris, Paul A. *-- Illinois State University*
Mechanisms of Amphetamine Action On Dopaminergic Signaling

Glenzer, Vicky Ann *-- Oregon Center for Applied Science, Inc.*
Interactive Training for Parents of At-Risk Children

Glenzer, Vicky Ann *-- Oregon Center for Applied Science, Inc.*
Internet Step-parent Training For Parents of Adolescents

Goldowitz, Daniel *-- University of Tennessee Health Science Center*
Gene To Phenotype Networks For Alcohol & Drug Addiction

Gorbach, Sherwood L. *-- Tufts University Boston*
HIV Infection In Drug Users In Two International Sites

Graham, Amanda L. *-- Society of Behavioral Medicine*

Society of Behavioral Medicine Annual Meeting & Scientific Sessions

Greenwald, Mark K. *-- Wayne State University*
Reducing Cocaine/Heroin Abuse With SR-Amphetamine and Buprenorphine

Grodzicker, Terri I. *-- Cold Spring Harbor Laboratory*
CSHL Conference On Channels, Receptors, Synapses

Gu, Howard H. *-- Ohio State University*
Cocaine and Monoamine Transporters

Gustafson, David H. *-- University of Wisconsin Madison*
RCT Evaluating Improvement Strategies for Addiction Treatment

Hall, Edward D. *-- University of Kentucky*
Therapeutic Strategies for Neurodegeneration Training Grant

Harris, Kathleen Mullan *-- University of North Carolina Chapel Hill*
The National Longitudinal Study of Adolescent Health

Hawrot, Edward *-- Brown University*
Role of Alpha3-Containing Nicotinic Receptors In Mediating Central Nicotine Effects

Hawrot, Edward *-- Brown University*
The Neuronal Nicotinic Acetylcholine Receptor Interactome Via A Knock-In Mouse

He, Johnny J. *-- Indiana University-Purdue University at Indianapolis*
Use A Novel Tat Transgenic Model To Develop Neuroaids Therapeutics

Heatherton, Todd F. *-- Dartmouth College*
Effects of Social Context On The Neural Correlates of Cue Reactivity

Henggeler, Scott W. *-- Medical University of South Carolina*
Vocational Outcomes For Youth With Substance Abuse Problems and High HIV Risk

Heninger, George R. *-- Yale University*
Substance Abuse Education for Medical Students

Hinds, Bruce J. *-- University of Kentucky*
Gated Carbon Nanotube Membrane Transdermal Drug Delivery

Hogle, Joanne M. *-- University of Wisconsin Madison*
Sex Differences In the Effect of Smoking Withdrawal on Emotion Response

Hohmann, Andrea G. *-- University of Georgia*
Endocannabinoid Analgesia: An In Vivo Gene Transfer - Lipidomics Approach

Hoshino, Yoshihiko *-- New York University School of Medicine*
RNAS Editing and Its Inhibition Of HIV-1 Replication In Human Macrophage

Howe, Chanelle J. *-- Johns Hopkins University*
Methods For Informative Censoring HIV/AIDS Cohorts

Howell, Leonard L. *-- Emory University*
PET Imaging and Cocaine Neuropharmacology In Monkeys

Huang, Yiyun *-- Yale University*
New PET Radioligand For the Serotonin Transporter

Hubert, George W. *-- Emory University*
Anatomy and Activation of Nucleus Accumbens CART Neurons

Hurt, Richard D. *-- Mayo Clinic College of Medicine, Rochester*

Efficacy of Methylphenidate For Treating Tobacco Dependence

Inciardi, James A. *-- University of Delaware*
Case Management Alternatives for African American Women At High Risk For HIV

Jackson-Newsom, Julia *-- Tanglewood Research, Inc.*
Drug Prevention for Children In After-School and Community Settings

Jacobs, Russell E. *-- California Institute of Technology*
In Vivo Detection of Neuronal Activity

Janowsky, Aaron J. *-- Oregon Health & Science University*
Methamphetamine Abuse Research Center

Jarcho, Johanna M. *-- University of California Los Angeles*
Dopamine's Role In Pain Sensivity & Placebo Analgesia

Kadden, Ronald M. *-- University of Connecticut School of Medicine and Dentistry*
Contingency Management for Marijuana Dependence

Kaestner, Klaus H. *-- University of Pennsylvania*
Development of C57bl/6 Es Cell Technology For High Thoughput Use

Kass, Robert E. *-- Carnegie-Mellon University*
Interdisciplinary Training In Computational Neuroscience

Kessler, John A. *-- Northwestern University*
Training For A New Interdisciplinary Research Workforce In Regenerative Medicine

Kim, Seong-Gi *-- University of Pittsburgh at Pittsburgh*
Multimodal Neuroimaging Training Program

Kirby, Lynn G. *-- Temple University*
Regulation of Serotonin Circuits In Opiate Addiction and Relapse

Knackstedt, Lori A. *-- Medical University of South Carolina*
Evaluating Models of Cocaine Self-Administration

Knowlton, Amy R. *-- Johns Hopkins University*
Informal Caregiving & Medical Adherence Among HIV+ IDUs

Knuepfer, Mark M. *-- Saint Louis University*
Effects of Chronic Stress Or Psychostimulants On CNS and ANS

Koodie, Lisa *-- University of Minnesota Twin Cities*
Morphine Induced Modulation of Tumor Growth

Kosterman, Richard *-- University of Washington*
Social Development and Psychopathology Into Adulthood

Kral, Alexander H. *-- Research Triangle Institute*
Correlates of Sexual Risk For HIV/STI Among Women Who Use Methamphetamine

Kushel, Margot B. *-- University of California San Francisco*
Pain and Misuse of Prescription Opioids In A Community-Based HIV-Infected Cohort

Labrie, Richard A. *-- Cambridge Health Alliance*
An Assessment of A Problem Gambling Self-Change Toolkit

Lahvis, Garet P. *-- University of Wisconsin Madison*

Social Approach Behaviors and Reward Pathways of Adolescent Mice

Lau, Elaine K. *-- University of California San Francisco*
Morphine-Regulated Phosphorylation of Opioid Receptors

Lee, Yue-Wei (David) *-- McLean Hospital, Belmont, MA*
Pharmacology and Metabolism Of Salvia Divinorum

Lee, Yun J. *-- Women and Infants Hospital-Rhode Island*
Massage for Methadone Exposed Infants

Levin, Frances R. *-- New York State Psychiatric Institute*
Combined Pharmacotherapies for Cocaine Dependence

Li, Chiang-Shan R. *-- Yale University*
Imaging Inhibitory Control In Cocaine Dependence

Liao, Dezhi *-- University of Minnesota Twin Cities*
Opioid Receptors In Excitatory Synapses

Lillie-Blanton, Marsha D. *-- George Washington University*
HIV/AIDS & Women of Color: Roles of Drug Use, Violence & Insurance In HAART Use

Lindsey, Kimberly P. *-- McLean Hospital, Belmont, MA*
Pharmacologic MRI of Smoked Tobacco: Effects of Abstinence and Dependence

Listman, Jennifer B. *-- New York University*
Population Genetics & Drug Dependence In Asian Isolates

Liu, Hongjie *-- Wayne State University*
A Pilot Study of School-Based HIV Intervention In China

Locey, Matthew L. *-- University of Florida*
Nicotine and the Behavioral Mechanisms of Impulsivity

London, Edythe D. *-- University of California Los Angeles*
Methamphetamine Abuse, Inhibitory Control: Implications for Treatment

Low, Walter C. *-- University of Minnesota Twin Cities*
Translational Research In Neurobiology of Disease Training Program

Lute, Brandon J. *-- Vanderbilt University*
Amphetamine Regulation of the Dopamine Transporter

Mahler, Stephen V. *-- University of Michigan at Ann Arbor*
Opioid Modulation of Cue-Triggered 'Wanting' In Amygdala

Malison, Robert T. *-- Yale University*
Genetics of Opioid Dependence In A Hmong (Thai) Isolate

Malow, Robert M. *-- Florida International University*
Multi-Level HIV Prevention for Pregnant Drug Abusers

Mao, Jianren *-- Massachusetts General Hospital*
Opioid-Induced Pain Sensitivity: Clinical Diagnosis and Management

Marcus, Bess H. *-- Miriam Hospital*
Using A YMCA Exercise Program To Enhance Nicotine Dependence Treatment For Women

Margiotta, Joseph F. *-- Medical University of Ohio at Toledo*
Altering Gene Expression and Function At Single Neuronal Nicotinic Synapses

Marians, Kenneth J. *-- Sloan-Kettering Institute for Cancer Research*
Integrated PhD Training Program In Cancer Biology

Marinelli, Michela *-- Rosalind Franklin University of Medicine & Science*
Adolescent Cocaine Abuse: Electrophysiology & Behavior

Marnett, Lawrence J. *-- Vanderbilt University*
Integrative Training In Therapeutic Discovery

Marota, John J. *-- Massachusetts General Hospital*
Effects of Cocaine Self-Administration: fMRI of Awake Non-Human Primates

Marsch, Lisa A. *-- National Development & Research Institutes*
Computer-Delivery of Effective, Psychosocial Interventions In Methadone

Treatment

Martin, Thomas J. *-- Wake Forest University Health Sciences*
Role of the Amygdala In Opioid Self-Administration In Rats With Chronic Pain

Martinez, Charles R. *-- Oregon Social Learning Center, Inc.*
A Culturally Specific Intervention for Latino Families

Marzluff, William F. *-- University of North Carolina Chapel Hill*
UNC-Chapel Hill Integrated Biomedical Research Training Program

Masson, Carmen L. *-- University of California San Francisco*
Hepatitis Care Coordination In Methadone Treatment

Mathew, Rano T. *-- Coastal Horizons Center, Inc.*
Improving Co-Occurring Disorder Care in Rural Areas Via Technology Enhancements

May, James C. *-- Richmond Behavioral Health Authority*
Organizational Factors Influencing Practice Improvement In Community-Based Care

Mayford, Mark R. *-- Scripps Research Institute*
CBP Acetyltransferase Function In Addictive Behavior

Mcginn, Thomas G. *-- Mount Sinai School of Medicine of New York University*
Prevention of Depression In HIV/HCV Co-Infected Substance Abuse Patients

Mcginnis, Marilyn Y. *-- University of Texas San Antonio*
Anabolic Androgenic Steroid Effects on Brain and Behavior

Mckay, James R. *-- University of Pennsylvania*
Effectiveness of Extended Treatments for Drug Dependence

Mcmanus, Michael T. *-- University of California San Francisco*
The Epigenetics of Small RNAs In the Mammalian Brain

Muehlbach, Britta *-- Daytop Village*
Technology Transfer: Promoting Change In The Therapeutic Community

Nagy, Andras *-- Mt. Sinai Hospital-Samuel Lunenfeld Research Institute*
Contribution to the Completion of Comprehensive Mouse Knockout Resource

Nair, Madhavan P. *-- State University of New York at Buffalo*
Immunopathogenesis of HIV-1 Infection: Role of Methamphetamine

Naleid, Amy M. *-- University of Washington*
VTA Opioid, GABA, and Insulin Effects on Sucrose Reward

Nelson, Christopher L. *-- Rosalind Franklin University of Medicine & Science*
Cellular Plasticity Following Repeated Amphetamine

Nemes, Susanna *-- Social Solutions International*

Buprenorphine

Nielsen, David A. *-- Rockefeller University*
DNA Methylation of Promoter CPG Dinucleotides In Opiate Addiction

Nunes, Edward V. *-- New York State Psychiatric Institute*
Opiate Dependence: Combined Naltrexone/Behavior Therapy

Ochsner, Kevin N. *-- Columbia University New York Morningside*
The Neural Bases of Affect Regulation in Drug Abuse

Oliveto Beaudoin, Alison *-- University of Arkansas Medical Sciences Little Rock*
Disulfiram for Cocaine Abuse In Methadone Patients

Ossipov, Michael H. *-- University of Arizona*
Proteasome Inhibitors: Therapeutics for Pain

Ouellet, Lawrence J. *-- University of Illinois at Chicago*
Psychiatric Disorders and HIV Risk Behaviors Among Young Injection Drug Users

Palmer, Abraham A. *-- University of Chicago*
Mouse QTL and Human Association Study of Methamphetamine Sensitivity

Palzkill, Timothy G. *-- Baylor College of Medicine*
Training In Biomedical Discovery from Large Scale Data Sets

Pantin, Debra Cherry-Ann *-- Palladia, Inc.*
Developing A CQI Intervention To Implement EBP Within A CBO

Patterson, Thomas L. *-- University of California San Diego*
Behavior Change and Maintenance Intervention for HIV+ MSM Methamphetamine Users

Paul, Robert H. *-- University of Missouri-St. Louis*
Functional Neuroimaging of Cognitive Dysfunction In HIV-HCV Co-Infection

Paulson, Autumn M. *-- University of Maryland College Park Campus*
Anxiety Vulnerabilities In Heroin Users

Pauly, James R. *-- University of Kentucky*
Prenatal Nicotine, Behavioral Teratogenicity and Dopamine

Pearlson, Godfrey D. *-- Yale University*
Reward, Impulsivity and Cocaine Addiction: fMRI Studies

Pearson, Zsuzsanna S. *-- New York University School of Medicine*
Modulation of Dopamine Release By CB1 Receptors

Perkins, Kenneth A. *-- University of Pittsburgh at Pittsburgh*
Tobacco Smoking, Nicotine and Negative Affect Relief

Perlman, David C. *-- Beth Israel Medical Center, New York*
Hepatitis Care Coordination In Methadone Treatment

Perron, Brian E. *-- Washington University*
Psychiatric Comorbidities and Outpatient Substance Abuse Treatment Retention

Perry, Jennifer L. *-- University of Minnesota Twin Cities*
Impulsivity and Drug Abuse: Sex and Hormonal Effects

Pinto, Elsa *-- Florida International University*
Dietary Patterns and Drug Use Among Latinas

Piomelli, Daniele *-- University of California Irvine*

Role of Endocannabinoids In the Behavioral Consequences of Social Isolation

Plant, Tony M. *-- University of Pittsburgh at Pittsburgh*
International Congress of Neuroendocrinology (ICN 2006)

Pouget, Alexandre *-- University of Rochester*
CRCNs: Bayesian Decision Making With Probabilistic Population Codes

Quintero, Gilbert A. *-- University of New Mexico Albuquerque*
Prescription Drug Abuse: The Role of the Internet

Raehal, Kirsten M. *-- Ohio State University*
Opioid-Induced Somatic Effects In Betaarrestin2-Ko Mice

Ramo, Danielle E. *-- University of California San Diego*
Developmental Models of Drug Abuse Relapse

Reith, Maarten E. *-- New York University School of Medicine*
The Dopamine Transporter and Ions, Substrates, Blockers

Reith, Maarten E. *-- New York University School of Medicine*
Dopamine Transporters: Mechanisms of Ligand Interaction

Reynolds, Jessica L. *-- State University of New York at Buffalo*
Mechanisms of Cocaine-Induced HIV-1 Infection In NHA

Rigotti, Nancy A. *-- Massachusetts General Hospital*
Bupropion for Smoking Cessation In Postpartum Women

Roe, Anna W. *-- Vanderbilt University*
Fast Optical Imaging of Cortical Signals In the Behaving Primate

Roget, Nancy A. *-- University of Nevada Reno*
NIDA Enters College: Infusing The Science of Addiction Into University Curricula

Rogge, George A. *-- Emory University*
Regulation of The CART Gene By Promoter CIS-Elements

Rosen, Bruce R. *-- Massachusetts General Hospital*
Advanced Multimodal Neuroimaging Training Grant

Rosenblum, Andrew Bruce *-- National Development & Research Institutes*
Sublingual Buprenorphine for Chronic Pain In Patients at Risk for Drug Abuse

Rosengard, Cynthia *-- Rhode Island Hospital, Providence, RI*
Partner-Specific HIV Risk Reduction for Drug Using Incarcerated Adolescents

Roth, Michael D. *-- University of California Los Angeles*
Effects of Marijuana on HIV and Viral Immunity

Rowland, Neil E. *-- University of Florida*
Cue Dependency With Intravenous Nutrients and Nicotine

Royal, Walter *-- University of Maryland Baltimore Professional School*
Opoid and Retinoid Interactions In the HIV-1 Transgenic Rat

Sadee, Wolfgang *-- Ohio State University*
Genetic and Epigenetic Regulation of Addiction Genes

Salom, David *-- Novasite Pharmaceuticals, Inc.*
Crystallization of the Human Cannabinoid Type 2 Receptor

Samet, Jeffrey H. *-- Boston Medical Center*
Clinical Addiction Research and Education (CARE) Program

Schacht, Joseph P. *-- University of Colorado at Boulder*
A Transdisciplinary Approach to Cannabis Addiction

Schank, Jesse R. *-- Emory University*
Dopamine Beta-Hydroxylase and Responses to Cocaine

Schramm-Sapyta, Nicole L. *-- Duke University*
Role of HPA Axis In Adolescent Vulnerability to Drug Addiction

Schwartz, Philip H. *-- Children's Hospital of Orange County*
Choc Human Embryonic Stem Cell Culture Training Course

Scott, David J. *-- University of Michigan at Ann Arbor*
Brain Reward Circuitry and Substance Use Risk

See, Ronald E. *-- Medical University of South Carolina*
Translational Research in Addiction Center

Shiffman, Saul *-- University of Pittsburgh at Pittsburgh*
Understanding Emerging Patterns of Non-Daily Smoking: Field and Lab Assessments

Simen, Arthur A. *-- Yale University*
Epigenetic Factors In Stress-Enhanced Acquisition of Cocaine Self-Administration.

Slesnick, Natasha *-- Ohio State University*
Evaluation of Treatments For Homeless Youth: CRA, MET and Case Management

Snedker, Karen A. *-- University of Washington*
The Impact of Neighborhood Context on Substance Abuse

Sofuoglu, Mehmet *-- Yale University*
GABA Medications for Tobacco Addiction

Sokhadze, Estate M. *-- University of Louisville*
Emotional and Attentional Biases to Drug and Trauma Cues In Addiction With PTSD

Sombers, Leslie A. *-- University of North Carolina Chapel Hill*
Functional Analysis of the Mesolimbic Dopamine System

Sood, Amit *-- Mayo Clinic College of Medicine, Rochester*
Gabapentin for Smoking Abstinence

Sorensen, James L. *-- University of California San Francisco*
Daart+ As A Structural HIV Intervention In Methadone Maintenance

Sorg, Barbara A. *-- Washington State University*
Cocaine, Electroconvulsive Seizure and Neural Plasticity

Spiess, Joachim *-- University of Hawaii at Manoa*
Emotion and Cognition On Gene, Cell, and Systems Levels

Stahl, Philip D. *-- Washington University*
21st-Century Imaging Sciences: Undergraduate and Graduate Student Training

Stefansson, Kari *-- Decode Genetics, Inc.*
Genes Contributing To Opioid Abuse In Humans

Stein, Michael D. *-- Rhode Island Hospital, Providence, RI*
Antidepressants During Office-Based Buprenorphine

Steinberg, Laurence *-- Temple University*

Peer Effects on Neural and Behavioral Markers of Risk-Taking

Stella, Nephi *-- University of Washington*
Novel Monoacylglycerol Lipase

Stenger, Victor A. *-- University of Hawaii at Manoa*
Parallel MRI for Substance Abuse Research

Stone, Laura S. *-- University of Minnesota Twin Cities*
Proteomic Studies of Human Chronic Pain

Strain, Eric C. *-- Johns Hopkins University*
Evaluation of Opioid Antagonist Activity In Humans

Sullivan, Mark D. *-- University of Washington*
Risks for Opioid Use and Abuse In Contrasting Chronic Pain Populations

Sun, Yi E. *-- University of California Los Angeles*
Epigenetic Gene Regulation In Morphin Addiction

Swanstrom, Ronald I. *-- University of North Carolina Chapel Hill*
UNC Center For AIDS Research

Szczytkowski-Thomson, Jennifer *-- University of North Carolina Chapel Hill*
Conditioned Effects of Heroin on Nitric Oxide

Tank, Arnold W. *-- University of Rochester*
Nicotine Effects on the Adrenal Medulla and Brain

Tank, David W. *-- Princeton University*
Training Program In Quantitative and Computational Neuroscience

Teplin, Linda A. *-- Northwestern University*
Drug Use, Disorder & HIV/AIDS Risk In Juvenile Justice Youth:A Longitudinal Study

Thompson, Alexis C. *-- State University of New York at Buffalo*
Evaluation of Neuropeptide Y As A Target for Cocaine-Dependence Treatment

Todorov, Alexandre A. *-- Washington University*
Genetic Epidemiology of Opioid Dependence In Bulgaria

Tranel, Daniel T. *-- University of Iowa*
Drug Abuse, Social Decision-Making, and Sex-Related Functional Brain Asymmetry

Troncale, Joseph A. *-- Caron Foundation*
Integrated Behavioral Program For Prescription Opiate Addiction and Chronic Pain

Tucker, Jalie A. *-- University of Alabama at Birmingham*
Telehealth Assessment of Risk Behaviors In Rural HIV+ Substance Users

Ulinski, Philip S. *-- University of Chicago*
Undergraduate Training In Computational Neuroscience

Umbricht, Annie *-- Johns Hopkins University*
Clinical Trial of Topiramate For Cocaine Addiction

Uteshev-Gaard, Victor V. *-- Southern Illinois University Carbondale*
Studying Nicotinic AChrs In Histaminergic Neurons

Valenzuela, David M. *-- Regeneron Pharmaceuticals, Inc.*
Production of Targeted Null Mutations For 10,000 Genes In C57bl/6 Es Cells

Vermund, Sten H. *-- Family Health International*

HIV Prevention Trials Network (HPTN) Coordinating and Operations Center

Volsky, David J. *-- St. Luke's-Roosevelt Institute for Health Sciences*
Effect of Morphine on HIV-1 Neuroinvasion and Brain Changes In Mice

Von Korff, Michael R. *-- Center for Health Studies*
Long-Term Opioid Management of Chronic Pain: Trends and Risks

Von Zastrow, Mark E. *-- University of California San Francisco*
Mechanisms Regulating Endocytosis of Opioid Receptors

Walsh, Sharon L. *-- University of Kentucky*
Evaluation of Atomoxetine for Cocaine Dependence: A Pilot Trial

Wang, Shaomeng *-- University of Michigan at Ann Arbor*
Design, Synthesis and Characterization Of Dopamine Receptor 3 Ligands

Watkins, Katherine E. *-- Rand Corporation*
Group CBT For Depression and AOD Disorders

Welch, Sandra P. *-- Virginia Commonwealth University*
Modulation of Opioid Antinociception and Tolerance By Sphingosine-1-Phosphate

Wells, Rebecca S. *-- University of North Carolina Chapel Hill*
How Child Welfare Inter-Agency Cooperation May Reduce Youth HIV Risk Behaviors

West, Anne Elizabeth *-- Duke University*
Epigenetic Regulation of Transcriptional Repression By Drugs of Abuse

West, Mark O. *-- Rutgers, The State University of New Jersey, New Brunswick*
Cue-Induced Relapse to Cocaine Seeking: Neuronal Activity In Accumbens Circuits

Westmaas, Johann L. *-- State University New York Stony Brook*
Gender, Social Support, and Stress Reactions In Smokers

Wilens, Timothy E. *-- Massachusetts General Hospital*
Juvenile Bipolar Disorder and Substance Abuse

Williams, Jason M. *-- Vanderbilt University*
Insulin Regulation of Amphetamine Action

Wirtshafter, David *-- University of Illinois at Chicago*
Lateral Hypothalamus, Dopamine and Ingestive Behavior

Wong, Dean F. *-- Johns Hopkins University*
Training for Clinician Scientists In Imaging Research

Woody, George E. *-- University of Pennsylvania*
Methadone Maintenance and HIV Risk In Ukraine

Wu, Z. Helen *-- University of Texas Medical Branch Galveston*
Does Stress Influence Drug Use In Young, Poor Women?

Xu, Jiansong *-- University of California Los Angeles*
Cigarette Smoking and the Efficiency of the Frontoparietal Attentional Network

Yoburn, Byron C. *-- St. John's University*
Prescription Opioid Agonists: Tolerance and Efficacy

Zhan, Chang-Guo *-- University of Kentucky*
Redesign of Butyrylcholinesterase for Cocaine Metabolism

Zhuang, Xiaoxi *-- University of Chicago*

Epigenetic Mechanisms In Motor Habits Stability

Zubieta, Jon-Kar *-- University of Michigan at Ann Arbor*
Neurochemistry of Opiate Abuse Risk In Chronic Pain

Zucker, Robert A. *-- University of Michigan at Ann Arbor*
International Substance Abuse Research Training Program

Director's Report to the National Advisory Council on Drug Abuse - February, 2007

Extramural Policy and Review Activities

Receipt, Referral, and Review

NIDA received 1052 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 841 applications.

OEA arranged and managed 17 grant review meetings in which 314 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 7 contract proposal reviews and 2 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 13 Special Emphasis Panels for a variety of reasons:

Conflicts with the chartered committees
Center Grant Applications
The Minority Institutions' Drug Abuse Research Development Program (MIDARP)
Program Project Grant applications
Behavioral Science Track Award for Rapid Transition (B/START)
Imaging Science Track Awards for Research Transition (I/START)
Conference Grants (R13)
NIH Pathway To Independence (PI) Awards (K99/R00)

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

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

- N01DA-7-8859: Preclinical Medications Discovery and Abuse Liability Testing for NIDA
- N01DA-7-5537: State and Local Epidemiology Planning and Information Development
- N01DA-7-8873: Purity Specifications, Storage and Distribution for Medications Development
- N01DA-7-8870: Pharmacokinetic Analysis Resource Center

Phase I SBIR Reviews

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N43DA-7-5536 (Topic 087): Development of State-of-the-Art Mechanisms for Epidemiological Research

- N43DA-7-4408 (Topic 090): Develop a Real-Time fMRI Feedback System that Allows Drug Abusers to Control their Cravings and Urges and/or Increase their Self-Control of their Drug Taking
- N43DA-7-5535 (Topic 086): Marketing Evidence-Based Prevention Interventions for Substance Abuse and Related HIV Prevention

R&D Concept Reviews

- N01DA-7-8870: Pharmacokinetic Analysis Resource Center
- N01DA-7-8873: Purity Specifications, Storage and Distribution for Medications Development

CTN-Related Review Activities

The Data and Safety Monitoring Board (DSMB) met:

- September 19, 2006 to review and discuss study 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).
- November 16, 2006 to review and discuss study protocols:
  - CTN 0027 Starting Treatment with Agonist Replacement Therapies (START); and
  - CTN 0031 (Twelve-Step Facilitation: Evaluation of an Intervention to Improve Substance Abuse Treatment Outcomes by Increasing 12-Step).

  The board discussed the Final Study Reports of two studies:
  - CTN 0018 (Reducing HIV/STD Risk Behaviors: A Research Study for Men in Drug Abuse Treatment); and
  - CTN 0019 (Reducing HIV/STD Risk Behaviors: A Research Study for Women in Drug Abuse Treatment).
- November 13, 2006 to review an update on 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).
- October 23, 2006 to review an interim analysis of protocol CTN 0014, Brief Strategic Family Therapy for Adolescent Drug Abusers (BSFT).
- October 6, 2006 to review an update on protocol CTN 0030, Prescription Opioid Addiction Treatment Study (POATS).

Certificates of Confidentiality

Between August 15, 2006 and December 7, 2006, OEA processed 85 Certificate applications, including 18 for extension of expiration dates and 4 for amended protocols.

Extramural Outreach

Dr. Rita Liu, OEA, co-chaired with Drs. David Shurtleff, DBNBR, and Cathrine Sasek, OSPC, the 2006 NIDA Miniconvention: Frontiers of Addiction Research held as a satellite of the Society for Neuroscience annual meeting in Atlanta on October 13, 2006. The meeting drew 455 domestic and international attendees.

Dr. Rita Liu co-chaired with Drs. David Shurtleff and Cathrine Sasek, the program for the 2006 Society for Neuroscience Jacob P. Waletzky Memorial

Planned Meetings

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Grantee Honors

Award that was given to Dr. Yavin Shaham from the NIDA Intramural Research Program.

Drs. Mark Green and Rita Liu of OEA, along with Drs. Cathrine Sasek of OSPC and Diane Lawrence of DBNBR participated in the NIH Electronic Submission Outreach Workshops on October 14 to 17 at the 2006 Society for Neuroscience Annual Meeting, Atlanta, GA.

Dr. Levitin, Director, OEA, continues to serve on several NIH-wide committees, including the committee to evaluate the CSR pilot for new investigators to allow them to resubmit their applications earlier in the review cycle and the committee to evaluate the pilot multi-principal investigator initiative.

In January 2007, Dr. Levitin spoke at two separate conversation hours on social psychological research at NIDA and on the grant review and funding process at NIH at the annual meeting of the Society for Personality and Social Psychology.

Dr. Meena Hiremath attended the Addiction Health Services Research conference in Little Rock on October 22-25, 2006 and presented a talk entitled "Study Sections and Review" to junior investigators.

Dr. Eliane Lazar-Wesley, OEA, helped organize the Research Training Directors Meeting, held November 3rd, 2006 at the North Marriott Hotel in Bethesda and also gave a presentation at the meeting entitled: "T32 Training Programs: A New Framework".

Dr. Gerald McLaughlin, OEA, continues to serve as the NIDA Liaison to the NIH-wide committee dealing with all aspects of the transition to electronic grant submission, committees recommending guidelines for R01's, U01's and Appendixes, and the Review User's Group.

Dr. Gerald McLaughlin presented talks at several national and regional specialty NIDA meetings and provided guidelines and materials to NIDA staff to for other meetings including the 2006 Society for Neuroscience.

Dr. Gerald McLaughlin has co-arranged sessions for review staff of NINDS/NIMH/NIDA to learn inter-Institute operating and training procedures in these Institutes' review units, including the new J2EE Web Peer Review module.

Dr. Mark Swieter participated in NIDA's Research Training Directors' meeting held at the North Bethesda Marriott on November 3, 2006, serving as co-Chair with Dr. Cindy Miner of a Best Practices Forum on Components of Successful Program Evaluation and Tracking.

Dr. Mark Swieter continues to serve as NIDA's representative on the NIH Review Policy Committee and was recently selected to be a member of the RPC Steering Committee.

OEA staff attending the Society for Neuroscience meeting in Atlanta, GA and working at the NIDA booth included Drs. Rita Liu and Mark Green.

Dr. Mark Green continues to participate on the NIH-wide Electronic Submission/424 Contingency Workgroup that deals with emerging issues related to the transition to electronic submission of grant applications.

Staff Training and Development

The OEA Symposium Series, a forum for staff training and sharing of ideas and information, continued through the fall. Topics included a presentations by Dr. Gerald McLaughlin of OEA on recent experiences with the review of the K99/R00 applications, by Tom Hilton of DESPR (who also serves as NIDA's

representative on the Program Module Update Group) on the Program Module in IMPAC, by Pam Fleming, the Chief of the Grants Management Branch and by Carol Krause, the recently hired Chief of the Public Information and Liaison Branch.

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Congressional Affairs (Prepared January 23, 2007)

Appropriations

On December 9, 2006, the President signed into law P.L. 109-383, the third Continuing Resolution for FY 2007, to provide funding for agencies including NIH without enacted appropriations. This CR will extend funding through midnight on February 15, 2007, and for NIH under the same terms and conditions as were in effect in FY 2006.

FY 2008 Outlook: House Appropriations Committee Chairman David Obey and Senate Appropriations Committee Chairman Robert Byrd announced in December that they intend to pass a "joint resolution" to fund government operations for the remainder of FY 2007. The exact terms of this resolution continue to be negotiated.

Bills Passed at the End of the 109th Congress

H.R. 864 - On December 9, 2006, both chambers of Congress passed H.R. 864, the STOP Underage Drinking Act. The President signed the bill into law on December 20, 2006, as Public Law 109-422. The law authorizes grants to reduce the rate of underage alcohol use and binge drinking among students at institutions of higher education, data collection to identify the scope of the problem and research into the effects of alcohol on developing brains. The NIDA Director would serve, with other agency heads, on an interagency coordinating and planning committee.

H.R. 6164 - On December 8, 2006, the House and Senate passed H.R. 6164, the National Institutes of Health Reform Act, as amended. Provisions would revise Title IV of the PHS Act and create the Division of Program Coordination, Planning, and Strategic Initiatives, to be supported by the Common Fund. The bill authorizes appropriations for NIH of $30,331,309,000 for FY 2007, $32,831,309,000 for FY 2008 and such sums as necessary for FY 2009. The bill calls for the establishment of a Scientific Management Review Board to review the structure of NIH every seven years. The bill also authorizes the NIH Director to award grants for demonstration projects for research bridging the biological sciences with the physical, chemical, mathematical, and computational sciences; and authorizes the establishment of demonstration programs that award grants, contracts, or engage in other transactions, for high-impact, cutting-edge research demonstration programs. The legislation was signed by the President on January 15, 2007, and is cited as Public Law 109-482, the National Institutes of Health Reform Act of 2006. (A complete summary of this bill, provided by the NIH Office of Legislative Policy Analysis, is included at the end of the Congressional Affairs section).

S. 3880 - On November 27, 2006, the President signed into law S. 3880, the

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Animal Enterprise Terrorism Act (P.L. 100-374). Senators James Inhofe (R-OK) and Dianne Feinstein (D-CA) introduced the bill to expand criminal prohibitions against the use of force, violence, and threats involving animal enterprises and increases penalties for violations of these prohibitions. Building upon the Animal Protection Act of 1992, the Animal Enterprise Terrorism Act will stiffen original penalties for crimes against commercial or academic enterprises that use or sell animals or animal products for profit, food or fiber production, agriculture, education, research, or testing. Further, the hallmark of the new law is protection for tertiary targets of such crimes. Specifically, the law extends protection to the immediate families, spouses or intimate partners, and those doing business with persons involved in an animal enterprise.

110th Congress

As a result of the November 2006 elections, both the Senate and House of Representatives are now under Democratic Party control. As a result of this shift, there are significant changes to both the leadership and membership of those committees most relevant to NIDA's work. Also, certain committee jurisdictions have changed.

Senate: In the Senate, primary focus is on the

- Committee on Appropriations (Subcommittee on Labor, Health and Human Services, and Education; Financial Services [now with ONDCP jurisdiction] and Commerce, Justice, Science;
- Committee on Health, Education, Labor, and Pensions (HELP) (subcommittees yet to be determined);
- Committee on the Judiciary; and the
- Caucus on International Narcotics Control (this is an officially recognized Caucus, established by law in 1985).

House: In the House, primary focus is on the

- Committee on Appropriations (Subcommittee on Labor, Health and Human Services, Education, and Related Agencies; Financial Services [now with ONDCP jurisdiction], and Commerce, Justice, Science and Related Agencies);
- Committee on Energy and Commerce (Subcommittee on Health); and the
- Committee on Oversight and Government Reform (formerly Government Reform). (Subcommittee on Domestic Policy - formerly Criminal Justice, Drug Policy, and Human Resources).

Subcommittee Rosters - Senate

Appropriations - Labor, Health and Human Services, and Education

Democrats	Republicans
Tom Harkin, IA (Chair)	Arlen Specter, PA (Ranking Member)
Daniel Inouye, HI	Thad Cochran, MS
Herbert Kohl, WI	Judd Gregg, NH
Patty Murray, WA	Larry Craig, ID
Mary Landrieu, LA	Kay Bailey Hutchison, TX
Richard Durbin, IL	Ted Stevens, AK
Jack Reed, RI	Richard Shelby, AL
Frank Lautenberg, NJ	

Appropriations - Financial Services

Democrats	Republicans

Richard Durbin, IL (Chair)	Sam Brownback, KS (Ranking Member)
Patty Murray, WA	Christopher Bond, MO
Mary Landrieu, LA	Richard Shelby, AL
Frank Lautenberg, NJ	Wayne Allard, CO
Ben Nelson, NE	

Appropriations - Commerce, Justice, Science

Democrats	Republicans
Barbara Mikulski, MD (Chair)	Richard Shelby, AL (Ranking Member)
Daniel Inouye, HI	Judd Gregg, NH
Patrick Leahy, VT	Ted Stevens, AK
Herbert Kohl, WI	Pete Domenici, NM
Tom Harkin, IA	Mitch McConnell, KY
Byron Dorgan, ND	Kay Bailey Hutchison, TX
Dianne Feinstein, CA	Sam Brownback, KS
Jack Reed, RI	Lamar Alexander, TN
Frank Lautenberg, NJ	

Health, Education, Labor, and Pensions (as of this writing, subcommittees pending)

Democrats	Republicans
Edward Kennedy, MA (Chair)	Mike Enzi, WY (Ranking Member)
Christopher Dodd, CT	Judd Gregg, NH
Tom Harkin, IA	Lamar Alexander, TN
Barbara A. Mikulski, MD	Richard Burr, NC
Jeff Bingaman, NM	Johnny Isakson, GA
Patty Murray, WA	Lisa Murkowski, AK
Jack Reed, RI	Orrin Hatch, UT
Hillary Rodham Clinton, NY	Pat Roberts, KS
Barack Obama, IL	Wayne Allard, CO
Bernard Sanders, (I), VT	Tom Coburn, OK
Sherrod Brown, OH	

Judiciary (as of this writing, subcommittees pending)

Democrats	Republicans
Patrick Leahy, VT (Chair)	Arlen Specter (Ranking Member)
Edward Kennedy, MA	Orrin Hatch, UT
Joseph Biden, DE	Charles Grassley, IA
Herbert Kohl, WI	John Kyl, Arizona
Dianne Feinstein, CA	Jeff Sessions, AL
Russ Feingold, WI	Lindsey Graham, SC
Charles Schumer, NY	John Cornyn, TX
Richard Durbin, IL	Sam Brownback, TX
Benjamin Cardin, MD	Tom Coburn, OK
Sheldon Whitehouse, RI	

Caucus on International Narcotics Control

Democrats	Republicans
Joseph Biden, DE	Charles Grassley, IA
Diane Feinstein, CA	Jeff Sessions, AL
Appointment pending	Norm Coleman, MN
Appointment pending	

Subcommittee Rosters - House

Appropriations - Labor, Health and Human Services, Education, and

Related Agencies

Democrats
David Obey, WI (Chair)
Nita Lowey, NY
Rosa DeLauro, CT
Jesse Jackson, IL
Patrick Kennedy, RI
Lucille Roybal-Allard, CA
Barbara Lee, CA
Tom Udall, NM
Michael Honda, CA
Betty McCollum, MN
Tim Ryan, OH

Republicans
James Walsh, NY (Ranking Member)
Ralph Regula, OH
John Peterson, PA
Dave Weldon, FL
Michael Simpson, ID
Dennis Rehberg, MT

Appropriations - Commerce, Justice, Science, and Related Agencies

Democrats
Alan Mollohan, WV (Chair)
Patrick Kennedy, RI
Chaka Fattah, PA
C.A "Dutch" Ruppersberger, MD
Adam Schiff, CA
Michael Honda, CA
Rosa DeLauro, CT
John Olver, MA

Republicans
Rodney Frelinghuysen, NJ
John Culberson, TX
Harold Rogers, KY
Tom Latham, IA
Robert Aderholt, AL

Appropriations - Financial Services

Democrats
Jose Serrano, NY (Chair)
Carolyn Kilpatrick, MI
C.A "Dutch" Ruppersberger, MD
Debbie Wasserman Schultz, FL
Peter Visclosky, IN
Robert "Bud" Cramer, Jr., AL
Maurice Hinchey, NY
Lucille Roybal-Allard, CA

Republicans
Ralph Regula, OH
Tom Latham, IA
Mark Kirk, IL
Dennis Rehberg, MT
Rodney Alexander, LA

Energy and Commerce - Health

Democrats
Frank Pallone, NJ (chair)
Henry Waxman, CA
Edolphus Towns, NY
Bart Gordon, TN
Anna Eshoo, CA
Gene Green, TX
Diana DeGette, CO
Lois Capps, CA
Tom Allen, ME
Tammy Baldwin, WI
Eliot Engle, NY
Jan Schakowsky, IL
Hilda Solis, CA
Mike Ross, AK
Darlene Hooley, OR
Anthony Weiner, NY
Jim Matheson, UT

Republicans
Nathan Deal, GA (Ranking Member)
Ralph Hall, TX
Charlie Norwood, GA
Barbara Cubin, WY
John Shadegg, AZ
Steve Buyer, IN
Joseph Pitts, PA
Mary Bono, CA
Mike Ferguson, NJ
Mike Rogers, MI
Sue Myrick, NC
John Sullivan, OK
Tim Murphy, PA
Michael Burgess, TX

Oversight and Government Reform - Domestic Policy

Democrats	Republicans
Dennis Kucinich, OH (Chair)	Darrell Issa, CA (Ranking Member)
Tom Lantos, CA	Dan Burton, IN
Elijah Cummings, MD	Christopher Shays, CT
Diane Watson, CA	John Mica, FL
Christopher Murphy, CT	Mark Souder, IN
Danny Davis, IL	Chris Cannon, UT
John Tierney, MA	Brian Bilbray, CA
Brian Higgins, NY	
Bruce Braley, IA	

HEARINGS, BRIEFINGS, AND EVENTS OF INTEREST

AAMC-Sponsored Briefing on Addiction

On January 22, 2007, the Association of American Medical Colleges (AAMC) sponsored a Capitol Hill briefing entitled "The Disease of Addiction: New Strategies for Prevention and Treatment." NIDA Director Dr. Nora Volkow updated the audience on recent developments in addiction science, and Dr. Chuck O'Brien from the University of Pennsylvania provided examples from his research to show how basic research can lead to further discovery and, eventually, clinical implementation. This briefing was part of a series that the AAMC started in 2005 to address an unfortunate knowledge gap among Congressional staff about the partnership between the NIH and the nation's medical schools and teaching hospitals.

Meeting with Senate Judiciary staff focusing on Criminal Justice populations

On January 22, NIDA Director Dr. Nora Volkow met with a dozen staff of the Senate Judiciary Committee to discuss the importance of providing addiction treatment to criminal justice populations. This meeting was originally suggested and organized by the Friends of NIDA. Dr. Volkow reviewed the research supporting drug treatment in criminal justice settings, as well as NIDA's "Principals of Drug Abuse Treatment for Criminal Justice Populations. A similar meeting will occur with staff of the House Judiciary Committee.

BILLS OF INTEREST

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

H.R. 3/S.5 - On January 5, 2007, Representative Diana DeGette (D-CO) introduced H.R. 3, the Stem Cell Research Enhancement Act of 2007. The Senate companion, S. 5, was introduced on January 4 by Senate Majority Leader Harry Reid (D-NV). The bills would require the Secretary of HHS to conduct and support research using human embryonic stem cells regardless of the date on which such cells were derived. H.R. 3 had 211 cosponsors upon introduction and was referred to the House Committee on Energy and Commerce; it is expected to be considered by the House on January 11, 2007. S. 5 had 31 cosponsors upon introduction and is expected to be considered by the Senate in February.

H.R. 322/S.51 - On January 4, 2007, Senator Johnny Isakson (R-GA) introduced S. 51, a bill to "derive pluripotent stem cells using techniques that do not knowingly harm embryos." The bill had no cosponsors upon introduction and was referred to the Senate Committee on Health, Education, Labor and Pensions. On January 9, 2007, Representative Roscoe Bartlett (R-MD) introduced the House companion measure, H.R. 322. The bill had 13 cosponsors upon introduction and was referred to the House Committee on Energy and Commerce. The bill would require NIH to fund research to develop techniques for the isolation and production of pluripotent stem cells, without

deriving such cells from human embryos.

National Institutes of Health Reform Act of 2006 -- Public Law 109-482

Background

The National Institutes of Health (NIH), part of the U.S. Department of Health and Human Services (DHHS), is the primary Federal agency for conducting and supporting medical research. Comprising 27 Institutes and Centers (ICs), NIH provides leadership and financial support to researchers in every State and around the world. Throughout its history, NIH's ICs, program offices within the Office of the Director (OD), and congressionally directed research programs were regularly reauthorized either through stand-alone or omnibus bills; the last omnibus NIH reauthorization bill was enacted in 1993 (P.L. 103-43). An attempt was made to reauthorize the agency in 1996 when the Senate passed S. 1897, the National Institutes of Health Revitalization Act of 1996; however, the House did not take action on the measure. It should be noted that because Section 301 of the Public Health Service Act provides the Secretary of Health and Human Services (HHS) with permanent statutory authority to conduct and sponsor research, NIH can continue to operate. The annual appropriations process provides a de facto reauthorization for NIH. When Representative Joe Barton (R-TX) became the chair of the House Committee on Energy and Commerce in May 2004, he vowed to reauthorize the agency and held numerous reauthorization and oversight hearings. When crafting legislation, the Chair took into account the 14 recommendations contained in the 2003 Institute of Medicine report entitled "Enhancing the Vitality of the National Institutes of Health: Organizational Change to Meet New Challenges".

Provisions of the Legislation/Impact on NIH In contrast to the last two omnibus reauthorization bills (P.L. 99-158 and P.L. 103-43), which expanded ICs, OD offices, and programs aimed at specific diseases, H.R. 6164 will cap the number of ICs at 27, provide the Director of NIH with expanded authority to manage the agency, encourage ICs to collaborate on trans-NIH research, and reform the agency's reporting system so that Congress can evaluate its research portfolio. Specific provisions of the bill address the following areas:

- **Office of the Director:** The bill provides the Director of NIH with new oversight and coordination responsibilities across ICs. For example, in consultation with Directors of the ICs, the Director of NIH will be responsible for program coordination across the ICs, including conducting priority-setting reviews, to ensure that NIH's research portfolio is balanced, free of unnecessary duplication, and takes advantage of collaborative, cross-cutting research. The Director of NIH will be require to assemble accurate data to be used to assess research priorities, including information to better evaluate scientific opportunity, public health burdens, and progress in reducing health disparities. The Director will also be required to ensure that scientifically based strategic planning is implemented in support of research priorities as determined by the ICs and that NIH's resources are sufficiently allocated for research projects identified in strategic plans. In coordination with Directors of the ICs, the Director of NIH will be required to ensure that investigator-initiated research is maximized, when appropriate. This portion of the bill contains a provision preserving current authorities of the ICs.
- **Reorganization:** The bill will reaffirm the Secretary of HHS's authority to reorganize ICs after notifying Congress 180 days in advance. The legislation will require that certain reorganizations be carried out pursuant to a regulatory notice and comment process and with congressional review. In addition, the Director of NIH will be authorized to reorganize the offices within the OD, following a series of public hearings and approval of the Secretary. ICs will be authorized to reorganize their divisions, centers, or other administrative units, including adding, removing, or transferring the

functions of such units, following a series of public hearings and approval of the Director of NIH.

- **Scientific Management Review Board:** The bill will establish a Scientific Management Review Board to conduct periodic organizational reviews. The Board, which must be established within 60 days of enactment, will be required to examine the use of NIH's organizational authorities at least every 7 years, provide a report on its review, and make recommendations regarding the use of such authorities. If the Board recommended an organizational change, the process to effect the change must begin within 100 days of the report, and the change must be fully implemented within 3 years. These requirements do not apply if the Director of NIH objects to all or part of the recommended organizational change within 90 days, and the objection includes a rationale.
- **Division of Program Coordination, Planning, and Strategic Initiatives:** The bill will establish a new Division of Program Coordination, Planning, and Strategic Initiatives within the OD. The following program offices will be moved within the Division: the Office of AIDS Research, Office of Research on Women's Health, Office of Behavioral and Social Sciences Research, Office of Disease Prevention, Office of Dietary Supplements, and Office of Rare Diseases. The bill contains a provision stating that these offices will retain the authorities in effect prior to enactment of the Act. The Director of NIH, acting through the Division, will be authorized to identify and report on research that represents important areas of emerging scientific opportunities, rising public health challenges, or knowledge gaps that deserve special emphasis and would benefit from conducting or supporting additional research that involves collaboration between two or more ICs, or would otherwise benefit from strategic coordination and planning. The bill will establish a common fund to pay for such research. The research proposals will be considered by a new Council of Councils, comprising members from IC advisory councils, individuals nominated by OD offices, and members of the Council of Public Representatives. Trans-NIH proposals will be required to include milestones and goals for the research activities and timeframes for funding the research. The bill stipulates that appropriate consideration be given to proposals for which the investigator is a first-time applicant to NIH.
- **Common Fund:** The Director of NIH will have the authority to allocate Common Fund money to the ICs to fund trans-NIH research. Common Fund amounts will be reserved by the Director and subject to appropriations, but the percentage constituted by the amount reserved relative to the total appropriation in any fiscal year (FY) may not be less than the percentage from the preceding fiscal year. The first year that the Common Fund reached the 5-percent mark, the Director, in consultation with the Council of Councils, will be required to submit recommendations to Congress for changes regarding amounts for the Common Fund.
- **Authorization of Appropriations:** Expired authorizations of appropriations sections relevant to NIH will be deleted from the statute and replaced with one authorization of appropriations for the entire agency for the following amounts: $30,331,309,000 for FY 2007, $32,831,309,000 for FY 2008, and such sums as may be necessary for FY 2009. Report language accompanying the House-passed bill states that the elimination of other authorizations of appropriations may not be construed as terminating the authority of the IC/OD office to carry out the program. Of the amount authorized to be appropriated for NIH, the bill authorizes for the OD such sums as may be necessary for each of the fiscal years 2007 through 2009.
- **Coding System:** The bill will require the establishment of an electronic system to uniformly code research grants and activities. This system will be required to be searchable by a variety of codes, such as type of research grant, research entity managing the grant, and public health area of interest. When permissible, the Secretary of HHS, acting through the

Director of NIH, will be required to provide information on relevant literature and patents that are associated with NIH's research activities.

- **Reporting:** ICs will be required to annually report to the Director of NIH the amount of the IC budget made available for trans-NIH research. The appropriations levels of ICs that fail to report trans-NIH funding will be held at the FY 2006 level. The Director of NIH will be allowed to waive the reporting requirement in certain circumstances.
  Most reports pertaining to NIH in current law will be deleted and replaced with one biennial report to Congress, with instructions on the information that will be required to be included. Additional reports with respect to collaboration with other DHHS agencies, clinical trials, human tissue samples, whistleblowers, and experts and consultants will be required. Reports will also be required from each institution receiving an NIH award for the training of graduate students for doctoral degrees.
- **Demonstration Programs:** The Director of NIH will be authorized, in consultation with the Director of the National Science Foundation, Secretary of the U.S. Department of Energy, and other agency heads, as necessary, to allocate funds for ICs to make grants for interdisciplinary demonstration projects designed to improve public health. The Director of NIH will also be authorized to allocate funds for ICs to make awards of grants or contracts or to engage in other transactions for demonstration projects for high-impact, cutting-edge research; in providing for such research, the Director of NIH or of the IC, as applicable, will be required to seek to facilitate partnerships between public and private entities. Such funds will be allocated from amounts appropriated to the OD. Grant applications must undergo both peer review and advisory council review.
- **Foundation for NIH:** The bill will make minor technical corrections regarding the Foundation for the NIH Board of Directors, as well as other clarifying amendments. The bill will require NIH to transfer between $500,000 and $1,250,000 to the Foundation annually.

Status and Outlook

A hearing was held on the unnumbered bill on September 19, 2006, and on September 20, 2006, the bill was marked up by the House Committee on Energy and Commerce and passed by a vote of 42 to 1. On September 26, 2006, H. Rept.109-687 was issued, and the bill was introduced as H.R. 6164. It was passed by the House by a vote of 414 to 2. The measure was passed by the Senate with an amendment by unanimous consent on December 8, 2006, and the amended version was passed by the House that same day. The legislation was signed by the President on January 15, 2007, and is cited as Public Law 109-482, the National Institutes of Health Reform Act of 2006.

Director's Report to the National Advisory Council on Drug Abuse - February, 2007

International Activities

NIDA-Supported Meetings

Drugged-Driving Experts Draft Research Standards
Experts from nine countries and three continents gathered September 8-12, 2006, to draft standards for drugged-driving research to ensure the comparability of data from country to country. IP Director Dr. Steven W. Gust co-chaired the meeting with Dr. Michael J. Walsh, The Walsh Group, and opened the meeting by reviewing previous recommendations on drugged driving data needs and research. Plenary and breakout sessions explored issues in epidemiology, behavioral aspects of drugs, toxicology and analytical chemistry. Dr. Marilyn Huestis, IRP, was an expert participant in the toxicology and analytical chemistry sessions. To solicit comments from the greater drug-impaired driving research community, the meeting organizers will post the draft standards on the websites of The Walsh Group; the International Council on Alcohol, Drugs and Traffic Safety (ICADTS); and the International Association of Forensic Toxicologists (TIAFT). Organizers plan to distribute the final version of the standards at the joint TIAFT/ICADTS meeting in August 2007. The meeting, held at the Tufts University European Center in Talloires, France, was organized by The Walsh Group and co-sponsored by NIDA, the European Commission, the European Monitoring Centre for Drugs and Drug Addiction, ICADTS, TIAFT, and the French Society of Analytical Toxicologists. NIDA supported the participation of the following speakers: Barry Logan, Ph.D., Washington State Patrol, Seattle; Jan Ramaekers, Ph.D., Maastricht University, The Netherlands; Patricia Dischinger, Ph.D., University of Maryland Shock Trauma Center, Baltimore; and Ms. Inger Marie Bernhoft, Danish Transport Research Institute. NIDA also provided travel support to the following participants: Olaf Drummer, Ph.D., Monash University, Victoria, Australia; Larry Gentilello, M.D., University of Texas Southwestern Medical School, Dallas; Jorg Morland, M.D., Norwegian Institute of Public Health, Oslo; Horst Schulze, Ph.D., Federal Highway Research Institute, Gladbach, Germany; Ms. Beitske Smink, Netherlands Forensic Institute, Rijswijk; and Mr. Rene Mathijssen, SWOV Institute for Road Safety Research, The Netherlands.

NIDA and CICAD Co-Sponsor Latin American Epidemiology Group and Iberoamerican Conference of National Observatories on Drugs
The initial meeting of the Latin American epidemiology group, Red Epidiemiologica de Drogas para Latinoamerica (REDLA), took place in Cartagena, Colombia, December 10 - 12, 2006. REDLA is a joint effort between NIDA and the Inter-American Drug Abuse Control Commission (CICAD) at the Organization of American States to create a drug epidemiology network for Latin America that parallels NIDA's Community Epidemiology Working Group (CEWG) in scope and purpose. NIDA's support for REDLA is part of the Institute's Latin American Initiative. The meeting was co-chaired by Ms. Marya Hynes Dowell, CICAD, and Dr. Ivan Montoya, DPMCDA. Representatives of

Planned Meetings

Publications

Staff Highlights

Grantee Honors

Argentina, Brazil, Canada, Chile, Colombia, Costa Rica, Mexico, Nicaragua, and the United States summarized the drug use situation in their countries, identifying reliable sources of information for future investigations. In addition to their discussions about drug use patterns in the hemisphere and future activities for REDLA, participants discussed ways to integrate REDLA activities with those sponsored by the National Observatories on Drugs. The REDLA participants then joined the Third Iberoamerican Conference of National Observatories on Drugs, which was held December 11-15, 2006, in Cartagena and cosponsored by NIDA, OAS/CICAD, the Spanish Plan Nacional Sobre Drogas, and the Agencia Espanola de Cooperacion Internacional. Dr. Montoya's plenary session presentations during the Iberoamerican Conference addressed the role of drug abuse research on public policy, U.S. methodologies to conduct surveys of students and the general population, and morbidity indicators. Participants in both meetings included Dr. Antonio Cepeda-Benito, Chair, International Collaborations, National Hispanic Science Network; 2004 DISCA Scientist Dr. Helena Barros, Brazil; and 2003-2004 Humphrey Fellow Dr. Vladimir Stempliuk, Brazil.

Research Training and Exchange Programs

Former INVEST and DISCA Scientist Wins NIH Support for HIV Research

Dr. Min Zhao, Shanghai, China, Mental Health Center, has received a Fogarty International Center award through the Global Health Research Initiative Program for New Foreign Investigators (GRIP). Dr. Zhao will longitudinally examine gender-related differences in sexual and drug use risk behaviors among injection drug users in Shanghai. GRIP awards support the return of NIH-trained foreign investigators to their home countries as part of a broader program to enhance the scientific research infrastructure in developing countries, and to stimulate research of high priority global health-related issues. The GRIP proposal was developed through a 2005 DISCA research exchange by Dr. Zhao and Dr. Clyde B. McCoy, University of Miami, and will lead to further expansion of collaboration on HIV/AIDS and drug abuse research between Shanghai and Miami. Dr. Zhao was also a 2001-2002 NIDA INVEST Fellow.

HHH Fellows Meet with NIDA, State Department Officials

Officials from NIDA, the U.S. Department of State, Johns Hopkins University (JHU), and Virginia Commonwealth University (VCU), welcomed the 2006-2007 Hubert H. Humphrey Drug Abuse Research Fellows in a series of meetings designed to introduce the new Fellows to the Humphrey Program, which includes academic study; a professional affiliation with a NIDA-funded scientist; participation in the NIDA International Forum, to be held June 15-18, 2007, in Quebec City, Canada; and additional professional development activities sponsored by NIDA and the State Department. NIDA International Program Director Dr. Steven W. Gust and Dr. Judith Babbits, Institute of International Education, met with the HHH Fellows at VCU in August. In September, NIDA International Program Analyst Dale Weiss and Dr. Babbits met with VCU officials as well as with each Fellow individually to help the Fellows set objectives and begin planning their professional affiliations. NIDA also demonstrated the NIDA International Virtual Collaboratory, an online resource under development to promote information sharing and support collaborative international research. In November, Ms. Weiss met with the HHH Fellows and university officials at JHU, summarizing NIH activities, NIDA-sponsored professional development activities, and professional affiliations for the substance abuse fellows. The 2006-2007 Hubert H. Humphrey Fellows at VCU include: Lala Margaryants, Armenia; Kevin Goulbourne, Jamaica; Peter Kenneth Ndege, Kenya; Giselle Gonzalez, Panama; Rehanna Kader, South Africa; Adham Hamd, Syria; Desiree Molina, Venezuela; and Duc Nguyen, Vietnam. The 2006-2007 Humphrey Fellows at JHU include: M. D. Alamgir,

Bangladesh; Magalie Personna Nelson, Haiti; Mehboob Singh, India; Fairuz Afran, Iraq; Violet Caroline Akoth Okech, Kenya; Cholpon Imanalieva, Kyrgyz Republic; Sudhir Khanal, Nepal; Joseph Navarro, Philippines; Yasantha Ariyaratne, Sri Lanka; Amani Kisanga, Tanzania; and Michelle Moore, Trinidad and Tobago.

Travel Support

International Researchers Present Posters at NIDA Society for Neuroscience Mini-Convention

Drs. Susan Volman, DBNBR, chaired an Early Career Investigators Poster Session on Friday, October 13, 2006, as part of NIDA's mini-convention at the Society for Neuroscience Research meeting in Atlanta, Georgia. Among the drug abuse and drug-related neuroscience research showcased at the invited poster session were presentations by 19 international researchers from 11 countries: Laura Milan-Lobo, Austria; Lin Lu, China; Lia Gelazonia, Republic of Georgia; Chiara Castiglioni, Maria Antonietta De Luca, Daina Economidou, Liana Fattore, Gloria Lazzeri, Paola Lenzi, and Anna Rizzi, Italy; Masami Suzuki, Japan; Michel Van den Oever, The Netherlands; Ma_gorzata Frankowska, Poland; Marina Rubio, Spain; Pernilla Fagergren, Sweden; Taner Dagci and Aysegul Keser, Turkey; and Alexis Bailey and Anushka V. Goonawardena, 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.

NIDA Supports Presentations at SALIS/ELISAD Joint Conference

NIDA provided support for two presenters at the Substance Abuse Librarians and Information Specialists (SALIS)/ European Libraries and Information Services on Alcohol and Other Drugs (ELISAD) joint conference, held September 26-30, 2006, in Newton, Massachusetts. Ms. Jane Shelling, Manager of the Resource Center for the Alcohol and Other Drugs Council of Australia (ADCA), provided a general overview on the current AOD situation in Australia, highlighting the work being done by ADCA to reach out to policy makers and researchers. Mr. Juan Carlos Vega, Information Specialist for the Praxis Project, Washington, D.C., discussed the role of information resources in traditionally marginalized communities, highlighting how the Praxis Project works to eliminate health disparities in our society. Other conference topics included open access resources for web based searching, using GIS for substance abuse information, NIDA's Clinical Trials Network, and methamphetamine use in the United States.

NIDA Supports Grantee Presentations at the Congress of Neuroimmunology

NIDA provided assistance to support the participation of two grantees at the Congress of Neuroimmunology, held October 14-19, 2006, in Nagoya, Japan. Dr. Linda Chang, University of Hawai'i, and Dr. Howard E. Gendelman, University of Nebraska Medical Center, participated in a symposium for international researchers that highlighted efforts by NIDA and the Society on NeuroImmune Pharmacology (SNIP) to promote research on the pharmacology, immunology, and neuroscience of the neuroimmune axis.

NIDA Grantee Presents at ICAA, Supports Multinational Research Group

NIDA supported the participation by Dr. Howard Schubiner, Providence Hospital, Wayne State University, at the International Council on Alcoholism and Addictions (ICAA) International Conference on Dependencies, September 3-8, 2006, in Edinburgh, Scotland. Dr. Schubiner discussed ADHD and substance use disorders and agreed to serve as a consultant to a multinational research group developing plans for an international study of the prevalence of

ADHD among individuals seeking substance abuse treatment. He reports that the study is expected to begin in 2007 and to involve sites in The Netherlands, Spain, England, Norway, and possibly Italy.

NIDA Supports Mexican Researcher's Participation at NHSN

NIDA supported the participation of Nuria Lanzagorta, Carracci Medical Group, Mexico, at the National Hispanic Science Network on Drug Abuse Sixth Annual Conference, Drug Use and HIV/AIDS: Implications for the Hispanic Population, held September 13-16, 2006, in Scottsdale, Arizona. The multidisciplinary scientific meeting addressed the AIDS pandemic on both the international and national scale, focusing on the intersection between drug use and HIV/AIDS among Latinos.

International Visitors

Dr. Yakov Marshak, scientific director of the Marshak Clinic for Drug Addiction in Moscow, Russia, and Dr. Sonia Marshak from University of California, Irvine visited NIDA on August 9, 2006. Representing NIDA at the meeting were Dr. Cecelia McNamara Spitznas, DCNBR, Drs. Kevin Conway, Richard Denisco, Sarah Duffy, DESPR and Ms. Dale Weiss, IP. Dr. Marshak discussed his clinic and treatment method with the group.

On August 28, 2006, Ms. Els van Gessele and Dr. Nick Ramsey from ZonMw, The Netherlands Organization for Health Research and Development visited NIDA. The visitors met with Dr. Steve Gust and Ms. Dale Weiss, IP and Drs. Cecelia McNamara Spitznas and Steve Grant, DCNBR and Dr. Wilson Compton, DESPR. Discussions centered on the ongoing U.S. - Netherlands research collaboration.

The U.S. State Department's International Visitor Program sponsored a visit to NIDA by a group from Uzbekistan on September 21, 2006. The 8 visitors are involved in Drug Demand Reduction and HIV/AIDS prevention activities in Uzbekistan. Meeting with the group from NIDA were Dr. Cecelia McNamara Spitznas, DCNBR, Dr. Katherine Davenny, ARP and Ms. Dale Weiss, IP.

On October 31, 2006 Mr. Geurt van de Glind, of the International ADHD and Substance Abuse Collaboration, Trimbos-institute, The Netherlands visited NIDA to discuss the progress his collaboration has made and to look for ways to continue and expand the collaboration. Meeting with Mr. van de Glind from NIDA were Dr. Cecelia McNamara Spitznas, DCNBR, Dr. Steve Gust and Ms. Dale Weiss, IP.

Mr. Paul Thewissen, recently appointed Counselor for Health, Welfare and Sport, Royal Netherlands Embassy visited NIDA on November 16, 2006. Mr. Thewissen met with Dr. Steve Gust, IP to introduce himself and learn more about the ongoing U.S. - Netherlands research collaboration.

A delegation from the Indonesian National Narcotics Board visited NIDA on November 29, 2006. Heading the delegation was General Made Mangku Pastika, Executive Director of the National Narcotics Board, Republic of Indonesia. Accompanying General Pastika was Dr. Sudirman Ma, Executive Director of the Indonesian National Institute on Drug Abuse (INIDA), General Djoko Satriyo, Head of Law Enforcement Center, National Narcotics Board, Brigadier General Indradi Thanos, Director, Criminal Investigation Bureau, Indonesian National Police and Mr. Russell Holke, DEA Country Attache, American Embassy Singapore. Meeting with the Delegation from NIDA were Drs. Liz Ginexi and Richard Jenkins, DESPR, Dr. Cecelia McNamara Spitznas, DCNBR and Dr. Steve Gust and Ms. Dale Weiss, NIDA.

Other Activities

In October 2006, a team of NIDA staff and several extramural researchers formed a delegation that visited Wuhan University (Hubei Province, China) and Peking University (Beijing, China). The purpose of the trip was to explore possible research collaborations for non-human primate studies of AIDS and drug abuse interactions. The "U.S.-China Symposium on Drug Abuse and Chinese Monkey Model for SIV Infection" was held on October 24, 2006 at Wuhan University, and included presentations by David Shurtleff, Director, DBNBR and Lynda Erinoff, Associate Director, ARP on NIDA's goals in HIV/AIDS research and international research funding opportunities. Diane Lawrence and Yu "Woody" Lin attended as program representatives from DBNBR. The delegation also visited the State Key Virology Laboratory in Wuhan, the Hubei Province CDC, and the laboratory of Hongkui Deng, recipient of a Grand Challenges in Global Health award to use stem cells to develop mouse models for use in testing HIV and HCV vaccines.

Dr. Betty Tai, Director, CCTN, was an invited panel speaker and participant in the 9th National Conference on Drug Dependence in Sanya City, China sponsored by the Chinese National Institute on Drug Dependence (NIDD) in Peking University from November 1-5, 2006. The theme of this year's conference was "Drug Abuse and HIV/AIDS." The meeting resembles the US Blending Conference in that Chinese drug abuse researchers meet jointly with Chinese community drug treatment practitioners in bi-directional communication.

On November 5, 2006, Dr. Tai was awarded the "Distinguished Public Service Award in Drug Abuse Treatment" by the Chinese NIDD and the Peiking University.

While in China, Dr. Tai also visited Shanghai Mental Health Hospital on October 31, 2006 and met with Hospital's Clinical Pharmacology faculty and the Director of Shanghai's CDC. She met with representatives of the Hospital's drug trial program and heard how Shanghai CDC plans to initiate its five methadone centers. Dr. Tai was received by Dr. Min Zhao, a former NIDA INVEST fellow and Distinguished Scientist fellow. Dr. Zhao is an Associate Professor, Director of the Shanghai Drug Abuse Treatment Center (SDATC)/Shanghai Mental Health Center. At the SDATC, located in a suburb of Shanghai, Dr. Tai met with the entire 35-member staff, comprising psychiatrists, nurses, counselors, and social workers. At the meeting, Dr. Tai gave a lecture on NIDA's effort in using the CTN to bridge research and practice, and how NIDA/NIH is addressing drug abuse and the HIV/AIDS public health threat. Staff there expressed intense interest in integrating behavioral treatment with methadone treatment and expressed the needs of training.

Dr. Jag Khalsa, DPMCDA, presented a symposium on Clinical Management of HIV/HCV Co-infections in Drug Abusers at the Annual Meeting of the International Society of Addiction medicine (ISAM), Oporto, Portugal, September 27-30, 2006, where NIDA/NIH-supported grantees presented research on the issue of dual infections in drug abusers. Dr. Frank Vocci gave a presentation originally slated for Dr. Glen Treisman of Johns Hopkins University. Dr. Vocci spoke on Overcoming Psychiatric Barriers to Effective Hepatitis C Treatment.

Dr. Frank Vocci, Director, DPMCDA, gave two presentations at the ISAM meeting in Porto. Dr. Vocci participated in a cannabis symposium and spoke on Developing Medications for Cannabis Dependence. Dr. Vocci also spoke at a methamphetamine symposium. His topic dealt with medications targets for methamphetamine dependence treatment arising from preclinical research. Dr. Frank Vocci gave the opening plenary lecture at the Australasian Professional Society on Alcohol and Other Drugs in Cairns, Australia on November 5, 2006. Dr. Vocci spoke on preclinical and clinical approaches to the development of medications for the treatment of cannabis dependence.

Dr. Jag Khalsa delivered two talks on Medical Consequences of Drug Abuse and Infections and research at NIDA at the International Symposium on Drug Abuse and HIV/AIDS, in Kerala, India, on November 6-7, 2006, and at the Global BioPharma Conference, in Hyderabad, India, November 9-10, 2006. Dr. Khalsa inaugurated the International Symposium as well as closed the meeting with closing remarks. He received a citation for his outstanding contributions to the field of drug abuse and infections. Dr. Khalsa also delivered an invited talk on Medical (metabolic/nutritional) Complications of Drug Abuse and Hepatitis C Infection: Research at NIDA, at the GB Pant Hospital, New Delhi, India, November 15, 2006.

On September 28, 2006, Dr. Ivan Montoya, DPMCDA, presented the paper entitled "Medications Development for Co-morbid Substance Abuse and Depression" at the Sixth World Congress on Depression and International Symposium on Addictive Disorders, in Mendoza, Argentina.

On November 3, 2006, Dr. Ivan Montoya chaired a symposium on Drug Abuse Treatment and presented a paper on Immunotherapies for Addiction, at the annual meeting of the Colombian Psychiatric Association, in Medellin, Colombia.

On November 28, 2006, Dr. Ivan Montoya made a presentation entitled "Cognitive Effects of Chronic Cocaine Use" at a pre-conference course on Advances in Drug Abuse Research. Lima, Peru. Dr. Frank Vocci made a presentation on the Neurobiology of Addiction- A Systems Perspective.

On November 29, 2006, Dr. Ivan Montoya made a presentation on Immunotherapies for Addiction at the Regional Meeting of the World Psychiatric Association and Annual Meeting of the Peruvian Psychiatric Association, in Lima, Peru. Dr. Frank Vocci presented on the Endocannabinoid System as a Drug Development Target for Substance Abuse Disorders and Obesity. Dr. Jag Khalsa delivered talks on Consequences of Drug Abuse and Infections including Hepatitis C at the XIX Peruvian Psychiatric Congress Meeting, Lima, Peru, on November 29-December 1, 2006.

On December 10-15, 2006, Dr. Ivan Montoya represented NIDA at a meeting of the Drug Abuse Monitoring Networks in Ibero-America, in Cartagena, Colombia.

In September, Wilson M. Compton, M.D., M.P.E., Director, DESPR, attended the ISBRA meeting held in Sydney, Australia and presented a paper on Item Response Models of Marijuana Use and Criteria at the NIAAA satellite meeting on diagnosing substance use disorders.

On November 8-10, 2006, Wilson M. Compton, M.D., M.P.E presented at the East Asia epidemiology workgroup meeting in Taipei, Taiwan. Participants in this workgroup included representatives from East and South Asian countries as well as Australia.

Moira O'Brien, DESPR, chaired the meeting of the US Mexico Border Epidemiology Work Group held in San Diego, California, September 21, 2006. Participants included representatives from the Mexican Ministry of Health and drug abuse researchers from the US border area.

Dr. Peter Hartsock, DESPR, participated in a meeting with the Minister of Health and Minister of AIDS Interventions of Vietnam in Washington, D.C. on July 19th, 2006. The meeting was held under the auspices of the Center for Strategic and International Studies and the Department of State. Drug abuse is a principal factor in the rapidly spreading Vietnamese HIV/AIDS epidemic. Vietnam is one of the 15 "focus" countries receiving special U.S. PEPFAR (President's Emergency Plan for AIDS Relief) funds to combat the epidemic. Dr. Hartsock presented on NIDA's HIV/AIDS modeling program and its domestic and foreign applications.

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Director's Report to the National Advisory Council on Drug Abuse - February, 2007

Meetings/Conferences

NIDA hosted a two-day Blending Conference at the Washington State Convention and Trade Center in Seattle, Washington on October 16-17, 2006, titled **"Blending Addiction Science & Practice: Bridges to the Future."** This successful event brought together more than 900 clinicians and researchers to present and discuss the most recent scientific findings related to science-based drug abuse and addiction treatment. In this sixth NIDA Blending Conference, all five Blending Team products were presented in separate sessions and included: Buprenorphine Treatment: Training for Multidisciplinary Addiction Professionals; Short-Term Opioid Withdrawal Using Buprenorphine; S.M.A.R.T. Treatment Planning: Utilizing the Addiction Severity Index (ASI); Motivational Interviewing Assessment: Supervisory Tools for Enhancing Proficiency (MIA:STEP) and Promoting Awareness of Motivational Incentives (PAMI). The NIDA planning committee of this conference included Drs. Timothy P. Condon, Cindy Miner, Denise Pintello, as well as Jane Smither and Carol Krause, OSPC.

NIDA hosted a **Research Training Directors Meeting** on November 3, 2006 at the North Bethesda Marriott Hotel. Over 40 Research Training Directors and 40 NIDA staff attended this meeting that provided an overview of the state of NIDA's research training program and updates on the new announcement and regulations. Dr. Timothy Condon presented a broad overview of NIH/NIDA priorities and the Office/Division Directors described their research training needs and directions. The hallmark of the meeting was a set of Best Practices Topic Forums facilitated by NIDA staff. Drs. Susan Weiss, Suman Rao King, Elaine Lazar-Wesley, Beth Babecki, and Kathy Etz organized the meeting on behalf of the Research Training Committee.

Drs. Karen Sirocco, Nicolette Borek, Laurence Stanford, and Vincent Smeriglio, all of DCNBR, in collaboration with Dr. Ellen Witt from NIAAA, organized an invited expert panel workshop entitled **Consequences of Marijuana Use on Brain and Behavioral Development** on December 15, 2006 in Bethesda, MD. The workshop was sponsored by the Office of Science Policy and Communications (OSPC), and co-funded by NIAAA. A major purpose of the workshop was to facilitate increased quality and efficiency in ongoing and future studies by information-sharing and methodological problem-solving among researchers implementing relevant research studies.

Dr. Nicolette Borek, DCNBR, presented a talk on NIH research funding and career opportunities at the George Washington University's Clinical Psychology Seminar Series on October 16th, 2006.

Yonette Thomas, Ph.D. chaired a workshop on November 1-2, 2006 on **Mapping the Environment: A Workshop on Measuring the Social Environment in Drug Abuse Research.** The workshop brought together experts in epidemiology, social and behavioral sciences, and genetics who are

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interested in linking the social, biological/genetic, and physical environments to better understand their interactions and influences on drug use and risk behaviors.

Drs. Eve Reider, Elizabeth Robertson, Gina Hijjawi, and Vince Smeriglio, in collaboration with a NIDA working group consisting of Drs. Jessica Campbell Chambers, Redonna Chandler, Aria Crump, and Belinda Sims, convened a meeting **Children of Parents in the Criminal Justice System: Children at Risk**. The meeting was sponsored by NIDA's Office of Science Policy and Communication; it was held November 6, 2006 at the Marriott Bethesda North Hotel and Conference Center in Bethesda, Maryland.

The National **CTN Steering Committee Meeting** was held October 16-20, 2006 in Seattle, Washington. The following meetings/committees convened:

Members of the CTN 0015 (Women's Treatment for Trauma and Substance Use Disorders)
study team
Special Interest Groups: Gender, Health Services Research, Pharmacotherapy, Behavior/Psychosocial, Design and Analysis Group
CTP and PI Caucuses
Executive Committee
Research Utilization Committee
Research Development Committee
Node Coordinator Workgroup
Steering Committee - included Web conference/presentation from Dr. Nora Volkow
Members of the CTN 0020 (Job Seekers) study team
Secondary Analysis Workshop

The CCTN presented a symposium entitled: **Co-morbid Pain and Addiction - Novel Treatments** at the 45th Annual Meeting of the American College of Neuropsychopharmacology (ACNP) in Hollywood, Florida, December 3-7, 2006. Dr. Charles O'Brien chaired the session together with Dr. Petra Jacobs. This symposium reviewed new findings on the neurophysiology of pain and addiction. Presenters included Dr. David Borsook, Dr. Nathaniel Katz, Dr. Gavril Pasternak and Dr. Jon-Kar Zubieta. Dr. Walter Ling was a discussant in the panel as well.

The Special Populations Office, National Institute on Drug Abuse (NIDA) and the Substance Abuse and Mental Health Service Administration (SAMHSA) hosted a research development workshop titled: **Substance Abuse, Criminal Justice and HIV in African Americans** in Silver Spring, Maryland on Dec 11 - 12, 2006. The two-day workshop, which was attended by over 300 people, was designed to address the unique concerns that arise when conducting research in criminal justice populations and systems. The workshop is part of a NIDA initiative to address the disproportionate occurrence of criminal justice involvement and HIV/AIDS among African Americans as a consequence of substance abuse. The workshop consisted of panels, discussions and roundtables, which were led by key researchers in the field and a host of NIDA staff.

The Special Populations Office convened a two-day meeting of NIDA's African American Researchers and Scholars Workgroup in Gaithersburg, Maryland on October 10-11, 2006.

The Special Populations Office convened a two-day meeting of NIDA's Native American and Alaskan Native Researchers and Scholars Workgroup in Gaithersburg, Maryland on November 28-29, 2006. Dr. Nora Volkow gave a welcoming presentation to the workgroup.

The Special Populations Office, along with the Division of Epidemiology Services and Prevention (DESPR), sponsored a presentation by Gail Wyatt, Ph.D. on Wednesday, November 15, 2006. The presentation, titled "Health, Mental Health and Drug Abuse Disparities for African American and Latina Women at Risk for Living with HIV," was part of the DESPR Seminar Series.

Dr. Timothy P. Condon, Deputy Director, NIDA, presented "Methamphetamine: How It Influences the Brain and Behavior of Users and Treatment Implications" at the Addiction Studies Program for State Legislatures on September 13, 2006 in Portland, Oregon.

Dr. Timothy P. Condon presented a training entitled "It's a Brain Disease: Beyond a Reasonable Doubt - The Neuroscience of Addiction & Judicial Decision Making" to the Circuit Court of Cook County on September 28, 2006 in Chicago, Illinois.

Dr. Timothy P. Condon presented a keynote address, "Advances in Drug Abuse and Addiction from NIDA: Implications for Treatment," at the California Society of Addiction Medicine's Addiction Medicine Review Course 2006 on October 6, 2006 in San Francisco, California.

Dr. Timothy P. Condon presented "An Update on NIH/NIDA Activities" at the Research Training Directors Meeting on November 3, 2006 in North Bethesda, Maryland.

Dr. Timothy P. Condon presented on the "Neurobiology of Addiction" at the 52nd Annual St. Paul's Hospital Continuing Medical Education Conference on November 14, 2006 in Vancouver, British Columbia.

Dr. Timothy P. Condon presented "Addiction as a Brain Disease: New Implications for Research and Practice" at the UN Office on Drugs and Crime/UCLA Integrated Substance Abuse Program on November 30, 2006 in Los Angeles, California.

Dr. Cindy Miner, Deputy Director, OSPC gave a keynote presentation "Improving Addiction Treatment: NIDA's Blending Research and Practice Initiative" at the NAADAC Annual Conference on September 29, 2006 in Burbank, California.

Dr. Cindy Miner co-chaired a "NIDA/NIMH Grantwriting Workshop" at the 53rd Annual meeting of the American Academy of Child & Adolescent Psychology on October 25, 2006 in San Diego, California.

Dr. Cindy Miner facilitated a Best Practices Forum: "Components of Successful Program Evaluation and Tracking" at the Research Training Director's Meeting on November 3, 2006 in Bethesda, Maryland.

Dr. Cindy Miner presented "Next Steps in the Grant Funding Process" at the Enhanced State Capacity to Foster Adoption of Science Based Practices Meeting on November 21, 2006 in Bethesda, Maryland.

Dr. Cindy Miner assisted with the planning and execution of the 2nd National Leadership Conference on Medical Education in Substance Abuse on November 30 - December 1, 2006 in Washington, D.C.

Dr. Gayathri Dowling, SPB, OSPC, gave a presentation entitled "Methamphetamine: The Science of Addiction and Recovery" as part of a panel, "Addressing Meth and Substance Abuse Comprehensively," at the West/Southwest Methamphetamine Legislative and Policy Planning Conference, convened by the Office of National Drug Control Policy, the Office of Justice Programs/Bureau of Justice Assistance, the Substance Abuse and Mental Health Services Administration and the National Alliance for Model State Drug Laws, in Salt Lake City, UT on October 5-6, 2006.

Dr. Ruben Baler, OSPC, made a presentation at the School of Public Health and Health Services, Department of Exercise Science, at George Washington University on October 10, 2006. The presentation was part of the "Drug Awareness" course offered every semester to incoming freshmen, and included a formal lecture entitled "Addiction is a Brain Disease" that highlighted the neurobiology of drug addiction, as well as NIDA's mission, strategies and achievements.

Mr. Brian Marquis, PILB, OSPC, attended a public forum in the state of New Hampshire. The forum entitled "Is Rockingham County and New Hampshire Losing the War on Drugs?" was hosted to discuss the growing problem of drugs in Rockingham County and how legislators can help solve it. Nine panelists, each with differing experiences in drug treatment, enforcement and surveillance, summarized their experiences and preferred strategies for combating drug abuse in front of 260 New Hampshire (Rockingham County) citizens. NIDA also provided copies of Principles of Drug Abuse Treatment for Criminal Justice Populations: A Research-Based Guide and a video message from Dr. Volkow addressing the citizens of New Hampshire.

Dr. Donald Vereen, M.D., M.P.H., Special Assistant to the Director, NIDA, gave the keynote address and ran a research dissemination workshop at the Illinois Alcoholism and Drug Dependence Association (IADDA) annual meeting in Chicago, IL on September 19, 2006.

Dr. Don Vereen accepted the "Celebration of Recovery Community Service Award for Dr. Nora Volkow from Vanguard Services Unlimited, a longstanding drug treatment provider based in Arlington, VA on September 27, 2006.

Dr. Don Vereen gave the Dean's Hour presentation at the University of North Dakota School of Medicine and Health Sciences. Dr. Joe Frascella gave an overview of NIDA's brain imaging research and a technical assistance seminar. Both met with representatives of the University Health Services to discuss college drug use, American Indian drug and alcohol use, and treatment research. Ongoing dialogues were started on future neuroscience projects, research training for Native Americans (Dakotas), and clinical research training. All presentations and meeting took place in Grand Forks, North Dakota on October 4 - 6, 2006.

Dr. Don Vereen gave a presentation on drug abuse and addiction and it's treatment at the Optimal Health Conference at Howard University School of Medicine in Washington, DC on October 21, 2006.

Dr. Don Vereen presented at the Annual Meeting of the U.S. Department of Education's Safe and Drug Free Schools grantees in Arlington, VA on October 22, 2006.

Dr. Don Vereen gave presentation on drug abuse and addiction research and recovery to the treatment and recovery community of Pittsburgh at the University of Pittsburgh School of Medicine on October 26, 2006.

Dr. Don Vereen presented to the National Child Traumatic Stress Network (a SAMHSA sponsored group) in Boston, MA on November 6, 2006.

Dr. Don Vereen gave a joint presentation with Drs. Lula Beatty and Dionne Jones on drug abuse, addiction, AIDS, and the criminal justice system at the Annual Meeting of the American Public Health Association in Boston, MA on October 7, 2006.

Dr. Don Vereen gave the keynote address at the annual Minnesota Safe and Drug Free Schools Conference in St. Cloud, MN on October 8, 2006.

Dr. Don Vereen presented on minority drug abuse and addiction at the Howard University School of Medicine Mental Health Conference in Washington, DC on

October 14, 2006.

Dr. Don Vereen gave the keynote address at the annual meeting of the South Carolina Association of Drug Counselors in Myrtle Beach, SC on October 29, 2006.

Dr. Don Vereen presented an overview of drug abuse research to The Public Defender Service of Washington, DC on December 4, 2006.

Dr. Don Vereen gave a presentation on drug abuse, addiction, and treatment principles to the DC Drug Court staff in Washington, DC on December 6, 2006.

Dr. Don Vereen gave a presentation to parents and students of the Alice Deal Junior High School in Washington, DC on January 18, 2007.

Lula Beatty, Ph.D., Chief, Special Populations Office (SPO), participated in the meeting of the Committee on Women in Psychology of the American Psychological Association in Washington, DC in September 2006.

Dr. Lula Beatty attended the Health Disparities Conference sponsored by the NIH Office of Behavioral and Social Science Research in Bethesda, MD in October 2006.

Dr. Lula Beatty participated as a moderator in two scientific meetings planned by the Division of Epidemiology, Services, and Prevention Research in November 2006: "Children of Parents in the Criminal Justice System: Children at Risk," and "Trajectories of Drug Use among African Americans."

Dr. Lula Beatty presented a talk titled "Developing Research and Researchers to Address Drugs and Criminalization in African Americans" at the convention of the American Public Health Association in Boston in November 2006.

Pamela Goodlow, SPO, chaired a two-day Special Populations Research Development Seminar Series, an ongoing research grants development technical assistance workshop for new minority investigators, on October 1-2, 2006 in Rockville, Maryland.

Dr. Laurence Stanford, DCNBR, is a member of the Neuroscience Blueprint Neurodevelopment Project Team and served as the NIH Liaison to the Developmental Plasticity Group at the NIH Blueprint for Neuroscience Research Workshop on Neurodevelopment held in Bethesda, MD in November 2006.

Dr. Laurence Stanford presented talks on grant writing strategies at the NIDA Special Populations Office Research Development Seminar Series in October, 2006 and at the NIDA Substance Abuse, Criminal Justice and HIV in African-American Research Development Seminar Series in December 2006.

Dr. Kevin Conway, DCNBR, attended and delivered a talk at the Study of the Social Contexts of Pathways into Crime Conference at the University of Cambridge, United Kingdom, December 5-8, 2006.

Dr. Kevin Conway attended and delivered a talk at the American Society of Criminology conference in Los Angeles, California, November 1-4, 2006.

Dr. Nicolette Borek presented two talks on NIDA research priorities at the 53rd annual meeting of the American Academy of Child & Adolescent Psychiatry, October 24-28, 2006 in San Diego. Dr. Borek also moderated a session organized by Dr. Ivan Montoya, DPMCDA, on "Cannabis Use in Adolescents: Onset and Outcome of Psychotic Disorders".

Dr. Nicolette Borek presented talks and coordinated training on collecting substance use and exposure data at the Pediatric HIV/AIDS Cohort Study (PHACS) Training meeting, November 13-15th, 2006 in Bethesda, MD. Dr. Borek also participated as a NIH scientific collaborator at the PHACS Steering

Committee meeting held in Bethesda on September 18-19th, 2006.

Drs. Steven Grant and Harold Gordon, both of DCNBR, represented NIDA at the annual meeting of the Society for Neuroscience held in Atlanta, Georgia, October 14-18, 2006.

Dr. Steven Grant was a discussant in a symposium titled: "Can Correcting Cognitive Deficits Improve Treatment Responses In Substance Abusing Patients ?" at the annual meeting of the American College of Neurospsychopharmacology held in Hollywood, Florida, December 3-7, 2006.

Dr. Melissa Racioppo, DCNBR, participated in a panel discussion of evaluation of interdisciplinary research at an NCI-sponsored meeting entitled "The Science of Team Science".

Dr. Cecelia Spitznas, DCNBR, participated in the roundtable discussions with potential applicants at the Jointly Sponsored NIH and IHS Native American Centers for Research Meeting.

Dr. Cecelia Spitznas gave a briefing to Indian Health Services Senior Staff on options for Treating Methamphetamine Use Disorders in Indian Country.

On November 28, 2006, Drs. Lisa Onken, Patty Mabry, Teri Levitin, and Gerald McLaughlin participated in an on-line technical assistance meeting for the RFA, "Facilitating Interdisciplinary Research via Methodological and Technological Innovation in the Behavioral and Social Sciences (R21)"

Dr. Joseph Frascella, Director, DCNBR, presented an overview of the DCNBR programs at the NIDA Training Directors Meeting in Bethesda, MD on November 3, 2006. He also was a co-facilitator along with Drs. Jacques Normand and Harold Perl for a forum entitled "Targeting New Program Areas for Enhanced Training Development."

Dr. Joseph Frascella was invited to give a presentation entitled "Interdisciplinary Research: The Future of NIH Research?" and also presented a seminar on the "NIH Grant Process" at the J. B. Pierce Laboratory at Yale University, November 10, 2006.

Drs. Joseph Frascella and Donald Vereen conducted a site visit to the University of North Dakota in Grand Forks, North Dakota, October 4-6, 2006. They toured the new brain imaging facilities and met with several faculty members within the neuroscience and related departments. They also discussed university programs for American Indians. Dr. Vereen gave a presentation on the biology of addiction at the University of North Dakota Medical School's Grand Rounds, and Dr. Frascella gave a presentation on interdisciplinary research and grant writing to a group of faculty and graduate students.

Dr. Rao Rapaka, DBNBR, organized a symposium on "Strategies to Enhance Drugability" at the 2007 Annual National Meeting of the American Association of Pharmaceutical Scientists (AAPS) on November 1, 2006 in San Antonio, Texas. His term as the Chair of the Drug Design and Discovery Section ends in December 2006.

Dr. Allison Chausmer, DBNBR, served as moderator for the "Evaluation of NIH Roadmap and Other TD Programs at NIH" session at NCI's "The Science of Team Science: Assessing the Value of Transdisciplinary Research" conference at NIH in October 2006.

Dr. Cora Lee Wetherington, DBNBR, gave a talk, "The Pervasiveness of Sex/Gender Differences in Drug Abuse," to members of NIDA's Center for Clinical Trials Network, November 9, 2006.

Dr. Cora Lee Wetherington chaired the session, "Sex and Gender Factors Affecting Health Behavior" at the Third Annual Interdisciplinary Women's Health

Research Symposium, sponsored by the NIH Office of Research on Women's Health, November 15, 2006, Bethesda, MD.

Dr. Cora Lee Wetherington was a presenter in the panel, "The Grants Process: Roles and Responsibilities," at the annual meeting of the Scholars of the Building Interdisciplinary Research Careers in Women's Health Program, NIH Office of Research on Women's Health. November 14, 2006, Bethesda, MD.

Drs. Rita Liu, David Shurtleff, and Cathrine Sasek co-chaired the NIDA/Society for Neuroscience (SfN) Frontiers in Addiction mini-symposium, Atlanta GA, October 13, 2006.

Drs. Jonathan Pollock and John Saterlee co-chaired a SfN mini-symposium: Molecular Mechanisms of Synapse Formation: Adhesion Molecules, Atlanta GA, October 13, 2006.

Drs. Joni Rutter and George Uhl co-chaired a NIDA/SfN mini-symposium Genome-wide Scans for Addiction Loci, Atlanta GA, October 13, 2006.

Drs. Jerry Frankenheim and Roy Wise co-chaired a NIDA/SfN mini-symposium: Roles of Hypothalamus Peptides in Addiction and Obesity, Atlanta, GA, October 13, 2006.

Drs. Paul Schnur and David Shurtleff Co-chaired a NIDA/SfN mini-symposium session on "Social Neuroscience: Application to Addiction" Atlanta, GA, October 13, 2006.

Drs. Nora Volkow and David Shurtleff Co-chaired a symposium at The American College of Neuropsychopharmacology, Hollywood FL, December 7, 2006.

Dr. David Shurtleff, DBNBR, chaired and gave presentation on grantsmanship and navigating the NIH grant review system at the USA-Caribbean HIV/AIDS and Drug Abuse Conference, San Juan, PR, December 8-12, 2006.

Dr. Diane Lawrence, DBNBR gave an overview and presentation of "Glial Cell Models in AIDS Research, and Integrative Approaches" at the USA-Caribbean HIV/AIDS and Drug Abuse Conference, San Juan, PR, December 8-12, 2006.

Dr. David Shurtleff gave a presentation on "Animal Models of HIV: Genetics & Molecular Neurobiology" at the USA-Caribbean HIV/AIDS and Drug Abuse Conference, San Juan, PR, December 8-12, 2006.

Dr. Paul Schnur moderated a panel discussion on funding opportunities at the Substance Abuse, Criminal Justice and HIV in African Americans: Research Development Workshop, Silver Spring, MD, December 11-12, 2006.

Dr. Jag Khalsa, DPMCDA, participated as a panel member to discuss Liver Disease in HIV-co-infected Drug Addicts at the NIAID/NIDDK/NIDA co-funded R13 Conference on Liver Disease in HIV Infection, Jackson Hole, WY, September 14-16, 2006.

Dr. Jag Khalsa presented a session known as "NIDA/NIH AASLD Corner" a Symposium on Liver Disease/HCV in Drug Addicts at the Annual Meeting of the American Association for the Study of Liver Disease (AASLD). Dr. Frank Vocci gave the introductory remarks to the Symposium. Dr. Khalsa also presented the Early Morning Workshop on Drug Interactions Among Antiretroviral Drugs and Drug Addiction Medications, October 27-29, 2006, Boston, MA.

On September 14, 2006, Drs. Ivan Montoya and Jag Khalsa, DPMCDA, co-chaired the symposium entitled "Pharmacotherapy for HIV Infection in Hispanic Populations" at the annual meeting of the National Hispanic Science Network on drug abuse in Scottsdale, Arizona.

On September 14, 2006, Dr. Ivan Montoya co-chaired a workshop on the

development of a Webportal for international researchers, at the annual meeting of the National Hispanic Science Network on Drug Abuse in Scottsdale, Arizona.

On October 19, 2006, Dr. Ivan Montoya give a presentation at the Smoke-free Families Conference entitled "NIDA Funding Opportunities to Evaluate Interventions to Help Women Quit Smoking", in Washington, DC.

October 19, 2006, Dr. Frank Vocci, Director, DPMCDA, spoke at a CPDD-NIDA-FDA Abuse Liability Conference in Annapolis Maryland. Dr. Vocci's talk was titled: Use of Preclinical Abuse Liability Testing.

Dr. Frank Vocci chaired a symposium: "Can Correcting Cognitive Deficits Improve Treatment Responses in Substance Abusing Patients?" at the ACNP meeting in Hollywood, Florida on December 6, 2006. Drs. Daniel Alkon, Fanny Botreau and Barbara Sahakian spoke in the symposium. Dr. Vocci also spoke on: Cognitive Deficits in Stimulant Users: Types of Deficits and Their Possible Modulation.

On October 26, 2006, Dr. Ivan Montoya organized the symposium entitled: "Cannabis Use and Psychotic Disorders" at the annual conference of the American Academy of Child and Adolescent Psychiatry in San Diego, CA.

In October 2006, Wilson M. Compton, M.D., M.P.E., Director, DESPR, presented at the Rollins School of Public Health on linking epidemiology with neuroscience.

In October 2006 Wilson M. Compton, M.D., M.P.E. presented on services research at the Clinical Trial Network Steering Committee meeting in Seattle, Washington.

In October 2006, Wilson M. Compton, M.D., M.P.E. presented at the Drug Abuse Health Services Meeting, Little Rock, Arkansas.

On November 1-2, 2006, Dr. Compton participated in the DSM-V Task Force meeting of the American Psychiatric Association.

In November 2006, Dr. Compton presented at the Prevention Research Center, Pennsylvania State University, State College, Pennsylvania.

In December 2006, Dr. Compton attended the COMAT meeting at the Treatment Research Institute and Wharton School, University of Pennsylvania, Philadelphia, Pennsylvania.

In December 2006, at the ACNP Annual Meeting, Dr. Compton Co-Chaired a Study Group on Research with Prisoners: Ethics and Opportunities.

At the AAAP Annual Meeting in December 2006, Dr. Compton co-chaired with Dr. Mark Willenbring of NIAAA a symposium on 12-Step approaches to treating substance use disorders.

Yonette Thomas, Ph.D., Chief of the Epidemiology Research Branch, DESPR, chaired a workshop on November 13, 2006 on "Drug Use Trajectories among African Americans." The workshop brought together researchers from a variety of disciplines to consider the basis for the (apparently) consistent finding of divergent trajectories in drug use between African Americans and their white counterparts, specifically whether this is a real phenomenon, whether there are environmental, cultural, and biological factors that might explain it, and whether within this phenomenon, there are specific influences or effects that suggest opportunities for targeting prevention interventions.

Samia Noursi, Ph.D., of DESPR's Office of the Director, chaired a workshop on December 7-8, 2006, on "Disasters and Substance Abuse." The workshop brought together a distinguished group of experts in epidemiology, prevention,

and services research to address several key objectives: (1) to review the current state-of-knowledge on the etiology and epidemiology of substance abuse in disaster situations; (2) to identify research gaps in the epidemiology, prevention, and services delivery needs of substance abusers in the context of disasters; and (3) to formulate strategies for the translation and implementation of research findings to measurably impact public health practice. In addition to Dr. Noursi, the DESPR Organizing Committee for the workshop included Elizabeth Lambert of ERB, Shakeh Kaftarian of PRB, and Jerry Flanzer of SRB.

Yonette Thomas, Ph.D. presented a two-part lecture series on the social epidemiology of drug abuse to the Department of Behavioral Sciences and Health Education in the School of Public Health at Emory University, on October 28-29, 2006.

Dr. Redonna Chandler, DESPR, presented a paper titled, "Addressing Public Health Treatment Need in Public Safety Settings," as part of a symposium on treatment needs of individuals involved in the criminal justice system at the 2006 Annual Meeting of the American Psychological Association, New Orleans, LA, August 10-13, 2006.

Dr. Redonna K. Chandler presented, "Responding to Katrina: Intervening with the New Orleans First Responder Community," as part of a symposium on crisis intervention in the aftermath of Hurricanes Katrina and Rita at the 2006 Annual Meeting of the American Psychological Association, New Orleans, LA, August 10-13, 2006.

Dr. Peter Hartsock, DESPR, participated in a ground-breaking ceremony by the Acting Surgeon General for a new research building at the Uniformed Services University for the Health Sciences, October 23, 2006 in Bethesda, MD. Dr. Hartsock spoke on research opportunities related to substance abuse, HIV/AIDS, emerging diseases, and international cooperation.

Dr. Peter Hartsock represented NIDA at the Fogarty International Center's ICOHRTA AIDS/TB (International Clinical, Operational, & Health Services Research Training for AIDS/TB) meeting in Bethesda, MD, on August 23, 2006. With other NIH ICs, NIDA contributes funding to ICOHRTA activities overseen by Fogarty. ICOHRTA grantees in Russia, funded in large part by NIDA, have offered to provide the venue for the next (2007) ICOHRTA meeting.

Dr. Peter Hartsock participated in a Pentagon-hosted planning meeting on September 9, 2006 in Arlington, Virginia, on social and political destabilization associated with drug trafficking, specifically the heroin trade, and HIV/AIDS, along the "Silk Road" in Central Asia. The increase in illicit drug trafficking has major implications for national and international security. The Department of Defense has given this matter priority status for research on the scope and causes of the problem. Dr. Hartsock reported on NIDA-supported molecular epidemiologic research on the heroin trade and HIV sub-types which follow the drug trade through Central Asia.

Dr. Dionne Jones, DESPR, organized and chaired two panel presentations, "Treating Drug Abuse in Vulnerable Populations: A Human Right"; and "Drugs, HIV and Incarceration Among African Americans: Research Needs and Intervention Strategies" at the American Public Health Association Annual Meeting in Boston, MA, November 4-7, 2006.

Drs. Dionne Jones and Aria Crump, DESPR, served as faculty/consultants to participants attending the NIDA Research Development Seminar, October 2-3, 2006 at the Doubletree Hotel, Rockville, MD.

Dr. Dionne Jones, DESPR, gave a presentation on "Effective Interventions for Substance Abusers at Risk for HIV/AIDS" at the CSAP/SAMHSA Grantee Training Institute, in Miami, Florida, September 21, 2006.

Dr. Dionne Jones, DESPR, organized and chaired a panel presentation on "Effective Interventions for Drug Abusing Women At Risk for HIV/AIDS" at the American Psychological Association, New Orleans, LA, August 10-13, 2006.

On September 28, 2006, Dr. Jody Sachs presented the CCTN Classroom Series. Dr. Sachs is a Scientific Project Officer at the National Center for Research Resources/NIH and supervised the development of the National Electronics Clinical Trials and Research (NECTAR) Network. She presented an update on the NIH Roadmap Clinical Research Networks and NECTAR. The goal of NECTAR is to provide the informatics infrastructure that will serve as the backbone for interconnected and inter-operable research networks.

Dr. Harold Perl, CCTN, was an invited participant in the conference titled "Implementing and Sustaining Evidence-Based Drug Treatment in Criminal Justice Settings", organized by the Center on Evidence-based Interventions for Crime and Addiction (CEICA) on December 6-7, 2006 in Philadelphia, PA.

On October 12, 2006, Dr. Paul Wakim, CCTN, discussed Site Effect at the CCTN Classroom series. Dr. Wakim is a Senior Statistician in the Center for the Clinical Trials Network (CCTN) at NIDA. He discussed the guidance document on site effect in multi-site clinical trials on substance abuse treatments. He summarized the main points of the guidance document at the Classroom Series and discussed this at the National CTN Steering Committee in Seattle, WA.

On November 9, 2006, Dr. Cora Lee Wetherington presented Gender Analysis and the Women and Gender Group at NIDA. Dr. Wetherington, NIDA's Women & Gender Research Coordinator, serves as Chair of NIDA's Women and Gender Research Group and as NIDA's representative to the NIH Office of Research on Women's Health.

On November 10, 2006, Dr. Janet Levy, CCTN, gave an invited seminar for students and staff in the quantitative psychology program at the University of Kansas in Lawrence Kansas. The topic of the seminar was the role of the quantitative psychologist in the development and implementation of clinical trials.

Dr. Petra Jacobs, CCTN, co-chaired a symposium entitled: "Interface between Pain and Opioids: New Horizons" along with Dr. Roger Weiss at the 17th Annual American Academy of Addiction Psychiatry (AAAP) Meeting & Symposium. The meeting was held in St. Pete Beach, Florida, December 7-10, 2006. Presenters included Dr. Walter Ling, Dr. Martin Angst and Dr. Steven Passik.

Dr. Jonathan Katz, IRP, was invited to give a talk entitled: Atypical Dopamine Uptake Inhibitors: Curious Clues about Cocaine from Dubious Drugs. Presentation to the Department of Pharmacology, University of Michigan Medical School, Ann Arbor, MI, September 2006.

Dr. Amy Newman, IRP, was invited to give a lecture at the Department of Chemistry, Howard University on December 1, 2006.

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Media and Education Activities

The National Institute on Drug Abuse released the results of the 2006 Monitoring the Future (MTF) survey of eighth, 10th and 12th graders on December 21, 2006. The survey findings were unveiled at a news conference at the National Press Club in Washington, D.C. Featured speakers included John P. Walters, Director, Office of National Drug Control Policy; Alberto R. Gonzales, Attorney General of the United States; NIDA Director Dr. Nora D. Volkow; and Dr. Lloyd D. Johnston, principal investigator of the study, Institute for Social Research, University of Michigan.

The press conference was well attended by national, local and trade reporters and generated extensive print and broadcast media coverage. Highlights included stories by the *Associated Press, Reuters, New York Times, Washington Post, Baltimore Examiner*, CNN, ABC National TV, Fox National Cable News, and a live broadcast of the press conference by C-SPAN. Distribution of wire service stories resulted in articles in local daily newspapers across the country. Television coverage included stories by TV stations in more than 60 large, medium, and small media markets nationwide.

Press Releases

November 9, 2006 - The National Institute on Drug Abuse Announces Summer Internship Opportunities.
The National Institute on Drug Abuse is offering summer research training opportunities at their facility in Baltimore, Maryland. Students who are accepted to the program will work side-by-side with some of the world's leading scientists, in an environment devoted exclusively to cutting-edge biomedical research.

November 6, 2006 - Incentive-Based Therapy Improves Outlook For Methamphetamine Abusers.
New research suggests that offering methamphetamine abusers an incentive-based behavioral therapy program called contingency management (CM - also known as Motivational Incentives), along with psychosocial therapy is more effective than psychosocial therapy alone. The study was published in the November 2006 issue of the American Journal of Psychiatry.

October 16, 2006 - NIDA Speeds Transfer of Research Findings into Clinical Tools.
Thousands of people in the United States seeking treatment for drug abuse will benefit from years of scientific research, thanks to new products announced at the 2006 Blending Conference in Seattle, a meeting hosted by NIDA. The Blending initiative encourages the rapid integration of research findings into clinical practice.

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Grantee Honors

December 21, 2006 - NIDA-Sponsored Survey Shows Decrease in Illicit Drug Use among Nation's Teens but Prescription Drug Abuse Remains High.
The 2006 Monitoring the Future (MTF) survey of eighth, 10th and 12th graders indicated that their past-month use of illicit drugs has dropped 23.2 percent since 2001 (from 19.4 percent in 2001 to 14.9 percent in 2006). By contrast, abuse of prescription opioids remains at unacceptably high levels. The study was funded by the National Institute on Drug Abuse.

October 13, 2006 - NIDA NewsScan #46 - Women and Substance Abuse Issue

- Scientists Review Data on Substance Abuse in Women
- Study Identifies Factors Associated with a History of Substance Abuse Treatment in Women
- Case Management May Help Adolescent Females Stay In Treatment
- The Nicotine Patch May Increase Short-Term Abstinence Among Postmenopausal Smokers
- HIV Prevention Interventions Among Poor Women Need To Address Substance Abuse, Relationship Abuse
- Pregnant Smokers: Don't Light Up During First Two Weeks of Cessation Program
- Toddlers of Mothers Who Smoked During Pregnancy Show Behavior Problems

September 21, 2006 - NIDA Announces Smoke-Free Meeting Policy.
NIDA announced it would enact a new policy requiring that all meetings and conferences organized or primarily sponsored by NIDA be held in a state or municipality that has adopted a comprehensive smoke-free policy, unless specific circumstances justify an exemption.

September 18, 2006 - NIDA NewsScan #45 - Back to School Issue

- School-Based Drug Prevention Program May Decrease HIV Risk Behavior in Young Adulthood
- Project Towards No Drug Abuse Associated With Long-Term Reduction in Abuse of Certain Drugs
- Risky Behaviors May Indicate Risk of Adolescent Depression
- ADHD With Specific Co-Occurring Disorders Increases Risk for Drug Abuse in Adolescence
- Anti-drug Messages May Be More Effective When Delivered In Tandem with Classroom-Based Prevention Curriculums
- Successful Youth Anti-Drug Media Campaign Focuses on Positive Messages

September 4, 2006 - Prevention Programs for Young Rural Teens Can Reduce Methamphetamine Abuse Years Later.
New research shows that prevention programs conducted in middle school can reduce methamphetamine abuse among rural adolescents years later. Because methamphetamine addiction leads to problems with social interactions and a wide range of medical conditions, research into early interventions such as this is critical to protecting the Nation's youth. The paper was published in the September issue of Archives of Pediatrics and Adolescent Medicine.

August 24, 2006 - NIH Researchers Complete Unprecedented Genetic Study That May Help Identify People Most at Risk for Alcoholism.
Researchers at the National Institute on Drug Abuse, have completed the most comprehensive scan of the human genome to date linked to the ongoing efforts to identify people most at risk for developing alcoholism. This study represents the first time the new genomic technology has been used to comprehensively

identify genes linked to substance abuse. The study was published in the December 2006 issue of the American Journal of Medical Genetics Part B (Neuropsychiatric Genetics).

August 7, 2006 - Imaging Study May Help Point Toward More Effective Smoking Cessation Treatments.
Results of a recent imaging study showed that the nicotine received in just a few puffs of a cigarette can exert a force powerful enough to drive an individual to continue smoking. Researchers found that the amount of nicotine contained in just one puff of a cigarette can occupy about 30 percent of the brain's most common type of nicotine receptors, while three puffs of a cigarette can occupy about 70 percent of these receptors. When nearly all of the receptors are occupied (as a result of smoking at least 2 and one-half cigarettes), the smoker becomes satiated, or satisfied, for a time. Soon, however, this level of satiation wears off, driving the smoker to continue smoking throughout the day to satisfy cigarette cravings.

Articles of Interest

December 21, 2006, *Washington Post* -- "Teens Use Medicines to Get High"--NIDA mention.

November 17, 2006, *CNN* -- "Are Antidepressants Good for a Boost if You're Already Healthy?"--Interview with Nora D. Volkow, M.D.

November 17, 2006, *Proto Magazine* -- "The Addicted Brain"--Interview with Nora D. Volkow, M.D.

October 25, 2006, *Kitsapsun.com* -- "Causes of Addiction, Prompts for Help Different for Women"--Interview with Nora D. Volkow, M.D.

October 20, 2006, *Scientific American* -- "Not Imagining It; Research into Hallucinogens Cautiously Resumes"--Interview with David Shurtleff, Ph.D.

September 26, 2006, *Chemical & Engineering News* -- "Scientists Drugs to Fight Addictions"--Interview with Frank Vocci, Ph.D.

Dr. Frank Vocci, Director, DPMCDA, was interviewed by John Fritze of the *Baltimore Sun* on the role of physician training in the implementation of buprenorphine for treatment of opiate dependence.

Dr. Frank Vocci was interviewed by Edyta Zielinska on clinical pharmacology studies involving substance abusers.

Dr. Frank Vocci was interviwed by Wesley Cropp of the *Daily Iowan* on the nicotine vaccine.

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 distribute eye-catching, informative, science-based articles on the health aspects of drug abuse and addiction to nearly two million students and teachers in grades 5 through 10 nationwide four times per year, with an emphasis on grades 7 and above. This is a very special relationship - NIDA is unique because *Heads Up* is the only regular "run-of-book" insert included in any Scholastic magazine. Also, 95 percent of the educators who distribute the articles in their classes rate them as "extremely valuable" or "very valuable" as a tool designed to teach students about the teen brain and the science behind drug addiction. Magazines that include Heads Up are ***Junior Scholastic®, Science World®, CHOICES®, SCOPE®, ACTION®,*** and ***Up Front®***. The first article for this school year, The Science of Addiction, was distributed in

September-October in CHOICES and followed in the remaining magazines in October 2006. The second and third articles, *The Deadly Effects of Tobacco Addiction*, and *Stress and Drug Abuse*, were distributed in November-December. Also, these articles are featured in the *Heads Up* website (www.scholastic.com/headsup) and have been supplemented with extra material.

NIDA's *Physician Outreach Project* made strides with the October 11, 2006 release of an RFP from the project's contractor to develop *NIDA Centers of Excellence* (NIDA COE's). The RFP was released via the American Medical Association, a subcontractor on the outreach project, to their newly-convened consortium of medical schools. The goals are (1) to develop research-based training resources for medical students and primary care resident physicians to advance the prevention, diagnosis, and treatment of drug abuse and addiction and (2) to empower the medical school and residency community with self-sustaining educational tools on drug abuse and addiction. Seven medical schools submitted proposals and awards were given to four schools in January 2006.

Recent Past and Upcoming Conferences/Exhibits*

National Hispanic Science Network (NHSN) on Drug Abuse Sixth Annual Scientific Conference -- September 13-17, 2006

Latino Behavioral Health Institute (LBHI) 12th Annual Conference -- September 19-21, 2006

American Academy of Family Physicians (AAFP) Scientific Assembly and Exposition -- September 27-October 1, 2006

Society for Neuroscience (SfN) 36th Annual Meeting -- October 14-18, 2006

NIDA Blending Conference -- October 16-17, 2006

American Academy of Child and Adolescent Psychiatry (AACAP) 54th Annual Meeting -- October 24-29, 2006

American Public Health Association (APHA) 134th Annual Meeting and Exposition -- November 4-8, 2006

Southeast Conference on Alcohol and Drug Addiction (SECAD) 2006 Conference -- November 29-December 2, 2006

American Academy of Addiction Psychiatry (AAAP) Annual Meeting and Symposium -- December 7-10, 2006

Community Anti-Drug Coalitions of America (CADCA) National Leadership Forum XVII -- February 11-15, 2007

American Association for the Advancement of Science (AAAS) 173rd Annual Meeting -- February 15-19, 2007

American Alliance for Health, Physical Education, Recreation and Dance (AAHPERD) 122nd National Convention and Exposition -- March 13-17, 2007

Society for Research in Child Development (SRCD) Biennial Meeting -- March 29-April 1, 2007

Lonnie E. Mitchell Historically Black Colleges and Universities (HBCU) 9th Annual Substance Abuse and Mental Health Conference -- March 29-April 1, 2007

American Society for Addiction Medicine (ASAM) Annual Medical-Scientific Conference -- April 26-29, 2007,/p>

Experimental Biology 2007 (EB 2007) -- April 28-May 2, 2007

*Conferences/Exhibits are subject to change.

Director's Report to the National Advisory Council on Drug Abuse - February, 2007

Planned Meetings

The National Institute on Drug Abuse (NIDA) will participate in a number of sessions at the **Community Anti-Drug Coalitions of America (CADCA) annual National Leadership Forum** in Washington, D.C., February 12-15, 2007. Dr. Lucinda Miner, Deputy Director, OSPC, NIDA, will conduct a workshop on The Neurobiology of Addiction and Dr. Joni Rutter, DBNBR, NIDA and Dr. Kevin Conway, DCNBR, NIDA will conduct a workshop on The Genes, Environment, and Development Initiative in Addiction: The GEDI Approach. In addition, NIDA Director, Dr. Nora Volkow, will participate in the plenary session.

The Neuroscience Consortium will present a **Symposium on Learning and Memory** on March 7, 2007 in the Neuroscience Center in Rockville, MD. Sessions will include: Dopamine's New Role as a Reinforcer for Learning and Memory - speakers Dr. Barry Everitt and Dr. Nora Volkow; Emotional Memory - speakers Dr. Kevin LeBar and Dr. Tony Grace; Cellular Mechanisms - speakers Dr. Antonello Bonci and Dr. Marina Wolf; and Molecular Alterations of Learning and Memory - speakers Dr. George Uhl and Dr. Peter Kalivas. The symposium is being organized by Dr. Cathrine Sasek, Dr. Susan Volman, and Dr. Steve Grant.

The National Institute on Drug Abuse (NIDA) is collaborating with the **American Psychiatric Association (APA) to hold a major research based track at the APA Annual Meeting** in San Diego, CA, May 19-24, 2007. The first major NIDA/APA track was held at the 1998 APA meeting in Toronto and then again at the 2004 APA meeting in New York City. NIDA has organized a number of sessions for the upcoming track, including 5 symposia, 5 workshops and two major lectures. NIDA anticipates another highly successful program at the meeting in 2007.

The National Institute on Drug Abuse (NIDA) is organizing a program at this year's **American Psychological Association (APA) Annual Meeting** in San Francisco, California, August 17-20, 2007. A number of NIDA staff throughout the Institute are involved in organizing and/or presenting on a wide range of session topics. NIDA will also co-sponsor an Early Career Investigator Poster Session with APA's Divisions 28 and 50 and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as part of the two Divisions' Social Hour.

The next **National CTN Steering Committee Meetings** are scheduled for March 19-23, 2007 and September 24-28, 2007 in Rockville, MD.

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NIDA Publications

Epidemiologic Trends in Drug Abuse - Community Epidemiology Work Group
Advance Report - June 2006 - NIH Pub. No. 06-5880A
This 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 2006 - NIH Pub. No. 06-5881A
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 2006 - NIH Pub. No. 06-5882A
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.

Mind Over Matter (8 Booklets - Spanish)
NIH Pub. Nos.: 06-3858; 06-4038; 06-3859; 06-4394; 06-4248; 06-3856; 06-3860; 06-3857
This series encourages young teens to reject drug use by helping them understand the effects of drugs on the brain. In each booklet, Sara Bellum--a budding science student--takes students on a scientific journey to learn about the brain's complex responses to specific drugs, including hallucinogens, inhalants, marijuana, methamphetamine, nicotine, opiates, steroids, and stimulants. This is the first time the series is available in the Spanish language.

COMING SOON!

Science of Addiction
NIH Pub. No. 07-5605
New advances in science demonstrate that addiction is a brain disease--a disease that is accompanied by disruption of the mechanisms responsible for generating, modulating and controlling an individual's cognitive, emotional, and social behavior.

NIDA Notes

Planned Meetings

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***NIDA Notes* Volume 21 Issue No. 1**
NIH Pub. No. 06-3478
The lead story looks at the effectiveness of low-cost incentives in a stimulant abuse treatment program. The Director's Perspective reports on the ongoing problem of steroid abuse and the many risks associated with steroids. Other research looked at ultra rapid detoxification programs; buprenorphine in adolescent opiate addiction; the brain mechanisms of memory in rats; and the potential respiratory consequences of marijuana abuse. This issue also reports on NIDA's July launch of the new criminal justice document in Chicago.

***NIDA Notes* Volume 21 Issue No. 2**
NIH Pub. No. 06-3478
The Director's Perspective addresses addiction and co-occurring mental disorders. The NIDA at Work feature looks at NIDA's Division of Basic Neuroscience and Behavioral Research. Research findings review how combination treatment of vouchers and cognitive-behavioral therapy extended marijuana abstinence; a study linking treatment outcome and brain response to cocaine cues; nicotine's effects on the development of rat brains, cocaine craving and high effects on brain activation patterns. The Bulletin Board reports on the use of Dialectical Behavior Therapy in deaf populations, and summarizes the recent NIDA-funded supplemental issue of Alcohol and Drug Dependence.

***NIDA Notes* Volume 21 Issue No. 3**
NIH Pub. No. 06-3478
The Director's Perspective examines genes and smoking, and NIDA's work with Perlegen Sciences. Research findings include how regional brain development contributes to adolescent risk-taking; animal studies looking at the serotonin system as a potential target for cocaine medications; endorphin derivative inhibiting reward from morphine and nicotine in rats; depot naltrexone's safety and efficacy for heroin addiction; and the use of standard treatments to help depressed smokers quit. The Bulletin Board discusses the NIDA International Program-sponsored special supplement to Drug and Alcohol Dependence, and What the Numbers Say looks at cocaine abstinence rates.

Science and Practice Perspectives

Science and Practice Perspectives Volume 3, Issue No. 2
Research Review articles include "Assessing Organizational Functioning as a Step Toward Innovation," by Drs. Dwayne D. Simpson and Donald F. Dansereau; "Imaging the Addicted Human Brain," by Dr. Joanna Fowler and NIDA Director Dr. Nora Volkow; Clinical Perspectives: One Program's Experience Incorporating Research-Based Strategies into Methamphetamine Treatment, by Jay Hansen; Quality and Performance Improvement: What's a Program To Do? by Dr. Frank McCorry. The Science and Practice in Action feature is "Attending to Emotional Cues for Drug Abuse: Bridging the Gap Between Clinic and Home Behaviors" by Drs. Michael Otto, Conall O'Cleirigh, and Mark Pollack.

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 2006 - This issue announced the dates and deadlines for the 2007 NIDA International Forum, discussed new budget rules for grant applications from non-U.S. institutions, and reported on research conducted by DISCA scientists.
- December 2006 - The issue discussed research results from a NIDA-

supported binational research team in Tanzania, reported that NIH support had been awarded to a former NIDA INVEST and DISCA scientist, and announced new Administrative Supplements for binational research co-funded by NIDA and the Dutch Addiction Program.

CTN-Related Publications

Seven editions of the CTN Bulletin Board were distributed. The Bulletin Board is an electronic report on the progress of the protocols, committees, and node activity in the CTN.

The CTN Data Sharing Web Site was established to support the NIH data sharing policy. The data sets of four protocols are available for public use; another four data sets will be available before the end of April 2007. These data sets are in compliance with HIPAA and CDISC (Clinical Data Interchange Standards Consortium) standards in support of the interoperability required by the NIH Roadmap.

Other Publications

Compton W.C., Conway K.P., Stinson F.S., and Grant B.F. Changes in the Prevalence of Major Depression and Comorbid Substance Use Disorders in the United States between 1991-1992 and 2001-2002. American Journal of Psychiatry 163: 2141-2147, 2006.

Dr. Rao Rapaka, DBNBR, guest edited a special themed issue of the AAPS (American Association of the Pharmaceutical Scientists) Journal entitled "Themed Issue: 2005 AAPS National Biotechnology Conference Symposium on Lipidomics."
http://www.aapsj.org/theme_issues/theme_issue17.asp

Drs. Rao Rapaka, DBNBR, and Jagitsing Khalsa, guest edited a special themed issue of the AAPS (American Association of the Pharmaceutical Scientists) Journal entitled "Themed Issue: NIDA/AAPS Symposium on Drugs of Abuse: Mechanisms of Toxicity, Toxicokinetics and Medical Consequences, November 4-5, 2005."
http://www.aapsj.org/theme_issues/theme_issue16.asp

Drs. Rao Rapaka, DBNBR, and Wolfgang Sadee, Ohio State University, guest edited a special themed issue of the AAPS (American Association of the Pharmaceutical Scientists) Journal entitled "Themed Issue: Drug Addiction - From Basic Research to Therapies."
http://www.aapsj.org/theme_issues/theme_issue10.asp

Rutter, J.L. Symbiotic Relationship of Pharmacogenetics and Drugs of Abuse. AAPS Journal, 8(1) pp. E174-E184, 2006.

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Khalsa, J.H., Vocci, F.J., and Dobs, A. Hormonal and Metabolic Disorders of Human Immunodeficiency Virus Infection and Substance Abuse. Am J Infectious Dis 2(3), pp. 125-129, 2006.

Khalsa, J., Vocci, F., Altice, F., Fiellin, D., and Miller, V. Buprenorphine and HIV Primary Care: New Opportunities for Integrated Treatment. Clin Infect, Dis. 15:Suppl 4:S169-172, 2006.

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Staff Highlights

Staff Honors and Awards

2006 NIDA DIRECTOR'S AWARD RECIPIENTS

Individual Awards
Betty Tai, Ph.D.
Allison Chausmer, Ph.D.
Cora Lee Wetherington, Ph.D.
Joyce Williams
Melissa W. Racioppo, Ph.D.
Vincent Smeriglio, Ph.D.
Dionne Jones, Ph.D.
Elizabeth Robertson, Ph.D.
Loretta A. Beuchert
David S. Daubert
David Anderson

GROUP AWARDS

NIH Neuroscience Blueprint Training Workgroup
Beth Babecki, M.A.
Allison Chausmer, Ph.D.
Gayathri Dowling, Ph.D.
Steven Grant, Ph.D.
Suman Rao King, Ph.D.
Teresa Levitin, Ph.D.
Kay Nimit, M.D.
Charlie Sharp, Ph.D.
David Shurtleff, Ph.D.
Karen Skinner, Ph.D.
Laurence Stanford, Ph.D.
Susan Volman, Ph.D.
Susan Weiss, Ph.D.

Jennica Database Team
Jessica Campbell Chambers, Ph.D.
Aria D. Crump, Sc.D.
Richard Denisco, M.D.
Gina Hijjawi, Ph.D.
Samia Noursi, Ph.D.
Belinda E. Sims, Ph.D.
Ming Shih, Ph.D.

COAC Initiative Team
Mary K. Affeldt

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Cindy Miner
Lisa Onken
Jeng-Jong Pan
Denise Pintello
Jonathan Pollock
Melissa Racioppo
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Carmen Rosa
Joni Rutter
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Hari Singh
Karen Skinner

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Larry Stanford
Betty Tai
Don Vereen
Frank Vocci
Susan Volman

2006 NIDA DIRECTOR'S AWARD FOR EEO, DIVERSITY AND QUALITY OF WORKLIFE

Mary K. Affeldt
Amy H. Newman Greig, Ph.D.

COMMISSIONED CORPS AWARDS

The Unit Commendation
CDR Carlo S. Contoreggi
LCDR Michelle K. Leff

ther Staff Awards

Dr. Betty Tai, Director of the CCTN was awarded the Meritorious Research Service Commendation by the Board of Scientific Affairs, American Psychological Association. Dr. Tai was honored for her leadership of the National Institute on Drug Abuse Clinical Trials Network and her instrumental role in defining future research issues and identifying new avenues for collaboration within the Network. She was presented with the award by then-APA President Gerald Koocher, PhD. at a ceremony held at the Capitol Hilton Hotel in Washington, DC on December 2, 2006.

Dr. Kevin Conway, DCNBR, received a Director's Award of Merit from the National Institute of Aging for his work on the Blueprint Committee on Neuroepidemiology.

Dr. Jerry Flanzer, DESPR, received a National Institute of Health Merit Award in recognition of his outstanding contribution in developing and implementing a trans-NIH program to support research on social work practice and concepts of health on November 5, 2006.

On September 14, 2006, **Dr. Ivan Montoya,** DPMCDA, received the National Award of Excellence in Public Service from the National Hispanic Science Network.

Dr. Frank Vocci, Director, DPMCDA, received the Vernelle Fox award from the California Society on Addiction Medicine, October 5, 2006.

Dr. Frank Vocci received an award from the Federazione Italiana Degli Operatori Dei Departmenti Dei Servici Delle Dipendenze for his research in furthering knowledge in addiction medicine, December 12, 2006.

Dr. Yavin Shaham, IRP, received the Society for Neuroscience: Jacob P. Waletzky Memorial Award for Innovative Research in Drug Addiction and Alcoholism.

Dr. George Uhl, IRP, was awarded the Gonzalo Rio Arronte award and lectureship at the October National Congress of Genomic Medicine in Mexico City, Mexico.

Dr. Amy Newman filed the following patent: Newman, A. H.; Zou, M.-F.; Katz, J. L. Benztropine Compounds and Uses Thereof. U.S. Patent Application filed August 24, 2006.

Staff Changes

Dr. Joni Rutter has assumed new responsibilities as Associate Director, DBNBR, for Human Population and Applied Genetics. In this role, she is responsible for all scientific and administrative activities in support of the Division-level population and applied genetics initiatives. Dr. Rutter also chairs the newly created NIDA Genetics Coordinating Committee (NGCC), which shapes the NIDA human genetics program to meet the changing needs of NIDA's multifaceted human genetics portfolio. Finally, she will continue to serve as Chair of the NIDA Genetics Consortium Steering Committee and will participate in a variety of trans-NIH genetics activities related to human genetics research.

Mimi Ghim, Ph.D., joined NIDA's Science Policy Branch as Deputy Research Training Coordinator in October 2006. She recently earned her doctoral degree from the Integrative Neuroscience Program at the University of Maryland, specializing in vision neuroscience using behavioral and electrophysiological techniques, with optical imaging experience acquired during her postdoctoral appointment at SUNY Update Medical University. Prior to arriving at NIDA, Dr. Ghim was involved in project-based administration and scientific writing at a local consulting company.

Dorie Hightower joined the Office of Science Policy and Communications as a Press Officer in October 2006. She began her career in television production, where she was a consumer reporter and news director for an ABC affiliate in Norfolk, Virginia, and an associate producer for a PBS affiliate in Milwaukee, Wisconsin. She moved to Washington, D.C., where her interest in health-related issues led to working as a public relations consultant for a number of organizations, including the Arthritis Foundation, National Pharmaceutical Council (NPC), the Spina Bifida Association and the National Association of Social Workers. Dorie went on to serve as a public affairs contractor for the Centers for Medicare and Medicaid (CMS), where she developed marketing materials in several languages to raise awareness about Medicare managed care options, created print and broadcast advertisements, handled media buying, and coordinated broadcast interviews. For the past five years, she has worked in the press office of the National Cancer Institute, where she was instrumental in press relations, media training, the science writers' seminar program, and science writing. Her new role is to lead the press efforts for NIDA. Dorie has a B.A. in Communications from Adelphi University and an A.A. in Interior Design from Montgomery College.

Petra Jacobs, M.D. joined the CCTN as a Medical Officer. Dr. Jacobs received her M.D. from Charles University in Prague, Czech Republic, and has a Board Certification in Psychiatry from the Prague Institute of Postgraduate Education. She has more than 10 years of experience developing treatment, research, education and training initiatives in drug abuse. In 2001 and 2002, Dr. Jacobs was a Fulbright-Hubert H. Humphrey Fellow in advanced Public Health studies at Johns Hopkins University, and served as a Distinguished Scientist at NIDA in the extramural program. Most recently, she has been working with the CCTN as a contractor, and has worked closely on several of the ongoing clinical trials, including both medication and behavioral treatments for drug abuse. Nadine Rogers, Ph.D. is a new Scientific Review Administrator in the NIDA Office of Extramural Activities. She joins NIDA from the US State Department where, for the last three years, she had worked in the recently established Office of the US Global AIDS Coordinator, the organization created to implement the President's Emergency Plan for AIDS Relief. Dr. Roger's activities with Global AIDS included establishing its Scientific Committee and associated subcommittees. She helped develop policies acceptable to participants including HHS, NIH, the CDC, USAID, DOD, the Census Bureau, the Peace Corps, and other national and international agencies. Nadine helped to define Global AIDS science evaluation practices and policies, recruited committee scientists, and managed and reported on committee recommendations and activities. Before work with Global AIDS, Nadine was Senior Program Manager

for Community-Based Health Strategies for The Academy for Educational Development which worked with the CDC and HRSA to develop HIV/AIDS Epidemiology guidelines. Prior to this Dr. Rogers worked for the American Red Cross and helped with study coordination including human subjects, review and assay development guidelines. Dr. Roger's Ph.D. is from The Johns Hopkins University School of Public Health in Health Policy and Management with a concentration in Health Education and Communication, and she has published in these areas.

Kristen Vaughan Huntley, Ph.D. has joined the NIDA Office of Extramural Affairs as a Scientific Review Administrator. Kristen is a Clinical Psychologist with academic medicine, market research, teaching, and clinical service experience. As an Instructor at Case Western Reserve Medical School, Department of Pediatrics, she provided clinical services, instructed medical residents, and directed research studying the use of prenatal cardiac diagnostic services. She managed research projects including an advertising effectiveness tracking study and consumer product concept tests in her role as Project Manager at Hauser & Associates, a market research firm in Paramus, New Jersey. Dr. Huntley has also worked as a psychologist in direct clinical care settings, such as community mental health centers, a hospital, and specialty care outpatient offices. Kristen is a graduate of the University of Texas at Austin, holds a Master of Science in Psychology from Texas A&M University, and a Ph.D. in Psychology from Texas A&M University. She completed an internship at the University of Texas Health Science Center, Houston, Department of Psychiatry and Behavioral Sciences, with rotations at Harris County Psychiatric Center, The Mental Sciences Institute, and MD Anderson Cancer Center.

Dr. Suman King, Deputy Research Training Coordinator, left the Office of Science Policy and Communication in October 2006 to become the Special Assistant to the Director of the Office of Extramural Research (OER), Dr. Sam Shekar. The Office of Extramural Research (OER) serves as the focal point for policies and guidelines for extramural research grants administration. In her new role, Suman will continue to be involved in NIH-wide research training and career development policy as well as other areas overseen by the OER.

Laura S. Rosenthal, NIDA's Executive Officer and Associate Director for Management, after 39 years of dedicated service--the last 17 with NIDA, retired from Government service on January 3, 2006. Laura began her career as a research assistant with NIMH, advancing from there to an appointment as Special Assistant to the Administrator of the Alcohol, Drug Abuse, and Mental Health Administration, where she received a Special Achievement Award for her exceptional contributions to the formation of ADAMHA as a major public health agency. In 1972, she joined NIAAA and a year later was selected as the Deputy Associate Director for Research, then in 1982 was appointed Deputy Director for the Division of Intramural Clinical and Biological Research. There she played a key role in catalyzing the integration of alcoholism with other health problems as a scientific area of medical study. Since joining NIDA in 1989, Laura has witnessed unprecedented growth and challenge, earning a reputation for effectively implementing several new national programs and policies and successfully integrating administrative and resource realities with program goals. Among her numerous noteworthy accomplishments is developing a program to link national research goals with the treatment needs of the DC community; helping establish the first Federal medications development program in the addiction field; and serving as a recognized leader of reinvention activities. In addition, Laura was listed in Who's Who of American Women in 1981, was awarded the Public Health Service Award for Superior Service in 1991, and is the recipient of two Presidential Meritorious Rank Awards for sustained SES accomplishment.

Donna M. Jones, NIDA's Budget Officer has been selected to serve as the

Acting Executive Officer for NIDA.

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Director's Report to the National Advisory Council on Drug Abuse - February, 2007

Grantee Honors

Dr. Frederick Altice, Director of Clinical and Community Research and Associate Professor of Medicine at Yale University, was awarded the HIV/AIDS Service Award by the Connecticut State Assembly for his clinical work and research with drug abusers and those involved in criminal justice.

Dr. Angela Bryan, Associate Professor in the Department of Psychology at the University of Colorado Boulder received the 2006 Award for Distinguished Scientific Early Career Contributions to Psychology from the American Psychological Association. Dr. Bryan was recognized for her theoretical and applied research on health behavior change. Dr. Bryan's research program includes a NIDA funded longitudinal study examining the effects of marijuana use on high risk adolescents' HIV/AIDS related sexual behaviors.

Howard B. Kaplan, Ph.D., received the American Sociological Association's Leo G. Reeder Award for "Distinguished Contribution to Medical Sociology" at the August 2006 ASA meetings in Montreal, Canada. Dr. Kaplan is Regents Professor, Distinguished Professor of Sociology, and the Mary Thomas Marshall Professor of Liberal Arts at Texas A & M University. The award honors his more than 40 years' work in the field of medical sociology and recognizes his leadership and effective advocacy for the significance of sociological research in addressing mental health and substance abuse problems.

As part of the second annual Science Leadership Conference of the Science Directorate of the American Psychological Association, two DBNBR grantees, Dr. Wendy Lynch, University of Virginia, and Dr. Colleen McClung, UT Southwestern Medical Center, were feted along with 20 other outstanding early career psychological scientists at a reception and poster session in honor of their achievements on December 1, 2006. Dr. Lynch's poster was entitled, "Influence of Sex and Ovarian Hormones on 'Binge' Cocaine Self-Administration," and Dr. McClung's poster was entitled, "The Molecular Mechanisms of Mood Disorders and Drug Addiction: Role of the Circadian Clock."

Dr. Flavio Marsiglia received the National Award of Excellence in Mentorship from the National Hispanic Science Network on Drug Abuse on September 14, 2006. This award recognizes a senior investigator who has provided outstanding mentorship in the area of Hispanic drug abuse.

Dennis McCarty, PI for the CTN Oregon/Hawaii Node, was elected to Fellow status in the American Psychological Association, Division 28 - Psychopharmacology and Substance Abuse (effective January 2007). Fellow status is awarded, in part, on the basis of evaluated evidence of outstanding contribution in the field of psychology.

Dr. Jody Sindelar of Yale University has been named the President of the

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American Society for Health Economists.

Dr. Richard Spoth received recognition for the NIDA supported PROSPER Project as a "Program of Distinction" by the National 4H Council.

Dr. Richard Spoth received recognition for the Strengthening Families Program--Parents and Youth 10-14--as a "Program of Distinction" by the National 4H Council.

Dr. Jose Szapocznik, Director of the University of Miami Center for Family Studies and Principal Investigator of the CTN Florida Node, made the rounds of the Hispanic media outlets in Miami to help launch the White House Office of National Drug Control Policy (ONDCP) Media Campaign. In addition to appearing on the nation's top Hispanic morning television show, "Despierta America", Dr. Szapocznik was also interviewed by Univision Radio, Telemundo Television Network and El Nuevo Herald. The El Nuevo Herald published a front-page story on the ONDCP's and Dr. Szapocznik's efforts to try to reach out to and educate Hispanic parents about the dangers of prescription drug abuse among their youth.

Dr. Jose Szapocznik, Director of the University of Miami Center for Family Studies and Chair of the National Hispanic Science Network on Drug Abuse, was featured for his scientific contributions to the U.S. Hispanic community during a Discovery en Espanol prime-time network special that aired on September 24, 2006. Intended to launch the celebration of Hispanic Heritage month, this original, four-part documentary series profiled prominent U.S. Hispanic scientists. Dr. Szapocznik and the other Pioneros were congratulated. The episode recounted the stories of sacrifice and successes [during their American journey] of Dr. Szapocznik and others, including Franklin Chang Diaz, the first Hispanic astronaut, Mario Molina, a Nobel prize winner in chemistry, Victor Penchaszadeth, Director of the World Health Organization's Collaborating Center in Community Genetics and Education, and renowned seismologist Ines Cifuentes. As Director of the University of Miami Center for Family Studies, Dr. Szapocznik developed the flagship program on basic and clinical research on family interventions for the prevention and treatment of Hispanic adolescent problem behaviors, including drug abuse.

University of Miami's Center for Family Studies was recognized as a "2006 Best Practice" by the State of Florida Department of Children and Families and the Florida Alcohol and Drug Abuse Association for "Brief Strategic Family Therapy TM", the intervention model developed by Dr. Jose Szapocznik and colleagues at the University. The award was accepted by Dr. Szapocznik at the Association's Annual Conference on August 17th in Orlando, Florida. The Center for Family Studies National Training Institute provides training and certification in BSFT TM, in Spanish or English, to agencies around the country.

Planned Meetings

Publications

Staff Highlights

Grantee Honors