Director's Report to the National Advisory Council on Drug Abuse - May, 2004

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Director's Report to the National Advisory Council on Drug Abuse - May, 2004

Research Findings - Basic Research

Design of Novel Peptide Ligands that have Opioid Agonist Activity and CCK Antagonist Activity for the Treatment of Pain

There is a need for a new paradigm in drug discovery for pathological conditions including disease states such as neuropathic pain and conditions of opioid analgesic tolerance. It is now known from multiple experimental approaches that many disease states lead to changes in expressed proteins (adaptation/neuroplasticity). Drug design based on normal states is inadequate or even possibly counter-indicated. Therefore the system changes that have occurred must be considered in any treatment for the disease. Such "systems changes" are clearly evident in neuropathic pain and in conditions of opioid tolerance where opioids can actually heighten pain. In these pain states there are increased levels and/or activity of pronociceptive neurotransmitters such as cholecystokinin (CCK) and their receptors. CCK and enkephalins and their receptors are co-localized in the CNS and, as a pronociceptive peptide, CCK acts as an "antiopioid" and alternate analgesic to diminish opioid antinociception. In view of these and other findings, NIDA grantee, Dr. Victor Hruby and colleagues have investigated a new paradigm for drug discovery aimed at treatment of pathological pain (such as neuropathic pain) and in conditions of opioid tolerance. In this approach a single peptide or peptidomimetic molecule that can interact with opioid receptors as agonists and at CCK receptors as antagonists is designed. Specifically, compounds that are agonists at opioid mu or delta receptors and antagonists at CCK-1 or CCK-2 receptors (preferably both representing a "balanced" CCK receptor antagonist) are developed. It is postulated that such a molecule would show superior efficacy to opioid agonists for the treatment of pathological pain states since it would block the antiopioid effects of CCK and be resistant to the development of paradoxical opioid-induced pain and antinociceptive tolerance. In this paper, Dr. Hruby and his colleagues report progress toward these objectives using various approaches to rational peptide ligand based drug design. De novo design based on the concept of overlapping pharmacophores was a central hypothesis of this design, and led to compounds such as H-Tyr-DPhe-Gly-DTrp-NMeNle-Asp-Phe-NH2 (i.e., RSA 601), which have the designed properties. Hruby, V.J., Agnes, R.S., Davis, P., Ma, S-W., Lee, Y.S., Vanderah, T.W., Lai, J. and Porreca, F. Design of Novel Peptide Ligands which have Opioid Agonist Activity and CCK Antagonist Activity for the Treatment of Pain. Life Sciences 73, pp. 699-704, 2003.

The Effect of Hair Color on the Incorporation of Codeine into Human Hair

The purpose of this study was to determine if codeine, as a model compound for abused drugs, would be incorporated into black, brown, blond, or red hair as a function of melanin concentration. Male and female Caucasians with black (n=6), brown (n=12), blond (n=8) or red hair (n=6) and non Caucasians with black hair (n=12), aged 21-40 years of age were administered oral codeine phosphate syrup in a dose of 30 mg three times a day for five days. Twenty-four hours after the end of the treatment period, a 30 mg codeine dose was administered and the subject's plasma area under the concentration time curve (AUC) for codeine was determined. Codeine and melanin were measured in the first 3 cm of hair closest to scalp prior to and 1,4,5, 6,and 7 weeks after dosing. The quantitative and qualitative melanin profiles were determined for each subject's hair to provide an objective measure of hair color. The plasma concentrations of codeine were measured to eliminate differences in the bioavailability and clearance of codeine as factors that might account for the differences in codeine hair concentrations. The mean hair codeine concentrations 5 weeks after dosing were 1,429 pg/mg in black hair; 208 pg/mg in brown hair; 99 pg/mg in blond hair; and 69 pg/mg in red hair. In black hair, codeine

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concentrations were 2,564 pg/mg for Asians and 865 pg/mg for Caucasians. Similar concentration relationships were observed at weeks 4, 6, and 7. A strong relationship between the hair concentrations of codeine and melanin was observed. These data demonstrate that the interpretation and reporting of hair test results for codeine are influenced by hair color. After this dosing protocol, the proposed federal guideline cut-off of 200 pg/mg of codeine would result in 100% of subjects with black hair and 50% of subjects with brown hair being reported as positive, and subjects with blond or red hair would be reported as negative. The incorporation of these drugs into hair should be studied carefully in humans to ensure the appropriate interpretation of drug concentrations. Rollins, D.E., Wilkins, D.G., Kruger, G.G., Augsburger, M.P., Mizuno, A., O'Neal, C., Borges, C.R. and Slawson, M.S. Journal of Analytical Toxicology, 27, pp. 545-551, 2003.

Morphine Tolerance and Development

In a recent paper, Dr. Gordon Barr and Dr. Hongbo Zhu report their findings on ontogeny of N-methyl-D-aspartate (NMDA) receptor mediated morphine tolerance in the postnatal rat. This study is the first to provide conclusive evidence that NMDA receptor antagonists are not effective in attenuating tolerance in the newborn rat and that there is a transition age, around the second postnatal week in the rat, for NMDA receptor antagonists to be effective in suppressing opiate tolerance and withdrawal. This study was undertaken because of the known effectiveness of NMDA receptor antagonists to inhibit the development of morphine tolerance in adults and the dramatic changes that occur in NMDA receptors during the first few weeks of postnatal life. Zhu, H. and Barr, G.A. Ontogeny of NMDA Receptor-Mediated morphine Tolerance in the Postnatal Rat. Pain. 104, pp. 437-447, 2003.

Mixed Mu Agonists/Delta Antagonists

There is a continuing effort and interest in developing ligands exhibiting agonist action at the mu receptor for purposes of chronic pain treatment, but which also possess antagonist properties at the delta receptor, in order to lessen or minimize the known side effects of mu ligands, such as respiratory depression and development of tolerance/dependence. Evidence has been provided by immunoprecipitation and immunoblotting results of an interaction or complex formation between mu and delta receptors, when they are co- expressed in COS cells. These co-expressed receptors showed altered binding profiles (reduced affinity of morphine, DAMGO, and DPDPE) as compared to the values reported in separate cell expressions of mu or delta receptors. Additionally, the development of acute tolerance and dependence in mice administered morphine could be inhibited by pretreatment with the delta antagonist naltrindole (NTI). More recently, it has been reported that the pseudopeptide TIPP[psi], a delta antagonist (lacking mu or kappa receptor antagonism), is quite effective in suppressing tolerance and dependence in rats during chronic morphine treatment. Previous efforts by Dr. Subramaniam Ananthan and associates have suggested that the binding properties of pyridomorphinans may be modified by the particular choice of 5' (meta) substituent on the pyridine ring, resulting, in one case, with a p-chlorophenylpyridine derivative of naltrexone, having in-vivo antinociceptive activity in mice, without the development of tolerance upon repeated injections. The compound also produced fewer signs of withdrawal than with naloxone, in a morphine-dependent rodent model. However, this compound, when tested in a GTPgammaS functional assay, showed very little stimulation activity as an agonist either in guinea pig membranes, or in cells expressing the mu or delta receptor. The authors have now reported the preparation and pharmacological evaluation of additional pyridomorphinans made from naloxone, oxymorphone, and hydromorphone, some of which show "mixed" mu agonism and delta antagonism. In terms of structure-activity relationships, an unsubstituted pyridine ring led to comparable affinity for the mu and delta receptors, while the introduction of an aryl substituent, particularly 4-chlorophenyl or 2,4-dichlorophenyl at the 5' position of the pyridine ring increased the delta antagonism, while retaining sufficient mu agonist potency. These latter two compounds showed nanomolar antagonist constants in the mouse vas deferens assay (displacement of the delta agonist DPDPE) and nanomolar inhibition constants in the functional GTPgammaS activity at the delta receptor, as well as nanomolar agonist IC50 constants in the guinea pig ileum assay (inhibition of the mu agonist PL-017). They both exhibited analgesic activity in the mouse tail-flick assay, and one of them retained its analgesic activity upon repeated icv injection. The design of these ligands, in which the binding at the delta receptor has been increased relative to that at the mu receptor, has resulted in several promising examples of combined in-vivo delta antagonism and partial to full mu agonism. Ananthan, S., Khare, N.K., Saini, S.K., Seitz, L E., Bartlett, J.L., Davis, P., Dersch, C.M., Porreca, F., Rothman, R.B., and Bilsky, E.J. Journal Medicinal Chemistry, 47, pp. 1400-1412,

2004.

Gestational Nicotine Exposure Attenuates Nicotine-Stimulated Dopamine Release in the Nucleus Accumbens Shell of Adolescent Lewis Rats

The effects of chronic gestational exposure to nicotine on the nucleus accumbens dopamine response to acute nicotine were determined during adolescence (postnatal day 29-36) in cross-fostered and noncross-fostered Lewis rats. In both males and females, gestational nicotine exposure diminished the adolescent nucleus accumbens dopamine response to 0.07 mg/kg nicotine i.v. However, dopamine responses to 0.105 mg/kg nicotine were unaffected by gestational nicotine treatment and were similar in both genders. Furthermore, in both female and male gestational nicotine and control groups, the dopamine response to nicotine (0.105) was the same as that observed to the lower dose of nicotine in gestational controls. Thus, in adolescent male and female Lewis rats, gestational nicotine exposure attenuated nucleus accumbens dopamine release to a maximally stimulative dose of nicotine. Unexpectedly, in female gestational controls cross fostering per se reduced nucleus accumbens dopamine secretion to 0.07 mg/kg nicotine. These investigations suggest that gestational nicotine exposure could modify the acute reinforcing effects of nicotine in adolescent rats, whereas early postnatal stressors, (e.g., cross-fostering) may affect nicotine-induced reinforcement in female but not male adolescents. Kane, V.B., Fu, Y., Matta, S.G. and Sharp, B.M. Gestational Nicotine Exposure Attenuates Nicotine-Stimulated Dopamine Release in the Nucleus Accumbens Shell of Adolescent Lewis Rats. JPET, 308(2), pp. 521-528, 2004.

Disproportionate Increase in the Up-regulation of the a6 Subunit nAChR During Long-term Self-administration of Nicotine

In male rats continually self-administering nicotine (approximately 1.5 mg free base/kg/day), Dr. Sharp and colleagues found a significant increase of nicotinic acetylcholine receptors (nAChRs) labeled by epibatidine (Epb) in 11 brain areas. A large increase of high affinity Epb binding sites was apparent in the ventral tegmentum/ substantia nigra, nucleus tractus solitarii, nucleus accumbens, thalamus/subthalamus, parietal cortex, hypothalamus, and amygdala. A smaller but significant up-regulation of high affinity Epb sites was seen in the piriform cortex, hippocampus, caudate/putamen, and cerebellar cortex. The up-regulation of nAChRs, shown by immunoadsorption and Western blotting, involved a4, a6, and b2 subunits. As a consequence of long-term self-administration of nicotine, the a6 immunoreactive (IR) binding of either labeled Epb or 125I-a-conotoxin MII increased to a much greater extent than did a4 or b2 IR binding of Epb. In addition, the b2 IR binding of Epb was consistently enhanced to a greater extent than was a4. These findings may reflect a larger surface membrane retention of a6-containing and, to some degree, b2-containing nAChRs compared with a4-containing nAChRs during long-term self-administration of nicotine. Parker, S.L, Fu, Y., McAllen, K., Luo, J., McIntosh, J.M., Lindstrom, J.M. and Sharp, B.M. Up-Regulation of Brain Nicotinic Acetylcholine Receptors in the Rat during Long-Term Self-Administration of Nicotine: Disproportionate Increase of the a6 Subunit. Mol Pharm, 65(3), pp. 611-622, 2004.

Morphine-Induced Pruritus Inhibited, and Analgesic Potency Enhanced, by the Kappa Opioid Receptor Agonist, U-50488H

Morphine is a potent analgesic used to treat moderate to severe pain. Though effective as an analgesic, morphine has side effects that limit its use. One side effect that can be especially severe is pruritus (itch), where morphine acts at central mu receptors to cause a maddening pruritus of the face and trunk. Dr. Ko and colleagues have found in monkeys that the kappa opioid receptor agonist, U-50488H, attenuated the scratching (an indication of pruritus) produced by morphine administration. Further, U-50488H enhanced the analgesic properties of morphine. These data suggest that a combination therapy of morphine and U-50488H may produce more analgesia with fewer side effects than morphine alone. Ko, M.C. et al., Activation of Kappa-Opioid Receptors Inhibits Pruritus Evoked by Subcutaneous or Intrathecal Administration of Morphine in Monkeys, JPET, 305, pp. 173-179, 2003.

Molecular Profiling of Midbrain Dopamine Regions in Cocaine Overdose Victims

Chronic cocaine use in humans and animal models is known to lead to pronounced alterations in neuronal function in brain regions associated with drug reinforcement. To evaluate whether the alterations in gene expression in cocaine overdose victims are associated with specific dopamine populations in the midbrain, cDNA arrays and western blotting were used to compare gene and protein expression patterns between

cocaine overdose victims and age-matched controls in the ventral tegmental area (VTA) and lateral substantia nigra. Scott Hemby and colleagues found significant up-regulation of numerous transcripts in the VTA, but not in the substantia nigra, of cocaine overdose victims. The up-regulated transcripts included several glutamate receptor transcripts (NMDAR1, GlurR2, GluR5, and KA2), and VTA-selective up-regulation of CREB protein was observed by western blot. The findings of these up-regulated mRNA and protein levels may be indicative of chronic cocaine use and/or cocaine overdose in humans. The observed changes may indicate alterations in the excitability of dopamine transmission underlying long-term biochemical and behavioral effects of cocaine. Tang, W-X., Fasulo, W.H., Mash, D.C., and Hemby, S.E. Molecular Profiling of Midbrain Dopamine Regions in Cocaine Overdose Victims. J. Neurochemistry, 85, pp. 911-924, 2003.

Homer1 Proteins and AMPA Receptors Modulate Cocaine-Induced Behavioral Plasticity

Homer proteins form functional assemblies in the excitatory postsynaptic density, and withdrawal from repeated cocaine administration reduces the expression of Homer1b/c in the nucleus accumbens. To determine if the reduction in Homer1b/c may be contributing to cocaine-induced behavioral sensitization, Dr. M.B. Ghasemzadeh and his research team at the Medical University of South Carolina infused antisense oligonucleotides over two weeks into the nucleus accumbens of rats to reduce Homer1 gene expression by approximately 35%. Infusion of antisense sequences (AS1 and AS2) caused a sensitization-like augmentation in the motor response to acute cocaine administration in naive rats. One of the sequences (AS1) also prevented the development of sensitization to repeated cocaine treatment, while AS2 was without effect. A panel of immunoblots for other proteins in the excitatory postsynaptic density revealed that AS1, but not AS2 reduced the level of the alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor subunit GluR1 protein. This posed the possibility that altered AMPA signaling may mediate the inhibitory effect of AS1 on the development of sensitization. To examine this possibility, rats were pretreated in the accumbens with drugs to block AMPA/kainate, N-methyl-d-aspartate, group 1 metabotropic glutamate or dopamine receptors prior to each daily injection of cocaine. Only AMPA/kainate receptor blockade prevented the development of behavioral sensitization to cocaine. These data indicate that the expression of behavioral sensitization arises in part from a reduction in Homer1 gene products in the accumbens, while the development of sensitization requires stimulation of AMPA/kainate receptors. Ghasemzadeh, M.B., Permenter, L.K., Lake, R., Worley, P.F., Kalivas, P.W. Homer1 Proteins and AMPA Receptors Modulate Cocaine-induced Behavioral Plasticity. Eur J. Neurosci.,18(6), pp. 1645-1651, September 2003.

Dopamine Neurons Release Transmitter via a Flickering Fusion Pore

It has been debated whether synaptic vesicles release all of their neurotransmitter into the synapse at once during a full fusion of the vesicular membrane with the neuron's outer membrane, or whether they "kiss-and-run" several times, releasing only part of their transmitter via transient fusion pores. A new study demonstrates that dopamine (DA) neuron synaptic vesicle fusion pores "flicker" (open and close) either once or multiple times in very rapid succession (4000 Hz), and each flicker (whether there is only one or several flickers per exocytic event) releases about 25-30% of vesicular DA. These researchers measured DA release from synaptic vesicles of cultured rat ventral tegmental area neurons using carbon fiber amperometry; this technique directly measures DA exocytosis with a time resolution 2-5 orders of magnitude greater than other techniques, and so was able, for the first time, to demonstrate the multiple flickering nature of DA release. The incidence of events with multiple flickers was decreased by a phorbol ester (protein kinase C (PKC) activator) and increased by staurosporine (kinase inhibitor), suggesting that this process is regulated by the PKC second messenger system. Thus, DA neurons regulate the amount of DA released by controlling the number of fusion pore flickers per exocytic event. This mode of exocytosis is a potential mechanism whereby neurons may rapidly re-use vesicles without undergoing the comparatively slow process of recycling. Staal, R.G.W., Mosharov, E.V. and Sulzer, D. Dopamine Neurons Release Transmitter via a Flickering Fusion Pore. Nature Neuroscience, published online 29 February 2004.

Marijuana Disrupted Signal Flow at Cortical Pyramidal Synapses -- The Entrypoint of Cognitive/Decision-Making Circuits

Marijuana affects cognitive functions, and is frequently abused by teenagers. Craving for drugs involves an interruption of the brain functions and a decision-making

process. As an endogenous modulator system widely present in areas related to cognition, memory, emotion and reward, what role do cannabinoid receptors and the endocannabinoids play in cognition and decision-making processes? These processes rely on the function of cortical pyramidal cells that are responsible for functional connections between cortical areas, and to subcortical structures. Signal encoding at cortical synapses is the fundamental process that integrates afferent inputs and initiates coordination in the cognitive circuit network. Dr. Levine's recent work focuses on the importance of the endocannabinoid system in the fine-tuning of the cortical synapse-by-synapse information flow, to provide cellular basis of endogenous cannabinoid signaling in the regulation of neocortical function. He showed that activity of the pyramidal cell was controlled by distinct classes of the inhibitory GABAergic interneurons, which innervated functionally segregated domains on pyramidal cells and regulated timing of the action potential, the efficacy of excitatory inputs, and synchronous activity. These interneurons fire at high frequency *in vivo* and provide potent inhibition to pyramidal cells. Endogenous cannabinoid ligands are synthesized and released from pyramidal neurons with a high degree of spatial and temporal specificity, and act at least in part by feedback binding to receptors on the presynaptic terminals of interneurons to regulate their release of GABA, which in turn modulated signal processing at the pyramidal cell. Levine's lab demonstrated that this micro-feedback circuit is the structural basis of the depolarization-suppression of inhibition in cortical pyramidal cells, a cannabinoid-mediated mechanism of signal disinhibition that involved synaptic plasticity, originally demonstrated in the hippocampus and then in the cerebellum. Trettel, J. and Levine, E.S. Endocannabinoids Mediate Rapid Retrograde Signaling at Interneuron -- Pyramidal Neuron Synapses of the Neocortex. J. Neurophysiol, 89, pp. 2334-2338, 2003.

D1 Receptors Increase GluR1 Surface Expression in Cultured Nucleus Accumbens Neurons via PKA Activation

In the first study to examine AMPA receptor trafficking in neurons of the striatal complex, Dr. Marina Wolf found that brief incubation with a D1 agonist increased GluR1 surface expression in cultured NAc neurons (Chao et al., J Neurochem 83, 704-12, 2002). In the present study, she used an immunocytochemical method for selectively detecting newly externalized GluR1 to demonstrate that the D1 agonist SKF 81297 increased the rate of GluR1 externalization. This trafficking was blocked by a D1 receptor antagonist and by two different cell-permeable PKA inhibitors, KT5720 and RpcAMPS, and this effect was reversed in the presence of a PKA activator. Her previous work had shown that D1 receptor stimulation increased GluR1 phosphorylation at the PKA site (Chao et al., J Neurochem 81, 984-992, 2002). Together, their findings suggest that PKA phosphorylation of GluR1 is required for GluR1 externalization in response to D1 receptor stimulation. These results establish a direct mechanism by which D1 DA receptors, stimulated during psychostimulant administration, may influence glutamate neurotransmission and glutamate-dependent neuroplasticity. During repeated psychostimulant administration, inappropriate activation of this mechanism may lead to maladaptive plasticity in PFC, NAc and other regions that receive convergent DA and glutamate inputs. Ultimately, this may contribute to rewiring of motivational circuits and a transition to compulsive drug use. Mangiavacchi, S. and Wolf, M.E. D1 Dopamine Receptor Stimulation Increases the Rate of AMPA Receptor Insertion onto the Surface of Cultured Nucleus Accumbens Neurons through a Pathway Dependent on Protein Kinase A, J. Neurochem, 88, pp. 1261-1271, 2004.

Psychostimulant Sensitivity Requires PSD-95, a Key Regulator of Dopamine-Mediated Synaptic Plasticity

Chronic cocaine exposure leads to a long-lived escalation in psychomotor responses via a process called behavioral sensitization. Adaptive changes in the nucleus accumbens, and two of its most important afferents (the ventral tegmental area and cortical glutamatergic imputs) are important in this process. Recent work by the Caron laboratory has identified the synaptic scaffolding protein PSD-95 as being a key mediator in an important aspect of the underlying molecular changes. PSD-95 (as well as five other commonly altered genes) was identified using a microarray approach, and its function was tested using homologous recombination. At the synaptic level, enhanced LTP of the frontal cortico-accumbal glutamatergic synapses was correlated with decreased PSD-95 in cocaine-sensitized mice, as well as three mice lines mutant for differing monoamine transports (vesicular monoamine transporter, DA transporter, and NE transporter). In the cortico-accumbal synapses of mutant mice, the absence of PSD-95 leads to a "supersensitivity" to cocaine, and an "uncoupling" of glutamatergic transmissions from modulation by the dopamine system. This work illustrates a portion of the means by which drugs of abuse can usurp reward circuits

by altering the cortical glutamatergic system. Furthermore since PSD-95 and LTP are also associated with learning and memory, this work provides solid evidence that the mechanism driving long-lasting, drug-induced behavioral plasticity may occur by using the same cellular machinery. Yao, W-D., Gainetdinov, R.R., Arbuckle, M.I., Sotnikova, T.D., Cyr, M., Beaulieu, J-M., Gonzalo, E.T., Grant, S.G.N. and Caron, M G. Identification of PSD-95 as a Regulator of Dopamine-Mediated Synaptic and Behavioral Plasticity. Neuron, 41, pp. 625-638, 2004.

Spatial Profiling with MALDI MS: Distribution of Neuropeptides within Single Neurons

The distribution of peptides and proteins within a neuron plays an important role in the functioning of those molecules. Currently, we do not know how different the molecular content of one region of a cell is from another region of the same cell. Through the NIDA Cutting Edge Basic Research Award (CEBRA), Dr. Sweedler and colleagues have developed protocols for subcellular analysis of peptide distribution in cell bodies and neuronal processes. The model system used in these studies was Aplysia californica. This sea slug has large neurons making it a good test bed for doing single cell analysis to see if current technology will allow us to distinguish peptide profiles from different regions of a single cell. One of the challenges the researchers faced is seawater surrounding the neurons is problematic for the mass spectrometry technology they were using to obtain peptide profiles. The research team was ultimately able to find conditions that are compatible with the technology and allowed them to preserve cell morphology and prevent neuropeptide redistribution. They are finding that profiles of peptides in specific neuronal processes and the cell bodies demonstrate a variety of differences that appear to be cell-specific. These developments will contribute to researchers' abilities to use this type of technology in higher order animal systems. Being able to profile peptides or proteins in a spatial context may ultimately help us understand similarities and differences between different neurons and indeed between different neuronal projections. Rubakhin, S.S., Greenough, W.T. and Sweedler, J.V. Anal Chem.,75(20), pp. 5374-5380, October 15, 2003.

Neuroimmunology and Drugs of Abuse

The recent J Neuroimmunol V. 247, issues 1-2, 2004 presents a number of NIDA publications focusing on drugs of abuse actions on neuroimmune activities. These include topics of delta-opioid activities and mechanisms (B. Sharp); evidence implicating cocaine as a possible risk factor for HIV infection (Tashkin et al.); how morphine influences SAIDS in a monkey model (Donohoe); mechanisms of cannabinoids actions on diseases in mice (Klein et al.); immune cell activity during the initial stages of withdrawal from chronic exposure to cocaine or morphine (Bayer et al.); cannabinoids and morphine differentially affect HIV-1 expression in CD4(+) lymphocyte and microglial cell cultures (Peterson et al.); and cannabinoid-mediated exacerbation of brain infection (Cabral et al.). It also has other drug studies by non-NIDA supported scientists.

Director's Report to the National Advisory Council on Drug Abuse - May, 2004

Research Findings - Behavioral Research

Social Experience Alters Sensitivity to the Rewarding Properties of Drugs of Abuse

Interactions between environmental and genetic factors influence individual responses to drugs of abuse, but in humans and many animal models it is not easy to determine the relative contribution of these influences. The use of mice for such studies is a clear advantage, because they are the best-developed vertebrate genetic model organism. However, until recently there have been relatively few studies of environmental influences on drug-abuse behaviors in the mouse. In the present study, investigators studied how the social group experience of mice with opposite aggressive and non-aggressive behavioral strategies modulates reinforcing effects of morphine and cocaine. Level of aggression was identified within the stock group and during encounters with unknown intruders. Then, aggressive, moderately aggressive, and non-aggressive male mice were housed together in social triads for two weeks and subsequently tested for drug self-administration using tail vein infusions during restraint. Conditioned place preference (CPP) procedures were also performed with morphine and cocaine for all animals. Results showed that highly aggressive mice self-administered morphine and cocaine in higher unit concentrations (1.5 and 1.5 mg/ml) than non-aggressive animals (0.5 and 0.25, 0.5, 1.0 mg/ml). Both morphine (2.5, 5.0, 10.0, and 20.0 mg/kg) and cocaine (2.5, 5.0, and 10.0 mg/kg) induced a CPP in non-aggressive mice at all doses. In contrast, morphine had no effect in highly aggressive mice, while cocaine-induced a CPP at only the highest doses (10 mg/kg). These results illustrate that social experience in a stable group alters sensitivity to the rewarding properties of drugs of abuse. Vekovischeva, O.Y., Semenova, S.G., Verbitskaya, E.V. and Zvartau, E.E. Effects of Morphine and Cocaine in Mice with Stable High Aggressive and Nonaggressive Behavioral Strategy. Pharmacology Biochemistry and Behavior, 77, pp. 235-243, 2004.

Repeated Social Defeat Stress -- Long Lasting Effects on Behavioral and Neural Response to Amphetamine

Previous studies have shown that repeated exposure to stress induces cross-sensitization to psychostimulants. In the present study, Dr. Elena Nikulina and her colleagues looked for changes in neural activation that might be responsible for this environment x drug interaction. Social defeat stress was induced by subjecting rats to short confrontations with an aggressive resident rat once every third day over a period of 10 days. The rats then received d-amphetamine injections either 7 or 60 days after the last stress exposure. Amphetamine induced significantly greater locomotor activity in stressed animals than in controls, even two months after the last social stress exposure. The investigators used immunohistochemical techniques for Fos-like proteins to identify neural activation due to stress with or without an amphetamine challenge. At one-week post-stress, there was a significant increase in Fos-like immunoreactive (Fos-LI) labeling in prelimbic and infralimbic cortical regions, NAc shell and core, medial, central and basolateral amygdala, and VTA, due to the stress itself. Amphetamine challenge produced much higher Fos-LI in the dorsal striatum, NAc core, and medial amygdala in stressed animals compared to controls, but it is not clear whether this is an additive effect or reflects a cross sensitization to amphetamine. However, after two months, Fos-LI was no longer different between the stressed and control animals, but amphetamine challenge revealed sensitized Fos-LI labeling in the VTA and the central amygdala. These results suggest that episodes of repeated social stress induce long-lasting changes in neural activity of the VTA and amygdala, which might represent a neurobiological mechanism for enduring cross-sensitization to the effects of psychostimulant drugs. Nikulina, E.M., Covington, III,

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H.E., Ganschow, L., Hammer, Jr., R.P. and Miczek, K.A. Long-Term Behavioral and Neuronal Cross-Sensitization to Amphetamine Induced by Repeated Brief Social Defeat Stress: Fos in the Ventral Tegmental Area and Amygdala. Neuroscience, 123, pp. 857-865, 2004.

Human Gene Polymorphisms Predict Caffeine-Induced Anxiety

Caffeine is the most widely used psychoactive drug in the world and its popularity is likely due to its subjective effects, including enhanced alertness and stimulation. Yet, there are large individual differences in acute response to caffeine, with some people experiencing increased stimulation whereas others experience anxiety, an undesirable effect. Although the mechanism underlying individual differences to caffeine is not known, there is evidence that some of this variability might have a genetic basis. One source of inherited variability might lie in variation in the genes that code for the adenosine receptor, as activation of this CNS receptor gives rise to caffeine's psychological effects. Polymorphisms in the A1 and A2a adenosine receptor may account for variations in subjective responses to caffeine. Interestingly, the adenosine receptor system is also thought to be involved in the regulation of anxiety. In this study, NIDA grantee Harriet deWit examined the association between variations in anxiogenic responses to caffeine and polymorphisms in A1 and A2a adenosine receptor genes. Healthy, infrequent caffeine users (N = 94), recorded their subjective mood states following a 150 mg oral dose of caffeine freebase or placebo in a double-blind study. Dr. deWit and colleagues found a significant association between self-reported anxiety after caffeine administration and two linked polymorphisms on the A2a receptor gene, the 1976C>T and 2592C>Tins polymorphisms. Individuals with 1976T/T and 2592Tins/Tins genotypes reported greater increases in anxiety after caffeine administration than the other genotypic groups. The study shows that an adenosine receptor gene polymorphism that has been associated with panic disorder is also associated with anxiogenic effects of caffeine. Identifying the genetic basis for individual variation in quality or magnitude of response to addictive drugs may aid in understanding the vulnerability and resiliency for developing drug addiction. Alsene, K., Deckert, J., Sand, P., and de Wit, H. Association Between A(2a) Receptor Gene Polymorphisms and Caffeine-Induced Anxiety. Neuropsychopharmacology, 28(9), pp. 1694-1702, 2003.

Prescription Drug Abuse Liability: Subjective Effects of Oral Oxycodone

National surveys have noted significant increases in the abuse of prescription opioids. One particular opioid, oxycodone, is a semisynthetic derivative of thebaine that is indicated for the relief of moderate-to-severe pain. It has been available for clinical use since 1915, and while information about this drug is available from preclinical studies and investigations in drug abusing populations, there are no studies that address abuse liability of oral oxycodone in non-drug-abusing subjects. The purpose of the present study was to investigate the subjective, psychomotor, and physiological effects of oxycodone in non-drug-abusing volunteers and to compare the effects to morphine, an opiate with documented abuse liability. Eighteen subjects received oral placebo, 10 mg oxycodone, 20 mg oxycodone, 30 mg oxycodone, 40 mg morphine, or 2 mg lorazepam in a balanced, cross-over design. Measures were taken pre-drug and for 5-h after drug administration. End-of-session and 24-h post-session measures were taken to assess residual drug effects and overall subjects' assessments of the drug effects. In general, oxycodone produced effects similar to those of other mu opioid agonists. Its subjective effects were found to be dose-related, with the majority of statistically significant effects found at the two highest doses tested. Oxycodone produced both pleasant and unpleasant effects, and morphine in general produced effects similar in magnitude to those of 10 mg and 20 mg oxycodone. Peak "liking" and "drug-wanting" was increased by all doses of oxycodone and by morphine, and ratings of "dislike" were lower with 20-mg and 30-mg oxycodone relative to placebo. Post-session ratings of overall liking and wanting were not statistically significant. Cognitive and psychomotor impairment were obtained with high doses of oxycodone, but to a much lesser degree than that of lorazepam. Nevertheless, this observation suggests that patients taking higher doses of oxycodone (e.g., 20-30 mg) might have difficulty with demanding cognitive or psychomotor tasks. Although oxycodone produced abuse liability-related subjective effects, it also produced unpleasant effects, as is typically observed with opioid drug administration to non-drug-abusing volunteers. Zacny, J.P. and Gutierrez, S. Characterizing the Subjective, Psychomotor, and Physiological Effects of Oral Oxycodone In Non-Drug-Abusing Volunteers. Psychopharmacology, 170(3), pp. 242-254, 2003.

Prescription Drug Abuse Liability: Oral Propoxyphene Effects in Non-Drug-

Abusing Subjects

Like morphine and methadone, other prescription opioids have a potential for human abuse. It is therefore important to assess liability-related subjective effects of some of the more commonly prescribed prescription opioids, such as propoxyphene. Propoxyphene napsylate (Darvon-N¨) is a centrally acting mu opioid, which is indicated for the relief of mild-to-moderate pain. It is available as a single entity product or as a compound product containing acetominophen, or aspirin and caffeine. A good deal has been learned about the psychopharmacology of propoxyphene from both preclinical and clinical studies. Its profile of subjective, physiological, cognitive and behavioral effects is similar to that of other mu opioids. However, the present study was designed to provide a systematic and comprehensive characterization of subjective, psychomotor, and physiological effects of this drug in a population of "non-drug-abusing" volunteers. Eighteen subjects received oral placebo; 50 mg propoxyphene napsylate; 100 mg propoxyphene napsylate; 200 mg propoxyphene napsylate; 40 mg morphine sulfate; and 2 mg lorazepam in a balanced, cross-over design. Measurements were taken pre-drug and for 300 min. after drug administration. Results indicated that both morphine and lorazepam produced subjective effects, but no statistically significant subjective effects were obtained with any dose of propoxyphene in the group as a whole. This was true even with doses twice as high as the typical clinically prescribed dose of 100 mg. When examining individual subject data, the investigators noted that approximately 30-50% of the subjects did report subjective effects from this drug. "Drug liking" was not consistently observed in this subset. Propoxyphene, unlike lorazepam, did not impair psychomotor or cognitive performance. In general, the present results suggest that patients differ in their sensitivity to subjective effects of this prescription opioid and therefore may be differentially vulnerable on liability for abuse. Zacny, J.P. and Goldman, R.E. Characterizing the Subjective, Psychomotor, and Physiological Effects of Oral Propoxyphene in Non-Drug-Abusing Volunteers. Drug & Alcohol Dependence, 73(2), pp. 133-140, 2004.

Early Life Events Increase Susceptibility for Cocaine Self-Administration: The Identification of "Sensitive Periods" in Development

Individual differences in susceptibility to drug abuse and addiction are influenced by both genetic and environmental factors, such as early life stressors and maternal care. In this study, the investigators compared the effects of manipulations during week 1 vs. week 2 of life on subsequent propensity to self-administer cocaine. Pups received daily subcutaneous saline injections, were handled briefly, or remained undisturbed during their respective treatment periods. The rats were then given the opportunity to self-administer cocaine when they were 70 days old. Only animals manipulated during the second week of life acquired drug-taking behavior. These effects were both stimulus- and gender-specific: Females handled during the second week of life acquired cocaine self-administration at the lowest dose, and females injected during the second week of life acquired at the intermediate dose. Males injected during the second week of life showed a similar, but more variable, drug-taking pattern. In addition, females that were either handled or saline injected during the first week of life were the most resistant to acquiring self-administration. The authors conclude that the second week of life represents a sensitive period in this preclinical model of environmental manipulations, for influencing the vulnerability to acquire cocaine self-administration, especially in females. The observed gender difference is consistent with findings from many other studies comparing vulnerability for self-administration in male versus female subjects. The results also support previous observations that increased maternal attention following stressful events during early development can confers protective effects for subsequent drug taking behaviors. This study makes a valuable contribution to understanding how early life events alter neurobiological substrates that may confer differential susceptibility to drugs of abuse in adolescents and adults. Flagel, S.B., Vazquez, D.M. and Robinson T.E. Manipulations During the Second, but not the First, Week of Life Increase Susceptibility to Cocaine Self-Administration in Female Rats. Neuropsychopharmacology, 28, pp. 1741-1751, 2003.

Stress Affects Response to Methamphetamine in Human Subjects

The present study by Dr. Harriet de wit and colleagues was designed to study the effects of acute stress on subjective and physiological responses to methamphetamine (METH) in human volunteers. Prior studies in laboratory animals indicate that both acute and chronic stress increase self-administration of psychostimulants such as amphetamine and cocaine. In this study healthy volunteers were exposed to an acute social stressor (using the Trier Social Stress Test (TSST), or

no stress, immediately before10mg of METH or placebo. In this test, subjects are asked to perform a challenging arithmetic test in the presence of other people. The TSST has been shown to reliably induce increases in cardiovascular and endocrine parameters as well as subjective ratings of stress. Based on the preponderance of preclinical data, it was hypothesized that stress would enhance the subjective responses to METH as a consequence activating the HPA axis. Twenty-eight male subjects participated in two sessions, one with stress and the other without. They were randomly assigned to two groups that received either METH (n=16) or placebo (n=12) on both sessions. During each session, subjects underwent the TSST or no TSST, and then ingested METH) or placebo (PLAC). Over the next 1.5 hr self-reported mood measures and physiological measures, including salivary cortisol, were collected at regular intervals. Results indicated that both acute stress and METH produced mood-altering and physiological effects. Stress increased ratings of anxiety immediately after the TSST and increased salivary cortisol levels 20 min later. METH increased feelings of stimulation, and decreased fatigue and sedation, beginning about 20 min after drug administration and peaking at 60 and 90 min. Most interesting and surprising was the finding that stress dampened some early responses to METH (i.e., at 20 min), in particular reports of "energetic" and "calming" effects. By contrast, the stress manipulation increased responses to METH early in the sessions was on ratings of "want more drug." These results suggest that acute stress can alter the subjective responses to a low dose of METH, but these effects are short-lived. In addition, it is not always possible to predict "wanting" more drug, from changes in other drug-induced subjective states. Furthermore, paradigms such as the one employed in this study may be useful for studying self-medication models of drug abuse and addiction. Soderpalm, A., Nikolayev, L., and de Wit, H. Effects of Stress on Responses to Methamphetamine in Humans. Psychopharmacology, 170 (2), pp. 188-199, 2003.

A Novel Self-Administration Paradigm for Assessing "Affective" Properties

Drugs of abuse produce a wide range of affective experiences, from the more familiar euphorigenic or reinforcing effects, to aversive subjective states. Little is known about how this range of effects influences vulnerability to initiate drug abuse or progress to compulsive, uncontrollable addiction. We do know that individuals vary greatly on their initial response to drugs such as psychostimulants, and these individual differences may be an important influence on vulnerability. Few preclinical behavioral paradigms are available for the assessment of affective drug effects that fall along an appetitive - aversive continuum. Dr. William Woolverton at the University of Mississippi has developed a novel choice procedure to measure these effects in non-human primates. Animals are given a choice to perform operant responses to receive food reward only, or food reward plus drug on a concurrent (VR10 VR10 schedule). With this procedure, the degree to which a drug produces "positive" subjective states has been shown to determine preference for the drug plus food option. For example, when histamine is offered, preferences for the drug+food option decreases in a dose-related manner. However, when the drug choice is cocaine, preference for the drug+food option increases in a dose-related manner. This approach provides a new behavioral assay to investigate the affective effects of drugs of abuse, and will be useful for studying changes in subjective state over repeated drug exposures, under varying contextual influences, and individual differences. Woolverton, W.L. A Novel Choice Method for Studying Drugs as Punishers. Pharmacol Biochem Behav, 76, pp. 125-131, 2003.

Malleability of Early Social and Environmental Enrichment Effects in the Rat

Early social and environmental enrichment experiences have been shown to have profound effects on subsequent responsivity and vulnerability to drugs of abuse in animals. For example, studies on opiates have shown that group-housed rats are more sensitive than isolates to both antinociceptive and reinforcing effects of opioid mu agonists such as morphine and heroin. Previous studies suggest that these effects may be due to differences in opiate receptor density, which is increased under conditions of group housing. The present study examined the effects of these environmental manipulations on sensitivity to kappa opioid agonists. Animals were obtained at weaning (21 days) and assigned to isolate (IC) or group housed (enriched or EC) conditions for seven weeks. EC rats were reared in an enriched environment with various objects for exploration and interaction. The EC group was subsequently found to be significantly more sensitive to analgesia produced by highly selective kappa agonists. When tested for conditioned place preference, all animals spent less time in the compartment previously paired with a kappa agonist (as has previously been reported), but enriched rats were more sensitive to this effect. At week fourteen, the investigators reversed housing conditions in these two groups - isolates

were switched to group housing with enrichment and group housed rats were switched to isolated housing. Seven weeks later tail-flick analgesia was re-determined and a reversal of the housing condition influence was observed. Hence, the kappa agonist produced less analgesia in previously EC animals switched to IC, and more analgesia in IC rats now living under EC conditions. While additional behavioral investigations need to be conducted to determine if this observation generalizes to direct measures of drug reinforcement and reward, it suggests that the effects of early, deleterious environmental conditions may be overcome by subsequent environmental stimulation. Smith, M.A., Bryant, P.S. and McClean, J.M. Social and Environmental Enrichment Enhances Sensitivity to the Effects of Kappa Opioids: Studies on Antinociception, Diuresis and Conditioned Place Preference. Pharmacol Biochem Behav, 76, pp. 93-101, 2003.

Exercise Effects Central Opioid Systems - Behavioral Evidence of Cross-Tolerance

Exercise stimulates the release of endogenous opioid peptides and increases nociceptive thresholds in humans and animals. This observation suggests that repeated exercise might induce a tolerance in endogenous opioid systems. To test this hypothesis, Dr. Mark A. Smith and colleagues recently conducted a study with rats assigned to either sedentary (S) or exercise (E) conditions, from the time of weaning at age 21 days. Rats in the E group were housed in cages with a 35cm diameter exercise wheel. These housing conditions remained in effect for six weeks, at which time weekly testing was conducted with tail flick measures to assess analgesia. E rats were found to have higher baseline tail-withdrawal latencies in warm water when tested in the dark phase of the light cycle. Morphine produced 1.6 to 2.7 times greater analgesia in the S group at 50 and 55 degrees, respectively. Similar results were obtained with levorphanol, buprenorphine, butorphanol and nalbuphine. A naloxone challenge revealed withdrawal symptoms in both E and S group, but the mean symptom withdrawal score for E rats was two times greater than seen under S conditions, with a significant group X treatment (naloxone versus saline) interaction. At 15 weeks, housing conditions were reversed and after 6 weeks under these new conditions, analgesia testing was repeated with buprenorphine. E rats now living in S conditions showed an enhanced sensitivity to the analgesic effects of this opiate, whereas S rats changed to E conditions now were less sensitive to buprenorphine in the tail flick test. These findings support the hypothesis that exercise produced functional changes in the mu-opioid receptor system. In addition, these receptor substrate alterations appear malleable to subsequent change in physical activity level. Smith, M.A. and Yancey, D.L. Sensitivity to the Effects of Opioids in Rats with Free Access to Exercise Wheels: _-Opioid Tolerance and Physical Dependence. Psychopharmacol, 168, pp. 426-434, 2003.

Early Environmental Enrichment Alters Nicotine's Behavioral Activating Effects

There are suggestions from the literature that adolescent animals may be more sensitive to both the behavioral stimulatory effects of nicotine, and to its reinforcing properties. Thus, it is important to investigate how environmental factors affect these differential sensitivities. Many previous investigations with animals have revealed that environmental enrichment (EC) conditions affect subsequent response to drugs of abuse. For example, EC rats are more sensitive to the acute behavioral and neurochemical effects of amphetamine than those raised in an impoverished (IC) environment. EC rats also exhibit less locomotor sensitization to repeated amphetamine treatment, probably due to this greater initial sensitivity. In the laboratory of Dr. Michael Bardo, investigators have been studying how early environmental conditions influence the behavioral effects of psychostimulants. In the present study, 21-day-old rats were assigned to EC, IC or a social (SC) enrichment condition. SC rats were group housed, and EC animals also had the additional stimulation of objects to explore in their environment. In two separate assessments, conducted at 51 days of age, animals were tested for locomotor effects of s.c. 0.2 or 0.8 mg/kg of nicotine, compared to a saline control injection. Eight drug challenges were performed -- one every 48 hours. On the ninth session, rats were tested for sensitization with 0.8 mg/kg nicotine. In Experiment 1, data from IC and EC rats were examined from the first and the last drug treatment (session 1 and 8). EC rats exhibited significantly less nicotine-induced locomotor change over the 60 min post injection than did IC animals. This was true of both early session hypoactivity, and later session hyperactivity produced by 0.2 mg/kg. On the high dose test for sensitization, EC rats again showed less locomotor effects from the nicotine injection. In Experiment 2, EC and SC groups were examined with only 0.2 mg/kg nicotine over a similar eight sessions. Neither group showed locomotor effects after nicotine on

session one and there were few changes from saline controls on session 8. On a day nine challenge with 0.8 mg/kg, only SC rats exhibited nicotine hyperactivity, suggesting that EC blocked the development of behavioral sensitization. Overall, these observations suggest that early environmental enrichment induces a neurobiological substrate change that subsequently renders an animal less sensitive to nicotine's behavioral stimulation. Additional studies are needed to determine the effect of EC on the reinforcing properties of nicotine. Green, T.A., Cain, M.E., Thompson, M. and Bardo, M.T. Environmental Enrichment Decreases Nicotine-induced Hyperactivity in Rats. Psychopharmacol, 170, pp. 235-241, 2003.

Compulsive Drug use and Behavioral Sensitization: Are They Related?

Enhanced dopaminergic activation and behavioral stimulation have been well documented in preclinical studies of repeated psychostimulant administration. This psychostimulant sensitization has been implicated in neurobiological substrate changes that may contribute to the process of addiction. As addiction involves an escalation of drug use over time, Dr. George Koob and colleagues at The Scripps Research Institute have suggested that a 6 hr drug access model may mimic the transition to compulsive abuse. In this procedure, groups of animals are initially trained to respond for food reward and then allowed to self-administer cocaine for either 1 (short access, SA) hr or 6 (long access, LA) hr periods per day. SA animals typically develop stable daily intake, whereas LA rats show dramatic increases in number of cocaine infusions taken. Recently Dr. Koob compared animals trained in these two procedures, versus saline control groups, on measures of brain c-fos activation and locomotor response to a challenge injection of cocaine. In this study, all groups self-injected for 8 days and then underwent a 14-day withdrawal. On day 14 animals were returned to the operant chambers and allowed to bar press for one cocaine infusion. For some rats, the lever was withdrawn and they remained in the operant chamber without further drug availability, for one hour, after which they were sacrificed for c-fos measurements. C-fos counts showed that SA rats (versus 1 hr saline animals) had a significant elevation of this intermediate early gene in the lateral habenula, the prefrontal cortex and the nucleus accumbens core. There were no significant differences in the ventral tegmental area, central nucleus of the amygdala, bed nucleus of the stria terminalis, striatum or nucleus accumbens shell. LA rats showed no changes in c-fos in any area of the brain. Other animals were transferred immediately after a single cocaine infusion to locomotor activity chambers. Locomotor activity measures were compared with baseline activity counts from the previous (non-drug) day (i.e., from day 13 of withdrawal). While all saline and drug groups had similar activity counts on the baseline test, SA rats showed elevated activity scores (significantly greater than 1 hr saline rats) after a single cocaine self-injection, indicating the development of sensitization. LA rats, however, failed to show locomotor activation to cocaine on withdrawal day 14 -- their locomotor activity was not significantly different from their own baseline or from a saline group that also received 1 cocaine infusion immediately before testing. The investigators suggest that LA animals underwent neuroadaptations that homeostatically countered the development of sensitization seen in the SA group. The mechanisms involved in this process remain to be identified. Ben-Shahar, L., Ahmed, S.H., Koob, G.F. and Ettenberg, A. The Transition from Controlled to Compulsive Drug Use is Associated with a Loss of Sensitization. Brain Res, 995, pp. 46-54, 2004.

Early Lead Exposure Enhances Vulnerability for Cocaine Self-Administration

Dr. Jack Nation at Texas A&M University has been studying the effects of prenatal exposure to metals and the subsequent effects of this exposure on indices of drug abuse vulnerability in an animal model. Previously he has demonstrated that developmental lead exposure enhances behavioral sensitization with repeated cocaine administration but reduces the behavioral effects of acute cocaine. In the present study, female rats received 30 days of 16mg oral lead exposure and were bred with non-exposed males. Lead dosing was continued during gestation and into the lactation period. Pups were weaned on post-natal day 21 and tested for i.v. cocaine self-administration beginning on day 70. After training on stable responding for doses between 0.030 and 0.500 mg/kg/infusion, a dose response curve was determined. Blood and tissue samples were then collected and analyzed for lead concentration. Comparisons between lead exposed rats and those from dams receiving only sodium acetate vehicle revealed that the lead group was more sensitive to low doses of i.v. cocaine. Thus, whereas little self-administration was seen with 0.030 mg/kg for either group, at 0.060 mg/kg lead exposed rats made responses to receive cocaine at a rate greater than two times that seen in vehicle exposed animals. Lead analysis indicated that high concentrations detected in littermates at post-natal days 1 and 21 had returned to control levels by the time of self-administration testing. These results

suggest that lead exposure during development may enhance the vulnerability to acquire drug abuse behaviors, because there is an enhanced sensitivity to the drug. The mechanism for this change in sensitivity remains to be determined but the authors suggest that either pharmacokinetic changes or alterations in central mesocorticolimbic dopaminergic systems produced by lead may be responsible. Nation, J.R., Smith, K.R. and Bratton, G.R. Early Developmental Lead Exposure Increases Sensitivity to Cocaine in a Self-Administration Paradigm. Pharmacol Biochem Behav, 77, pp. 127-135, 2004.

Are There Critical Periods for the Effect of Methamphetamine-Induced Cognitive Deficits?

In an animal model of postnatal methamphetamine (MA) administration, exposure during post-natal (PN) days 11 to 20 produces lasting deficits in spatial learning and memory, while early exposure (PN days 1-10) is without effect. PN days 1-20 represent a pre-weaning period in the rat that corresponds to the third trimester of human gestation, and it is likely that drug effects on brain hippocampal development in particular underlie these cognitive effects. In particular, rapid neuronal growth and differentiation is seen in the hippocampus during PN days 11-15. The investigators suggest that since MA produces prolonged elevations of corticosterone on PN day 11, neurotoxic effects of this stress hormone on hippocampal development may be responsible for subsequent cognitive deficits. In the present study, Dr. Vorhees used the Morris water maze as a behavioral test of hippocampally-mediated learning and memory. MA in a dose of 10 mg/kg was administered to pregnant dams four times daily on either PN days11-15 or PN days 16-20. Behavioral testing in offspring began on PN day 50 using a modified Morris maze procedure with a small platform to test learning. Animals were first trained with the platform in a familiar underwater location, and then assessed in a "shifted platform" version of the task where they have to learn a new platform location. During acquisition several dependent measures of learning are collected, including time to locate the platform, path length and distance from the platform. "Probe" tests were conducted following acquisition to assess memory. Average distance from the platform and percent time in the target quadrant of the pool were measured during the probe tests. MA administration impaired the ability of animals to learn the maze task following PN exposure on days 11-15, and during probe tests MA rats tended to be further from the former platform site. Animals exposed later during the PN period showed no deficits in learning the task. When tested with the shifted platform, again rats exposed on PN days 11-15 showed deficits in learning, but there were no treatment-related group differences on the probe test for memory. No effects were seen on learning or memory in this shifted-platform test by animals exposed later during the PN period. These differences reveal a critical window for MA exposure to produce cognitive deficits seen in adulthood. Thus, spatial navigation deficits in both 'learning' and 'shifting' response sets were apparent in animals exposed to MA on PN days 11-15, whereas drug exposure beginning five days later was without effect. As this critical period corresponds to development in the central HPA axis that influences hippocampal integrity, it is possible that MA compromises this integrity via glucocorticoid release and its ensuing neurotoxic effects on hippocampal neurons. Williams, M.T., Moran, M.S. and Vorhees, C.V. Refining the Critical Period for Methamphetamine-Induced Spatial Deficits in the Morris Water Maze. Psychopharmacology, 168, pp. 329-338, 2003.

Serotonin Challenge Reveals Long-Term Cognitive Deficits in a Primate Model of MDMA Abuse

Numerous recent reports have suggested that MDMA (ecstasy) abuse in human abusers may produce long-term cognitive deficits, most notably in short-term memory. However, studies on human abusers are fraught with problems of "street drug" contamination, the unreliability of self-report, and high rates of poly-drug abuse. Studies with non-human primates can assess drug effects on complex cognitive function under strictly controlled conditions where typical street doses of MDMA can be administered. In the research program of Dr. Michael Taffe at The Scripps Research Institute, investigators have been studying the effects of repeated, high dose MDMA (4 days, 10 mg/kg i.m., b.i.d., as the salt). The present study was conducted 11 months after drug administration to three male rhesus monkeys, with three others serving as controls for yoked vehicle administration. This regimen reduced CSF 5-HIAA (the major metabolite of serotonin) approximately 50% for up to 17 weeks. Upon sacrifice at 5-8 months after completion of this study, postmortem analyses revealed 76-93% reductions in neocortical and hippocampal 5-HT content in the MDMA exposed animals versus controls. The six monkeys were treated with a rapid tryptophan depletion (RTD) procedure that dramatically lowers tryptophan in

plasma and CSF in both humans and nonhuman primates. The control procedure involved oral administration of a balanced amino acid mixture. Electrophysiological measures of brainstem auditory evoked potentials (BSAEP) were taken following gavage with either the RTD mixture or the amino acid control, and behavioral testing was conducted on memory (SOSS, DNMS), reinforcer efficacy (with Progressive Ratio responding), reaction time and BMS. In addition, cognitive assessments were made with a modified CANTAB battery, previously used by this investigator. The RTD treatment produced significant reductions in P4 latencies on BSAEP in animals with a MDMA drug history, while not affecting latencies in vehicle treated monkeys. On self-ordered spatial search (SOSS), performance of control animals was significantly improved by the RTD, but there were no changes in performance of MDMA monkeys. No other differences were noted. These findings suggest that heavy MDMA use may produce long-lasting neurobiological changes, with cognitive consequences that do not become evident until unmasked by a challenge to the central 5-HT system. The observation that differences were seen on SOSS measures only might indicate that working memory is more sensitive to alterations of the serotonergic system. Furthermore, the RTD-induced impairment of early auditory processing in MDMA treated monkeys resembles P4 latency decreases seen during original drug exposure - an effect that persisted for 13 weeks post-drug. Overall, these observations are significant because challenges to the central 5-HT system later in the life of young ecstasy abusers, (e.g., stroke, degenerative disease or central transmitter changes with normal aging), may unmask the appearance of long-lasting MDMA-induced cognitive and central processing deficits. Taffe, M.A., Huitron-Resendiz, S., Schroeder, R., Parsons, L.H., Henriksen, S.J. and Gold, L.H. MDMA Exposure Alters Cognitive and Electrophysiological Sensitivity to Rapid Tryptophan Depletion in Rhesus Monkeys. Pharmacol Biochem Behav, 76, pp. 141-152, 2003.

Estrogen Enhances Stimulant-Induced Behavioral Activity in Female Rats

It is well established that locomotor activating effects of cocaine are greater in female than male rats. Several observations suggest that this sex difference is mediated by estrogen: For example, these sex differences emerge after puberty; cocaine-induced locomotion is greater during proestrus (when estrogen is highest) and estrous, than during diestrus; and cocaine-induced locomotion in ovariectomized rats is enhanced by the chronic administration of estrogen. Drs. Kathryn Cunningham, Mary Thomas and colleagues at the University of Texas Medical Branch have found evidence that the locomotor hyperactivity induced by 3,4methylenedioxymeth-amphetamine (MDMA, ecstasy) is also greater in female than male rats. They previously reported greater locomotor hyperactivity in female than male rats in response to 4 mg/kg doses of (+)-MDMA (Bubar, Thomas, & Cunningham, 2001). In a follow-up study, these researchers compared locomotor activity induced by either (+)-MDMA or cocaine, in rats that were ovariectomized (OVX) and in rats that were ovariectomized plus given a 17_-estradiol (E2) implant (OVX+E2). Locomotor activity was examined for two hours following (+)-MDMA (1, 2, 4 mg/kg ip) or cocaine (5, 10, 20 mg/kg ip). During initial habituation to the open field activity chambers, activity declined from Day 1 to Day 3. The investigators observed that the OVX+E2 group displayed retarded habituation of vertical and horizontal activity relative to the OVX group, although this difference did not achieve statistical significance. Both MDMA and cocaine administration dose-dependently increased locomotor activity. Both horizontal and vertical activity were elevated in the OVX+E2 group relative to the OVX group at the highest MDMA dose (4 mg/kg) and at the highest two cocaine doses (10 and 20 mg/kg), indicating E2 enhancement of MDMA-induced and cocaine-induced locomotor activation at those doses. Examination of the time course of locomotor activation indicated differential effects of MDMA and cocaine. Within 5-min of cocaine administration, both OVX and OVX+E rats exhibited hyperactivity followed by a decline over the 2-hr session. In contrast, MDMA activity increased only slightly in the first 20 min followed by hyperactivity between 20 and 40 min following injection. These differences appear in part to be related to the pharmacokinetic profiles of MDMA and cocaine. Although both drugs potentiate efflux of dopamine (DA) and 5-hydroxytryptamine (5-HT, serotonin), the drugs have different time courses for this potentiation -- MDMA produces an immediate increase in 5-HT, but a delayed increase in DA, whereas cocaine produces an immediate increase in both 5-HT and DA. Thus, the present data suggest that E2 may play a greater role in altering DA activity than 5-HT activity. Zhou, W., Cunningham, K.A., and Thomas, M.L. Estrogen Effects on the Hyperactivity Induced by (+)-MDMA and Cocaine in Female Rats. Behavioral Neuroscience, 117, pp. 84-94, 2003.

Sex-Dependent Effects of Δ9-tetrahydrocannabinol on Locomotor Activity in Mice

Prior research on the locomotor-altering effects of Δ9-tetrahydrocannabinol in rodents has shown suppressive effects at higher doses, facilitation at lower doses, and tolerance to the suppressive effects with repeated dosing. In the present study, Dr. Jenny Wiley of the Virginia Commonwealth University examined sex differences in Δ9-tetrahydrocannabinol's locomotor effects in mice. A range of single-injection doses, 1 - 30 mg/kg ip, was delivered to separate groups of mice on two separate test days. On Day 1, males did not exhibit increased locomotor activity compared to vehicle at any dose. Females, on the other hand, exhibited elevated locomotion at 1, 3, and 10 mg/kg. The enhancement at 1 and 10 mg/kg were each statistically higher than vehicle effects, and statistically higher than effects seen in males. Following 3 days of daily injections of 10 mg/kg (two injection on Days 2 and 3 and one injection on Day 4), on Day 5, the dose-response curve was re-determined. Again, males did not exhibit increased locomotor activity compared to vehicle at any dose. Females, however, exhibited statistically significantly increased locomotor activity with the 3, 10, and 30 mg/kg dose. However, at the 1mg/kg dose, no enhancement of locomotor activity was observed, suggesting the development of tolerance. At none of the doses was activity-suppression observed in either males or females. Δ9-tetrahydrocannabinol's activity-inducing effects in females, but not in males, observed in the present study is consistent with prior observations from rats showing greater female sensitivity to Δ9-tetrahydrocannabinol's locomotor-suppressive effects, antinociceptive effects, and cataleptic effects. Wiley, J.L. Sex-Dependent Effects of Δ9-tetrahydrocannabinol on Locomotor Activity in Mice. Neuroscience Letters, 352, pp. 77-80, 2003.

Director's Report to the National Advisory Council on Drug Abuse - May, 2004

Research Findings - Treatment Research and Development

High Levels of Prize Reinforcement makes a Difference for Treating Cocaine Users

Dr. Nancy Petry and colleagues at University of Connecticut Health Center and Yale University randomly assigned cocaine users to three levels of a motivational incentive intervention. In the first condition participants received standard counseling for drug abuse. In the second condition participants received standard counseling plus they could earn up to $80 worth of prizes through random drawings. In the third condition participants could earn up to $240 worth of prizes through random prize drawings. Prize drawing opportunities were contingent upon submitting a cocaine-free urine sample. Individuals in the high value ($240) condition achieved more abstinence from cocaine than those in the other conditions. Individuals who initiated treatment with negative urinalysis generally remained abstinent regardless of treatment condition assignment. Participants with positive urinalysis were most responsive in the high pay condition. These results suggest that relatively low cost motivational incentive programs may be appropriate for use in community treatment programs but that results may be magnitude dependent. Petry, N.M., Tedford, J., Austin, M., Nich, C., Carroll, K.M., Rounsaville, B.J., Addiction, 99(3), pp, 349-360, March, 2004.

Improvements in Counseling Session Punctuality with Contingency Management during Methadone Treatment

Dr. Charles Schuster at Wayne State University and colleagues conducted two studies to investigate the effectiveness of contingency management techniques in promoting punctual counseling attendance among methadone maintenance patients. In the first study, on-time attendance was reinforced with the chance to draw for prizes ranging in value from 0-$100.00. Those methadone maintenance patients who exhibited poor attendance initially demonstrated a significant positive response during the contingency management intervention phase. In the second study, participants were randomized to either a fixed or random value of voucher reinforcement. There were no differences between either group. Overall the results indicate that targeting poor attendance with contingency management may be effective. This is significant because attendance is consistently linked with abstinence outcomes. Rhodes, G.L., Saules, K.K., Helmus, T.C., Roll, J., Beshears, R.S., Ledgerwood, D.M., Schuster, C.R., Am J Drug Alcohol Abuse, 29 (4) pp, 759-773, 2003.

Pilot Study Shows Integrated Group Therapy May Improve Drug Use Outcomes for Bipolar Substance Dependent Patients

Dr. Roger Weiss and colleagues at McLean Hospital conducted surveys of bipolar patients showing that many initiate substance use because of at least one bipolar disorder symptom and most believe their drug use improves their bipolar symptoms. Among those who believe drug use improves their bipolar disorder symptoms, a new treatment, Integrated Group Therapy in which bipolar and substance dependence symptoms are concurrently treated produced fewer days of drug use. These results are preliminary due to design and sample size limitations. Weiss, R.D., Kolodziej, M., Griffin, M.L., Najavits, L.M., Jacobson, L.M., Greenfield, S.F., J. Affect. Disord, 79 (1-3), pp. 279-283, April 2004.

Smoking Among Female Prisoners: An Ignored Public Health Epidemic

The Mississippi Department of Corrections surveyed 866 female prisoners about tobacco use and interest in a smoking cessation program with a 27-item questionnaire. The majority of female inmates (73.9%) were current tobacco users

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with a mean of 14.6 cigarettes per day. Approximately 12.5% of current smokers reported a tobacco-related medical problem. Most (60.6%) had made at least one attempt to quit smoking and only 24.5% felt "very confident" that they could quit if they made an attempt. Overall, 64.2% of the smokers reported interest in participating in the smoking cessation program, with heavier smokers (71.4 %) reporting the most interest in enrolling in the program. The high percentage of current tobacco users, high level of interest in smoking cessation, and presence of smoking-related health problems indicate a tremendous public and correctional health problem that is being ignored. Cropsey, K., Eldridge, G.D., and Ladner, T. Addictive Behaviors, 29, pp. 425-431, 2004.

Disulfiram and Cognitive Behavior Therapy Effectively Reduce Cocaine Use

Dr. Kathleen Carroll and colleagues at Yale University evaluated the efficacy of disulfiram in general populations of cocaine users in a randomized placebo-controlled trial. They also compared the effectiveness of two active behavioral therapies, cognitive-behavioral therapy (CBT) and interpersonal psychotherapy (IPT). Participants (n=121) meeting criteria for current cocaine dependence were assigned to receive either disulfiram (250mg/day) plus CBT, disulfiram (250mg/day) plus IPT, placebo plus CBT, or placebo plus IPT. Both behavioral therapies were manual-guided and delivered in individual sessions for 12 weeks. Participants assigned to disulfiram reduced their cocaine use significantly more than those assigned to placebo, and those assigned to CBT reduced their cocaine significantly more than those assigned to IPT ($P<.01$ for both). Findings were consistent across all study samples (e.g., intention to treat, treatment initiators, and treatment completers). Benefits of disulfiram use and CBT were most pronounced for participants who were not alcohol dependent at baseline or who fully abstained from drinking alcohol during treatment. Thus, disulfiram and CBT are effective therapies for general populations of cocaine-dependent individuals. Further, disulfiram seems to exert a direct effect on cocaine use rather than through reducing concurrent alcohol use. Carroll, K.M., Fenton, L.R., Ball, S.A., Nich, C.N., Frankforter, T.L., Shi, J.S., and Rounsaville, B.J. Arch Gen Psychiatry. 61, pp. 264-272, March 2004.

Changes in the Meaning of Sexual Risk Behaviors Among Gay and Bisexual Male Methamphetamine Abusers Before and After Drug Treatment

This study combined the quantitative and qualitative research methodologies to examine risk behaviors among gay and bisexual male methamphetamine abusers as they entered treatment and at 1-year follow-up evaluations. Findings from the quantitative follow-up data demonstrate that gay and bisexual men reduce sexual risk behaviors and sustain those reductions following substance abuse treatment, and qualitative data reveal the meaning of these behavior changes from the perspective of the participant. At 1-year follow-up evaluations, associated behaviors of methamphetamine use and sexual risk behaviors were lessened. Although condom use decreased slightly, participants reported fewer anonymous sexual partners, reductions in episodes of both receptive and insertive anal intercourse, and an increased sense of responsibility to disclose their HIV status. This study further demonstrates the value of coupling quantitative and qualitative data in understanding the meaning behind reductions in high-risk behaviors. Reback, C.J., Larkings, S., and Shoptaw, S. AIDS and Behavior, 8, pp. 87-98, 2004.

Targeting HIV-Related Outcomes with Intravenous Drug Users Maintained on Methadone: A Randomized Clinical Trial of a Harm Reduction Group Therapy

In this study, investigators from Yale University evaluated the efficacy of a 12-session harm reduction group intervention for injection drug users, based on the Information-Motivation-Behavioral skills model of behavior change, that focused on reducing both drug and sex risk. Two hundred and twenty patients entering an MMP were randomized to receive either standard care (SC)-2 hours of counseling per month and a single-session risk reduction intervention-or SC plus the harm reduction group (HRG). Results showed that during treatment, patients receiving HRG were most likely to be abstinent from cocaine and to report fewer unsafe sexual practices. Post-treatment, HRG patients scored higher on a sexual risk quiz and reported increased self-efficacy in high-risk sexual situations. Enhancing methadone maintenance with a weekly harm reduction group treatment was somewhat more expensive but can bring positive changes in behaviors and attitudes that are associated with the transmission of HIV. Avants, K., Margolin, A., Usubiaga, M., and Doebrick, C. Journal of Substance Abuse Treatment, 26, pp. 67-78, 2004.

Psychiatric Co-morbidity Among Adolescent Substance Abusers Effects Response to Behavioral Treatment

Dr. Cindy Rowe of the University of Miami and colleagues continue their work to clarify the connection between psychiatric co-morbidity and treatment of adolescent substance abuse. Building on previous work highlighting the importance of both externalizing and internalizing disorders among adolescent substance abusers, this newest study examined whether adolescents with different psychiatric co-morbidities differed in clinical presentation and treatment response. Among 182 adolescent drug abusers in a randomized clinical trial comparing family and individual cognitive-behavioral therapy, more severe co-morbidity was associated with greater family dysfunction and being female and younger at intake. Regarding treatment response, adolescents with mixed externalizing and internalizing co-morbidities initially responded to treatment but returned to intake levels of substance use by 1 year post-discharge. Rowe, C.L., Liddle, H.A., Greenbaum, P.E. and Henderson, C. Impact of Psychiatric Comorbidity on Treatment Outcomes of Adolescent Drug Abusers. Journal of Substance Abuse Treatment, 26, pp. 1-12, 2004.

Mothers Entering Drug Treatment Appear to be Successful at Maintaining or Re-establishing Co-residency with their Children

Dr. Danica Knight and colleagues at Texas Christian University conducted a study of the degree to which mothers who enter residential drug treatment are successful in maintaining or re-establishing their role as parents during the course of treatment. The sample included 152 female clients admitted to a residential drug treatment program for women with dependent children. Among the 152 women in the study, there was a significant increase in child co-residency from admission to follow-up. Women who entered treatment with all children, or who were reunited with children previously in others' care at admission, were over five times more likely to co-reside with all children at follow-up. At follow-up, mothers who reported complete co-residence were more likely to be 30 years old or younger, live independently, and have fewer than two parenting challenges. This study documents the status of child co-residence prior to, during, and following treatment, which may have implications for the practice of providing child care and family residency options in drug abuse treatment. Knight, D.K. and Wallace, G. Where Are the Children? An Examination of Children's Living Arrangements when Mothers Enter Residential Drug Treatment. Journal of Drug Issues, 33(2), pp. 305-324, 2003.

HIV-Risk Behaviors Appear to be Connected to Violence and Clinical Depression Among Some Female Drug Users

Drs. Johnson, Cunningham-Williams, and Cottler recently published a paper describing the connection between sexual HIV-risk behaviors and exposure to violence and/or depression among 420 African-American out-of-treatment female drug users. Sexual risk behaviors were compared for women in mutually exclusive groups based on exposure to violence and the presence of clinical depression. Results showed that women with a history of sexually transmitted diseases were more likely to experience violence and depression, both alone and jointly. Women who had two or more sexual partners in the last 30 days and women who had an early onset of alcohol use were at an increased risk for having drug use, violence and depression. Never being married was a protective factor for drug use, violence and depression. As expected, more risk factors were found among women who had the full tripartite than among women with one or two of the factors. Johnson, S., Cunningham-Williams, R.M. and Cottler, L.B. A Tripartite of HIV-risk for African-American Women: The Intersection of Drug Use, Violence, and Depression. Drug and Alcohol Dependence, 70(2), pp. 169-175, 2003.

There May be Variations in the Progression from Abuse to Dependence for Different Substances

Drs. Ridenour and colleagues conducted a study meant to clarify the degree to which progression from abuse to dependence for marijuana, cocaine, and opiates mirrors the progression for alcohol. Re-analyzing data from the DSM-IV Substance Use Disorders Work Group (n = 1226) using McNemar's chi2, configural frequency analyses and survival analyses, these investigators found variations in progression from abuse to dependence for different substances. While for all substances, lifetime dependence in the absence of lifetime abuse was rare, results were consistent with a progression occurring for alcohol and cannabis, but not for cocaine and opiates. For cocaine users, abuse and dependence occurred in the same year for 66% of the cocaine users who experienced both disorders (57% of users with any cocaine disorder). For opiate users, abuse and dependence occurred in the same year for 65% who experienced both disorders (46% of users with any opiate disorder). Ridenour, T.A., Cottler, L.B., Compton, W. M., Spitznagel, E.L. and Cunningham-Williams R.M. Is There a Progression from Abuse Disorders to Dependence Disorders? Addiction, 98,

pp. 635-644, 2003.

The Minnesota Multiphasic Personality Inventory-Adolescent Version (MMPI-A) Detected Under-Reporting of Teens' Substance Abuse

Drs. Lynda Stein and colleagues continue to tackle the difficult issue of accurate assessment of drug use among adolescents. Incarcerated, substance abusing (n = 67) and non-substance abusing (n = 59) adolescents completed the MMPI-A under two different sets of instructions. Assessments completed according to standard instructions correctly classified 60 - 85% of substance abusers. Assessments completed when adolescents were instructed to "fake good" produced lower scores on substance abuse overall, although the Lie scale detected over 75% of the under-reported profiles. Additionally, when used in combination with the best substance abuse scale, the Lie scale detected 82% of substance abusers. Given that accurate assessment is vital to effective treatment and treatment research, this study suggests that the MMPI-A may be a tremendously useful tool in adolescent substance abuse research. Stein, L.A.R.and Graham, J.R. Ability of Substance Abusers to Escape Detection on the MMPI-A in a Juvenile Correctional Facility. Paper presented at the 38th Annual Symposium on Recent Developments in the Use of the MMPI (MMPI-2 and MMPI-A), Minneapolis, MN, June 2003.

Developing a Brief Version of the Marijuana Effect Expectancy Questionnaire (MEEQ)

Drs. Griffin and other NIDA-funded colleagues collaborated on the development of a brief version of the 70-item MEEQ for use with incarcerated teens. A single item was generated to represent each of the 6 scales of the original instrument. A total of 124 incarcerated teens completed the brief version of the instrument (MEEQ-B). Psychometric analyses suggested that the MEEQ-B had two factors: a positive expectancies factor accounting for 29% of the variance in responses, and a negative expectancies factor accounting for 23% of the variance in responses. Further, the internal reliabilities of each of these factor-scales were 61% and 38%, respectively. The investigators conclude that researchers should continue to use the longer version of the instrument, but that the brief version may be useful as a clinical tool to generate discussion about marijuana use expectancies. S. Griffin, L. Stein, S. Colby, N. Barnett, P. Monti, and C. Golembeske. Validation of a Brief Version of the Marijuana Effect Expectancy Questionnaire. Poster presented at the 8th Annual Research Symposium on Mental Health Sciences, Brown University, Providence, RI, March 2004. Assessment of Substance Use and Treatment Implications for Incarcerated Teens Dr. Lynda Stein of Brown University and colleagues assessed the substance use patterns, and other factors with potential treatment implications, of incarcerated teens. Among the 82 teens participating in the investigators' randomized treatment outcome study, there were high rates of alcohol, marijuana, and nicotine use, and high rates of depressive symptoms. Regarding drug use expectancies, overall, teens do not expect alcohol to have very much impact upon them, aside from "liquid courage," and teens felt confident in their ability to resist alcohol. However, teens expected marijuana to have a positive impact and very little negative impact on them, but they were not confident in their ability to resist marijuana use. Many teens appeared to be interested in changing their use of marijuana and/or alcohol. Stein, L.A.R., Colby, S., Barnett, N., Monti, P., Lebeau-Craven, R. & Golembeske, C. Assessment of Substance Use and Treatment Implications for Incarcerated Teens. Proceedings from the 65th Annual Meeting of the College on Problems of Drug Dependence, Bal Harbour, FL., June 2003.

Improving Parenting and Drug Use Among Drug-Dependent Mothers

Dr. Suchman of Yale University and colleagues developed and tested a 12-week parenting intervention for drug-dependent mothers. The investigators compared 20 mothers receiving Emotionally-Responsive Parenting (ERP) to a historical control group of 23 mothers that received standard treatment. Mothers receiving ERP mothers had better weekly attendance, and completion rates, and were more compliant with clinical advice. At post-treatment, 83% of women receiving ERP vs. 70% of comparison mothers were abstinent, but this difference was non-significant. Importantly, ERP mothers' capacity to acknowledge their own and their children's cognitive and affective states also improved significantly. This pilot study suggests that a parenting intervention focused on increasing parents' emotional availability to children can be effective in contributing both to abstinence and to emotional responsiveness. Suchman, N. E., Altomare, M., Moller, F., Slade, A., & Mayes, L. Emotionally Responsive Parenting: A New Parenting Intervention for Drug Dependent Mothers. Invited poster presentation, College on Problems of Drug Dependence Annual Meeting, Bal Harbour, FL, June 2003.

Social Relationships Appear to be Integral to Successful Treatment for Women in Drug Abuse Treatment

Dr. Danica Knight and colleagues at Texas Christian University presented a paper on the role of social relationships for women in drug abuse treatment. Findings documented significant associations between interpersonal relationship measures and key treatment process indicators among 152 women in long-term residential drug abuse treatment. For example, clients who were motivated at treatment entry were more likely to develop healthy relationships with fellow clients during treatment, and those who reported healthier family relationships were more likely to complete treatment requirements. Relationships with peers were important in the development of counselor rapport, and in perceived support for treatment. Relationships with family members impacted psychosocial functioning and completion, and relationships with counselors facilitated compliance, longer retention, and completion. This study provides additional evidence for the importance of building and maintaining positive social networks during the course of treatment. Knight, D.K., Joe, G.W, and Simpson, D.D. Is the Treatment Process Different for Women in Residential Treatment? Presented at the annual meeting of the American Psychological Association, Toronto, Canada, August 2003.

Genetic and Environmental Influences on Substance Initiation, Use, and Problem Use in Adolescents

Dr. Thomas Crowley and colleagues at the University of Colorado conducted a sibling/twin/adoption study of substance initiation, use, and problem use, estimating the relative contribution of genetic and environmental influences on these phenotypes in adolescents. The participants were 345 monozygotic twin pairs, 337 dizygotic twin pairs, 306 biological sibling pairs, and 74 adoptive sibling pairs. Results showed that there were moderate to substantial genetic influences, with the exception of alcohol use and any drug use, and modest to moderate shared environmental influences on substance initiation, use, and problem use. For alcohol and any drug, heritability was higher and the magnitude of shared environmental influences was lower for problem use than for initiation or use. Environmental influences shared only by twin pairs had a significant effect on tobacco initiation, alcohol use, and any drug use. For tobacco use, tobacco problem use, and marijuana initiation, heritability was higher and the magnitude of shared environmental influences was lower in female than in male adolescents. There was no evidence for sex-specific genetic or shared environmental influences on any variable. The moderate to substantial heritabilities found for adolescents in the present study are comparable to those found in twin studies of adult substance use and substance use disorders. The finding that problem use is more heritable than initiation and use is also consistent with the results of adult twin studies. The significance of environmental influences shared only by twin pairs on tobacco initiation, alcohol use, and any drug use suggests the influences of peers, accessibility of substances, and sibling interaction. Soo Hyun Rhee, S.H, Hewitt, J.K, Young, S.E., Corley, R.P., Crowley, T.J. and Stallings, M.C. Archives of General Psychiatry, 60, pp. 1256-1264, 2003.

Affect Differences Between Non-Abusers of Drugs Who Made a Preferred (Blind) Selection of Amphetamine Over Placebo

Dr. Frances Gabbay at the Uniformed Services University of Health Sciences (USUHS) compared a group of self-selected choosers of amphetamine over placebo to those who avoided amphetamine on a series of questions assessing subjective feelings. While taking amphetamine (blinded), choosers had increased ratings on energy, cognitive efficiency and well being, with reduction of fatigue and sedation. Non-choosers reported none of these effects though had an increase in dysphoria. Under placebo the ratings decrease while sedation ratings increased. The fact that these groups react to amphetamine differently (without knowing what it is they are ingesting) could be related to important differences in risk for drug use. Gabbay, F.H. Experimental and Clinical Psychopharmacology, 11(1), pp. 91-101, 2003.

Reduced Serotonin Uptake Sites among Cocaine Patients: Negative Correlation with Aggression, Impulsivity, and Sensation Seeking

Dr. Ashwin Patkar and associates at Thomas Jefferson University assessed binding (Bmax) values of paroxetine in platelets-a measure of serotonin uptake sites-in treatment-seeking male and female cocaine dependent patients. While Kd between subjects and controls were not different, Bmax was significantly ($p < .001$) lower in the patients while higher were several measures of aggression (Buss-Durkee battery), depression (Beck Depression Inventory), impulsivity (Barrett) and sensation seeking. The results may have limited generalizability since the subjects were all African-

American. There was no difference in craving. These results suggest that the densities of serotonin uptake sites may be reduced among cocaine abusers and related to impulsive-aggressive behavioral dimensions. Patkar, A.A., Gottheil, E., Berretini, W.H., Hill, K.P., Thornton, C.C. and Weinstein, S.P. The American Journal of Addictions, 12, pp. 432-447, 2003.

Sex Differences in rCBF Induced by Cue-induced Craving

Using verbal scripts to induce craving in patients with cocaine dependence (most, but not all who were in treatment), Kilts and colleagues at Emory University found, using PET, rCBF increases in the superior temporal gyrus, dorsal anterior and posterior cingulate cortex, nucleus accumbens area, and the central sulcus. However, in comparison to an identical study in men, women showed less activation of the amygdala, insula, orbitofrontal cortex, and ventral cingulate cortex but greater activation of the central sulcus and widely distributed frontal cortical areas. These findings suggest sex differences in the functional anatomy associated with cue-induced cocaine craving. Whether these differences are physiological or perceptual or both cannot be determined but once characterized may have implications for treatment. Kilts, C.D., Gross, R.E., Ely, T.D. and Drexler, K.P.G. American Journal of Psychiatry, 161(2), pp. 233-241, 2004.

Linkage Evidence for Two Chromosomal Regions Associated with Substance Dependence Vulnerability

Drs. Stallings, Crowley, and collaborators found a location on chromosome 3 (3q24-25, near markers D3S1279 and D3S1614) and chromosome 9 (9q34, near marker D9S1838) that had LOD scores above 1.0 suggesting possible linkage and providing a basis for a replication study. The measure "phenotype" used was determined empirically-having the greatest heritability as determined in their twin and community samples-and based on responses to diagnostic interviews. Specifically, it was the average number of symptoms of substance use over all substances (i.e., total number of symptom counts for all substances divided by the number of substances used). These results were obtained on adolescents and match findings reported by others on adults. Stallings, M.C., Corley, R.P., Hewitt, J.K., Krauter, K.S. Lessem, J.M. Mikulich, S.K., Rhee, S.H., Smolen, A., Young, S.E. and Crowley, T.J. Drug and Alcohol Dependence, 70, pp. 295-307, 2003.

Linkage Evidence for One Chromosome Region: Suggestive for Several Others for Nicotine Dependence

Dr. Ming D. Li and collaborators analyzed data from the Framingham Heart Study population using number of cigarettes smoked from on time period and a genome scan of 401 markers at an average spacing of 7.5 cM. Significant linkage was found at locus GGAA5C04 &GATA90D07 on chromosome 11 with suggestive loci found on 4, 7, 9, 14, & 17 by one of two methods. Loci on 7, 11, and 17 were found by both methods. Li, M.D., Ma, J.Z., Cheng, R., Dupont, R.T., Williams, N.J., Crews, K.M., Payne, T.J. and Elston, R.C. BMC Genetics, 4(Suppl 1) S103, 2003.

Opiate Addicts Lack Error-Dependent Activation of Rostral Anterior Cingulate

Dr. Steven Forman and colleagues at University of Pittsburgh used functional Magnetic Resonance Imaging (fMRI) to determine whether brain regions involved in error detection, such as the anterior cinglulate cortex, are dysfunctional in substance abusers. Normal individuals performing response suppression tasks activate anterior cingulate cortex with occurrence of false alarm error responses to non-targets. In contrast, methadone maintained opiate addicts exhibited an attenuated anterior cingulate cortex error signal and significantly poorer task performance. In controls but not opiate abusers, the individual level of event-related anterior cingulate cortex activation accompanying false alarm errors positively predicted task performance, particularly sensitivity in discriminating targets from non-targets. These results suggest that the attenuation of error signals in anterior cingulate cortex may play a role in loss of control in addiction and other forms of impulsive behavior. Forman, S.D., Dougherty, G.G., Casey, B.J., Siegle, G.J., Braver, T.S., Barch, D.M., Stenger, V.A., Wick-Hull C., Pisarov L.A. and Lorensen, E. Biological Psychiatry, 55(5), pp. 531-537, 2004.

Prefrontal Responses to Drug Cues: A Neurocognitive Analysis

Dr. Julie Fiez and colleagues at the University of Pittsburgh reviewed neuroimaging studies of cue-elicited craving in the context of a framework drawn from behavioral research indicating that perceived drug use opportunity significantly affects responses to the presentation of drug cues. They report that activation of the prefrontal cortex

was consistently found in studies using non-treatment seeking substance abusers. In contrast, prefrontal activation was largely absent in studies using treatment-seeking subjects. Using this framework provides a way to reconcile discrepant findings among brain imaging studies of cue-elicited craving. Wilson, S.J., Sayette, M.A., Fiez, J.A. Nature Neuroscience, 7(3), pp. 211-214, 2004.

Oral D-Amphetamine Causes Prolonged Displacement of [C-11]Raclopride as Measured by PET Source

Dr. Usula Busto and colleagues at the University of Toronto used PET imaging to determine whether orally administered D-amphetamine would inhibit [C-11]raclopride binding to the same extent as intravenously administered D-amphetamine. Twelve healthy human volunteers were scanned at baseline and 2 hrs after D-amphetamine administration (n = 5); at baseline, 2 and 6 hrs post drug (n = 4); or at baseline, 2 and 24 hrs post drug (n = 3). The study found that orally administered D-amphetamine caused a reliable and prolonged [C-11]raclopride displacement, the magnitude of which is similar to that observed after intravenous administration. Orally administered D-amphetamine caused a significant decrease in [C-11]raclopride binding at 2 h (13% +/- 5%). Receptor availability was still decreased at 6 hrs (18% +/- 6%), even though physiological effects of amphetamine had completely returned to baseline. [C-11]Raclopride binding returned to baseline at 24 hrs. The percentage of [C-11]raclopride displacement was not correlated with plasma D-amphetamine concentrations. Cardenas, L., Houle, S., Kapur, S. and Busto, U.E. Synapse, 51(1), pp. 27-31, 2004.

Attributes of Long-term Heavy Cannabis Users: A Case-control Study

Dr. Harrison Pope and colleagues at McLean Hospital examined the attributes of long-term heavy cannabis users. Using a case-control design, they obtained psychological and demographic measures on 108 individuals, age 30-55, who had smoked cannabis a mean of 18,000 times and a minimum of 5,000 times in their lives and compared these heavy users to 72 age-matched control subjects who had smoked at least once, but no more than 50 times in their lives. Although no significant differences between the two groups were found with respect to reported levels of income and education in their families of origin, heavy users reported significantly lower educational attainment ($P<0.001$) and income ($P=0.003$) than the controls, even after adjustment for a large number of potentially confounding variables. The majority of heavy users (66-90%) also reported that cannabis had a 'negative effect' on cognition, memory, career, social life, physical health and mental health. Finally, heavy users also reported significantly lower levels of satisfaction than controls on several measures of quality of life. It remains to be determined why heavy cannabis users continue to smoke regularly for years, despite acknowledging these negative effects on their quality of life. Such an understanding may guide the development of strategies to treat cannabis dependence. Gruber, A.J., Pope, H.G., Hudson, J.I. and Yurgelun-Todd, D. Psychological Medicine, 33(8), pp. 1415-1422, 2003.

What Is Odd in the Oddball Task? Prefrontal Cortex Is Activated by Dynamic Changes in Response Strategy

Drs. Scott Huettel and Gregory McCarthy at Duke University used functional Magnetic Resonance Imaging (fMRI) in normal human subjects to determine whether the transient activation in the prefrontal cortex in response to infrequent target stimuli is due to selection of an infrequent response or to changes in response strategy. Subjects viewed a series of circles and squares that required left and right button presses, respectively. On 90% of trials ("standard" trials), the stimuli were presented in the same visual hemifield as the hand of response, but on 10% of trials ("strategy-change" trials) they were presented in the opposite visual hemfield. Behavioral results indicated that subjects developed a position-based response strategy during the standard trials, which was inhibited on the strategy-change trials. Significant activation to the infrequent strategy-change trials was found in the anterior middle frontal gyrus (MFG), the posterior inferior frontal gyrus (IFG) and adjacent insular cortex, and in the anterior cingulate gyrus (ACG). Activity within the MFG and ACG was much greater on error trials than on correct trials, while IFG activity was similar between error and correct trials. These results suggest that the dorsolateral prefrontal cortex (dlPFC) is associated with dynamic changes in the mapping of stimuli to responses (e.g. response strategies), independently of any changes in behavior. These findings provide a basis for interpreting the functional changes in these brain regions observed in substance abusers in brain imaging studies of drug action, craving, and response inhibition deficits. Huettel, S.A.and McCarthy, G. Neuropsychologia, 42(3), pp. 379-386, 2004.

Conformationally-Flexible Benzamide Analogues as Dopamine D-3 and Sigma(2) Receptor Ligands

Dr. Robert Mach and colleagues at Wake Forest University have determined the affinities of a new series of ligands for D2-like dopamine (D-2, D-3 and D-4) receptors using receptor binding assays. One compound was identified that bound with high affinity (Ki value = 2 nM) and moderate selectivity (30-fold) for D-3 compared to D-2 receptors. A number of the compounds also showed high affinity and excellent selectivity for sigma(2) versus sigma(1) receptors. These novel compounds may useful platforms for developing novel PET ligands for imaging D-3 receptors and sigma receptors. Mach, R.H., Huang, Y.S., Freeman, R.A., Wu, L., Vangveravong, S. and Luedtke, R.R. Bioorganic & Medicinal Chemistry Letters, 14(1), pp. 195-202, 2004.

Impaired Decision Making Related to Working Memory Deficits in Individuals with Substance Addictions

Drs. Antoine Bechara of University of Iowa and Eileen Martin of University of Illinois at Chicago examined whether impaired performance of substance abusers on a laboratory test of decision-making is related to impairments in working memory. Decision-making was indexed by the gambling task (GT) paradigm and working memory was indexed using a Delayed Non-Match to Sample task (DNMS). Impaired performance on the Gambling Task was seen in 11% of healthy control participants and 61% of substance abusers. Substance abusers performed significantly lower than controls on the DNMS task, irrespective of whether substance abusers were impaired on the GT, even if the substance abusers were matched with controls who were equally impaired on the GT. Substance abusers were impaired across all delay times on the DNMS task, suggesting the deficit may not lie in working memory per se, but rather in the "executive" processes. The results suggest that there are multiple distinct mechanisms of decision-making and inhibitory control and that substance abusers may be affected in any one or combinations of them. Bechara, A. and Martin, E.M. Neuropsychology, 18(1), pp. 152-162, 2004.

Event-Related Functional Magnetic Resonance Imaging of Reward-Related Brain Circuitry in Children and Adolescents

Dr. Julie Fiez and colleagues at the University of Pittsburgh used functional magnetic resonance imaging to investigate the brain reward systems of normal children and adolescents. Regions and time-courses of reward-related activity were similar to those observed in adults with condition-dependent BOLD changes in the ventral striatum and lateral and medial orbital-frontal cortex. Reward-related activity in these regions exhibited larger responses to positive than to negative feedback. These results provide further a baseline from which to understand the pathophysiology of reward-related disorders, such as substance abuse, in youth. May, J.C., Delgado, M.R., Dahl, R.E., Stenger, V.A., Ryan, N.D., Fiez, J.A. and Carter, C.S., Biological Psychiatry, 55(4), pp. 359-366, 2004.

Trend Detection Via Temporal Difference Model Predicts Inferior Prefrontal Cortex Activation During Acquisition of Advantageous Action Selection

Dr. Martin Paulus and colleagues at the University of California, San Diego used functional magnetic resonance imaging (fMRI) to investigate the role of the inferior prefrontal cortex in detecting changes in the association between an action and an outcome. FMRI scans were conducted on normal subjects while the performed a task based on the common game of Rock Paper Scissors (RPS) that required the development of an advantageous strategy over trials. Activations in the medial frontal gyrus (BA 10) left ventrolateral frontal gyrus (BA 11/47), and left pallidum were significantly higher during trials in which subjects acquired the advantageous action. The time course of individually derived trend detection functions was found to be time-locked to the hemodynamic changes in the inferior frontal gyrus. These findings are consistent with the hypothesis that the inferior prefrontal cortex computes a trend from previously experienced action-outcome sequences based on a value function derived from the temporal difference model. These findings have important implications for the understanding of substance abuse since substance abuse is characterized by an inability to alter drug-taking behavior based on adverse outcome, and since substance abusers have been found to exhibit impairment in activation of the inferior prefrontal cortex. Paulus, M.P., Feinstein, J.S., Tapert, S.F. and Liu, T.T. Neuroimage, 21(2), pp.733-743, 2004.

Artifactual fMRI Group and Condition Differences Driven by Performance Confounds

Drs. Hugh Garavan and Kevin Murphy of the Medical College of Wisconsin and Trinity College examined how differences in task performance across groups could confound functional imaging results. Specifically, the presence of disproportionate numbers of errors in one group may either introduce noise into the signal of interest or confound the signal of interest with an additional signal associated with specific error-related processes. To test this possibility two inhibitory task datasets involving young and aged subjects were analyzed twice using event-related techniques. In one analysis, correct and error response trials were analyzed separately. In the other analysis, error responses were treated as if they were correct. It was found that the activation maps differed considerably, with the inclusion of errors leading to many false positive and false negative activation clusters. These differences were not corrected with an analysis of covariance (ANCOVA) using performance as a covariate. Data simulations that varied the number of errors included in the analyses found that surprisingly few errors could significantly alter activation maps. Consequently, brain-imaging investigations that do not accommodate error contributions to functional signals are at risk of misinterpreting activation patterns. Given that studies have shown that substance abusers may exhibit higher error rates than normal subjects, these findings suggest that brain imaging studies of drug addiction that combine correct and incorrect trials in a single analysis need to be interpreted with caution. Murphy, K. and Garavan, H. Neuroimage, 21(1), pp. 219-228, 2004.

Modulation of Caudate Activity by Action Contingency

Dr. Julie Fiez and colleagues at the University of Pittsburgh used functional Magnetic Resonance Imaging (fMRI) to determine whether human striatal activation is driven solely by the hedonic properties of rewards or whether such activation is reliant on other factors, such as anticipation of upcoming reward or performance of an action to earn a reward. Normal human subjects performed a task during fMRI scans in which monetary gains and losses were displayed either 1) randomly in time, 2) following an anticipatory cue, or 3) following a button press response. Robust and differential activation of the caudate nucleus occurred only when a perception of contingency existed between the button press response and the outcome. This finding suggests that the caudate is involved in reinforcement of action potentially leading to reward, rather than in processing reward per se. Tricomi, E.M., Delgado, M.R. and Fiez, J.A. Neuron, 41(2), pp. 281-292, 2004.

Study Suggests Methamphetamine Withdrawal is Associated with Brain Changes Similar to Those Seen in Depression and Anxiety

Dr. Edythe London and her colleagues at the UCLA, UCI, and NIDA's IRP used positron emission tomography (PET), to compare glucose metabolism in the brains of 17 methamphetamine abusers (MA) who had stopped using the drug 4-7 days before their participation in the study, and 18 non-abusers. The PET scans identified regional brain differences in glucose metabolism. In MA, glucose metabolism was lower in the limbic and paralimbic regions that are linked to depressive disorders, depressed mood, and sadness and higher in brain regions linked to anxiety and drug cravings. The ACG appears dysfunctional in MA abusers compared to healthy subjects. The most robust group difference in rCMRglc was in the infragenual ACG, where MA abusers showed relative hypoactivity compared with control subjects, and the ventral striatum, where MA abusers showed relative hyperactivity. MA provided higher self-ratings of depression and anxiety than control subjects, and differed significantly in relative regional glucose metabolism: lower in the anterior cingulate and insula; higher in the lateral orbitofrontal area, mid- and posterior cingulate, amygdala, ventral striatum, and cerebellum. In MA, self-reports of depressive symptoms co-varied positively with relative metabolism in limbic regions (e.g., perigenual anterior cingulate gyrus and amygdala), and ratings of state and trait anxiety covaried negatively with relative activity anterior cingulate cortex and left insula. London, E.D., Simon, S.S., Berman, S.M., Mandelkern, M.A., Lichtman, A.M., Bramen, J., Shinn, A.K., Miotto, K., Learn, J., Dong, Y., Matochik, J.A., Kurian, V., Newton, T., Woods, R., Rawson, R., and Ling, W. Mood Disturbances and Regional Cerebral Metabolic Abnormalities in Recently Abstinent Methamphetamine Abusers. Archives of General Psychiatry, 61, pp. 73-84, January 2004.

Gray Matter Differences Between Smokers and Non-Smokers

Imaging studies have shown structural changes (i.e., ventricular enlargement and atrophy) in cigarette smokers when compared to nonsmokers. Functional differences appear in the lateral prefrontal cortex (PFC), anterior cingulate cortex (ACC), ventral striatum, and thalamus. Using magnetic resonance imaging, one group of NIDA supported researchers at UCLA evaluated brain regions for differences in gray matter between smokers and nonsmokers. Results showed smokers had smaller relative

cortical gray matter volumes and lower gray matter densities than nonsmokers in the prefrontal cortices at the dorsal and ventral lateral levels. Smokers also had smaller left dorsal ACC volumes and lower right cerebellar gray matter densities than nonsmokers. No regions were significantly larger or had significantly higher gray matter densities in smokers when Regions of Interest (ROI's) were compared with nonsmokers. There was also a positive association between pack-year smoking history (9-70 pack years) and gray matter density, with smokers who had a greater number of pack years having smaller cortical densities. Strengths of the study included the use of relatively stringent thresholds for significance, and similarities in study findings with the use of two independent methods of MRI analysis. Results indicate significant regional gray matter volume and density differences between smokers and nonsmokers, a potentially important association with smoking behavior that has not yet been widely studied. Brody, A.L., Mandelkern, M.A., Jarvik, M.E., Lee, G.S., Smith, E.C., Huang, J.C., Bota, R.G., Bartzokis, G. and London, E.D. Differences Between Smokers and Non-smokers in Regional Gray Matter Volumes and Densities. Biological Psychiatry, 55(1), pp. 77-84, January 2004.

Parametric Manipulation of Conflict and Response Competition Using Rapid Mixed-trial Event-related fMRI

Dr. B.J. Casey and colleagues investigated the fMRI activation patterns of a number of brain areas while subjects performed a task in which they were to signal an incompatibility in a presented stimulus. A goal in this study was to determine how the preceding context (i.e., the number of compatible or incompatible trials) affected the response to an incompatible stimulus and the regions of the brain that contributed to the response. It was found that reaction times increased as the number of preceding compatible trials increased and that an increase in activation in the anterior cingulate, dorsolateral prefrontal, and superior parietal cortices paralleled this change. The temporal aspects of the changes in activation differed, however, with increased activity in the anterior cingulate cortex preceding that in the dorsolateral prefrontal cortex, which, in turn, preceded that in the superior parietal cortex. These findings are consistent with the theory that the anterior cingulate cortex detects conflict, the superior parietal cortex controls attention to the stimulus and the prefrontal cortex modulates the latter's influence. Durston, S., Davidson, M.C., Thomas, K.M., Worden, M.S., Tottenham, N., Martinez, A., Watts, R., Ulug, A.M., and Casey, B.J. NeuroImage, 20, pp. 2135-2141, 2003.

Tissue Immunoassay for 19F-tagged 5-Hydroxytryptophan

Dr. Sherry Dingman and colleagues have synthesized a new tool for magnetic resonance imaging, L-6-heptafluorobutyryl-5-hydroxytryptophan, that has the potential for greatly increasing the detection of the neurotransmitter, serotonin. To assess whether this compound would be useful as an imaging agent, experiments were performed to determine if it crossed the blood brain barrier and became concentrated in vesicles in serotonergic neurons. This is a necessary step if the compound is to accumulate in sufficient quantity for *in vivo* detection. L-6-heptafluorobutyryl-5-hydroxytryptophan was administered in ova to domestic chicks (Gallus domestics) to investigate its bioavailability and uptake dynamics. It was found that the compound accumulated in higher quantities in neural and liver tissue than in heart tissue and that, in the brain, the midbrain contained more tagged compound than the frontal lobe, and the frontal lobe contained more than the occipital or cerebellum samples, thus demonstrating that the compound follows the pathway of endogenous serotonin. Dingman, S., Hurlburt, L., Thomas, R. and Guo, C. J Immunoassay Immunochem., 24(4), pp. 325-344, 2003.

Director's Report to the National Advisory Council on Drug Abuse - May, 2004

Research Findings - Research on AIDS and Other Medical Consequences of Drug Abuse - AIDS Research

Methamphetamine Dependence Increases Risk of Neuropsychological Impairment in HIV Infected Persons

HIV infection and methamphetamine (METH) dependence can each be associated with brain dysfunction. Little is known, however, about the cognitive effects of co-occurring HIV infection and METH dependence. NIDA researchers studied four groups of 200 participants: HIV+/METH, HIV-/METH, HIV+/No METH, and HIV-/ No METH. The groups were similar in age, education, and ethnicity, although there were significantly more females in the HIV-/No METH group. A comprehensive, demographically corrected neuropsychological battery was administered yielding a global performance score and scores for seven neuro-behavioral domains. Rates of global impairment were higher in the HIV+/METH (58%), HIV-/METH (40%) and HIV+/No METH (38%) groups compared to the HIV-/No METH (18%) group. A significant monotonic trend for global cognitive status was seen across groups, with the least impairment in the HIV-/No METH group and highest in the HIV+/METH+ group. The results indicate that HIV infection and METH dependence are each associated with neuropsychological deficits, which suggests that these factors in combination are associated with additive deleterious cognitive effects. This additivity may reflect common pathways to neural injury involving both cytotoxic and apoptotic mechanisms. Rippeth, J.D., Heaton, R.K., Carey, C.L., Marcotte, T.D., Moore, J.D., Gonzalez, R. and Wolfson, I.G., The HNRC Group. Methamphetamine Dependence Increases Risk of Neuropsychological Impairment in HIV Infected Persons. Journal of the International Neuropsychological Society. 10(1), pp.1-14, January 2004.

Effects of Hepatitis C virus on Neurological Injury HIV+ Methamphetamine Abusers

Given the increased risk for brain injury among methamphetamine abusers (MA), researchers at UCSD questioned whether the addition of Hepatitis C virus (HCV) infection would have a further detrimental effect. In a preliminary study, concentrations of the metabolites NAA, Cho, Ins, and Cr were compared in three groups: HCV+/METH, HCV+/No METH, HCV-/ METH and HCV-/No METH controls. It was expected that NAA would be lowest in HCV+/METH, followed by HCV-/METH and would be highest in HCV-/No METH with a selective increase in the inflammatory markers Ins and Cho in HCV+/METH only, reflecting putative inflammation due to HCV. The preliminary results indicate that HCV infection may worsen METH-associated neuronal injury in white matter. NAA was lower in the white matter region of the right anterior centrum semiovale in the HCV+/METH compared to controls and HCV-/Meth groups. In addition, reduction in this marker of neuronal integrity was correlated with worsening global neuropsychological deficit in the combined METH groups. However, Cho and Ins were not elevated in the HCV+/METH group. Larger studies should determine if this disagreement is due to inadequate power, or whether the combination of methamphetamine and HCV alters the neuropathogenesis of the latter. Taylor, M.J., Letendre, S.L., Schweinsburg, B.C., Alhasson, O.M., Brown, G.G., Gongvatana, A., Grant, I. and The HNRC. Hepatitis C Virus Infection is Associated with Reduced White Matter N-acetylaspartate in Abstinent Methamphetamine Users. Journal of the International Neuropsychological Society. 10(1) pp.110-113, January 2004.

Affects of HIV Infection Coupled with Hepatitis C Virus in Drug Abusers

Hepatitus C virus (HCV) can be detected in the brain and several investigators

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speculate that HCV has neuroinvasive properties with direct effects on cerebral function. 1MRS studies show that the basal ganglia and white matter of individuals with HCV have abnormal choline/creatine ratios, indicating CNS inflammation or infection and deficits in working memory and IPS have been documented similar to those seen in HIV seropositive individuals. Investigators at the University of Illinois, Chicago, conducted a preliminary study to examine whether HCV co-occurring with HIV exerts additive effects on brain dysfunction. One hundred fifty nine HIV +/- and/or HCV +/- male drug users participated in a reaction time (RT) version of the Stroop task which has been found to be sensitive to HIV-associated cognitive dysfunction. Results revealed a significant monotonic trend for poorer performance among subject groups ordered hierarchically according to infection status, (seronegative, monoinfected, dually infected) and this trend was significant for Congruent and Incongruent conditions. This finding is consistent with the hypothesized additive effects of HIV and HCV on neurocognition. Multiple Comorbid Conditions Appear to Confound Effects on Cognition. Martin, E.M., Novak, R.M., Fendrich, M., Vassileva, J., Gonzalez, R., Grbesic, S., Nunnally, G., and Sworowski, L. Stroop Performance in Drug Users Classified by HIV and Hepatitis C Virus Serostatus. Journal of the International Neuropsychological Society. 10(2), 298-300, March 2004.

Association of Drug Abuse with Inhibition of HIV-1 Immune Responses: Studies with Long-term of HIV-1 Non-Progressors

Recreational drug use has been proposed to affect the course of human immunodeficiency virus (HIV) infections. To investigate the effects of substance abuse on HIV infections, we compared virus-specific cytotoxic T lymphocyte (CTL) responses and the expression of IL-16, TGF-beta1, and CXCR4 in three different cohorts of HIV-infected patients: (1) long-term non-progressors (LT-NPs) of HIV infection who do not use recreational drugs; (2) non-drug using normal progressors (NPs), and (3) drugs using NPs. Our results show that LT-NPs manifest increased CTL activity and IL-16 expression and decreased expression of TGF-beta1 and CXCR4 compared to NPs, regardless of recreational drug usage. Furthermore, drug- using NPs showed significantly lower levels of CTL and IL-16 expression and increased TGF-beta1 and CXCR4 expression compared to non-drug using NPs. Our results suggest that recreational drug use may reduce CTL and IL-16 expression and increase the expression of TGF-beta1 and CXCR4, all of which may facilitate progression of HIV infection. Nair, M.P., Mahajan, S., Hewitt, R., Whitney, Z.R. and Schwartz, S.A. J. Neuroimmunol, 147 (1-2), pp. 21-25, 2004.

Fat Distribution in Relation to Drug Use, Human Immunodeficiency Virus (HIV) Status, and the Use of Antiretroviral Therapies in Hispanic Patients with HIV Infection

Human immunodeficiency virus (HIV)-associated fat-redistribution syndrome is still a subject of controversy. There is, as yet, little agreement on the definition, etiology, and prevalence of the syndrome. Many studies have examined medication or disease-related factors. Fewer studies have examined patient-related factors. Illicit drug use is an important risk factor for HIV infection, yet the role of drug use in fat distribution has not been well described. We examined fat distribution, measured by dual energy x-ray absorptiometry, in relation to drug use, smoking, and alcohol use in Hispanic patients with HIV infection and a control group of HIV-negative drug users. Our results suggest that neither drug use nor alcohol consumption is a predictor of fat distribution. However, among men, smoking was independently associated with less total fat, less trunk fat, and more appendicular fat. The role of patient-specific factors in the etiology of HIV-associated fat-redistribution syndrome warrants further investigation. Forrester, J.E. and Gorbach, S.L., CID, 37(suppl 2), s62-s68, 2003.

Determinants of Health Care Use Among Puerto Rican Drug Users

Researchers sought to identify factors accounting for differences in health care and drug treatment utilization between Puerto Rican drug users residing in two separate locations. Survey findings from 334 drug users in Puerto Rico and 617 in New York City showed that those in Puerto Rico were 6 times less likely than their counterparts in New York to have used inpatient medical services and 13 to 14 times less likely to have used outpatient medical services or methadone. They also were less likely to have health insurance or past drug treatment. After controlling for site-related variables, health insurance and previous use of physical or mental health services remained significant predictors of health care and drug treatment utilization. Although Puerto Rican drug users in Puerto Rico are not an ethnic minority, they reported significant disparities in health services use compared with Puerto Rican drug users in New York, and were less likely to use physical health services, mental health services, and drug treatment. By contrast, drug users in East Harlem reported more chronic

medical problems and more HIV/AIDS diagnoses, that is, more health care needs, than did Puerto Ricans residing in Puerto Rico. This might explain the differences in utilization of physical health care between the two study groups. Puerto Rican islanders, although significantly younger, were more likely to be drug injectors and to inject drugs more frequently, behaviors related to HIV/AIDS and other infectious disease. Puerto Rican drug users in Puerto Rico were also less likely to have health insurance than were their counterparts in New York. This may account for the significant lack of health care utilization among drug users, and has implications for reducing drug use and HIV/AIDS risk behaviors in Puerto Rico and in many sites on the US mainland. Robles, R., Matos, T., Col—n, H., Deren, S., Reyes, J., Andia, J., Marrero, C. and Sahai, H. Determinants of Health Care Use Among Puerto Rican Drug Users in Puerto Rico and New York City. Clin Infect Dis, 37(Suppl 5), S392-S403, 2003.

Designing an HIV Counseling and Testing Program for Bathhouses

Researchers describe the process through which HIV testing was initiated at bathhouses for high risk men who have sex with men in Seattle and make recommendations for the optimal design of an HIV counseling and testing program in the bathhouse environment. They examined logistical considerations that had previously been identified as influencing the initiation, effectiveness, and maintenance of HIV testing programs in bathhouses for men who have sex with men, including building alliances with community agencies, hiring and training staff, developing techniques for offering testing, and providing options for counseling, testing, and disclosure of results. The design included ways to provide client support and follow-up for partner notification and treatment. Bathhouse clients were found to engage in multiple high-risk behaviors: of 437 clients tested, 159 (36%) reported past month drug use and 118 (27%) reported past month binge drinking; 36% reported engaging in more sexual risks while drinking alcohol or taking drugs; 77% reported 4 or more sex partners since their past HIV test; and 25% reported engaging in unprotected sex during the past 2 months. The researchers found that early detection of HIV infection and HIV prevention can be achieved for some high-risk MSM through an acceptable and accessible HIV counseling and testing program in bathhouses. Spielberg, F., Branson, B., Goldbaum, G., Kurth, A. and Wood, R. Designing an HIV Counseling and Testing Program for Bathhouses: The Seattle Experience with Strategies to Improve Acceptability. Homosexuality, 44(3/4), pp. 203-220, 2003.

HIV Prevention Among Drug Users: An International Perspective from Thailand

All too often in reviews of HIV prevention needs, the role of drugs is summarily dismissed, especially in contexts where the heterosexual epidemic is the primary mode of transmission. Substance use and abuse, particularly injection drug use, play a paramount role in maintaining the heterosexual spread of HIV, as well as in maintaining epidemics where heterosexual spread of the infection has come under control due to prolonged and concerted HIV prevention activities. This paper presents several themes to place in the developing country context what we have learned about substance use-related HIV prevention and the special problems of HIV interventions. First, the paper briefly examines the international production and trade routes of opium and heroin, and their role in the HIV epidemic, as well as the importance of substance abuse in heterosexual epidemics. Second, it presents a case study of HIV control that has been internationally acclaimed as one of the few successes in achieving a meaningful reduction in heterosexually transmitted HIV--Thailand. The Thai response to the injection drug use HIV epidemic, however, has been muted, and its impact on future epidemic dynamics is evaluated. It concludes with a discussion of existing research gaps concerning the role of drug use in HIV epidemics in the developing world, with Thailand as an example. Celentano, D. HIV Prevention Among Drug Users: An International Perspective from Thailand. J Urban Health, 80(4), suppl 3, pp. 97-105, 2003.

HIV Prevention Among IDUs: The Need for Integrated Models

Opportunistic infections (OIs) were first recognized among injection drug users (IDUs) in New York City in 1981. By the mid-1980s, OIs had become associated with HIV infection and attention began to focus on efforts to prevent HIV transmission among IDUs. Since then, a range of prevention strategies have been implemented and evaluated in an attempt to reduce the spread of HIV infection among drug users. Evaluations of these strategies have provided substantial evidence of effectiveness, and have helped to inform network-based and structural interventions. Despite the cumulative empirical evidence, however, research findings have yet to be widely disseminated, adopted, and implemented in a sustained and integrated fashion. The

reasons for this are unclear, but point to a need for improved communications with program developers and community planners to facilitate the implementation and evaluation of integrated intervention strategies, and for collaborative research to help understand policy, legal, economic, and local barriers to implementation. This paper reviews the research findings on core strategies of HIV prevention that have targeted IDUs and concludes with a discussion of the potential association between substance abuse treatment completion and reductions in risky sexual behaviors among drug users. Metzger, D. and Navaline, H. HIV Prevention Among IDUs: The Need for Integrated Models. J Urban Health, 80(4), suppl 3, pp. 59-66, 2003.

Risk Reduction Among Drug-Using Men Who Have Sex With Men

This paper focuses on sexual risk reduction interventions for HIV-positive men who have sex with men (MSM), the largest group of HIV-positive individuals in the U.S. It reviews factors associated with high-risk behaviors, and discusses some findings from research with HIV-positive methamphetamine users, including: 1) data from a small qualitative study and its implications for the development of new interventions; and 2) baseline data from an ongoing large-scale study of the efficacy of a theory-based sexual risk reduction intervention for HIV-positive methamphetamine-using MSM. Currently, less than one percent of the total U.S. population is infected with HIV. Targeting behavioral interventions to this smaller group of HIV-positive individuals has the potential for making cost-effective reductions in the number of new infections. In this era of highly active antiretroviral therapy (HAART), interventions for HIV-positive individuals are more critical than ever to address the unique challenges and issues they face regarding disclosure and partner notification, use of HAART and sexual risk behavior, and HIV-related stigma. Patterson, T. and Semple, S. Sexual Risk Reduction Among HIV-Positive Drug-Using Men Who Have Sex With Men. J Urban Health, 80(4), suppl 3, pp. 77-87, 2003.

Sex Work and Drug Use in a Subculture of Violence

In this paper, researchers examine the subculture of violence thesis as it relates to female street sex workers in Miami. Interview and focus group methods were used to study the intersection of childhood trauma, drug use, and violent victimization among 325 women. Using targeted sampling, crack- and heroin-using sex workers were recruited through street outreach into an HIV-prevention research program. Interviews used standard instrumentation and focused on drug-related and sexual risk for HIV, sex work, violence, childhood trauma, and health status. Past drug use among the women was found to be substantial, and large percentages reported high levels of substance use in the past month, including use of alcohol. Nearly half of the respondents reported physical (44.9%) and/or sexual (50.5%) abuse as children, and over 40% experienced violence from clients in the prior year: 24.9% were beaten, 12.9% were raped, and 13.8% were threatened with weapons. Consistent relationships between historical and current victimization suggest that female sex workers experience a continuing cycle of violence throughout their lives. Surratt, H., Inciardi, J., Kurtz, S. and Kiley, M. Sex Work and Drug Use in a Subculture of Violence. Crime and Delinquency, 50(1), pp. 43-59, 2004.

Sharing of Non-Injection Drug Use Implements as a Risk Factor for Hepatitis C

Researchers examined sharing of non-injection drug implements as a risk factor for hepatitis C (HCV) infection among women drug users (n=123) with no history of drug injection. Participants were street-recruited from East Harlem, New York City, between October 1997 and June 1999. They were administered a survey measuring risk factors for HCV. Prevalence of HCV and HIV infections was 19.5% and 14.6%, respectively. Multiple logistic regression determined significant associations between sharing non-injection drug use implements and HCV infection. "Ever shared both oral and intranasal non-injection drug implements" was independently associated with HCV infection (OR 2.83, CI 1.04, 7.72; p=0.04); "ever shared non-injected heroin implements with an injector" was a trend (OR 3.06, CI .85, 10.79; p=0.08). The strongest association between sharing non-injection drug use implements and HCV infection was found among HIV positive individuals (chi square=8.8, p<0.01). The strong association between HIV and HCV seropositivity among women reporting no history of injecting drugs indicates that HIV may facilitate the transmission of HCV through non-injecting routes. These findings suggest that sharing non-injection drug implements, either for intranasal or oral drug use, may be a risk factor for HCV and may explain the higher than expected prevalence of HCV infection observed in this sample. Tortu, S., McMahon, J., Pouget, E. and Hamid, R. Sharing of Non-Injection Drug Use Implements as a Risk Factor for Hepatitis C. Subst Use & Misuse, 39(2), pp. 211-224, 2004.

The Dynamics of Substance Use and Sex Networks in HIV Transmission

This paper reviews the research literature to identify mechanisms that may underlie HIV heterosexual transmission in developed and developing countries; examines linkages between sex and substance use HIV transmission risks; and describes sex network measurement issues relevant to developing HIV preventive interventions. It describes how the research contributions of developed countries to understanding sexually transmitted HIV have long recognized the influence of substance use and sex networks. By comparison, research in developing countries has contributed significantly to the environmental and biological understanding of HIV sexual transmission dynamics, but few studies have explicitly examined the relationship between HIV sex risk and substance use in these contexts. Given that HIV sexual transmission dynamics are linked to interactions between substance use and sex network factors, it is critical to examine substance use as a framework within which HIV sexual transmission occurs, particularly in developing countries that focus on either substance use or sex-mediated HIV transmission though not on both. The characteristics of network members and structural relationships within and across sex networks have identifiable roles in the spread of HIV. These characteristics and relationships are measurable at the individual level and can contribute substantively to improving network and community surveillance. They are also essential for the development and evaluation of network- and community-based interventions. Miller. M. The Dynamics of Substance Use and and Sex Networks in HIV Transmission. J Urban Health, 80(4), suppl 3, pp. 88-96, 2003.

The Role of Sexual Transmission of HIV Among IDUs and Non-Injecting Drug Users

Many early studies of injecting drug users (IDUs) suggested that most HIV infections in this population were due to needle sharing, and that sexual transmission was negligible or was overshadowed by parenteral routes. A few of the early studies suggested a potentially important role for heterosexual transmission, but these tended to be limited to cross-sectional data or had only a few years of prospective follow-up. Studies of sexual risk factors for HIV infection among non-injecting drug users are similarly sparse. Recently, investigators prospectively examined both drug-related and sexual risk factors for HIV seroconversion among male and female IDUs with an adequate number of person-years to identify statistically significant associations. Other studies among never and former IDUs have identified associations suggesting that sexual transmission accounts for a substantial number of HIV seroconversions in these populations. Herein, highlights are discussed from recent investigations among IDUs in Baltimore, Maryland and corroborating findings from the literature. Results from a ten-year prospective analysis of the ALIVE study and an analysis of the REACH studies spanning a seven year period indicate that sexual risk factors for HIV infection are important in both female and male IDUs. These findings underscore the need for HIV interventions among drug users that incorporate sexual risk reduction. Based on the existing literature, a narrow focus on injection-related risks is an ineffective prevention strategy. Interventions that target specific subgroups of high-risk IDUs, such as men who have sex with men and inject drugs, sex worker-IDUs and HIV-infected IDUs deserve special attention. Strathdee, S. and Sherman, S. The Role of Sexual Transmission of HIV Among IDUs and Non-Injection Drug Users. J Urban Health, 80(4), suppl 3, pp. 7-14, 2003.

The Social Course of Drug Injection and Sexual Activity Among YMSM and Other High-Risk Youth

The cumulative epidemiological literature indicates that many injecting drug users (IDUs) initiate injection as a mode of drug administration during late adolescence or early adulthood. Recent studies have shown that IDUs are often exposed to viral infections relatively early in the course of injection, highlighting the importance of understanding this initiation process for both epidemiology and prevention. Epidemiological evidence similarly suggests that at least some youth populations, most notably young men who have sex with men (YMSM), are at substantial risk for exposure to HIV and other sexually transmitted diseases (STDs) from early sexual activity. Despite the importance of this issue for both epidemiology and prevention, however, there is surprisingly little information available on the social course of injection initiation, including the individual, social, or ecological factors that might mitigate or exacerbate transmission risks within the critical phase of early injection drug use. Similarly, little is known about the ways that YMSM and other high-risk youth understand risk, the kinds of exchanges and relationships in which they participate in the context of initiating sexual activity, or how drug use is operant in these exchanges and early sexual experiences. In this paper, researchers explore key

dimensions of the early initiation of injection and sexual risk, and discuss how a social network approach might be instrumental in understanding the social course of drug injection and sexual activities among youth and young adult populations. Clatts, M., Goldsamt, L., Neaigus, A. and Welle, D. The Social Course of Drug Injection and Sexual Activity Among YMSM and Other High-Risk Youth: An Agenda for Future Research. J Urban Health, 80(4), suppl 3, pp. 26-39, 2003.

Transmission of STIs/HIV at the Partnership Level: Beyond Individual-Level Analyses

Mathematical modeling of transmission dynamics of sexually transmitted infections (STIs) and HIV has considerably advanced HIV research by highlighting the importance of certain types of partnerships in epidemic spread. Concurrent partnerships, defined as a sexual partnership in which one or more of the partnership members have other sexual partners while continuing sexual activity with the original partner, have been shown to play a fundamental role in potentiating the spread of STIs and HIV. Risk behaviors such as concurrency and sex without condoms as well as STI/HIV prevalence vary with physical, social, and emotional factors within partnerships. The efficiency of HIV/STI transmission appears to vary across types of concurrent partnerships according to the differing dynamics within them. Previous research on partnership dynamics has improved our understanding of the multidimensional aspects of sexual partnering, but little is understood of how these aspects of sexual partnering interact and increase risks for HIV, nor how types of partnerships, partnership dynamics, and concurrency work together to affect both the behavior of condom use and the biological transmission of disease. In this paper, researchers discuss the need to extend our understanding of concurrency to include partnerships among men who have sex with men (MSM) and to differentiate between types of partnerships and to develop interventions to modify risk within partnerships. They also introduce a conceptual framework that reflects how individual and partner characteristics influence partnership dynamics that, in turn, influence risk behaviors, such as concurrency and not using condoms, and associated risks for STIs and HIV. Gorbach, P. and Holmes, K. Transmission of STIs/HIV at the Partnership Level: Beyond Individual-Level Analyses. J Urban Health, 80(4), suppl 3, pp. 15-25, 2003.

Contextual Determinants of Drug Use Risk Behavior: A Theoretical Framework

Over the past two decades, public health research has emphasized the role of individual risk behaviors, primarily injection and sexual risk behaviors, in the spread of HIV infection. Much less emphasis has been given to understanding the determinants of these risk behaviors. Although individual characteristics are partly responsible for risky injection and sexual behaviors, they do not explain all the inter-personal variability in risk behavior. Contextual factors associated with HIV risk behavior may include structural factors (e.g., availability of services), social norms and attitudes (e.g., social trust), disadvantage (e.g., neighborhood socio-economic status), and features of the physical environment (e.g., housing quality). This paper presents a conceptual framework that incorporates some of the key contextual domains that may affect drug use behavior. It also presents data from a study of street-recruited drug users as an example of the relations between social contextual factors and frequency of injecting drug use, and discusses some methodological challenges in the study of contextual determinants of drug use behavior. Galea, S., Ahern, J. and Vlahov, D. Contextual Determinants of Drug Use Risk Behaviors: A Theoretic Framework. J Urban Health, 80(4), suppl 3, pp. 50-58, 2003.

Social Network Correlates of Self-Reported Non-Fatal Overdose

The leading cause of death among heroin users is drug overdose. This study examined the relationship between history of self-reported drug overdoses and social network characteristics among cocaine and opiate users. Data were from cross-sectional surveys administered from March 2001 through February 2003 as part of follow-up of an experimental network oriented HIV prevention intervention. A total of 838 participants with histories of cocaine and opiate use completed the survey. Several social network variables were found to be significantly associated with drug overdose in the prior 2 years, including larger number of network members who were injection drug users and more conflicts among the network members. Even after controlling for age, gender, frequency of injection drug and alcohol use, and health status, network variables continued to have a strong association with history of recent overdose. Specifically, the number of injectors in the network and the number of networks that the index had conflict with was associated with recent overdose. Social network factors have been found to be associated with other health conditions among drug users, such as HIV and STIs, and behaviors such as sharing needles and using

shooting galleries. The data suggest that large drug networks should be targeted for drug overdose prevention interventions. For example, key network members or several network members could be trained in overdose prevention and in treating overdose victims with Naloxone (Narcan). Using peer-based prevention models have been shown to be successful among drug users in reducing needle sharing behavior. Latkin, C., Wei, H. and Tobin, K. Social Network Correlates of Self-Reported Non-Fatal Overdose. Drug and Alcohol Depend., 73(1), pp. 61-67, 2004.

Director's Report to the National Advisory Council on Drug Abuse - May, 2004

Research Findings - Research on AIDS and Other Medical Consequences of Drug Abuse - Non-AIDS Research

Relation of Coronary Artery Calcium to Left Ventricular Mass in African-Americans

Both coronary artery calcium (CAC) deposits and increased ventricular (LV) mass are important risk factors for coronary heart disease, but the relation between these two factors has rarely been studied. The investigators (Dr. Shenghan Lai and his colleagues at Johns Hopkins) examined the correlation of coronary artery calcium and left ventricular mass in 159 young to middle-aged African-Americans, and found that the average left ventricular mass indices were bigger in the CAC-positive groups than in CAC-negative groups in both genders [p=0.0004 in men and p=0.08 in women]. Studies are in progress to examine if drug abuse (e.g., cocaine) has an impact on cardiovascular disease (coronary artery calcium/ventricular function) in African-Americans. Tong, W., Lima, J.A., Lai, H., Celentano, D.D., Dai, S. and Lai, S. Am J. Cardiol., 93, pp. 490-492, 2004.

Assessment of Neurobehavior in Drug-Exposed and High-Risk Infants

A recently-published supplement to the journal Pediatrics provides information and data for the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS). The NNNS was developed to assess the neurobehavior of drug-exposed and high-risk infants, as part of the multisite, prospective longitudinal study of in-utero drug exposure, the Maternal Lifestyle Study (MLS). MLS has been jointly-supported by NICHD and NIDA since it began in the early 1990s. The NNNS was developed because of a concern that existing instruments were not sensitive to the neurobehavioral effects of prenatal drug exposure and for infants at risk. The Pediatrics supplement provides the rationale for the NNNS and its procedures. It also includes NNNS data from the MLS and from a low-risk term sample, as well as a discussion of clinical uses. Lester, B.M., and Tronick, E.Z. (Eds.). The Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS). Pediatrics, 113(3), pp. 631-699, 2004.

Severity of Prenatal Cocaine Exposure and Child Language through Age 7 Years

Results of data analyses from a longitudinal cohort study at the University of Miami suggest that greater severity of prenatal cocaine exposure is associated with increased (although modest) deficits in aptitude for language performance, but not with a trajectory of language development through 7 years of age. Within the framework of the latent growth curve analysis utilized, the intercept of the language growth curve was interpreted as reflecting a relatively time-invariant aptitude for language performance, and the slope was interpreted as indicating a time-varying trajectory of language performance. Language was assessed at ages 3, 5, and 7 years. The observed association was independent of multiple other possible sources of variation in language development, including the child's intellectual functioning and language stimulation in the home. Severity of prenatal cocaine exposure was characterized using a construct combining maternal self-report of cocaine use during pregnancy with maternal and infant bioassays. The statistical analytical model included gender, and prenatal alcohol, tobacco, and marijuana among the covariates. The researchers note that although the study has many strengths, the sample is relatively homogeneous (e.g., full-term, relatively healthy African-American children residing in socially disadvantaged inner-city neighborhoods), and caution should be exerted in generalizing the cocaine-language estimate to other populations or settings. Furthermore, they call for further investigation in other scientifically rigorous

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studies with sufficient sample sizes, in order to understand mechanisms by which prenatal cocaine exposure may affect child language functioning. Bandstra, E.S., Vogel, A.L., Morrow, C.E., Xue, L., and Anthony, J.C. Severity of Prenatal Cocaine Exposure and Child Language Functioning Through Age Seven Years: A Longitudinal Latent Growth Curve Analysis. Substance Use and Misuse, 39(1), pp. 25-59, 2004.

Relationships between Marijuana Exposure and Response Inhibition in 18-22 Year-Olds

Researchers from the Ottawa Prenatal Prospective Study (OPPS) have reported initial fMRI results in an investigation of the effects of prenatal exposure to marijuana, and current use of marijuana, on response inhibition in 18-22 year-old study participants. OPPS participants have been assessed longitudinally on behavioral outcomes at multiple times since birth. Those who were prenatally-exposed to marijuana have been found to show differential performance, relative to non-exposed participants, on an aspect of executive functioning that involves inhibition of prepotent responses. In light of literature showing associations between executive functioning and maturation of the prefrontal cortex, the purpose of the fMRI analyses was to examine the putative association between prefrontal cortex activity of young adults and prenatal exposure to marijuana. fMRI analyses were also carried out relative to current marijuana use among the study participants. Thirty-five OPPS subjects were imaged using a 1.5 T Siemens MR scanner. A go/no go task was used to measure response inhibition. Results suggest that both prenatal exposure and current use were related to neurophysiological aspects of response inhibition. Prenatal marijuana exposure was most related to increased activity in left dorsolateral-prefrontal-cortex (DLPFC), and attenuated right DLPFC activity. Current marijuana use was most associated with right DLPFC activity. This is the first report of fMRI data relative to response inhibition in young adults prenatally exposed to marijuana. These investigators are continuing their fMRI explorations in this cohort. Smith, A., Fried, P., Hogan, M., and Cameron, I. The Effects of Prenatal and Current Marijuana Exposure on Response Inhibition: A Functional Magnetic Resonance Imaging Study. Brain and Cognition, 54(2), pp. 147-149, 2004.

Director's Report to the National Advisory Council on Drug Abuse - May, 2004

Research Findings - Epidemiology and Etiology Research

Community Epidemiology Work Group

The 55th meeting of the Community Epidemiology Work Group (CEWG), chaired by Moira O'Brien, DESPR, was held in Atlanta, Georgia, on December 9-12, 2003. The CEWG is composed of researchers from 21 metropolitan areas of the United States who meet semiannually to report on patterns and trends of drug abuse in their respective areas, emerging drugs of abuse, vulnerable populations and factors that may place people at risk for drug abuse, and negative health and social consequences. Reports are based on a variety of drug abuse indicator data such as morbidity and mortality information, treatment data and local and State law enforcement data. Additional sources of information include criminal justice, correctional, medical and community health data, local and State survey information, and findings from qualitative research studies.

Polydrug abuse, where different drugs are used in combination or sequence to achieve specific desired effects, was identified during meeting discussions as a significant and troubling trend across localities. Examples of polydrug abuse reported include the mixture of MDMA and Viagra known as "sextasy" (Atlanta), combination of PCP, opium, and crystal methamphetamine known as "red devil dust" (Texas), and the practice by some dealers of pulverizing OxyContin pills and mixing the powder with heroin to enhance the high (New York City).

Methamphetamine abuse was identified as an issue of great concern by CEWG members. Abuse indicators remain high in Hawaii and west coast areas, and show methamphetmine use is spreading eastward. Seizures of methamphetamine labs were reported in most CEWG areas/States, and reports of methamphetamine abuse came from as fareast and south as Miami, New Orleans, New York and Philadelphia. "Ice," the most potent form, has increased in availability in areas of North Texas, Minneapolis, Phoenix, and San Diego.

Cocaine/Crack continues to be widely available and a major problem in most CEWG areas. Rates of ED mentions per 100,000 population in 2002 were higher for cocaine than for any other drug in 17 CEWG areas. Two exceptions were San Francisco and Newark where rates of heroin mentions were higher than those for cocaine. In Philadelphia, crack users report use of the drug in combination with malt liquor, or other drugs including marijuana, heroin, or alprazolam.

Heroin abuse indicators remained relatively stable in most CEWG areas, continuing at high levels in particular areas and relatively low levels in others. Heroin indicators tended to be highest in northeastern/mid-Atlantic areas where high purity powder from South America was available. However, heroin indicators were also relatively high in two west coast areas (San Francisco and Seattle) where black tar heroin predominates and purity levels are comparatively low.

Opiates (other than heroin) abuse indicators continue to trend upward. Rates of ED narcotic analgesic/combinations mentions per 100,000 population rose significantly in 14 CEWG areas from 2000 to 2002 with rates particularly high in Baltimore, New Orleans, Boston, Detroit and Seattle.

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Marijuana abuse indicators remained at high, but fairly stable levels, in most CEWG areas. In 2002, rates of marijuana ED mentions per 100,000 populations were highest in Philadelphia (150), Detroit (146), St. Louis (124) and Boston (119). From 2001 to 2002, rates of marijuana ED mentions increased significantly in three areas (Baltimore, Miami and Newark), but decreased significantly in four (Chicago, Dallas, San Francisco, and Seattle).

MDMA (methylenedioxymethamphetamine) or ecstasy abuse showed some evidence for declines in use and/or consequences. MDMA ED mentions decreased significantly in nine CEWG areas from 2001 to 2002 and increased significantly between 2001 and 2002 in only one CEWG area: New Orleans. Concern remains regarding the spread of use to new populations (increased use reported among African-American and Hispanic populations in Atlanta, Chicago, New York, Texas, and Washington, DC), use of MDMA in combination or sequence with other drugs, and "unintentional" combinations or unknown content of pills taken since ecstasy tablets often contain drugs other than MDMA and users may not know what drug or drugs they are taking.

PCP abuse was identified as a trend emerging in some metropolitan areas that bears watching. In 2002, rates of PCP ED mentions per 100,000 increased significantly for the coterminous US and in 6 CEWG areas including Washington, DC (31), Philadelphia (25), Baltimore (5), Dallas (4), Newark (7) and St. Louis (6). A high DAWN ED was also reported for Los Angeles (11). A panel was convened during the December 2003 CEWG meeting to explore the issue of PCP abuse. A DEA representative provided current information on PCP production and distribution in the US. CEWG members from Washington DC and Los Angeles discussed PCP abuse in their respective areas. A presentation by a NIDA grantee conducting research in Hartford, CT, described the emergence of PCP abuse in the Hartford area. Panel presentations and discussions reported that PCP in liquid form is often combined with other substances, including formaldehyde, and then added to marijuana or tobacco cigarettes. Often users do not know the exact contents of the substance they are using. The panel stressed the importance of coordinating information from police labs in localities where PCP is reported as a problem to learn more about the actual ingredients of substances purported to be or to include PCP. The panel stressed the need for educational strategies to alert users and their networks to the risks of using PCP and PCP-related substances.

Neurobehavior Disinhibition in Childhood Predicts Substance Use Disorder in Young Adulthood

The development of substance use disorder (SUD) was prospectively investigated in 66 boys having fathers with SUD and 104 boys having fathers with no adult psychiatric disorder. Evaluations were conducted to determine the context in which neurobehavior disinhibition in relation to parental SUD, parental neglect of the child and child's social maladjustment culminated in a DSM-III-R diagnosis of SUD. A neurobehavior disinhibition latent trait reflecting prefrontal cortex disturbance was derived using indicators of behavior undercontrol, affect dysregulation and executive cognitive functioning in the boys when they were 10-12 and again at 16 years of age. The data were analyzed to determine whether the score on the neurobehavior disinhibition construct mediates the association between father's and mother's SUD and son's SUD. Several key results emerged. First, SUD in the mother and father predicted neurobehavior disinhibition in the son. Second, the neurobehavior disinhibition score of the sons at ages 10-12 predicted SUD at age 19. Third, neurobehavior disinhibition, in conjunction with social maladjustment and drug use frequency, mediated the association between paternal and maternal SUD and son's SUD. Fourth, neurobehavior disinhibition was unrelated to neglect of the child by either the father or mother; however, paternal but not maternal neglect at age 10-12 predicted SUD at age 19. These findings suggest that prefrontal cortex dysfunction contributes to SUD liability. Tarter R.E., Kirisci L., Habeych M., Reynolds M. and Vanyukov M. Neurobehavior Disinhibition in Childhood Predisposes Boys to Substance Use Disorder by Young Adulthood: Direct and Mediated Etiologic Pathways. Drug and Alcohol Dependence, 73, pp. 121-132, 2004.

SUD Among Mental Disorders Increases Risk for Later Depression

The authors used retrospective psychiatric data from population-based samples of

men and women to assess degree and time periods of risk for major depressive disorder posed by prior or co-occurring psychiatric disorder. The disorders studied included psychoactive substance use disorders, alcohol dependence, generalized anxiety disorder, panic disorder, phobia, and conduct disorder. Although the highest risk for depression was associated with co-occurring disorder, elevated risk for depression was associated with prior episodes of any of the studied disorders, regardless of the length of time from the first disorder to depression. Thus, SUD, like the anxiety and conduct disorders also studied, poses a lifetime increase in risk for depression. This suggests that the public health impact of preventing substance use disorders may extend to a possible impact on rates of depression, which is also a very costly and debilitating disorder. Hettema, J.M., Prescott, C.A., and Kendler, K.S. The Effects of Anxiety, Substance Use and Conduct Disorders on Risk of Major Depressive Disorder. Psychological Medicine, 33, pp.1423-1432, 2003.

Family Transmission of Marijuana Use, Abuse, and Dependence

This is the first family study to specifically examine the familial aggregation of marijuana use, abuse, and dependence. Subjects included adolescents recruited from residential and day treatment programs for youths with conduct and substance problems, matched controls, and all available family members. A total of 2,546 individuals from 781 families were interviewed with structured research instruments. Risk ratios of relatives of clinical cases were calculated compared with controls, for marijuana use, abuse, or dependence. Spousal, parent-offspring, and sibling correlations and the proportion of variance attributable to parent-offspring transmission were estimated using structural equation modeling. The results indicated that, for all three measures, the risk ratios were elevated in the family members of clinical probands, with estimates ranging from 1.5 to 3.3. Spousal correlations ranged from 0.33 to 0.70. Parent-offspring correlations ranged from 0.17 to 0.30. Sibling correlations ranged from 0.34 to 0.44. The proportion of variance attributable to factors transmitted from parents to children ranged between 25% and 44%. Results demonstrate significant parent-offspring transmission of risk, sibling environmental influences, and assortative mating for all three levels of marijuana use. Hopfer C.J., Stallings M.C., Hewitt J.K., and Crowley T.J. Family Transmission of Marijuana Use, Abuse, and Dependence. Journal of the American Academy of Child and Adolescent Psychiatry, 42, pp. 834-834, 2003.

Substance Use Among Adults 35 Years of Age: Prevalence, Adulthood Predictors, and Impact of Adolescent Substance Use

Using national longitudinal panel data from the Monitoring the Future study, this study examines the prevalence of substance use among American adults aged 35 years, and assesses the impact of adolescent substance use and adulthood predictors. Logistic regressions were conducted to assess the impact of demographics, life experiences, and adolescent substance use on smoking, heavy drinking, prescription drug misuse, marijuana use, and cocaine use at 35 years of age. Results indicate that factors related to increased likelihood of substance use include high school use, unemployment, and non-custodial parenthood. Lower use was associated with being female, a college graduate, a professional, married, or a custodial parent. Among those aged 35 years, substance use was still fairly prevalent and was a function of adulthood roles, experiences, and previous use. Merline A.C., O'Malley P.M., Schulenberg J.E., Bachman J.G. and Johnston L.D. Substance Use Among Adults 35 Years of Age: Prevalence, Adulthood Predictors, and Impact of Adolescent Substance Use. American Journal of Public Health, 94(1), pp. 96-102, 2004.

How Academic Achievement, Attitudes, and Behaviors Relate to the Course of Substance Use During Adolescence: A 6-Year, Multiwave National Longitudinal Study

Self-report data regarding alcohol, cigarette, and marijuana use were collected biennially from ages 14 to 20 in a nationally representative panel sample of adolescents (N = 1,897) from the Monitoring the Future study. Growth curve analyses were performed using hierarchical linear modeling to consider psychosocial background, motivation and school attitudes, and parental and peer influences at age 14 as predictors of concurrent substance use and change in substance use. Results indicate that school misbehavior and peer encouragement of misbehavior were positively associated with substance use at age 14 and with increased use over time; school bonding, school interest, school effort, academic achievement, and parental help with school were negatively associated. The protective effects of positive school attitudes and perceptions of high status connected to academics were stronger for low-achieving compared with high-achieving youth. Implications for a developmental perspective on substance use etiology and prevention are discussed. Bryant A.L.,

Schulenberg J.E., O'Malley P.M., Bachman J.G., and Johnston L.D. How Academic Achievement, Attitudes, and Behaviors Relate to the Course of Substance Use During Adolescence: A 6-Year, Multiwave National Longitudinal Study. Journal of Research on Adolescence, 13(3), pp. 361-397, 2003.

Common Predictors of Cigarette Smoking, Alcohol Use, Aggression, and Delinquency Among Inner-City Minority Youth

The present study examined the prevalence rates and common predictors of substance use, aggression, and delinquency among inner-city minority youth entering middle school. A survey was administered to 6th grade students (N = 5423) from 42 New York City schools. Aggressive behaviors were reported most frequently, followed by delinquent behaviors, alcohol use, and cigarette smoking. Across all behavioral outcomes, social and environmental influences explained the largest proportion of variance, followed by individual characteristics and skills, bonding to conventional institutions, and demographic variables. For the majority of predictor variables there was substantial overlap in patterns of prediction across outcomes. These findings indicate that several factors that correspond to the predominant psychosocial theories of adolescent development explain variation across different problem behavior outcomes among inner-city minority youth. Griffin, K.W., Botvin, G.J., Scheier, L.M., Doyle, M.M., and Williams, C., Common Predictors of Cigarette Smoking, Alcohol Use, Aggression, and Delinquency Among Inner-City Minority Youth. Addictive Behaviors, 28, pp. 1141-1148, 2003.

Stress Exposure, Race, and Young Adult Male Crime

A recent revision of strain theory, Robert Agnew's (1992) general strain theory (GST), has stimulated research testing its principles, central to which is the notion that exposure to stressors is positively associated with criminal behavior. The present research extends prior scholarship in three important ways: (1) assessing the role that race and ethnicity play in understanding the stress-crime relationship, (2) testing GST principles on an underexamined group of crime prone individuals (i.e., young adults), (3) examining the stress-crime association with a substantially more comprehensive set of measures of stressors than prior evaluations. Central to the study's findings is the result that racial differences in criminal involvement are largely reducible to exposure differences, with blacks typically exposed to significantly more stressful events over their lifetimes than members of other racial/ethnic groups. Eitle, D. and Turner, R.J. Stress Exposure, Race, and Young Adult Male Crime. Sociological Quarterly, 44, pp. 243-269, 2003.

Patterns of Sexual Risk Behaviors and Psychiatric Disorders in a Community Sample of Young Adults

This cross-sectional study documents significant associations between patterns of sexual risk behaviors and psychiatric diagnoses in a multiethnic community sample of young adults (N =1803) in South Florida. Self-report data regarding sexual behavior and psychiatric symptoms were collected in structured interviews in a follow-up of an earlier school-based study. Cluster analysis was used to group participants with regard to levels of sexual risk behaviors during the past year. Chi-square analysis and ANOVA identified significant associations between cluster membership and (a) lifetime and (b) past year diagnoses for affective disorders, conduct disorder, antisocial personality disorder, alcohol abuse/dependence, marijuana abuse/dependence, and other drug abuse/dependence. In addition, higher levels of sexual risk behaviors were associated with higher levels of cumulative lifetime psychiatric disorders. Implications for selected prevention of sexually transmitted diseases (STDs) and the treatment of psychiatric disorders in young adulthood are discussed. Tubman, J.G., Gil, A.G., Wagner, E. F., and Artigues, H. Patterns of Sexual Risk Behaviors and Psychiatric Disorders in a Community Sample of Young Adults. Journal of Behavioral Medicine, 26, pp. 473-500, 2003.

Cumulative Adversity and Post-Traumatic Stress Disorder: Evidence From A Diverse Community Sample Of Young Adults

The authors hypothesized that history of adversities, whether objectively traumatic or not, predicts risk for first-onset of PTSD. Survival analysis in a community sample of 1803 young adults revealed risk is associated with retrospectively reported adverse experiences that occurred in years prior to the focal traumatic event. Analyses control for clustering of events proximal to onset. Implications for etiology and preventive intervention are noted. Lloyd, D.A. and Turner, R.J. Cumulative Adversity and Post-Traumatic Stress Disorder: Evidence From A Diverse Community Sample Of Young Adults. American Journal of Orthopsychiatry, 73, pp. 381-391, 2003.

The Deterrence Hypothesis Reexamined: Sports Participation and Substance Use Among Young Adults

The widely held notion that sports participation reduces subsequent risk of substance use is evaluated with longitudinal survey data of a representative sample of 1,172 youth when they were in their preteen and young adult years. Unlike previous inquiries into the deterrence hypothesis, the present study controls for other major factors previously found to be predictive of alcohol and drug use, such as family structure and stress exposure. Results of analyses revealed that contrary to the deterrence hypothesis, playing high school sports does not appear to be a protective factor that lowers one's involvement in young adult alcohol or drug use--with one exception. Subgroup analyses revealed that among blacks, the greater the extent of high school sports participation the less the risk of substance use. In direct contradiction to the deterrence hypothesis, playing high school sports was found to be positively associated with alcohol use for whites, even in the context of other major predictors of alcohol use. Further analyses revealed that the positive association between sports participation and alcohol use appeared to exist only for white males. These findings cast doubt about the contention that playing high school sports is protective against alcohol and illegal substance use. Eitle, D., Turner, R.J. and Eitle, T.M. The Deterrence Hypothesis Reexamined: Sports Participation and Substance Use Among Young Adults. Journal of Drug Issues, 33, pp. 193-222, 2003.

BIS/BAS Levels and Psychiatric Disorder: An Epidemiological Study

Behavioral inhibition and behavioral activation levels have been theorized to relate to a broad range of psychopathologies. To date, however, studies have focused on a single diagnosis, and the measures used to assess different psychopathologies have varied greatly. This study assessed how levels of behavioral inhibition and behavioral activation relate to lifetime diagnoses of depression, anxiety, drug abuse and dependence, alcohol abuse and dependence, attention deficit hyperactivity disorder, and conduct disorder. A representative community sample of 1803 individuals between the ages of 19 and 21 in the Miami area was surveyed with the Composite International Diagnostic Interview and the Behavioral Inhibition and Behavioral Activation Scales (BIS/BAS; Carver & White, 1994). Results supported the role of BIS as a vulnerability factor for depression and anxiety and for BAS Fun-Seeking for drug abuse and non-comorbid alcohol diagnoses. Other models were not supported. Goals in understanding BIS and BAS are described, including the need for prospective studies with a broader array of behavioral indices. Johnson, S.L., Turner, R.J. and Iwata, N. BIS/BAS Levels and Psychiatric Disorder: An Epidemiological Study. Journal of Psychopathology and Behavioral Assessment, 25, pp. 25-36, 2003.

The Pursuit of Socially Modifiable Contingencies in Mental Health

The effort to understand the meanings of the well-demonstrated linkages between mental health and one's locations in the social structure has commanded a great deal of research attention over the past half century. Findings support the conclusion that differences in exposure to social stress represent a much more critical contingency in mental health and substance use outcomes than has generally been assumed. In addition, reported results indicate that the lifetime experience of multiple adversities is quite common among young people in South Florida and, presumably, elsewhere and the likelihood that the compelling linkage observed between cumulative adversity and risk for psychiatric and substance disorders is causal in nature. Evidence also suggests that differences in exposure to adversity may account for much of the observed association between psychiatric disorder and substance dependence. It is suggested that the development of interventions in the service of stress prevention or reduction should command a greater proportion of the attention of researchers and interventionists. Turner, R.J. The Pursuit of Socially Modifiable Contingencies in Mental Health. Journal of Health and Social Behavior, 44, pp. 1-17, 2003.

Cumulative Adversity and Drug Dependence in Young Adults: Racial/Ethnic Contrasts

This study assesses the effects of cumulative exposure to stressors as a risk factor for drug dependence, and evaluates whether race/ethnic differences in exposure to stressful events contributes to race/ethnic differences in prevalence of drug dependence. Data were analyzed cross-sectionally from a community survey of lifetime adverse experiences and substance and psychiatric disorders among young adults. Data were collected between 1997-2000 in Miami-Dade County, Florida. The sample size is 1,803 former Miami-Dade Public School students, 93% of whom were between ages 19 and 21 when interviewed. Males and females of Cuban origin, other Caribbean basin Hispanics, African-Americans, and non-Hispanic Whites are equally

represented. Drug dependence disorder was assessed by DSM-IV criteria using the Composite International Diagnostic Interview, and a 41-item checklist of lifetime exposure to major and potentially traumatic experiences was used to measure cumulative adversity. Both measures include age at time of first occurrence. The lifetime rate of drug dependence disorder (total 14.3%) did not vary significantly ($p>.05$) by socioeconomic group. The rate for males (17.6%) was significantly greater than female rate (10.9%). The African-American rate (6.5%) was dramatically lower than non-Hispanic White (17.0%), Cuban (18.1%) and non-Cuban Hispanic (16.0%) rates despite their dramatically higher exposure to adversity. Twenty eight of 33 individual adversities were associated with the subsequent onset of drug dependence ($p<.05$). Cumulative lifetime exposure was greatest for males and for African-Americans, and was inversely associated with socioeconomic level. Multivariate discrete-time event history analysis revealed significant independent effects of distal (>1 year earlier) and proximal (previous year) exposure to adverse events ($p<.05$), controlling for childhood conduct disorder, ADHD, and prior psychiatric disorder. Lifetime cumulative exposure to distant as well as more recent adversity predicts risk of subsequent drug dependence, though it does not explain ethnic group differences in risk. Implications are that distal and proximal stressful events should both be included when measuring stress exposure. Turner, R.J., and Lloyd, D. Cumulative Adversity and Drug Dependence in Young Adults: Racial/Ethnic Contrasts. Addiction, 98, pp. 305-315, 2003.

Status Variations in Stress Exposure Among Young Adults: Implications for the Interpretation of Prior Research

Life Events checklists have been the predominant method for estimating variations in stress exposure. It is unknown, however, whether such inventories are equally meaningful for estimating differences in exposure between men and women, African-Americans and Whites, and those in lower and higher SES categories. In this paper, we employ a wider range of measures of stress - recent life events, chronic stressors, lifetime major events and discrimination stress - to examine the extent to which these dimensions collectively yield conclusions about status variations in stress exposure that are similar to or different from estimates based only on a life events checklist. Our analyses of data collected from 899 young men and women of African American and non-Hispanic White ancestry suggest that status differences in exposure to stress vary considerably by the measure of stress that is employed. Although women are more exposed to recent life events than men, males report more major events and discrimination stress than females. Our results also reveal that life event measures tend to substantially under-estimate differences between African-Americans and non-Hispanic Whites in exposure to stress. A similar pattern also holds for SES. When stress is more comprehensively estimated, level of exposure profoundly affects ethnic differences in depressive symptomatology, accounts for almost half of the difference by SES but contributes little to the explanation of the gender difference in distress. The implications of these findings for the debate over the relative mental health significance of exposure and vulnerability to stress are discussed. Turner, R.J., and William A. Journal of Health and Social Behavior, 44, pp. 488-505, 2003.

Substance Use, Dependence, and Service Utilization Among the US Uninsured Non-Elderly Population

Investigators examined the prevalence and correlates of substance use, dependence, and service utilization among uninsured persons aged 12 to 64 years. Using the 1998 National Household Survey on Drug Abuse, the investigators found an estimated 80% of the uninsured non-elderly persons reported being uninsured for more than 6 months in the prior year. Within this data sample, only 9% of the uninsured persons who were dependent on alcohol or drugs had received any substance abuse services in the past year. Non-Hispanic Whites were estimated to be 3 times more likely than Blacks to receive substance abuse services. In conclusion, compared with the privately insured, uninsured persons had increased odds of having alcohol/drug dependence and appeared to face substantial barriers to health services for substance use problems. Wu, L.T., Kouzis, A.C., and Schlenger, W.E. Substance Use, Dependence, and Service Utilization Among the US Uninsured Non-Elderly Population. American Journal of Public Health, 93(12), pp. 2079-2085, 2003.

Intravenous Drug Use Among Street-Based Sex Workers: A High-Risk Behavior for HIV Transmission

The goal of this study was to determine the correlates and prevalence of intravenous drug users among Street-Based Sex Workers (SSW's) in Ho Chi Minh City. A cross sectional study was conducted among SSW's in Ho Chi Minh City during December 2000. The SSW's were interviewed and tested for HIV-1. HIV prevalence among sex

workers in Ho Chi Minh City has increased rapidly, from 6.5% in 1999 to 18.1% in 2000. This study examined whether injecting drug use among street-based sex workers (SSW's) in Ho Chi Minh City is a high-risk factor for HIV infection. The study findings showed HIV-1 seroprevalence was 16.3%. Regression analysis indicated that injecting drugs and being younger than 25 years of age were independently associated with HIV seropositivity. The investigators concluded that young SSW's who inject drugs are at the greatest risk of contracting HIV and acting as a bridge for HIV to the sexually active population. Nguyen, A.T., Nguyen, T.H., Pham, K.C., Le Truong, G., Bui, D.T., Hoang, T.L., Tobi, S., and Roger, D., Intravenous Drug Use Among Street-Based Sex Workers: A High-Risk Behavior for HIV Transmission. Sexually Transmitted Diseases, 31(1), pp. 15-19, 2004.

Substance Use References in the Lyrics of Favorite Songs of African-American Adolescents

Concerns have been raised regarding the effect of media messages on health risk behaviors, particularly given that media with explicit content are often marketed toward adolescents under the age of 18 (Federal Trade Commission 2000). The goal of this study was to investigate the extent to which drug-related references were present in popular songs nominated by a sample of African-American adolescents. To address this issue, secondary data analyses were performed using data originally collected by the Reaching Adolescents, Parents, and Peers project (Project RAPP). In the spring of 1997, participants reported their five favorite songs. Songs that were nominated five or more times by the sample (popular songs) were coded for genre and drug-related content. Of the 93 popular songs, the most popular genres were R&B (34%), gangsta rap (32%), and non-gangsta rap (27%). The majority of rap (68%) and gangsta rap (80%) songs contained at least one reference to illicit drugs, whereas few R & B songs did (6%). Marijuana and stimulants were the most commonly referred to drugs. These findings substantiate the need for more research on the potential relationship between exposure to media messages and drug use among adolescents. Brookshire, C.D., Stevens, E., Bryant, S., Browne, D.C., and Clubb, P. Substance Use References in the Lyrics of Favorite Songs of African-American Adolescents. Journal of Young Investigators, 1(1), pp 1-7, 2003.

Inner-City, Welfare-Needy, Drug-Using Households and Welfare Reform

This study reports ethnographic observations made from 1995-2001 on welfare-needy subjects, i.e., subjects lacking long-term stable employment and with little prospect of attaining it, who use illicit drugs or are members of a household containing a drug user. The authors suggest that the prevalence of drug-using, welfare-needy households has been greatly underestimated in the literature because subjects such as these have been unable to maintain continuous AFDC/TANF support, avoid participating in surveys, or do not disclose the full extent of their substance use in surveys. This study suggests that welfare reform is not helping welfare-needy, drug-using subjects gain economic independence through employment. Rather, subjects experience welfare reform "incentives" as "punishments" by a welfare system that does not understand their needs. Welfare reform has resulted in drug-using subjects in the inner city being cut off welfare, and this in turn has caused hardship and increased reliance on the underground economy. Dunlap, E., Golub, A. and Johnson, B.D. The Lived Experience of Welfare Reform in Drug-Using Welfare-Needy Households in Inner-City New York. Journal of Sociology and Social Welfare, 30(3), pp. 39-58, 2003.

Childhood Compelled Sex and Its Relationship to Structural Disadvantage, Subcultural Norms, Violence, and Illicit Drug Use in Inner City Households

There are a number of studies that have linked child sexual abuse to various adverse outcomes, including substance abuse. This study is a retrospective, qualitative study that seeks to understand the etiology, significance, and response to early compelled sex within the social context of poor, inner-city, predominantly African-American households (approximately 72 households) in New York City. Adult sexual contact with girls was widespread, even the norm in many impoverished households, although it is not accepted behavior by everyone living in the inner city. 61% of female subjects reported having compelled sex by age 13. Typically this activity took place regularly over time and fit within the young girl's sexual development pathway leading to independent sexuality. Many adults do not regard compelled sex as a major problem, and compelled sex is consistent with other subcultural behaviors, including violence and the ever-present threat of violence. The primacy of drug use in the lives of many inner-city residents also supports the acceptance of these subcultural norms and the commodification of sexual behavior (exchange of sex for food, rent money, drugs). Dunlap, E., Golub, A. and Johnson, B. Girls' Sexual Development in the Inner

City: From Compelled Childhood Sexual Contact to Sex-for-Things Exchanges. Journal of Child Sexual Abuse, 12(2), pp. 73-96, 2003.

Drug Use by Juvenile Detainees: Comparison of Self-Report and Urinalysis Data

1,829 youth in the Cook County Juvenile Temporary Detention Center were interviewed using the Diagnostic Interview Schedule for Children (DISC 2.3) to gather information on substance use, and 1,745 of these subjects provided urine samples for drug analysis using Enzyme-Multiplied Immunoassay Tests (EMIT-10 panel). Most subjects knew they would be urine tested when they were interviewed. 77.3% reported cannabis use in the past 6 months, 90.1% reported lifetime use. Self-report of other substances was less common, 8.0% reported use of other substances in the past 6 months, 13.0% lifetime. Two-thirds of detainees' urines tested positive for any drug; 65.9% tested positive for cannabis, 4.8% for cocaine, and 1.1% for hallucinogens. Overall, the veracity of self-report was high; among those who tested positive for any substance, 87.7 had reported use in the past 6 months and 94.1% had reported lifetime use. The veracity figures for cannabis were quite similar, 87.6% past 6 months, 94.1% lifetime; and these numbers account for the high veracity seen overall. Veracity figures for drugs other than cannabis were 27.5% for past 6 months and 37.8% lifetime. In general, younger detainees, African-American detainees, and detainees with recent drug arrests lacked veracity in self-reporting drug use. The authors suggest that self-report and urinalysis should be used together along with other data such as information about substance abuse treatment, records of drug-related arrests and charges, and information from families and schools to identify those youth in greatest need of intervention. McClleland, G.M., Teplin, L.A., and Abram, K.M. Detection and Prevalence of Substance Use Among Juvenile Detainees. OJJDP Juvenile Justice Bulletin, March, pp. 1-14, 2004.

Substance Use Disorders Related to Attempted Suicide in Adolescents

This study examined the effects of psychiatric disorders on attempted suicide among adolescents with substance use disorders (SUD). Age of onset for psychiatric disorders, age of first suicide attempt, and the relationship of psychiatric disorder with attempted suicide were investigated in a sample of 503 adolescents with DSM-IV defined SUD (age range: 12.2-19.0 years). Results indicated that males who attempted suicide had a significantly earlier onset of alcohol use disorders (AUD) and significantly more mood, AUD, and disruptive behavior disorder symptoms compared to non-attempting males. Females who attempted suicide had a significantly earlier onset and higher counts of mood disorders and SUD symptoms compared to non-attempting females. Hazard analysis revealed that mood disorders represent the highest psychiatric risk for attempted suicide in both the genders. Attention deficit-hyperactivity disorder (ADHD) increased the risk for attempted suicide among males. The interaction of mood disorder and AUD increased the risk for attempted suicide among females. The investigators conclude that clinicians should closely monitor SUD adolescents for suicide risk and be aware of gender differences for suicidal behavior based on course and severity of psychiatric disorder in this population. Kelly, T.M., Cornelius, J.R. and Clark, D.B. Psychiatric Disorders and Attempted Suicide Among Adolescents with Substance Use Disorders. Drug And Alcohol Dependence, 73(1), pp. 87-97, 2004.

Substance Use Related to Early Marriage

Prior work indicates that substance use is related to adolescent marriage. This study describes two different processes that may account for this relationship and hypothesize patterns of association that would be consistent or inconsistent with each. Using data from a study that followed west coast youth from 7th grade to young adulthood (N = 3,324), investigators assessed the effects of cigarette, alcohol, and marijuana use in 7th and 10th grade on the probability of marriage prior to age 20. When gender, race, and SES were controlled, cigarette use in adolescence, but not other substance use, was associated with early marriage. Low educational attainment and early unwed parenthood each uniquely mediated this association. These results suggest that the link between substance use and early marriage reflects a disposition toward risky or unconventional behavior, not the judgment-impairing effects of drug and alcohol use. Martino, S.C., Collins, R.L., and Ellickson, P.L. Substance Use and Early Marriage. Journal of Marriage and the Family, 66(1), pp. 244-257, 2004.

Higher Rates of Consent Obtained When Consent Forms Returned in School

Many school-based research efforts require active parental consent for student

participation. Maximizing rates of consent form return and agreement is an important issue, because sample representativeness may be compromised when these rates are low. This article compares two methods for obtaining active parental consent: return of consent forms in the mail versus return by students to their classrooms. The methods were tested in a pilot study of 46 schools (1,058 students), with half of the schools randomly allocated to each of the alternative methods. A hierarchical nonlinear model of consent form return and agreement rates suggests that the student delivered method is more successful at producing higher rates of consent form return and agreement to participate in the study, after controlling for school-level characteristics. McMorris, B.J., Clements, J., Evans-Whipp, T., Gangnes D., Bond, L., Toumbourou, J.W., and Catalano, R.F. A Comparison of Methods to Obtain Active Parental Consent For An International Student Survey. Evaluation Review, 28(1), pp. 64-83, 2004.

Predictors of Offspring Nonparticipation in a Twin-Family Study

This study examines an important methodologic issue for family studies of substance abuse - whether parents' alcoholism is associated with offspring nonresponse to telephone interviews. In 1999, the first wave of a longitudinal study of offspring of alcoholic twins was conducted via telephone interview with members of the Vietnam Era Twin Registry. The target offspring sample consisted of 2,096 male and female children, of whom 1,270 were successfully interviewed. Offspring response status was classified as participation, refusal or unavailable/no consent. Stepwise logistic regression models were used to identify variables that were significantly associated with one or both types of offspring nonparticipation. A multinomial logit procedure with backward deletion was then used to build a model of the three levels of child response. The results showed that paternal alcoholism was not significantly associated with offspring nonresponse. However, offspring nonparticipation because of not being located, or being deceased, disabled or unavailable was associated with current paternal smoking, paternal divorce and paternal marital status. The most important conclusion to be drawn from current results is that the alcohol abuse and dependence history of fathers should not bias analyses in family studies of alcoholism when data are collected via telephone interview. Scherrer, J.E., Waterman, B.M., Heath, A.C., Bucholz, K.K., True, W.R. and Jacob, T. Are Substance Use, Abuse and Dependence Associated with Study Participation? Predictors of Offspring Nonparticipation in a Twin-Family Study. Journal of Studies on Alcohol, 65, pp. 140-144, 2004.

Alcohol, Tobacco, and Other Drug Use among Asian American and Pacific Islander Adolescents in California and Hawaii

Prior research suggests that the lowest rates of alcohol, tobacco, and other drug (ATOD) use are often reported for Asian Americans/Pacific Islanders (AAPIs), compared to other Whites. These low rates are, however, often based upon samples with small representations of AAPIs, or represented by only one or two AAPI groups. This study investigates drug use among specific AAPI subgroups (Chinese, Filipino, Japanese, and Pacific Islander/Native Hawaiian) using data from school surveys collected from nearly 82,000 9th grade students in California and nearly 5,000 10th grade students in Hawaii. Results showed that ATOD rates were lowest for the Chinese adolescents and highest among the White and Pacific Islanders/Native Hawaiians reported among the highest. Similar variation was found for need for alcohol and other drug treatment for these groups. In summary, AAPIs clearly constitute heterogeneous groups characterized by a wide range of ATOD behaviors and treatment needs. Wong, M.M., Klingle, R.S., and Price, R.K. Alcohol, Tobacco, and Other Drug Use among Asian American and Pacific Islander Adolescents in California and Hawaii. Addictive Behaviors, 29, pp.127-141, 2004.

Antisocial Behavior, Depressive Symptoms, and Partner Violence

This study examined the extent to which antisocial behavior and depressive symptoms were associated between romantic partners, and whether the partner's antisocial behavior and depressive symptoms affected the individual's aggression toward the partner. Questions were examined concurrently and longitudinally for 79 couples from a young, at-risk sample. There were reliable associations between partners' antisocial behavior and depressive symptoms. Women's antisocial behavior and depressive symptoms were significantly related to concurrent levels of men's physical and psychological aggression. Women's depressive symptoms remained significant in predicting men's psychological aggression over time. Overall, men's risk factors had little effect on their partners' aggression. Findings suggest that interventions to reduce partner violence need to consider the potential influence of partner, as well as perpetrator characteristics. Kim, H.K., and Capaldi, D.M. The Association of Antisocial Behavior and Depressive Symptoms between Partners and

Risk for Aggression in Romantic Relationships. Journal of Family Psychology, 18, pp. 82-96, 2004.

Review of Twin and Adoption Studies of Adolescent Substance Use

This paper reviews studies of adolescent substance use and abuse with twin and adoption studies. Results were presented by design, sample, and stage of drug use. Of 19 studies that used adolescent samples, 18 examined initiation or use of substances and 1 examined abuse. Of the 7 retrospective studies using adult samples, 6 examined problematic behaviors such as substance dependence. Genetic and shared environmental influences on adolescent substance use appear to be moderated by the specific substance, age, gender, specific contexts, religiousness, and region. There is some evidence for a common genetic influence on substance use across substances. Genetic influences on adolescent substance use may act through an influence on disinhibited behavior. Shared environment contributed to adolescent substance use consistently across all adolescent samples and common shared environmental factors influenced initiation into tobacco and alcohol use. While parental alcohol use had a small influence on adolescent shared environment, sibling influences were substantial. In summary, twin and adoption studies have increased our understanding of genetic and environmental influences on adolescent substance use and its initiation, although more studies focusing on clinical syndromes of abuse and dependence are needed. Hopfer, C.J., Crowley, T.J., and Hewitt, J.K. Review of Twin and Adoption Studies of Adolescent Substance Use. Journal of the American Academy of Child and Adolescent Psychiatry, 42, pp. 710-719, 2003.

Daily Smoking and the Subsequent Onset of Psychiatric Disorders

Recent research has demonstrated that smokers are at an elevated risk for psychiatric disorders. This study extends the enquiry by examining the specificity of the psychiatric sequelae of smoking, and the variability in the likelihood of these sequelae by proximity and intensity of smoking. Data come from the National Comorbidity Survey (NCS), a representative sample of the US population 15-54 years of age. The Smoking Supplement was administered to a representative subset of 4,414 respondents. A modified World Health Organization-Composite International Diagnostic Interview was used to measure DSM-III-R disorders. Age of onset was determined by retrospective reports. Survival analysis with smoking variables as time-dependent covariates was used to predict the subsequent onset of specific psychiatric disorders. Results indicated that the estimated effects of daily smoking varied across psychiatric disorders. For mood disorders, daily smoking predicted subsequent onset, with no variation between current versus past smokers or by smoking intensity. In the case of panic disorder and agoraphobia, current but not past smoking predicted subsequent onset; furthermore, the risk of these disorders in past smokers decreased with increasing time since quitting. For substance use disorders, current but not past smoking predicted subsequent onset, with no variation by time since quitting or smoking intensity. The data suggest that smoking cessation programs would not prevent the onset of mood disorder, as ex-smokers do not differ from current smokers in their risk for these disorders. In comparison, daily smoking might be a risk factor in panic disorder and agoraphobia, conditions that might be preventable by smoking cessation. Additionally, current smoking might serve as a marker for targeting interventions to prevent alcohol and drug disorders. Breslau, N., Novak, S.P., and Kessler, R.C. Daily Smoking and the Subsequent Onset of Psychiatric Disorders. Psychological Medicine, 34, pp. 323-333, 2004.

Psychiatric Disorders and Stages of Smoking

This study examined the role of DSM-III-R psychiatric disorders in predicting the subsequent onset of daily smoking, smokers' progression to nicotine dependence, and the persistence of smoking. The Tobacco Supplement of the National Comorbidity Survey was administered to a representative subsample of 4,414 persons 15-54 years of age. Psychiatric disorders and information on age of onset of psychiatric disorders, daily smoking, and smoking cessation were ascertained with the World Health Organization's Composite International Diagnostic Interview. Age of onset was determined by retrospective reports. Results showed that active psychiatric disorders predicted an increased risk for the first onset of daily smoking and for smokers' progression to nicotine dependence. The increased risk applied across most of the disorders examined in the study, including major depression, anxiety disorders, and substance use disorders. Persons with four or more active disorders were at higher risk for daily smoking (O.R.: 2.1 vs. 1.4) and for nicotine dependence (O.R.: 2.9 vs. 1.4) than were persons with one active disorder. With few exceptions, remitted (i.e., past) disorders did not predict the subsequent onset of daily smoking. Preexisting psychiatric disorders did not influence smokers' potential for quitting; the persistence

of smoking in the year preceding the interview was unrelated to history of psychiatric disorders. The results suggest the possibility of additional and previously unrecognized public health benefits in that early treatment of mental disorders may be beneficial in preventing daily smoking. Breslau, N., Novak, S.P., and Kessler, R.C. Psychiatric Disorders and Stages of Smoking. Biological Psychiatry, 55, pp. 69-76, 2004.

Smoking Progression and Physical Activity

This study examined the association between changes in physical activity and changes in smoking among adolescents. Smoking progression, physical activity, demographic factors, and covariates were assessed in 978 high school students participating in a longitudinal cohort study of the predictors of smoking adoption. Analyses used latent growth modeling with the parallel processes smoking progression and physical activity as our method, with smoking progression measured as an ordered categorical variable. Results indicated that higher levels of physical activity reduced the odds of progressing to smoking or a higher level of smoking by nearly 1.5. Although no race differences were found, being male increased the odds of smoking progression by 1.32. These findings indicate that higher levels of physical activity may reduce the risk of smoking during adolescence, and that youth smoking prevention initiatives should consider incorporating strategies to promote physical activity to prevent smoking experimentation and escalation. Audrain-McGovern, J., Rodriguez, D., and Moss, H.B. Smoking Progression and Physical Activity. Cancer Epidemiology, Biomarkers, and Prevention, 12, pp. 1121-1129, 2003.

Development and Validation of the Michigan Nicotine Reinforcement Questionnaire

Positive- and negative-reinforcement consequences of smoking were assessed using a self-report inventory. Data from 429 current smokers (348 women, 81 men) were subjected to an exploratory factor analysis, with concurrent validation of resulting scales in 288 current smokers (235 women, 53 men), controlling for sex and age. The solution with three factors - positive reinforcement, negative reinforcement, and smoking patterns - provided the clearest and most interpretable factor solution. The Michigan Nicotine Reinforcement Questionnaire (M-NRQ), which yields positive- and negative-reinforcement scales, was developed based on these results. Positive-reinforcement smoking was associated with higher scores on novelty seeking, reward dependence, alcohol dependence, and pleasurable sensations upon early smoking experimentation, and with lower scores on displeasurable sensations and nausea upon early smoking experimentation. Negative-reinforcement smoking was associated with higher scores for nicotine dependence, depression, anxiety, and harm avoidance. The M-NRQ has potential as a diagnostic tool for individualizing behavioral intervention and pharmacotherapy and also may be useful in identifying new phenotypes for genetic research on smoking. Pomerleau, O.F., Fagerstrom, K.O., Marks, J.L., Tate, J.C., and Pomerleau, C.S. Development and Validation of a Self-Rating Scale for Positive- and Negative-Reinforcement Smoking: The Michigan Nicotine Reinforcement Questionnaire. Nicotine and Tobacco Research, 5, pp. 711-718, 2003.

Correlates of Pathological Gambling

This study examined correlates of gambling among respondents of a random-digit-dial telephone survey that was conducted in 1999-2000 with a representative sample of the U.S. population aged 18 or older. This report uses data from the 2,168 respondents who gambled in the year before the interview. Gambling measures included the Diagnostic Interview Schedule (DIS)-IV for pathological gambling, frequency of 15 types of gambling, and size of win or loss on the last occasion. Other measures included the quantity and frequency of alcohol consumption, frequency of illicit drug use and criminal offending, and the DIS-IV for alcohol and drug abuse and dependence. Results showed that casino gambling is associated with a high risk of gambling pathology. Lottery, cards, and bingo are associated with a moderately high risk of gambling pathology. Participation in a greater number of types of gambling is strongly predictive of gambling pathology, even after frequency of gambling and size of win or loss are taken into account. Alcohol abuse is strongly predictive of gambling pathology, even with gambling behaviors held constant. Minority and low socioeconomic status (SES) group members have higher levels of gambling pathology than other groups after all other factors are considered. Welte, J.W., Barnes, G.M., Wieczorek, W.F., Tidwell, M.C., and Parker, J.C. Risk Factors for Pathological Gambling. Addictive Behaviors, 29, pp. 323-335, 2004.

Drug Test Feasibility in a General Population Household Survey

This study focuses on evaluating the feasibility of drug testing in a general population survey. First the PIs explore the nature of drug test participation and refusal among survey participants drawing comparisons across different procedures. They examine three factors that may potentially influence drug test participation in epidemiological surveys: drug disclosure concerns, test-specific factors, and factors associated with the decision to participate in surveys and variables associated with participation and reaction. Their analyses evaluate the impact of the main experimental condition of the study, subject incentives, on drug test refusal and subjects' reactions to drug test participation, and provide test-specific comparisons. Models of the drug test reactions are compared with models of drug test refusal. Participants, ages 18-40 years residing in Chicago, were recruited to participate in three different biological tests (hair, oral fluid, and urine) presented in random order subsequent to completing an interview. Subjects had the option of participating in zero to three different tests and were randomly assigned to a low (US $10 per test) or high (US $20 per test) incentive condition. Over 90 percent of the sample participated in at least one test, usually the oral fluid test. Associations between refusal status and two variables, socioeconomic status and presence of children in the household, provided partial support for the notion that drug test participation parallels the survey response process in general. Incentive level did not directly increase drug test participation. Reporting of recent illicit drug use was associated with participation in only one procedure, hair testing. Type of test offered and individual differences in willingness to be drug tested were important predictors of drug test refusal and subject reaction to testing requests. Compared with urine and hair testing, oral fluid testing had lower refusal rates and was generally more acceptable to respondents in a general population survey. The overall findings underscore the feasibility of conducting multiple drug tests with modest incentives in the context of epidemiological surveys on drug abuse. Despite specific between-test differences, overall drug test participation rates were high in this study. Fendrich, M., Johnson, T.P., Wislar, J.S., and Hubbell, A. Drug Test Feasibility in a General Population Household Survey. Journal of Drug and Alcohol Dependence, 73, pp. 237-250, 2004.

The Culture of Affluence: Psychological Costs of Material Wealth

This study collates evidence on the nature of problems among the wealthy and their likely causes, specifically, disturbances among affluent children and the characteristics of their families and neighborhoods. Children of affluence are generally presumed to be at low risk. However, recent studies have suggested problems in several domains - notably, substance use, anxiety, and depression, with two potential causes: pressures to achieve and isolation from parents (both literal and emotional). The PI concludes that, although a few samples of high-SES teenagers have shown elevated levels of depression, anxiety, and substance use, it is possible that these problems reflect normative complaints in the culture of upper-class suburbia rather than serious psychopathology. Longitudinal research will be critical in illuminating this issue, identifying the degree to which high self-reported distress among suburban teens does in fact presage subsequent deterioration in critical domains, by affecting their school grades, for example, or leading to diagnosable mental illness. Also, it is not clear whether the problems suggested represent a largely suburban phenomenon or might generalize to high-SES children in large cities. Luthar, S.S. The Culture of Affluence: Psychological Costs of Material Wealth. Child Development, 74, pp. 1581-1593, 2003.

Director's Report to the National Advisory Council on Drug Abuse - May, 2004

Research Findings - Prevention Research

Evaluation of the National Youth Anti-Drug Media Campaign: 2003 Report of Findings

The National Youth Anti-Drug Media Campaign (NYAMC) was funded by the Congress to reduce and prevent drug use among young people both directly, by addressing youth and indirectly, by encouraging their parents and other adults to take actions known to affect youth drug use. The major intervention components include television, radio, and other advertising, complemented by public relations efforts including community outreach and institutional partnerships. The goals of the evaluation are to determine: 1) if there is change in the behaviors, attitudes and beliefs targeted by the Campaign and 2) determine if such change can be attributed to the Campaign. The findings summarized below are from the fifth Evaluation report; the first three waves of data collection involved enrolling nationally representative samples of about 8,100 youth from 9 to 18 and 5,600 of their parents. The 2003 report includes the second (of three) follow-up interviews of the initial samples. The new report covers the period from September 1999 through June 2003. For the youth component of the Campaign, the Report focuses on evidence concerning the possible effects of the Marijuana Initiative that began in late fall 2002 and refocused the Campaign to emphasize marijuana use among youth. The report examines 1) exposure of youth and their parents to anti-drug messages (general exposure and specific exposure to ads run in the 2 months prior to the interview that are played on a computer to respondents); 2) effects on parents in terms of beliefs and behaviors associated with talking about drugs, and beliefs and behaviors regarding monitoring their child, and doing fun activities with their child; and 3) effects on youth cognitions, intentions, and initiation of marijuana use.

- Recall of Campaign Messages:
  As in the 5th Report, most parents and youth recalled exposure to Campaign anti-drug messages. About 70 percent of parents and nearly 80 percent of youth report exposure to one or more messages through all media channels every week. Recall of TV advertising has climbed across the 3.5 years of the Campaign. In 2000, 24 percent of parents and 37 percent of youth recalled weekly exposure to specific TV ads; in 2002, before the Marijuana Initiative, recall among parents reached 51 percent and among youth reached 52 percent; in 2003, after the launch of the Marijuana Initiative recall rates had moved to 58 percent and 76 percent respectively. Both parents and youth also reported substantial recognition of the Campaign's "anti-drug" brand phrases. The 2003 youth component of the Campaign focused on strong marijuana Negative Consequences ads; they were evaluated positively by youth at a level comparable to most of the previous ads.
- Effects on Parents:
  There continues to be evidence suggesting a favorable Campaign effect on parents. Overall, there are favorable changes on 4 of 5 parent belief and behavior outcome measures including talking about drugs with their children, doing fun activities with children and beliefs about monitoring of children. Evidence for Campaign effects on parents' monitoring behavior was much weaker. Lack of influence on monitoring behavior is a concern because it has been the focus of the parent Campaign for the past several years and is the parent behavior most strongly associated with youth nonuse of marijuana. In addition, there is no evidence for favorable indirect effects on youth behavior or beliefs as the result of

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parent exposure to the Campaign.

- Effects on Youth:
  There is little evidence of direct favorable Campaign effects on youth, either for the Marijuana Initiative period or for the Campaign as a whole. The trend data in marijuana use is not favorable and for the (new) primary target audience, 14- to 16-year olds, past year use increased from 2000 through 2003, although the increase was already in place prior to the start of the Marijuana Initiative. However, an independent source of trend information, the Monitoring the Future Study, showed a decline in use for some age groups. In any case, youth who were more exposed to Campaign messages are no more likely to hold favorable beliefs or intentions about marijuana than are youth less exposed to those messages, both during the Marijuana Initiative period and over the entire course of the Campaign.

Because the Marijuana Initiative began just before the final wave of data collection, it is not possible to supplement the same-time comparisons of exposure and outcomes with delayed-effects comparisons of Marijuana Initiative exposure with later outcomes. These delayed-effects analyses will be examined in the final report planned for December, 2004.

Effects of the Early Risers Program on Young Aggressive Children's Peer Relations

Peer nominations for behavioral reputation, likeability, and friendship were examined after 4 years of an ongoing randomized, controlled prevention trial designed to interrupt the developmental trajectory of young aggressive children by improving peer relations. Participants included 125 moderately to highly aggressive children (program and control) and 1,489 of their 4th-grade classmates. Results indicated that program children (compared to controls) obtained higher reputation scores on leadership and social etiquette and chose friends with lower aggression. Self-reported quality of friendship also differed between groups, with program children reporting more companionship and recreation, program girls reporting more validation and caring, and severely aggressive program children reporting less aggression toward others than their control counterparts. These findings provide evidence for the generalization of program effects to a natural peer setting. Four Years of the Early Risers Early-Age-Targeted Preventive Intervention: Effects on Aggressive Children's Peer Relations. August, G.J., Egan, E.A., Realmuto, G.M., and Hektner, J.M. Behavior Therapy, 34(4), pp. 453-470, 2003.

The Early Risers Effectiveness Study

This study evaluated the effectiveness of the Early Risers "Skills for Success" Program when implemented by neighborhood family resource centers available to urban children and their families. Kindergarten and first-grade children (n=327) enrolled in 10 schools were screened for aggressive behavior, and randomized to two model variations of the Early Risers Program or a no-intervention control condition. The full-strength model (CORE + FLEX) included child and parent/family components; the partial model (CORE-only) offered only the child component. The intervention was delivered over two continuous years. CORE + FLEX children showed higher levels of program attendance than their CORE-only counterparts but no differences on outcomes measures were observed between models. When both program models were collapsed and compared to controls, program children showed significant gains on measures of school adjustment and social competence, the most aggressive program children showed reductions in disruptive behavior, and program parents reported reduced levels of stress. August, G.J., Lee, S.S., Bloomquist, L., Realmuto, G.M., and Hektner, J.M. Dissemination of an Evidence-Based Prevention Innovation for Aggressive Children Living in Culturally Diverse, Urban Neighborhoods: The Early Risers Effectiveness Study. Prevention Science, 4(4), pp. 271-286, 2003.

Effectiveness of the Coping Power Program and of Classroom Intervention with Aggressive Children at One-Year Follow-Up

This study examines key substance use, delinquency, and school-based aggressive behavior outcomes at a 1-year follow-up for a cognitive-behavioral intervention delivered to aggressive children and their parents at the time of these children's transition to middle school. This effectiveness study explored whether a classroom intervention directed at teachers and at all of the parents in the intervention classrooms enhanced the effects of the Coping Power program with at-risk children. The at-risk sample of boys and girls was identified through 4th-grade teacher ratings, and intervention took place during the 5th- and 6th-grade years. The Coping Power

child component included school-based groups focusing on anger management and social problem solving skills, and the Coping Power parent component addressed parenting and stress-management skills. The current results indicate that prior findings of post-intervention improvement for this sample (Lochman & Wells, 2002b) has led to preventive effects on delinquency and on substance use for older and moderate-risk children. The Coping Power program, in conjunction with a classroom-level intervention, also reduced school aggression one year after the intervention was completed. In addition, it appears that the classroom intervention facilitates radiating effects on reduced substance use for other at-risk children in the same classrooms who did not receive Coping Power. Lochman, J.E. and Wells, K.C., Effectiveness of the Coping Power Program and of Classroom Intervention with Aggressive Children at One-Year Follow-Up. Behavior Therapy, 34(4), pp. 493-515, 2003.

Reasons for Teachers' Adaptation of Prevention Curricula for Non-White Students

There is increasing evidence to suggest that the adaptation of classroom-based prevention curricula in the nation's middle schools is widespread. This study investigated the reasons for teachers' adaptation of prevention curricula. A randomly selected sample of nationally representative lead middle school substance abuse prevention teachers from 50 states and the District of Columbia answered questions concerning eight student problems or needs (i.e., poverty; violence; gang activity; discipline problems; sexual activity; various racial/cultural groups; special needs/disabilities; student and parent substance use) that were hypothesized to constitute reasons for curriculum adaptation. Controlling for a variety of school and teacher characteristics, teachers in high minority schools were more likely to adapt curricula in response to three of the eight characteristics presented (i.e., youth violence; limited English proficiency; and various racial/ethnic or cultural groups within classroom). It is suggested that curriculum developers make a systematic effort to understand how teachers are adapting their curricula in high minority schools and incorporate these modifications, if found effective, into their curricula. Ringwalt, C.L., Vincus, A., Ennett, S., Johnson, R., and Rohrbach, L.A. Reasons for Teachers' Adaptation of Substance Use Prevention Curricula in Schools With Non-While Student Populations. Prevention Science, 5(1), pp. 61-67, 2004.

An Acute Post-Rape Intervention to Prevent Substance Use and Abuse

Rape trauma frequently is associated with extreme acute distress increasing the risk of developing psychopathology and substance use or abuse post-rape, with the degree of internal distress positively predicting future problems. The nature of post-rape forensic evidence collection procedures may exacerbate initial distress, thus potentiating post-rape negative emotional sequelae. Substance use may increase in an effort to reduce this distress. To address this outcome, a two-part video intervention was develop for use in acute post-rape time frames with two goals: to minimize anxiety during forensic rape examinations, thereby reducing risk of future emotional problems; and to prevent increased post-rape substance use and abuse. Pilot data with 124 rape victims who completed a police report and were brought for medical care immediately following such a report and who completed a 6-week post-rape assessment are included in this article. Half the women saw a 17-minute video immediately prior to the forensic examination. The data indicated that the low-cost, easily administered intervention was effective in reducing risk of marijuana abuse at six weeks. Trends also were noted in favor of the intervention in the subgroup of women who were actively using substances pre-rape (among pre-rape alcohol users, 28% of viewers versus 43% nonviewers met criteria for post-rape alcohol abuse; among pre-rape marijuana users, the rates of post-marijuana use were 17% and 43% respectively). While still preliminary, these data support the use of immediate, brief intervention via the video to target substance abuse within a vulnerable population. Acierno, R., Resnick, H.S., Flood, A. and Holmes, M. An Acute Post-Rape Intervention to Prevent Substance Use and Abuse. Addictive Behaviors, 28, pp. 1701-1715, 2003.

Drug Abuse Prevention Program Development - Results Among Latino and Non-Latino White Adolescents

Five program development studies from Project Towards No Drug Abuse (TND) were reanalyzed to discern Latino versus non-Latino Whites similarities and differences in receptivity to a wide variety of high school-based drug abuse prevention activities. In most of the program development studies, these youth attended alternative (continuation) high schools in Southern California. Although there were a total of 46% Latino students in these schools, 99% of the students indicated English as the main language spoken at school and home. Thus, taken together, almost all Latino youth in

the various studies analyzed preferred to respond to survey questions in English. Latinos were relatively low in socioeconomic status (SES) and used drugs less frequently than non-Latino whites. Still, this group of highly acculturated Latinos and non-Latino Whites (37% of the school population) perceived that they were attending alternative schools for the same reasons (e.g., lack of credits, truancy). Very few differences in receptivity ratings of proposed TND activities were found as a function of ethnicity. In other words, the data suggest that the same types of lessons are applicable to older teens in both ethnic groups. Sussman, S., Yang, D.Y., Baezconde-Garbanati, L., and Dent, C.W. Drug Abuse Prevention Program Development - Results Among Latino and Non-Latino White Adolescents. Evaluation & The Health Professions, 26(4), pp. 355-379, 2003.

Preventing Early Onset Substance Use by Parental Monitoring

The Family Check-Up (FCU) is a brief family-centered intervention focused on family management practices. Within the context of a randomly assigned multilevel family intervention, high-risk youth and families (n = 71) were selected for videotaped home observation that includes a task to assess parent monitoring. Parents in the intervention group were offered annual feedback on the yearly assessment, including their home observation. Using an intention-to-treat design, analyses revealed intervention effects on early-adolescent substance use and observed parent monitoring by the first year of high school (Year 4 of follow-up). As in previous research, parents of high-risk adolescents were observed to decrease monitoring from Grades 7 to 9. However, families randomly assigned to the family intervention maintained their monitoring practices. Regression analyses revealed the prevention effect of the FCU on substance use was mediated by changes in parental monitoring. Dishion, T.J. Nelson, S.E. and Kavanagh, K. The Family Check-Up with High-Risk Young Adolescents: Preventing Early Onset Substance Use by Parent Monitoring. Behavior Therapy, 34, pp. 553-571, 2003.

Advocacy Activities to Address Environmental Influences Led to Less Smoking among Teenagers

Most smoking prevention and cessation interventions for adolescents show little sustained effects on smoking behavior. Since behavior change is embedded in the social context, the authors designed an intervention that involved adolescents in advocacy about social and environmental factors that influence smoking as a way to test an alternative approach. Ten continuation high schools were randomized to receive an advocacy curriculum where 11th and 12th grade students carried out activities to counter environmental influences on smoking in their communities (i.e., the treatment) or a curriculum where students learned about drug and alcohol abuse prevention (control). Compared with control schools, students in treatment schools showed significant net changes from baseline to the end of the semester (post intervention) for regular smoking, involvement in community-advocacy activities. The findings were significant for students who were regular smokers but not for those who were non-smokers or light smokers. Regular smoking decreased 3.8% in treatment schools and increased 1.5% in control schools. Regular smoking continued to decrease at 6-months post-intervention in treatment schools, with a total change in prevalence from 25% to 20%. Involvement in community-advocacy activities and three measures related to social cognitive theory --- perceived incentive value, perceived self-efficacy, and outcome expectancies also showed significant net changes between treatment and control schools that were maintained at 6-months post-intervention. Winkleby, M.A., Feighery, E.C., Dunn M., Ahn, D. and Killen J. Effects of an Advocacy Intervention to Reduce Smoking Among Teenagers. Archives of Pediatric Adolescent Medicine, 158, pp. 269-275, 2004.

Monetary Incentives Increase Community-Based Prevention Participation Rates

This investigation was designed to examine the influence of a research incentive ($100) and requirement (videotaping) on decisions to participate in prevention research. The participants were 685 parents of 6th graders from 36 rural Iowa schools who completed a telephone survey prospectively assessing factors relevant to their participation in a prevention intervention research project. The parents were later recruited for actual participation in the project. Individuals were significantly attracted by the incentive and marginally deterred by the requirement. Interaction analyses revealed that the positive incentive effect was stronger among prospective participants with less education and who were otherwise less likely to participate. These findings indicate that monetary incentives can be useful for increasing participation rates and may help reduce sampling bias by increasing rates most strongly among individuals who are typically less likely to take part in research

projects. Guyll, M., Spoth, R., and Redmond, C. The Effects of Incentives and Research Requirements on Participation Rates for a Community-Based Preventive Intervention Research Study. The Journal of Primary Prevention, 24, pp. 25-41, 2003.

What Works in Media Strategies Targeting High Sensation Seekers

This review examines media strategies used in effective drug prevention campaigns targeting high sensation seekers. Both experimental lab and field studies have been used to establish and test SENTAR (i.e., sensation-seeking targeting) approaches to segment the audience. The SENTAR principles for designing campaigns include: use the sensation seeking trait as a key targeting variable; design prevention messages that are high in sensation value; use pre-campaign research with high sensation seeking members of the target audience; and place prevention messages in high-sensation value contexts. In earlier studies this targeting strategy has resulted in significant drops in 30-day marijuana use by adolescents. Having established that SENTAR works, new studies focused on the factors that were influencing the processing and persuasiveness of the ads including emotional responses; visual and sound effects, storyline and consequences of drug use portrayed in ads. The influence of these mediating factors was expected to differ in youth. High sensation seekers reported a much stronger negative reaction to the consequences of marijuana than low sensation seekers, but their emotional reactions were inconsequential in affecting attitudes whereas low sensation seekers' emotional reaction was the only factor affecting attitudes. Together these studies suggest that sensation seeking is a risk factor influencing drug use that can be addressed through ads that appeal to the sensation seeker's need for arousal and stimulation. Stephenson, M.T. Mass Media Strategies Targeting High Sensation Seekers: What Works and Why. Am J Health Behav 27 (Supplement 3), pp. S233-S238, 2003.

Sensation Seeking is a Moderator of Peer Effects and Perceived Peer Marijuana Use on Cigarette and Marijuana Use

This study tested the concurrent effects of peer influence and protective cognitive variables on marijuana and cigarette use to determine if they are contingent on adolescent sensation seeking. It tested two hypotheses: (1) low sensation-seekers would be more likely to resist pressures from risk-taking peers than their high-sensation-seeking counterparts and (2) low sensation seekers are more likely to be deterred from cigarette and marijuana use by the perceived negative consequences of harm than high sensation-seekers. Data are based on survey responses of 3127 eighth graders from 10 small towns and rural communities. Findings indicate that sensation seeking is a risk factor for drug use among high but not low sensation seekers; however, sensation seeking does not become a risk factor in the absence of social pressures to use substances. Aspirations inconsistent with marijuana use appeared protective for high sensation seekers. Since low sensation seekers appear to be at relatively low risk even in the presence of peer risk factors or the absence of cognitive factors, the primary audience for substance use prevention efforts should be the sensation-seeking young adolescents and should seek to channel this group into alternative arousing and risk taking activities with nonsubstance-using peers. Slater, M.D. Sensation-Seeking as a Moderator of the Effects of Peer Influences, Consistency with Personal Aspirations, and Perceived Harm on Marijuana and Cigarette Use among Younger Adolescents. Substance Use and Misuse 38, pp. 865-880, 2003.

Familism, Parental Monitoring & Knowledge as Predictors of Adolescent Drug Use

The authors investigated relationships between marijuana and inhalant use and measures of familism, parental monitoring, drug use knowledge and acculturation as well as demographic factors in 1,094 Anglo and Hispanic youth from 5 school districts in southwest Arizona. Outcome measures addressed lifetime and 30-day marijuana and inhalant use. Hispanics exhibited higher use across all measures. Among Hispanic youth, high acculturation was associated with low marijuana but high inhalant use. In both Hispanics and Anglos positive family relations and parental monitoring were strongly associated with reduced marijuana use but only among youth most knowledgeable about drugs. Familism and monitoring were not associated with diminished use among the less knowledgeable. For inhalants, monitoring combined with high knowledge or with high familism was associated with attenuated use. The role of knowledge in reducing drug use suggests continuing to disseminate factual material. Prevention strategies also should incorporate a family component to inform parents and open lines of communication. Ramirez, J.R., Crano, W.D., Quist, R. Burgoon, M., Alvaro, E.M. and Grandpre, J. Acculturation, Familism, Parental Monitoring, and Knowledge as Predictors of Marijuana and Inhalant Use in Adolescents. Psychology of Addictive Behaviors. 18(1), pp. 3-11, March 2004.

Comparing African American and Caucasian Marijuana Use from Early Adolescence Through Young Adulthood

Although epidemiological studies have consistently reported that African American adolescents are less likely to use drugs than their Caucasian counterparts, few researchers have examined the developmental trajectories of drug use to identify whether and when differences in marijuana use appear and the nature of these differences. This study compared marijuana use patterns for African American and Caucasian youth across 7 waves of data using a community based dataset collected as part of the evaluation of Project DARE. Because the DARE intervention was found to have no effects on any program targets, this dataset provides an appropriate community sample for investigating developmental changes in drug use over time. 1,354 students (49.7% male, 77.4% Caucasian) were interviewed once a year in the sixth through tenth grades and again at age 20. Consistent with prior research, early onset of substance use was associated with low church involvement, low peer pressure resistance, high sensation seeking, and high positive and low negative expectancies about the effects of marijuana. These relationships held true for both African American and Caucasian adolescents. Relationships between marijuana use patterns and other outcomes including psychological problems, aggression and arrests were also examined. Among Caucasian adolescents, those with the earliest onsets reported more negative outcomes, whereas adolescents with the latest onsets reported fewer. However, the pattern was different for African American adolescents. The early-onset and late-onset African American groups were similar on outcome variables and, by age 20, these groups were using marijuana at rates that were low and indistinguishable from each other. By contrast, African American adolescents who began using marijuana around the ninth grade were significantly higher on these outcomes than were any of the other groups. Thus, initiation of marijuana use in mid-adolescence among African Americans poses the greatest risk for continued use. Brown, T.L., Flory, K., Lynam, D.R., Leukefeld, C., and Clayton, R.R. Comparing the Developmental Trajectories of Marijuana Use of African American and Caucasian Adolescents: Patterns, Antecedents, and Consequences. Experimental and Clinical Psychopharmacology, 12, pp. 47-56, 2004.

Maternal Influences on Urban Adolescent Girls' Smoking Intentions

Prior research has shown that parents who smoke are more likely to have children who smoke. Moreover, adolescents have been found to overestimate the number of adults and teenagers who smoke. This overestimation produces an expectation of smoking as normative and has been associated with an increase use of cigarettes among adolescents. This study examined maternal social influences on cigarette usage among urban minority girls with interview data from 450 mother-daughter dyads recruited from 30 New York City public and parochial middle schools. Girls in this sample ranged in age from 11 to 15 years and reported smoking rates of about 18% and smoking intention rates of 24%. Most of the sample was either Black or Latina, with smaller percentages of other groups (White, Native American, Asian). Neither mothers' reports of their own smoking nor maternal attitudes toward children's smoking were predictive of girls' experimental smoking and intentions to smoke in the next year. However, girls who perceived their mothers to be smokers were more likely to have tried smoking and to say that they intend to try smoking compared to girls who perceived their mothers to be nonsmokers. Compared to girls with low normative expectations of adult smoking, girls with high normative expectations were 2.89 times more likely to have tried cigarettes and 2.32 times more likely to intend to smoke. These findings suggest that preventive interventions aimed at correcting normative expectations of smoking among parents and youth may be helpful in deterring smoking among children. Nichols, T.R., Graber, J.A., Brooks-Gunn, J., and Botvin, G.J. Maternal Influences on Smoking Initiation Among Urban Adolescent Girls. Journal of Research on Adolescence, 14, pp. 73-97, 2004.

Ethnicity and Training Affects Observer Ratings of Family Interactions

Observer ratings are frequently used alone or in combination with other methods to provide more accuracy in measurement of health related behaviors. The present study illustrates the use of generalizability theory (Cronbach, Gleser, Nanda, & Rajarantnam, 1972) to assess possible sources of bias in observer ratings, as this approach allows for simultaneous examination of the contributions of multiple sources of error in the variance of observer ratings. In this study, two factors that may affect the level of rater agreement are examined: coder race and the interaction between coder race and observed family member (i.e., "target") race. Thirty behavioral scales were rated on three occasions during an initial 5-week training period. African-American and European-American coders observed videotaped interactions occurring

in one African-American and one European-American parent-child dyad. For each scale, levels of rater bias and rater agreement were examined over time. Although most scales showed decreasing levels of bias with training, some did not. For scales showing a main effect for coder race, European-American coders rated targets more favorably than African-American coders. For scales susceptible to coder race by target race interactions, coders tended to favor other-race rather than same-race targets. Melby, J.N., Hoyt, W.T., and Bryant, C.M. A Generalizability Approach to Assessing the Effects of Ethnicity and Training on Observer Ratings of Family Interactions. Journal of Social and Personal Relationships, 20(2), pp. 171-191, 2003.

Brief Measures of Sensation Seeking for Screening and Large-Scale Surveys

Sensation seeking is central to research on the prevention of risky health behaviors, but most measures of sensation seeking are fairly long. To increase the chances of inclusion of sensation seeking in research projects, the authors developed and evaluated two brief indices of sensation seeking, a four-item measure that retains the framework of the Sensation Seeking Scale-Form V (which is an 8-item measure), and a two-item measure focused on the risk-taking elements of sensation seeking. The performance of these new indices was compared with that of two well-documented longer measures of sensation seeking, based on data provided by more than 5,000 youth in grades seven through eleven. Psychometric analyses indicated that the internal consistency of the two new measures was very good overall and across grade and sex categories. Additionally, the new indices correlated with a series of risk and protective factors as well as tobacco, alcohol, and marijuana use. Since both indices performed in ways remarkably similar to the established measures of sensation seeking, they should prove useful for future research involving risky health behaviors. Stephenson, M.T., Hoyle, R.H., Palmgreen, P., Slater, M.D. Brief Measures of Sensation Seeking for Screening and Large-Scale Surveys Drug and Alcohol Dependence, 72, pp. 279-286, 2003.

Anger, Aggression, Risky Behavior, and Crash-Related Outcomes

This research sought to map the characteristics of high anger drivers who perceive they have a problem with driving anger (HAP drivers) and high anger drivers who perceive they have no problem with driving anger (HAPN drivers). Participants were 153 introductory psychology students (median age=19). Participants completed self-report measures of driving anger and a driving survey to characterize driving style in addition to other psychological measures. In addition, participants recorded driving miles, driving anger, and aggressive and risky driving in a log. There was some evidence that HAP drivers were somewhat angrier than HANP drivers. However high anger drivers did not differ from one another in terms of their anger during rush hour traffic, in their personally most angering situations, or on the frequency and intensity of anger in day-to-day driving. Analyses support the construct validity of the Driving Anger Scale. Deffenbacher, J.L., Lynch, R.S., Filetti, L.B., Dahlen, E.R., and Oetting, E.R. Anger, Aggression, Risky Behavior, and Crash-Related Outcomes in Three Groups of Drivers. Behaviour Research and Therapy, 41, pp. 333-349, 2003.

Director's Report to the National Advisory Council on Drug Abuse - May, 2004

Research Findings - Services Research

Long-Term Response to Treatment is Influenced by Early Response to Treatment and Participation in Aftercare

For many individuals substance use is a chronic, relapsing condition that can last for decades and require multiple treatment episodes. The objectives of this study were to (a) explore the relationships between initial severity, participant characteristics, treatment, recovery environment and initial and long-term response to treatment and (b) illustrate the need for long-term evaluation over multiple episodes of care. Data were collected from 1,054 adults seeking publicly funded substance abuse treatment. The final path analysis fit the data well (CFI = 0.99, RMSEA = 0.043). The effects of the initial treatment on long-term outcomes were entirely mediated by the initial response to treatment, participation in aftercare and 12-step support groups. This suggests the importance of evaluating outcomes in the context of (a) multiple episodes of care and (b) the extent to which a given episode of care produces initial changes in behavior and participation in a supportive recovery environment. Scott, C.K., Foss, M.A., and Dennis, M.L. Factors Influencing Initial and Longer-term Responses to Substance Abuse Treatment: A Path Analysis. Evaluation and Program Planning, 26, pp. 287-295, 2003.

Response to Substance Abuse Treatment Can Predict Subsequent Substance Use and Criminal Activity

Changes in criminal activity following substance abuse treatment were examined among 941 individuals. The estimated cost to society of crimes committed in the 6 months prior to intake was used to classify participants into three groups: no-, low-, and high-cost. Logistic regression was used to predict criminal activity at 6 and 24 months following intake as a function of (a) intake status, (b) treatment, and (c) outcome status and changes. The three groups varied significantly at intake and what predicted subsequent criminal activity. Treatment effects on criminal activity were mediated by the extent to which treatment reduced substance use. Outcomes were also predicted by other factors (e.g. housing, employment, medical problems, psychological distress, and social support). The results support the need for multidimensional assessments for predicting the risk of illegal activity, the need for reassessments following treatment, and the value of addressing other problems in reducing subsequent criminal activity. Scott, C.K., Foss, M.A., Lurigio, A.J., and Dennis, M.L. Pathways to Recovery after Substance Abuse Treatment: Leaving a Life of Crime Behind. Evaluation and Program Planning, 26, pp. 403-412, 2003.

Recovery Management Checkups Can Improve Long-term Outcomes of Chronic Substance Users

The majority of people presenting for publicly-funded substance abuse treatment relapse and receive multiple episodes of care before achieving long-term recovery. This Early Re-Intervention experiment evaluates the impact of a Recovery Management Checkup (RMC) protocol that includes quarterly recovery management checkups (assessments, motivational interviewing, and linkage to treatment re-entry). Data are from 448 adults who were randomly assigned to either RMC or an attention (assessment only) control group. Participants were 59% female, 85% African American, and 75% aged 30-49. Participants assigned to RMC were significantly more likely than those in the control group to return to treatment, to return to treatment sooner, and to spend more subsequent days in treatment; they were significantly less likely to be in need of additional treatment at 24 months. This demonstrates the importance of post-discharge recovery management checkups as a

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means to improve the long-term outcomes of people with chronic substance use disorders. Dennis, M., Scott, C.K. and Funk, R. An Experimental Evaluation of Recovery Management Checkups (RMC) for People with Chronic Substance Use Disorders. Evaluation and Program Planning, 26, pp. 339-352, 2003.

Drug Treatment Instrumental in Reducing Homelessness

The course of homelessness was examined among adult substance abusers entering treatment in the Chicago Target Cities treatment sample. The research objectives were to: (1) examine client movement in and out of homelessness over 2 years post entry into the index treatment episode, and (2) determine the treatment and non-treatment factors that predict achieving and sustaining residential stability. The sample, recruited from treatment programs on Chicago's West Side, was 59% female and predominantly African-American (87%), unemployed (86%), and unmarried (90%). Approximately one-third self-presented as homeless. Descriptive results showed that 73% of initially homeless clients had improved their residential status at 6 months, and 60% were stably housed at 24 months. By contrast, 28% of initially housed clients were not stably housed at 6 months (the majority of these had gone into residential treatment), and only 16% were homeless at 24 months. Sample-wide, homelessness was reduced by 37% between baseline and the 2-year follow-up. The high percentage of homeless substance abusers that achieved and maintained stable housing is consistent with a conclusion that treatment reduced homelessness in the Chicago Target Cities sample. Alternative explanations cannot be entirely ruled out, but are insufficient to nullify the general conclusion. Factors discriminating homeless and housed clients at baseline were consistent with prior literature. Several treatment and non-treatment factors predicted 6- and 24-month housing outcomes in conditional logistic regression models, although the significance and direction of effect estimates varied across conditions. The most consistent predictors were crack as the primary substance, which appears to be a persistent risk factor for becoming and remaining homeless, and whether or not the participant reported that persons were dependent on him/her for food/shelter, which appears to be a persistent protective factor for achieving housing and preventing homelessness. Orwin, RG., Scott, C.K., and Arieira, C.R. Transitions Through Homelessness and Factors that Predict Them: Residential Outcomes in the Chicago Target Cities Treatment Sample. Evaluation and Program Planning, 26, pp. 379-392, 2003.

Workplace Drug Testing Programs Can Discourage Employee Drug Use

Despite resistance among labor and consumer groups and a lack of rigorous empirical evidence regarding effectiveness, drug testing programs have remained popular with employers throughout the 1990s and into the current century. This study analyzed nationally representative data on over 15,000 US households to determine whether various types of workplace drug testing programs influenced the probability of drug use by workers. The study estimated several empirical specifications using both univariate and bivariate probit techniques, and specification tests favored the bivariate probit model. Estimated marginal effects of drug testing on any drug use were negative, significant, and relatively large, indicating that drug testing programs are achieving one of the desired effects. The results were similar when any drug use was replaced with chronic drug use in the models. These results have important policy implications regarding the effectiveness and economic viability of workplace anti-drug programs. French, M.T., Roebuck, M.C. and Alexandre, P.K. To Test or Not to Test: Do Workplace Drug Testing Programs Discourage Employee Drug Use? Social Science Research, 33(1), pp. 45-63, 2004.

Factors Supporting Innovation in Private Treatment Organizations

A study of 322 privately-funded substance abuse treatment centers participating in the University of Georgia National Treatment Center Study, found that provider organizations high in their capacity to absorb external knowledge via such activities as journal reading, participation in external seminars, staff professional association involvement, and various career development activities; as well as engaging in "environmental scanning" activities such as regularly seeking satisfaction input from patients and associated service support organizations were most likely to adopt therapeutic innovations. Larger provider organizations were significantly more likely to be high in absorptive capacity and environmental scanning. Knudsen, H.K., and Roman, P.M. Modeling the Use of Innovations in Private Treatment Organizations: The Role of Absorptive Capacity. Journal of Substance Abuse Treatment, 26, pp. 353-361, 2004.

Management Practices Have Potential to Reduce Turnover in Substance Abuse Counselors

A study of 1,107 substance abuse treatment counselors from 345 privately-funded substance abuse treatment centers participating in the University of Georgia National Treatment Center Study found that in clinics where management provided high job autonomy, supported counselor creativity, and rewarded good job performance counselors expressed higher levels of commitment to the organization and high levels of intent to remain in the organization. Results demonstrate that management practices in substance abuse treatment clinics have potential to reduce job turnover, thereby avoiding personnel costs associated with job turnover (recruiting, hiring, and training replacements) and lost treatment resources due to disruption of continuity of care for patients. Knudsen, H.K., Johnson, J.A. and Roman, P.M. Retaining Counseling Staff at Substance Abuse Treatment Centers: Effects of Management Practices. Journal of Substance Abuse Treatment, 24, pp. 129-135, 2003.

Cost-Effectiveness of Post-Release Substance Abuse Treatment For Criminal Offenders

A study of Delaware's CREST Outreach Center, a work release therapeutic community (TC) and aftercare program for criminal offenders estimated the cost-effectiveness over an 18-month post-release follow-up for four study groups: CREST work release TC completers, CREST work release TC noncompleters, CREST work release completers who also participated in aftercare treatment, and a comparison group of standard work release participants. The 6-month CREST program cost $1,937 for the average participant, and led to 30 fewer days incarcerated (29% less) than the average participant in a standard work release program. This implies that the CREST program reduced incarceration for criminal offenders at an average cost of $65 per day. The additional investment of $935 per client to provide aftercare services led to 49 fewer days incarcerated (43% less) than CREST work release-only participants. This suggests that by adding an aftercare component to the CREST work release program, a day of incarceration is avoided at an average cost of $19 per day. These results indicated that completing the CREST work release TC program and participating in aftercare were cost-effective treatment strategies. McCollister, K.E., French, M.T., Inciardi, J.A., Butzin, C.A., Martin, S.S. and Hooper, R.M. A Cost-Effectiveness Analysis of Post-release Substance Abuse Treatment for Criminal Offenders. Journal of Quantitative Criminology, 19(4), pp. 389-407, 2003.

Cost-Effectiveness of Addiction Treatment: Paradoxes of Multiple Outcomes

This paper identifies and illustrates the challenges of conducting cost-effectiveness analysis of addiction treatments given the multiple important outcomes of substance abuse treatment. Potential problems arise because cost-effectiveness analysis is intended primarily for single outcome programs, yet addiction treatment results in a variety of outcomes such as reduced drug use and crime and increased employment. Methodological principles, empirical examples, and practical advice are offered on how to conduct an economic evaluation given multiple outcomes. An empirical example is provided to illustrate some of the conflicts in cost-effectiveness ratios that may arise across the range of outcomes. The data are from the Philadelphia Target Cities quasi-experimental field study of standard versus "enhanced" (e.g. case management and added social services) drug treatment. Outcomes are derived from the Addiction Severity Index, while cost data were collected and analyzed using the Drug Abuse Treatment Cost Analysis Program. While the results are illustrative only, they indicate that cost-effectiveness ratios for each of several different outcomes can produce conflicting implications. These findings suggest that multiple outcomes should be considered in any economic analysis of addiction treatments because focusing on a single outcome may lead to inadequate and possibly incorrect policy inferences. However, incorporating multiple outcomes into a cost-effectiveness analysis of addiction treatment is difficult. Cost-benefit analysis may be a preferable and more appropriate approach in some cases. Sindelar, J.L., Jofre-Bonet, M., French, M.T., and McLellan, A.T. Cost-Effectiveness Analysis of Addiction Treatment: Paradoxes of Multiple Outcomes. Drug and Alcohol Dependence, 73(1), pp. 41-50, 2004.

Adolescent Substance Abuse: Under-reported or Under-detected by Health Plans?

This article examines whether health plans are adequately identifying adolescents with substance use problems. Three measures developed by the Washington Circle, a group focused on the development of substance use performance measures, have been adapted for the 2004 Health Plan Employer Data and Information Set. One measure-the identification rate-can be used to examine the extent to which private health plans are able to identify adolescent enrollees with substance abuse problems. Using MarketScan, a database of private health plan claims for selected employers maintained by the MEDSTAT Group, researchers calculated a 0.5 percent rate of

adolescents (ages 12-18 years) identified with substance abuse problems among those enrolled in 1997. This rate is low compared to the 6.8 percent rate of substance dependence reported by a subset of adolescents covered by commercial insurance who were included in the 1998 National Household Survey on Drug Abuse. Researchers detected no meaningful variation across health plan type. Researchers suggest that the low identification rate may be due to (a) providers' reluctance to record substance abuse diagnoses due to stigma or legal issues, or (b) providers' failure to identify substance abuse because they lack adequate training in or incentives for screening and diagnosis. Lee, M.T., Garnick, D.W., Miller, K. and Horgan, C.M. Adolescents with Substance Abuse: Are Health Plans Missing Them? Psychiatric Services, 55(2), p. 116, 2004.

Preventive Interventions for Externalizing Disorders in Adolescents

Adolescent externalizing dimensions refer to the cluster of highly co-occurring behaviors and disorders that include conduct disorders, oppositional defiant disorders, Attention Deficit Hyperactivity Disorder, substance use disorders and-more recent to the literature-problem gambling. Externalizing disorders are likely influenced by several personal (e.g., personality, attitudes, values) and environmental (e.g., peers, parenting practices, intervention or treatment experiences) factors. The emerging discipline of developmental psychopathology provides a conceptual framework that is applicable to the study of the etiology, prevention and intervention of externalizing disorders of youth. Developmental psychopathology is a macroparadigm, which emphasizes the contrast between typical and atypical development. This conceptualization allows for qualitative changes in functioning over time, and the influence by mediator and moderator variables at varying developmental stages from adolescence to young adulthood. In the past, preventive interventions for youth with externalizing disorders, many of which have focused on substance abuse, were designed as one-size-fits-all. The disappointing results have drawn attention to the complexity and multiplicity of the risk factors involved. In order to prevent the onset, maintenance and course of externalizing behaviors among adolescents, a prevention framework must include strategies crafted to respond to the unique risk profiles of various subgroups of the population. Consequently, prevention efforts that are initiated early in a child's life, adjusted with emerging developmental tasks and sustained over time, are the best possible tools available today. Winters, K.C., August, G.E., and Leitten, W. Preventive Interventions for Externalizing Disorders in Adolescents. In D. Rowe (Ed.), Reducing Adolescent Risk: Toward An Integrated Approach. Newbury Park, CA: Sage Press, 2003.

Runaway Youth's Use of Federally-Funded Crisis Services Differs by Region

This study examined national and regional differences between runaway shelter users and national census norms on demographic and high-risk characteristics. Data collected from federally-funded youth shelters nationwide (n = 16,652) were compared with U.S. adolescent populations (n = 26,735,028). Runaway youth were more likely to be female, minority and older than respective national figures; ethnicity varied greatly from one region of the U.S. to another. Proportions of youth with high-risk characteristics, such as illicit drug use and selling, suicidal behaviors, and physical and sexual abuse were strikingly different across regions. Development of policies and services that target particular issues of youth in specific regions is needed. Thompson, S., Maguin, E., and Pollio, D. National and Regional Differences Among Runaway Youth Using Federally-Funded Crisis Services. Journal of Social Services Research, 30(1), pp. 1-17, 2003.

Women More Vulnerable than Men to Relapse Because of Substance-Using Partners

Gender differences in the characteristics of individuals entering drug treatment and their post-treatment substance use were examined among 904 individuals, the majority of whom were female (63%) and predominantly African American (93%), who were admitted into the Chicago Target Cities Project. Bivariate relationships were examined in background characteristics, addiction and treatment career parameters, family and social relationships, psychosocial functioning, and treatment/social interventions received. Path analysis was used to determine the predictors of drug/alcohol use at 6- and 24-months following intake at a central referral agency, by developing separate path models for males and females. Drug/alcohol use was significantly reduced for men and women at 6- and 24-months, dropping by about 50% for both. Women had more episodes of subsequent treatment and men had higher rates of incarceration during the follow-up periods. The path analyses showed that at 6-months following intake, living with someone with a drug/alcohol problem was related to higher rates of drug/alcohol use for women, but not for men. For both

men and women, psychological distress was related to higher levels of substance use at the 6-month follow-up, whereas having an improved living situation and participating in 12-step groups were related to lower levels of use at both follow-up points. The findings suggest that, although there are some similarities in the factors related to recovery for both men and women, women are more vulnerable to relapse because of having substance-using partners. Grella, C.E., Scott, C.K., Foss, M.A., Joshi, V. and Hser, Y. Gender Differences in Drug Treatment Outcomes Among Participants in the Chicago Target Cities Study. Evaluation and Program Planning, 26, pp. 297-310, 2003.

Epidemiology of Substance Use Disorders in Women

This article reviews the current epidemiology and patterns of substance use, abuse, and dependence, and the course, medical consequences, and treatment-related issues of substance disorders in women of all ages. There are approximately 15.1 million individuals who abuse or depend on alcohol in the United States; approximately 4.6 million (nearly one third) of these individuals are women. In 2001, an estimated 15.9 million Americans aged 12 years or older were current illicit drug users, and more than a third were women. In 1999, almost 4% of pregnant women were past-month users of illicit drugs. Research suggests that women are more susceptible than men to substance-related interpersonal difficulties, trauma, and medical consequences, heightening their risk of morbidity and mortality. In an early study of 100 alcohol-dependent women, 31% were dead at the 11-year follow-up, with most deceased from alcohol-related causes. The lifespan of these alcohol-dependent women was shortened by an average of more than 15 years. In a more recent study, heavily drinking women (> 4 standard alcoholic drinks/day) died significantly earlier compared with non-alcohol-dependent women (consume <4 standard alcoholic drinks/day), and there was also a trend toward earlier mortality rates compared with the heavily drinking men (>8 standard alcoholic drinks/day). In addition to these data on alcohol disorders, other studies indicate a broad range of health-related consequences in women with substance use disorders. For example, in 1986, mortality for lung cancer in women surpassed breast cancer mortality to become the leading cause of cancer death for women in the United States. These and other illnesses and accidents that can be attributed to substance use and abuse in women accounted for $68 billion in health care costs in 1995 (12.3% of the total health care expenditure for women). Despite these statistics, women are underrepresented in traditional substance abuse treatment settings. This may be partly because women tend to pursue avenues of treatment other than traditional substance abuse programs, such as mental health or primary care services. One study of obstetrics and gynecology practices found that 12% to 16% of patients had an alcohol disorder. The obstetrician gynecologist (OB-GYN) may be the only clinician and primary care provider for many women through the life cycle. Many of these women come for a myriad of problems that may or may not be related to their substance abuse, including routine physical examinations, prenatal care, and sexual problems. Discussions about infertility, pregnancy, or birth control provide the OB-GYN with an opportunity to assess and advise patients about their alcohol or drug use. From a public health and clinical perspective, this presents an enormous opportunity to detect and counsel these patients and refer them to appropriate treatment as indicated. Greenfield, S.F., Manwani, S.G. and Nargiso, J.E. Epidemiology of Substance Use Disorders in Women. Obstetrics and Gynecology Clinics of North America, 30(3), pp. 413, 2003.

Methamphetamine Use Behaviors and Gender Difference

This analysis describes methamphetamine (MA) use behaviors in a broad cross-section of (N = 350) former clients from a large publicly funded treatment system and examines differences between males and females in drug use history, MA initiation and motivators, MA-related problems, acquisition, distribution, manufacture, and treatment characteristics. Results describe the prevalence of polydrug use, prolonged MA use before treatment, initiation primarily through friends, common sensation-seeking motivators (to have fun, get high, and experiment), numerous problems related to MA use (including paranoia, violent behavior, hallucinations, financial problems, and legal and work problems), and a majority who have sold MA. Gender differences appear in selected aspects of motivators and routes of initiation, access to MA, use patterns, and MA-related problems. Males were more likely than females to report work problems (70% vs. 48%) and high blood pressure (31% vs. 16%), and females were more likely to report skin problems (47% vs. 27%). Such description of behaviors and gender differences can provide a basis for development of treatment strategies and points of departure for future research. Brecht, M.L., O'Brien, A., von Mayrhauser, C. and Anglin, M.D. Addictive Behaviors, 29(1), pp. 89-106, 2004.

Burden of Medical Illness in Drug and Alcohol Dependent Persons without Primary Care

Little is known about the frequency, severity and risk factors for disease in drug and alcohol dependent persons without primary medical care. This article assesses the burden of medical illness and identifies patient and substance dependence characteristics associated with worse physical health in order to compare measures of illness burden in this population. Researchers conducted a cross-sectional study among alcohol, heroin or cocaine dependent persons without primary medical care admitted to an urban inpatient detoxification unit (mean age = 35.7 years; 76% male; 46% Black). Forty-five percent reported being diagnosed with a chronic illness, and 80% had prior medical hospitalizations. The mean age-adjusted SF-36 Physical Component Summary (PCS) score was significantly lower than the general U.S. population norm (44.1 vs. 50.1). In multivariable analysis, the following factors were associated with worse health: female gender, problem use of hallucinogens, heroin, other opiates, living alone, having medical insurance, and older age. Alcohol and drug dependent persons without primary medical care have a substantial burden of medical illness compared to age and gender matched U.S. population controls. While the optimal measure of medical illness burden in this population is unclear, a variety of health measures document this medical illness burden in addicted persons. De Alba, I., Samet, J.H. and Saitz, R. Burden of Medical Illness in Drug and Alcohol Dependent Persons without Primary Ccare. American Journal of Addiction, 13, pp. 33-45, 2004.

Similarities and Differences in Rural and Urban Substance Abuse Treatment

Using three waves of longitudinal data from a nationally representative sample of 450 privately-funded substance abuse treatment centers, this research found that rural and urban centers were similar in their increasing provision of inpatient psychiatric levels of care and their decreasing provision of more intensive services for chemical dependency between 1995 and 2001. Rural and urban centers were increasingly likely to offer specialty treatment tracks for women, adolescents, clients with HIV/AIDS, and relapsing clients over time, but rural centers were less likely to offer a treatment track tailored to substance-abusing women. The use of treatment innovations was similar at rural and urban treatment centers with the exception of lesser use of acupuncture at rural centers. Rural and urban centers did not differ in their average charges for treatment services. Knudsen, H.K., Johnson, J.A., Roman, P.M. and Oser, C.B. Rural and Urban Similarities and Differences in Private Substance Abuse Treatment Centers. Journal of Psychoactive Drugs, 35, pp. 511-518, 2003.

Medical and Psychiatric Conditions of Alcohol and Drug Treatment Patients in an HMO

This study compares the prevalence of medical and psychiatric conditions among 747 substance-abuse patients with 3,690 demographically-matched controls from the same health maintenance organization (HMO), and examines whether comparisons vary among demographic and substance-type subgroups. Approximately one-third of these comorbid conditions were more common among alcohol and drug patients than among matched controls, and many of these were among the most costly conditions. Researchers also found that pain-related diagnoses, including arthritis, headache, and lower back pain, were more prevalent among alcohol and drug patients, and particularly among those dependent upon narcotic analgesics. Findings point to the importance of examining comorbid medical and substance abuse in both primary care and specialty care. Findings regarding pain-related diagnoses among those dependent upon narcotic analgesics highlight the need for linkages between primary care and substance abuse treatment. Mertens, J.R., Lu, Y.W., Parthasarathy, S., Moore, C. and Weisner, C.M. Medical and Psychiatric Conditions of Alcohol and Drug Treatment Patients in an HMO: Comparison to Matched Controls. Archives of Internal Medicine, 163(20), pp. 2511-2517, 2003.

Perceived Accessibility and Coordination of Service for Persons With Co-Occurring Substance Abuse and Mental Disorders

Several initiatives in the past 20 years have been implemented in Los Angeles County to improve service delivery across the mental health and substance abuse treatment systems, with the goal of increasing access to and coordination of services for individuals with co-occurring substance abuse and mental disorders. To examine the current status of service delivery to this population, a survey was conducted with administrators of mental health and substance abuse programs that provide services to dually diagnosed patients and with the treatment staff in those programs. Administrators (n = 15) and staff (n = 99) in substance abuse programs rated the accessibility and coordination of services to dually diagnosed patients significantly

lower than the mental health administrators (n = 10) and staff (n = 136). Efforts to coordinate service delivery across the two systems need to address these divergent perceptions between staff in programs that are increasingly called upon to work together to jointly deliver services. Grella, C.E., Gil-Rivas, V. and Cooper, L.J. Perceptions of Mental Health and Substance Abuse Program Administrators and Staff on Service Delivery to Persons with Co-occurring Substance Abuse and Mental Disorders. Behavioral Health Services Research, 31(1), pp. 38-49, 2004.

Increased Prevalence of Psychiatric Illness Among Homeless, 1980-2000

Researchers examined the prevalence of psychiatric illness among 3 homeless populations in St. Louis, MO, in approximately 1980, 1990, and 2000. The prevalence of mood and substance use disorders and the number of minorities within these populations has increased over the two decades. Service systems need to be aware of potential prevalence changes, the increasing severity of their clientele's care needs and the growing health disparities that impact treatment service needs. North, C.S., Eyrich, K.M., Pollio, D.E. and Spitznagel, E. A Comparison of Psychiatric Prevalence of Homelessness Across Three Decades. American Journal of Public Health, 94(1), pp. 103-108, 2004.

HIV Testing For Homeless Women Indicated

This study describes the prevalence and predictors of HIV testing in a probability cluster sample of urban homeless women. Researchers analyzed data from the University of California Los Angeles-RAND Access to Health Care for Homeless Women of Reproductive Age Study, a survey conducted in six waves from January 1997 through November 1997 at shelters and soup kitchens in Los Angeles (LA) County. The sampling unit consists of homeless woman-visits, and data were collected using structured face-to-face interviews for which respondents were paid $10. Each sampling unit was weighted to account for the frequency with which respondents used shelters or meal programs. The main outcome measure was receipt of HIV test in the past year. With a response rate of 83%, the final sample size was 970. Sixty-eight percent reported receiving an HIV test in the past year, and 1.6% reported ever being diagnosed with HIV. HIV testing in the past year was most strongly associated with pregnancy in the past year and with having a regular source of care. Approximately 25% of homeless women with indications for HIV testing had not been tested in the past year. The reported HIV seroprevalence of greater than 1% suggests that providers should offer and encourage HIV testing for all homeless women in LA County. These data, which show a high rate of testing and few statistically significant independent predictors, indicate that this may be what is happening in practice. Herndon, B., Asch, S.M., Kilbourne, A.M., Wang, M., Lee, M., Wenzel, S.L., Andersen, R. and Gelberg, L. Prevalence and Predictors of HIV Testing Among a Probability Sample of Homeless Women in Los Angeles County. Public Health Rep., 118(3), pp. 261-269, 2003.

Posttraumatic Stress Disorder Among Minority Drug Users

This study explores cocaine abuse/dependence with physiological dependence and posttraumatic stress disorder diagnosis differences between out-of-treatment Hispanic and African American adults, in order to identify cultural differences in how experiences and attitudes affect cocaine use behaviors. Data was collected between February and November 2000, as part of a three-year longitudinal study. A cohort of 347 out-of-treatment, Hispanic and African American cocaine-using adults from the Houston metropolitan area were interviewed to measure differences between cocaine users who are dually diagnosed and those that are not. For the dual diagnoses categories, 102 (29%) participants met the requirements. Logistic regression models were used with age, race, gender, and income as the independent variables. Results indicate that individuals with higher income have a greater probability of developing a diagnosis. Results also indicate that being female increases the likelihood of developing both types of dual diagnoses. However, being an older female decreases the probability that an individual would develop these dual diagnoses. No differences were found for race/ethnicity among the dually diagnosed Hispanics and African Americans, however, gender differences were found. Treating high-risk substance abusers who are members of minority groups may require varied protocols depending on differences among minority groups. Montoya, I.D., Covarrubias, L.D., Patek, J.A., and Graves, J.A. Posttraumatic Stress Disorder among Hispanic and African-American Drug Users. American Journal of Drug and Alcohol Abuse, 29 (4), pp. 729-741, 2003.

HCV Antibody Testing in Drug-Free and Methadone Maintenance Treatment Programs

Drug treatment programs are uniquely situated to screen patients for antibodies for hepatitis C virus (HCV), an infectious disease that has reached epidemic proportions among drug users. The researchers compare the accessibility of and patients' use of opportunities for HCV antibody testing in a large sample of methadone and drug-free treatment programs (N=256) in the U.S. The researchers found that almost all methadone and about 2/3 of drug-free programs in the sample provided HCV antibody screening to at least some patients in 2001. While about 2/3 of the methadone and close to 1/3 of the drug-free programs offered this service to all patients, these programs report that only about 3/5 of their patients actually provided specimens for testing for HCV antibodies. These results can inform policymakers who advocate for increased HCV antibody screening in drug treatment programs about the current level and future plans for implementing these services, illuminating where resources and motivational efforts need to be targeted. Strauss, S.M., Astone, J.M., Des Jarlais, D.C. and Hagan, H. A Comparison of HCV Antibody Testing in Drug-free and Methadone Maintenance Treatment Programs in the United States. Drug and Alcohol Dependence, 73(3), pp. 227-236, 2004.

Self-Reported Health Status Among Treated Methamphetamine Users

Little research has examined how drug abuse is related to general health status over the long term among young and middle-aged adults. Researchers investigate how self-reported health status is related to prolonged methamphetamine (MA) use in a diverse sample of MA users from ages 18 to 52 who have been treated for drug abuse in Los Angeles County. Using retrospective data, the researchers investigated how prolonged MA use within younger and older age groups is related to two self-reported measures of current health status: the presence of a health condition that began after starting illegal drug use, and overall health. After controlling for the effects of drug use history, social and demographic factors, and other early experiences (e.g., early sexual abuse) that might be obstacles to achieving good health later in life. The researchers found that having a current health condition is predicted by greater age and by more prolonged MA use, especially among younger people. Early sexual abuse predicts both measures of poor health. Current health status is predicted by several measures of drug use history and early experiences, but by fewer social and demographic factors. The results suggest that reduction of MA use among younger people is important in promoting their later health and that MA treatment services could be improved by a greater understanding of how early experiences influence later health. Greenwell, L. and Brecht, M.L. Self-Reported Health Status among Treated Methamphetamine Users. American Journal of Drug and Alcohol Abuse, 29(1), pp. 75-104, 2003.

Trends of Criminal Activity and Substance Use in Welfare Recipients

The Personal Responsibility and Work Opportunity Reconciliation Act (PRWORA) of 1996 instituted a compulsory work mandate for welfare recipients. However, recipients who experience difficulties finding employment may increase their involvement in criminal activities and their frequency of substance use as a means to deal with changes precipitated by PRWORA. This study used a four-wave panel design to analyze the criminal behaviors and substance-use frequency of 534 welfare recipients in Houston, Texas. Data were collected from the Attitudes, Behaviors, and Skills Assessment (ABSA) instrument designed specifically for this study. Results show that a minority of welfare recipients were involved in criminal activity. Furthermore, although participants were losing their welfare benefits, both criminal activity and substance use declined over time. Brown, V.L., Montoya, I.D., Dayton-Shotts, C.A., Carroll-Curtis, T.L., and Riley, M.A. Trends of Criminal Activity and Substance Use in a Sample of Welfare Recipients. Crime and Delinquency, 50(1), pp. 6-23, 2004.

Predictors of Self-Reported HIV Infection Among Drug Injectors in Ukraine

The spread of HIV infection in Eastern Europe has been most intense in Ukraine where the number of cases has grown from 1,500 in 1994 to over 230,000 in 2002. Much of this rise in infection has been attributed to injection drug use. Researchers interviewed 212 IDUs (mean age = 29 years; 28% female) from Makeevka/Donetsk, Kiev, and Odessa. Responses indicated that 89% had injected drugs within the past 30 days, and that most respondents engaged in unsafe needle use. No gender differences were found. HIV positive respondents reported increased safe sex behavior, but were more likely to engage in unsafe needle use. Less than 25% reported receiving information about AIDS or risk reduction. Injection with others was common regardless of HIV status. Results suggest that HIV infection in Ukraine will continue to grow fueled to a large extent by unsafe injection drug use. Booth, R.E., Mikulich-Gilbertson, S.K., Brewster, J.T., Salomonsen-Sautek, S. and Semerik, O.

Predictors of Self-Reported HIV Infection Among Drug Injectors in Ukraine. Epidemiology and Social Science, 35(1), pp. 82-88, 2004.

Screening and Assessing Youth for Drug Involvement

Inclusion of this new chapter in the handbook underscores a growing recognition that the adolescent assessment literature has a significant body of research on alcoholism and drug addiction. The chapter provides an overview of several issues pertinent to evaluating adolescents for AOD use and related problems. It is organized around four major themes: Developmental issues that highlight the importance of assessing young people from a theoretical perspective and with instruments that are distinct from adult models; validity of self-report; types of instruments available for a range of assessment goals; and research needs in the field. Winters, K.C. Screening and Assessing Youth for Drug Involvement. In J. Allen and M. Colombus (Eds.), NIAAA Handbook on Assessment Instruments for Alcohol Researchers (2nd edition). Rockville, MD: National Institute on Alcohol Abuse and Alcoholism, 2003.

Director's Report to the National Advisory Council on Drug Abuse - May, 2004

Research Findings - Intramural Research

Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Cannabinoid CB1 Receptor and Serotonin 3 Receptor Subunit A (5-HT3A) are Co-expressed in GABA Neurons in the Rat Telencephalon

Among all described serotonin (5-HT) receptors in mammals, the type three (5-HT3) is the only ligand-gated ion channel receptor for serotonin. By using double in situ hybridization histochemistry, we found co-expression of the functional 5-HT3A subunit of the 5-HT3 receptor and the central CB1 cannabinoid receptor in neurons of the rat telencephalon. Double-labeled 5-HT3A/CB1 neurons were found in the anterior olfactory nucleus, superficial and deep layers of the cortex, hippocampal formation (hippocampus, dentate gyrus, subiculum, and entorhinal cortex) and amygdala. Analysis of the proportion of neurons co-expressing 5-HT3A and CB1 receptors in the cortex and amygdala showed that, depending on the brain region, 37-53% of all neurons expressing the 5-HT3A subunit also expressed CB1 transcripts; 16-72% of the total population of neurons expressing CB1 mRNA co-expressed the 5-HT3A subunit. By using a combination of double in situ hybridization and immunohistochemistry, we demonstrated that 5-HT3A/CB1-expressing neurons contained the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). These results imply that in distinct regions of the telencephalon, GABA neurons that react to cannabinoids may also be responsive to serotonin through 5-HT3 receptors. Cellular coexistence of 5-HT3A and CB1 transcripts in interneurons of the cortex, hippocampal formation, and amygdala suggest possible interactions between the cannabinoid and serotonergic systems at the level of GABA neurotransmission in brain areas involved in cognition, memory, and emotion. Morales, M., Wang, S.D., Diaz-Ruiz, O., and Jho, D.H. Journal of Comparative Neurology, 468, pp. 205-216, 2004.

Electrophysiology Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Cocaine Inhibits Cromakalim-Activated K(+) Currents in Follicle-Enclosed Xenopus Oocytes The effect of cocaine on K(+) currents activated by the K(ATP) channel opener cromakalim was investigated in follicular cells of Xenopus oocytes. The results indicate that cocaine in the concentration range of 3-500 microM reversibly inhibits cromakalim-induced K(+) currents. The IC(50) value for cocaine was 96 microM. Inhibition of the cromakalim-activated K(+) current by cocaine was noncompetitive and voltage independent. Pretreatment with the Ca(2+) chelator BAPTA did not modify the cocaine-induced inhibition of cromakalim-induced K(+) currents, suggesting that Ca(2+)-activated second messenger pathways are not involved in the actions of cocaine. Outward K(+) currents activated by the application of 8-Br-cAMP or forskolin were also inhibited by cocaine. The EC(50) and slope values for the activation of K(+) currents by cromakalim were 184+/-19 microM and 1.14 in the absence of cocaine as compared to 191+/-23 microM and 1.03 in the presence of cocaine (300 microM). Cocaine also blocked K(+) currents mediated through C-terminally deleted form of Kir6.2 (KirDeltaC26) in the absence of sulfonylurea receptor with an IC(50) value of 87 microM, suggesting that cocaine interacts directly with the channel forming Kir6.2 subunit. Radioligand binding studies indicated that cocaine (100 microM) did not affect the binding characteristics of the K(ATP) ligand, [(3)H]glibenclamide. These results demonstrate that cromakalim-activated K(+) currents in follicular cells of Xenopus oocytes are modulated by cocaine. Oz, M., Zakharova, I., Dinc, M., and Shippenberg, T. Naunyn Schmiedebergs Archives of Pharmacology, 369, pp. 252-259, 2004.

Index

Molecular Neuropsychiatry Section, Molecular Neuropsychiatry Research Branch

Chronic Methamphetamine Increases Fighting in Mice A propensity for violent behaviors to develop in chronic methamphetamine (METH) abusers has been noted. The idea that increased aggressiveness might result from chronic METH administration was tested in mice after chronic (long-term intermittent, 8 weeks) or single exposures to the drug. A single injection of METH (6 mg/kg) did not augment fighting. In contrast, chronic METH administration significantly increased the number of animals that initiated bite attacks. This regimen also shortened the latency before the first attack. Latency before the first attack was shorter at 20 h after the METH injection than at 15 min after injection. Locomotor activity was not different at 20 h after METH injection, indicating that increased fighting was not secondary to METH-induced hyperactivity. METH-induced increases in fighting were not related to the duration of persistent sniffing after the initial encounter with an intruder since the duration of this behavior was significantly increased at 15 min after METH but not at 20 h post drug. These results indicate that repeated injections of METH can increase fighting behaviors and also alter social interactions in mice. Thus, intermittent administration of METH might be useful as a pharmacological model to study the biochemical and molecular bases of aggressiveness. Sokolov, B.P., Schindler, C.W. and Cadet, J.L. Pharmacology Biochemistry and Behavior, 77, pp. 319-326, 2004.

Methamphetamine Induces Neuronal Apoptosis via Cross-talks Between Endoplasmic Reticulum and Mitochondria-dependent Death Cascades Methamphetamine (METH) is an illicit drug that causes neurodegenerative effects in humans. In rodents, METH induces apoptosis of striatal glutamic acid decarboxylase (GAD) -containing neurons. This paper provides evidence that METH-induced cell death occurs consequent to interactions of ER stress and mitochondrial death pathways. Specifically, injections of METH are followed by an almost immediate activation of proteases calpain and caspase-12, events consistent with drug-induced ER stress. Involvement of ER stress was further supported by observations of increases in the expression of GRP78/BiP and CHOP. Participation of the mitochondrial pathway was demonstrated by the transition of AIF, smac/DIABLO, and cytochrome c from mitochondrial into cytoplasmic fractions. These changes occur before the apoptosome-associated pro-caspase-9 cleavage. Effector caspases-3 and -6, but not -7, were cleaved with the initial time of caspase-3 activation occurring before caspase 9 cleavage; this suggests possible earlier cleavage of caspase-3 by caspase-12. These events preceded proteolysis of the caspase substrates DFF-45, lamin A, and PARP in nuclear fractions. These findings indicate that METH causes neuronal apoptosis in part via cross-talks between ER- and mitochondria-generated processes, which cause activation of both caspase-dependent and -independent pathways. Jayanthi, S., Deng, X., Noailles, P.A., Ladenheim, B. and Cadet, J.L. FASEB Journal, 18, pp. 238-251, 2004.

Molecular Neurobiology Branch

Estimating the Burden of Complex Genetics in Brain Disorders Few data estimate the impact of complex genetics in neuropsychiatric illness, making it likely that this impact could be underappreciated. Investigators provide estimates of the impact of complex genetics in neuropsychiatric disorders in the United States, based on estimates of disease costs to US society, disease heritability, and mendelian contributions to disease. Costs were estimated from literature sources and Lewin-National Foundation for Brain Research estimates updated for population growth and consumer price index inflation. Heritability estimates came from available twin data. Estimates of mendelian contributions came from the Online Mendelian Inheritance in Man database and our perspectives. Brain and nervous system disorders may cost the United States as much as $1.2 trillion annually, and affect many millions of Americans each year. Twin data suggest that more than 40% of the societal burden of brain disorders is likely to be genetically mediated. Most of this disease burden arises from complex multigene genetics as well as from environmental influences. The large sizes of these complex genetic burdens should encourage careful molecular and clinical work to link disease vulnerability allelic variants with the pathogenesis, nosologic characteristics, prevention, diagnostics, and therapeutics of brain disorders. Uhl, G.R. and Grow, R.W. Archives of General Psychiatry, 61, pp. 223-229, 2004.

Psychobiology Section, Medications Discovery Research Branch

What is Represented by Vertical Shifts in Self-administration Dose-response Curves? Several recent papers have made suggested mechanisms for changes in the drug self-administration dose-effect curve. In particular, a substantial amount of theory construction surrounds the observations of vertical shifts in dose-effect curves.

In this paper, IRP investigators make suggestions regarding ways in which these changes can be conceptualized so that they become subject to objective rational study. Importantly it should be appreciated that there are many factors that contribute to the shape of the curve, including the potential for tolerance to various effects of the drug being self administered. Potential mechanisms thought to underlie changes in the self administration of cocaine are discussed from a perspective based on clinical findings. These findings suggest some problems resulting from the unfettered extrapolation of some preclinical theories, providing a focus for refinements in theory. Katz, J.L. and Higgins, S.T. Psychopharmacology, 171, pp. 360-361, 2004.

Medicinal Chemistry Section, Medications Discovery Research Branch

Synthesis and Monoamine Transporter Binding of 2-(Diarylmethoxymethyl)-3_-aryltropane Derivatives A series of 3_-aryl tropane analogues wherein the 2-position was substituted with various diarylmethoxyalkyl groups was synthesized and evaluated for binding at the dopamine (DAT), serotonin (SERT), norepinephrine transporter (NET) and muscarinic (M1) receptors. The 2_-analogues generally demonstrated high to moderate binding affinities (Ki = 34 -112 nM) at the DAT with good selectivity over SERT, NET and M1 receptors. Alternatively, the 2_-isomers were 10-fold less potent at the DAT with poor selectivity over SERT. These Structure-Activity Relationship (SAR) studies provide further evidence for the varied binding requirements of structurally diverse tropane-based ligands and support future studies to elucidate DAT binding requirements in relation to cocaine-like behavioral endpoints. Xu, L., Kulkarni, S. S., Izenwasser, S., Katz, J. L., Kopajtic, T., Lomenzo, S. A., Newman, A. H., and Trudell, M. L. Journal of Medicinal Chemistry, 47, pp. 1676-1682, 2004

Neurobiology of Relapse Section, Behavioral Neuroscience Research Branch

A Single Infusion of BDNF into the Ventral Tegmental Area Induces Long-lasting Potentiation of Cocaine-seeking After Withdrawal Cocaine addiction in humans is associated with long-term propensity to relapse. Using a rat relapse model, IRP scientists found that cocaine-seeking induced by exposure to cocaine-associated cues progressively increases after withdrawal. This progressive increase is associated with increases in brain-derived nerve growth-factor (BDNF) levels within the mesolimbic dopamine system. Based on these findings, we studied whether BDNF infusions into the ventral tegmental area (VTA), the cell body region of mesolimbic dopamine neurons, would potentiate cocaine-seeking after withdrawal. Rats were trained to self-administer cocaine for 10 days and cocaine-seeking was measured in extinction tests 3, 10 or 30 d after withdrawal. During testing, rats were exposed to contextual cues that had predicted cocaine availability during training and lever-presses resulted in contingent presentations of a discrete tone-light cue that was previously temporally paired with cocaine infusions. BDNF (0-0.75 µg/site) or nerve growth factor (NGF, 0-0.75 µg/site) was infused into the VTA 1-2 h after the last self-administration session. To examine the role of the mitogen-activated protein kinase (MAPK) pathway in BDNF effects, U0126 (1 µg/site), a MEK inhibitor, was used. A single intra-VTA infusion of BDNF, but not NGF, induced long-lasting enhancement of cocaine-seeking for up to 30 days, an effect reversed by U0126. In contrast, neither BDNF infusions into the substantia nigra, nor acute intra-VTA BDNF infusions 2 h prior to testing on day 3 of withdrawal, were effective. These data suggest that BDNF-mediated neuroadaptations in mesolimbic areas are involved in the persistent cocaine-seeking induced by exposure to drug cues after withdrawal. Lu, L., Dempsey, J., Liu, S., Bossert, J. and Shaham, Y. The Journal of Neuroscience, 24, pp. 1604-1611, 2004

Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch

Exposure to D-9-Tetrahydrocannabinol (THC) Increases Subsequent Heroin Taking but not Heroin's Reinforcing Efficacy: A Self-Administration Study in Rats One concern about the widespread use of cannabis is that exposure to its active ingredient, Delta-9-tetrahydrocannabinol (THC), might increase future reinforcing effects of other abused drugs such as heroin. In this study, IRP scientists investigated the effects of pre-exposure to THC on subsequent intravenous self-administration of heroin by Sprague-Dawley rats. We studied (1) acquisition of heroin self-administration behavior using a continuous-reinforcement (fixed-ratio (FR) 1) schedule, (2) heroin dose-response relationships using a FR1/variable-dose schedule, and (3) reinforcing efficacy of heroin using a progressive-ratio schedule. The number of rats pre-exposed to THC that subsequently learned to self-administer 50_g/kg injections of heroin within 10 daily sessions did not differ from vehicle-pretreated controls. In contrast, rats pre-exposed to THC subsequently self-administered

significantly more heroin injections per session and showed significantly shorter post-injection pauses over a range of heroin doses (12.5-100 microg/kg/injection) using the variable-dose schedule. Interestingly, the maximum effort rats would exert to receive an injection of the different doses of heroin under the progressive-ratio schedule was not altered by THC pre-exposure. In other rats, we varied the 'price' of heroin (responses required/dose), by manipulating FR response requirements at different doses of heroin across sessions, to calculate demand and response output curves. Again, consumption was significantly higher in the THC-treated rats at the lowest prices of heroin (FR1/100_g/kg and FR1/50_g/kg) but there were no differences in the reinforcing efficacy of heroin between THC- and vehicle-pretreated rats. These results demonstrate that pre-exposure to THC alters some pharmacological effects of heroin that determine frequency of heroin taking, but offer no support for the hypothesis that pre-exposure to THC alters heroin's efficacy as a reinforcer. Solinas, M., Panlilio, L.V. and Goldberg, S.R. Neuropsychopharmacology DOI:10.1038/sj.npp.1300431

Sigma1 Receptor Upregulation after Chronic Methamphetamine Self-Administration in Rats: A Study with Yoked Controls Sigma-1 receptors (Sig-1R) are implicated in behavioral sensitization, conditioned place preference, and cellular restructuring induced by psychostimulants. IRP investigators previously reported that rats that actively self-administered methamphetamine for 5 weeks and were then withdrawn from methamphetamine for 24 h showed downregulation of dopamine D2 autoreceptors (approximately 30%) in the midbrain and this was not seen in rats that passively received injections of methamphetamine or saline at the same time (yoked controls). Involvement of Sig-1R in the self-administration of psychostimulants, however, has never been reported. This study examined neuroadaptive changes in Sig-1R in the brains of rats self-administering methamphetamine. Three groups of rats were tested simultaneously 5 days per week, for 5 weeks (25 daily sessions). Two groups served as yoked controls and passively received an injection of either 0.1 mg/kg methamphetamine or saline (not contingent on responding) each time a response-contingent injection of 0.1 mg/kg methamphetamine was actively self-administered by the first group of rats. Protein and mRNA levels of Sig-1R were then measured by Western and Northern blottings, respectively. Results showed a marked upregulation of Sig-1R proteins (50%) in the midbrain and altered levels of Sig-1R mRNA in the frontal cortex and hippocampus of rats that learned to actively self-administer methamphetamine, but not in yoked methamphetamine- or saline-control rats. The authors conclude that neuroadaptive increases in Sig-1R seen in this study may contribute to the reinforcing effects of methamphetamine. This upregulation of Sig-1R may be mediated by increased protein kinase A activity due to downregulation of dopamine D2 autoreceptors. Stefanski, R., Justinova, Z., Hayashi, T., Takebayashi, M., Goldberg, S.R. and Su, T-S. Psychopharmacology DOI 10.1007/s00213-004-1779-9

The Opioid Antagonist Naltrexone Reduces the Reinforcing Effects of D9-Tetrahydro- cannabinol (THC) in Squirrel Monkeys Experimental evidence from animal studies suggests reciprocal functional interactions between endogenous brain cannabinoid and opioid systems. There is recent evidence for a role of the opioid system in the modulation of the reinforcing effects of synthetic cannabinoid CB1 receptor agonists in rodents. Since _9-tetrahydrocannabinol (THC), the natural psychoactive ingredient in marijuana, is actively and persistently self-administered by squirrel monkeys, this provides an opportunity to directly study involvement of opioid systems in the reinforcing effects of THC in non-human primates. The objective of this study was to assess the effects of naltrexone, an opioid antagonist, on THC self-administration behavior in squirrel monkeys. Monkeys pressed a lever for intravenous injections of THC under a 10-response, fixed-ratio (FR) schedule with a 60-s time-out after each injection. Effects of pre-session treatment with naltrexone (0.03-0.3 mg/kg intramuscularly, 15 min before session) for 5 consecutive days on self-administration of different doses of THC (2 to 8 µg/kg/injection) were studied. Self-administration responding for THC was significantly reduced by pretreatment with 0.1 mg/kg of naltrexone for five consecutive daily sessions. Naltrexone pretreatment had no significant effect on cocaine self-administration responding under identical conditions. Self-administration behavior under a fixed-ratio schedule of intravenous THC injection was markedly reduced by daily pre-session treatment with naltrexone, but remained above saline self-administration levels. These findings demonstrate for the first time the modulation of the reinforcing effects of THC by an opioid antagonist in a non-human primate model of marijuana abuse. Justinova, Z., Tanda, G., Munzar, P. and Goldberg, S. R. Psychopharmacology DOI: 10.1007/s00213-003-1693-6

Neuropsychopharmacology Section, Behavioral Neuroscience Research Branch

Cocaine Exposure Increases the Expression of a Newly-Identified Brain Protein in Brain Areas Relevant to Addiction IRP scientists have previously described a family of brain-specific catecholamine-regulated proteins, which bind the addiction-relevant neurotransmitter dopamine in brain areas that are involved in the brain changes that accompany drug addiction. Now, they have identified a new member of that family by molecular cloning - a 40 kDa catecholamine-regulated protein termed CRP40. CRP40 is dopamine-inducible and has properties similar to previously-identified members of the family. The effects of acute and chronic cocaine treatment on CRP40 in brain areas relevant to addiction have now been studied in laboratory animals. Acute and chronic cocaine treatment significantly increased CRP40 expression in the nucleus accumbens and neostriatum, whereas chronic cocaine treatment increased CRP40 expression in the nucleus accumbens only. No effects were seen in prefrontal cortex or medulla. Pretreatment with anisomycin, a protein synthesis inhibitor, blocked cocaine-induced expression of CRP40, suggesting that cocaine's effects on CRP40 involves protein synthesis. Cocaine treatment did not affect levels of other brain proteins studied. These findings suggest that CRP40 is associated with high extracellular dopamine levels, and could play a neuroprotective role against cocaine-induced oxidative stress. Sharan, N., Chong, V.Z., Nair, V.D., Mishra, R.K., Hayes, R.J. and Gardner, E.L. Synapse, 47, pp. 33-44, 2003.

Dopamine D3 Receptor Antagonists as Potential Anti-Addiction, Anti-Craving and Anti-Relapse Medications for the Treatment of Addiction IRP scientists have previously found that acute blockade of the dopamine D3 receptor in the rat brain (which is neuroanatomically restricted to the mesolimbic dopamine system, implicated in drug-induced reward and drug-seeking behavior) dose-dependently attenuates cocaine-enhanced brain-stimulation reward, acquisition of cocaine-induced conditioned cue preference, expression of cocaine-induced conditioned cue preference, acquisition of heroin-induced conditioned cue preference, expression of heroin-induced conditioned cue preference, and cocaine-triggered relapse to cocaine-seeking behavior in animals pharmacologically detoxified and behaviorally extinguished from their intravenous cocaine-taking behavior. Now, these researchers have found that SB277011A, a high-potency high-selectivity dopamine D3 receptor antagonist inhibits intravenous cocaine self-administration if the work-demand to receive intravenous cocaine is increased from low to moderate, or if the unit-dose of intravenous cocaine received is lowered from 1.0 mg/kg to 0.75 mg/kg, 0.5 mg/kg, 0.25 mg/kg, or 0.125 mg/kg. Also, the break-point for intravenous cocaine self-administration under progressive-ratio reinforcement is lowered by SB277011A, suggesting that dopamine D3 receptor antagonism lowers cocaine's reward value. These findings suggest that dopamine D3 receptor antagonists are worthy of further investigation as potential anti-addiction, anti-craving, and anti-relapse medications for the treatment of drug abuse. Gilbert, J., Xi, Z.-X., Campos, A.C., Ashby, C.R. Jr., Heidbreder, C.A. and Gardner, E.L. Poster, 2003. Abstract 422.10. Society for Neuroscience Annual Meeting, New Orleans, LA, November 8-12, 2003.

Dopamine D3 Receptor Antagonists as Potential Anti-Addiction, Anti-Craving and Anti-Relapse Medications for the Treatment of Addiction IRP scientists have found that SB277011A, a high-potency high-selectivity dopamine D3 receptor antagonist dose-dependently inhibits nicotine-enhanced brain-stimulation reward. As drug-enhanced brain reward is believed to be a neural substrate for addiction, these findings suggest that dopamine D3 receptor antagonists are worthy of further investigation as potential anti-addiction, anti-craving, and anti-relapse medications for the treatment of drug abuse. These findings also suggest a specific utility for dopamine D3 antagonists - to assist cigarette smokers in breaking their nicotine dependence and to quit smoking. Campos, A.C., Xi, Z.-X., Gilbert, J., Ashby, C.R. Jr., Heidbreder, C.A. and Gardner, E.L. Poster, 2003. Abstract 322.8. Society for Neuroscience Annual Meeting, New Orleans, LA, November 8-12, 2003.

Dopamine D3 Receptor Antagonists as Potential Anti-Addiction, Anti-Craving and Anti-Relapse Medications for the Treatment of Addiction IRP scientists have previously found that blockade of dopamine D3 receptors in the rat brain by the high-potency high-selectivity dopamine D3 receptor antagonist SB277011A dose-dependently attenuates cocaine-enhanced brain-stimulation reward and cocaine-triggered relapse to cocaine-seeking behavior in animals pharmacologically detoxified and behaviorally extinguished from their intravenous cocaine-taking behavior. Now, these researchers have found that NGB2904, another high-potency high-selectivity dopamine D3 receptor antagonist, likewise dose-dependently attenuates cocaine-enhanced brain-stimulation reward and cocaine-triggered relapse to cocaine-seeking behavior in animals pharmacologically detoxified and behaviorally extinguished from their intravenous cocaine-taking behavior. These confirmatory findings with a new D3 receptor antagonist suggest that dopamine D3 receptor antagonists are worthy of

further investigation as potential anti-addiction, anti-craving, and anti-relapse medications for the treatment of drug abuse. Xi, Z.-X., Gilbert, J., Campos, A.C., Ashby, C.R. Jr., Gardner, E.L. and Newman, A.H. Poster, 2003. Abstract 422.9. Society for Neuroscience Annual Meeting, New Orleans, LA, November 8-12, 2003.

The Basolateral Amygdaloid Nucleus in the Brain Mediates the Modulation of Brain-Reward by Drug-Associated Environmental Cues Environmental cues (sights, smells, sounds) that have been previously associated with drug-taking or alcohol-taking are powerful triggers that provoke relapse to drug-seeking and drug-taking behavior. IRP scientists have previously reported that the ability of such environmental cues to trigger relapse depends upon the intact functioning of the basolateral amygdaloid nucleus in the brain. IRP scientists have also previously shown that such environmental cues alter brain-stimulation reward, and that electrical stimulation of the amygdaloid nucleus in the brain alters brain-reward functions. Now, these researchers have discovered that the ability of drug-associated environmental cues to alter brain-reward functions depends upon the intact functioning of the basolateral amygdaloid nucleus in the brain. Thus, the basolateral amygdala is necessary for cues associated with previous drug or alcohol exposure to modulate reward functions within the classically-described reward circuitry of the brain. These findings have implications for understanding the brain substrates that underlie the motivation to engage in drug-taking behavior, and may help to elucidate the brain mechanisms underlying drug craving. Hayes, R.J. and Gardner, E.L. Poster, 2003. Abstract 421.6. Society for Neuroscience Annual Meeting, New Orleans, LA, November 8-12, 2003.

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

Positive Chemical ionization Gas Chromatography-Mass Spectrometry Method Development IRP scientists have developed a new method for the simultaneous analysis of tetrahydrocannabinol, the primary psychoactive component of cannabis, and two of its metabolites. This method has been applied to the analysis of cannabinoids in plasma following controlled oral administration. The oral route of administration is important not only as a route for cannabis abuse, but also for hemp products containing active cannabinoids and for therapeutic use of Dronabinol for AIDS wasting disease and as an anti-emetic. Plasma concentrations following the oral route are very low compared to those following smoked cannabis. Gustafson, R.A., Moolchan, E.T., Barnes, A., Levine, B., and Huestis, M.A. Journal of Chromatography B, 798, pp. 145-154, 2003.

Oral Fluid Testing for Drug Impaired Driving Drug impaired driving is a major safety issue in the United States and internationally. IRP scientists have contributed important information on the disposition of cocaine, methamphetamine and opiates and metabolites into oral fluid, a new alternative matrix for the detection of drug use, following controlled drug administration. These data help to provide a science-based rationale for setting policy, identifying drugged drivers, and identifying individuals for treatment based interventions. These data are useful for interpreting the results of oral fluid drug tests. Kacinko, S.L., Barnes, A.J., Kim, I., Moolchan, E.T., Wilson, L., Cooper, G.A., Reid, C., Baldwin, D., Hand, C.W. and Huestis, M.A. Forensic Science International, 141, pp. 41-48, 2004.

In Utero Drug Exposure In utero exposure to cocaine and heroin poses significant health and behavioral development risks to the unborn fetus. IRP investigators are conducting several clinical protocols directed at improving monitoring of drug use by the pregnant addict during gestation and in improving the detection of drug exposure at birth. These data are essential for determining the relationship between the magnitude, frequency and timing of drug use and maternal and neonatal outcomes. It is not yet clear to what degree each of these factors contributes to adverse outcomes. In addition, these data are essential for differentiating drug from non-drug exposed infants in research addressing physiological and developmental outcomes of in utero drug exposure. Dams, R., Huestis, M.A., Lambert, W.E. and Murphy, C.M. Journal of the American Society for Mass Spectrometry, 14, pp. 1290-1294, 2003.

Nicotine Serves as an Effective Reinforcer of Intravenous Drug-Taking Behavior in Human Cigarette Smokers Although numerous studies have documented that nicotine can function as an effective reinforcer of intravenous self-administration behavior in animals, it has not been clearly shown to maintain intravenous self-administration behavior above vehicle placebo levels in humans. Here, IRP scientists compared the reinforcing effectiveness of nicotine versus saline placebo in human research volunteers responding under fixed-ratio (FR) schedules of intravenous drug self-administration while systematically increasing response

requirements. Eight male cigarette smokers resided in an inpatient research unit. During 3-hr sessions, intravenous injections of nicotine and saline were available concurrently and were contingent on responding (pulling a lever). Nicotine dose (0.75, 1.5, 3.0 mg/injection), time-out (TO) value after each injection (1 to 20 min) and FR response requirement (10 to 1600) were varied in different subjects over consecutive sessions. Number of nicotine injections/session significantly decreased as dose/injection increased and the number of self-administered nicotine injections was significantly greater than the number of self-administered saline injections across conditions. When FR value was progressively increased over sessions, response rates for nicotine, but not saline, injections increased, with maximal rates at the highest FR values. Rates of responding and injections/session were markedly and significantly higher for nicotine than for saline at FR values of 200 and above. Subjects rated effects of nicotine as both significantly more positive and more negative than saline placebo, with positive ratings significantly higher than negative ratings. Nicotine functioned as a prototypic drug of abuse, serving as an effective reinforcer of intravenous drug-taking behavior in human cigarette smokers. Subjects adjusted their responding to response requirements in a way that maintained relatively constant levels of nicotine injections per session. Harvey, D.M., Yasar, S., Heishman, S.J., Panlilio, L.V., Henningfield, J. E. and Goldberg, S.R. Psychopharmacology DOI: 10.1007/s00213-004-1818-6.

Treatment of Adolescent Tobacco Dependence Over 1,300 adolescent smokers were screened and 156 patients enrolled. This first study is now completed showing both the feasibility and practicality of an outpatient clinical laboratory for highly-dependent smokers who are motivated to quit. Of the 50 completers (age 15.4±1.5 years, 64% female, 66% Caucasian, 53% at least one psychiatric diagnosis, 41% current marijuana use), biochemically-confirmed (exhaled carbon monoxide less than 6 ppm) continuous and point prevalence abstinence rates at 3 months were 24% and 44% respectively (10% and 19% of 120 randomized); mean decrease in self-reported cigarette consumption was 14.4±8.3 CPD (85%) across groups for completers at 3 months. Findings demonstrated that adolescent smokers randomized to the nicotine patch, compared to those receiving placebo, have significantly higher prolonged abstinence (quit) rates (18% vs. 2.5% Chi square p= 0.028) (OR 8.36 CI 0.95- 73.1). In this first study of the gum in teenage smokers, compliance rates were suboptimal indicating the need for higher instructional support for use of this treatment modality. Overall, the study showed reduced cigarette consumption but not smoke exposure indicating compensatory smoking among adolescents who did not quit. While the effect of behavioral intervention in our study might have exceeded that of NRT, cessation rates for this highly dependent sample of comorbid adolescents are somewhat encouraging. Several analyses (e.g., adequacy of nicotine and cotinine concentrations) are pending. Moolchan, E.T., Robinson, M.L., Schroeder, J.R., Ernst, M., Heishman, S.J., Pickworth, W.B., Cone, E.J., Cadet, J.L. and Henningfield, J.E. Oral presentation at the 10th Annual Meeting of the Society for Research on Nicotine and Tobacco, Scottsdale, AZ 2/10-15, 2004.

Director's Report to the National Advisory Council on Drug Abuse - May, 2004

Program Activities

New NIDA PAs and RFAs

In October 2003, the Behavioral Treatment Development Branch released a Notice (NOT-DA04-002) calling for applications for **Administrative Supplements** to study the mechanisms of action of behavioral treatments in existing treatment studies. The Notice provided for support for developing, adding, or expanding on measures of the key ingredients, mediators, moderators, and mechanisms of behavioral treatment, as well as data analyses to clarify the mechanisms by which behavioral treatments produce their effects.

On March 9, 2004, NIDA reissued a Program Announcement entitled **Collaborative Clinical Trials In Drug Abuse (PAR-04-073)**. The purpose of this announcement is to increase the collaboration of investigators at different sites in order to address critical issues in the treatment of substance-related disorders that require sample sizes greater than a single site can reasonably attain. This new announcement replaces PAR-01-039 in its entirety.

On May 3, 2004, NIDA issued a Program Announcement entitled **Epidemiology of Drug Abuse (PA-04-100)**. This announcement replaces PA-99-002, Epidemiologic Research on Drug Abuse, published in the NIH Guide October 2, 1998; PA-99-113, Drug Use and Related Adverse Behavioral and Social Consequences, published in the NIH Guide June 18, 1999; and PAR-99-168, Research on the Origins and Pathways to Drug Abuse. This new PA encourages a broad range of epidemiologic research on drug use, abuse and dependence. It highlights new areas for research that emphasize the vital public health role of epidemiologic research in drug abuse.

On April 30, 2004, NIDA issued an RFA entitled **Developmental Centers for Translational Research on the Clinical Neurobiology of Drug Addiction (RFA-DA-05-003)**. Through this RFA, NIDA invites applications to support the development of translational research centers on the neurobiology of drug abuse that have a strong clinical/human neurobiology focus and the capability to integrate preclinical/animal studies that will serve to directly inform the direction of the clinical research. Letter of Intent Receipt Date for this RFA: October 18, 2004; Application Receipt Date: November 17, 2004.

PAs/RFAs Issued With Other NIH Components/Agencies

On February 12, 2004, NIDA, in collaboration with the National Institute of Mental Health (NIMH), issued a Program Announcement entitled **Research on Rural Mental Health and Drug Abuse Disorders (PA-04-061)**. Though this PA, NIDA and NIMH invite grant applications for research that will ultimately lead to a reduction in the burden of mental illness and drug abuse in rural and frontier populations. The purpose of this PA is to stimulate research on mental health and/or drug abuse problems in rural and frontier communities that will: (1) enhance understanding of structural, cultural, and individual factors that may limit the provision and utilization of prevention and treatment services in these communities; and (2) generate knowledge to improve the organization, financing, delivery, effectiveness, quality and outcomes of mental health and drug abuse services for diverse populations in rural and frontier populations.

On February 24, 2004, NIDA, in collaboration with the National Institute on Alcohol Abuse and Alcoholism (NIAAA) issued a Program Announcement entitled **Pharmacotherapies for Comorbid Alcohol and Drug Use Disorders (PA-04-067)**. Through this PA, NIDA and NIAAA are seeking research grant applications on

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pharmacological treatment for patients with alcohol use disorder (AUD) and a comorbid substance use disorder (SUD). Substance use disorder may include the abuse/dependence of heroin, prescription narcotics, cocaine, methamphetamine and other stimulants, hallucinogens, sedative hypnotics, marijuana and other substances of abuse. Alcoholic abuse/dependent patients may have a co-occurring nicotine dependence, but must also meet the criteria for other types of SUD.

On May 4, 2004, NIDA in collaboration with a number of other NIH Institutes, issued a Program Announcement entitled **Characterization, Behavior and Plasticity of Pluripotent Stem Cells (PA-04-101)**. Stem cells appear to possess great plasticity, but the cellular mechanisms regulating their behavior and fate are not understood. If these mechanisms can be harnessed to obtain cell specifically required for therapy, diagnosis or drug discovery, it may be possible to restore function to tissues and organ systems that have been compromised by congenital disorders, developmental malfunction, age, injury, disease or drug exposure. Through this PA the participating Institutes invite applications for studies on the characterization, behavior and plasticity of human and non-human stem cells, regulation of their replication, differentiation, integration and function in the nervous system, and the identification and characterization of normal and tumor cells.

On May 5, 2004, NIDA, in collaboration with the National Cancer Institute (NCI) issued a Program Announcement entitled **Testing Tobacco Products Promoted to Reduce Harm (PA-04-103)**. The purpose of this PA is to stimulate multidisciplinary research on potential reduced-exposure tobacco products, both smoked and smokeless, through the interplay of basic, biological, and behavioral research, surveillance, and epidemiology. The tobacco industry is currently promoting some new products with claims that they are less harmful or less addictive because these products purportedly deliver lower amounts of toxic, carcinogenic, and/or addictive agents to the user compared with conventional products. However, to date, the scientific evidence is insufficient to evaluate whether these new products actually reduce the users' exposure or risk for tobacco-related diseases. Research studies funded through this PA should help to determine whether or not potential reduced-exposure tobacco products provide a truly less harmful alternative to conventional tobacco products, both on the individual and population levels.

On April 2, 2004, NIDA, in collaboration with NIMH and the NIH Office of Dietary Supplements (ODS), issued a Program Announcement entitled **Psychopharmacology of Widely Available Psychoactive Natural Products (PA-04-084)**. Under this PA, the participating NIH components invite research grant applications that characterize the chemistry, pharmacology and/or toxicology of acute and chronic exposure to psychoactive natural products, as well as the transition in the use of these products to licit or illicit drugs of abuse. For the purposes of this PA, psychoactive natural products are defined as fungus- or plant-derived products that are taken primarily for their effects on the central nervous system rather than for treatment, medicinal or therapeutic effects.

On January 15, 2004, NIDA, in collaboration with NIMH issued an RFA entitled **HIV/AIDS, Drug Use, and Highly Vulnerable Youth: Targeting Research Gaps (RFA-DA-04-012)**. Through this RFA, NIDA and NIMH invite innovative applications to address critical gaps in research on HIV/AIDS prevention, treatment, and related health issues among highly vulnerable youth. For the purpose of this RFA, highly vulnerable youth are those children, adolescents, and young adults aged 10-24 years who are using or are at high risk for using drugs and who are (1) at high risk for HIV and other infectious diseases (2) living with HIV/AIDS and/or (3) affected by HIV/AIDS. Letter of Intent Receipt Date for this RFA: February 17, 2004; Application Receipt Date: March 16, 2004.

On March 12, 2004, NIDA and NIMH issued an RFA entitled **Molecular Markers and Mechanisms of HIV-Associated Dementia (RFA-MH-05-002)**. Through this RFA, NIMH and NIDA invite applications proposing to identify and characterize novel molecular and genetic markers associated with distinct stages of progression of HIV-associated nervous system disease in the context of highly active antiretroviral therapy (HAART). Research on the role of unique molecular and genetic markers in defining mechanisms of neuropathogenesis, host genetic susceptibility to development of central nervous system (CNS) disease, and response to treatment are also important areas of focus of this RFA. The use of state-of-the-art microarray technology, proteomics, molecular genetics, and neuroimaging techniques to define and characterize novel molecular and genetic markers associated with HIV-induced nervous system disease are encouraged. Letter of Intent Receipt Date for this RFA: April 12, 2004; Application Receipt Date: May 11, 2004.

On April 9, 2004, NIDA in collaboration with NIMH and NIAAA, issued an RFA entitled **Gene-Environment Effects and Epigenesis in Depression (RFA-MH-05-006)**. The goal of this RFA is to solicit applications to identify epigenetic mechanisms and characterize gene-environment interactions that produce vulnerability to depression. Novel approaches to gene discovery, the identification of epigenetic mechanisms, elucidation of environmental risk factors, characterization of the genetic aspects of response to environmental change, and the use of bimarkers and other intermediate phenotypes correlated with the clinical disorder are encouraged. Letter of Intent Receipt Date for this RFA: June 16, 2004; Application Receipt Date: July 16, 2004.

On April 16, 2004, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Additional Genotyping for the Human Haplotype Map (RFA-HG-04-005)**. This RFA solicits applications for a cooperative agreement to augment the International HapMap Projects by supporting the genotyping of approximately 2.25 million single nucleotide polymorphisms (SNPs) across the genome in 270 samples from 4 populations, at high quality and at a cost of about 1 cent per genotype. The data from this effort will contribute to the development of a map, called the HapMap, of the haplotype patterns in the human genome and of a set of SNPs that are informative about these patterns and the associations among the SNPs. The HapMap is expected to be a key resource that researchers will use to find genes that affect health, disease, and response to drugs and environmental factors. Letter of Intent Receipt Date for this RFA: May 28, 2004; Application Receipt Date: June 25, 2004.

On April 27, 2004, NIDA, in Collaboration with the Substance Abuse and Mental Health Services Administration (SAMHSA) issued an RFA entitled **Enhancing State Capacity to Foster Adoption of Science-Based Practices (RFA-DA-05-002)**. This initiative is designed to strengthen State Agencies' capacity to support and engage in research that will foster statewide adoption of meritorious science-based policies and practices. Specifically, NIDA, with support from SAMHSA, will provide grants to State Agencies to conduct preliminary or pilot research that helps to create, implement, expand, and/or sustain a process of continuous science-based practice improvement in publicly supported drug abuse prevention and treatment programs. This initial research should serve as a foundation for more in-depth services research to be conducted subsequently by the State Agency and its collaborators to enhance continuous practice improvement in the prevention and treatment of drug abuse and to foster implementation of proven innovative therapeutic and management policies and practices. Letter of Intent Receipt Date for this RFA: July 17, 2004; Application Receipt Date: August 17, 2004.

Other Program Activities

CTN Protocol Update

Wave 1 Protocols:

- Five CTN studies have closed enrollment. A total of 5,583 patients have been screened with 2,705 of those enrolling in all the trials. Other studies as listed below are starting in the next few months.

  Protocol CTN-0004 (Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome in Subjects Seeking Treatment for Substance Abuse) is actively enrolling at one site. A total of 480 participants have enrolled in this study so far. Three of the five participating sites have reached their targeted enrollment of 100 clients. This study is expected to close in the 3rd Quarter 2004.

Wave 2 Protocols:

- **Protocol CTN 0003 (Bup/Nx: Comparison of Two Taper Schedules)** began enrollment June 30th. This study will be carried out at 11 sites across 8 nodes. Nine of the eleven sites are actively enrolling. The targeted enrollment is 480 participants. Participation is at 20% of the targeted enrollment.
- **Protocol CTN 0008 (Baseline Survey)** has been actively collecting survey information in all 17 Nodes since January 2002.
- **Protocol CTN 0009 (Smoking Cessation Treatment With Transdermal Nicotine Replacement Therapy in Substance Abuse Rehabilitation Programs)** started enrolling April 9, 2003. This study will be carried out at 12 Community Treatment Programs across 7 Nodes. The targeted enrollment is 864 participants. The enrollment to date is about 12% of the target figure. Ten of the twelve sites are active

at this time.

- **Protocol CTN 0010 (Buprenorphine/Naloxone Facilitated Rehabilitation for Opioid Dependent Adolescents/Young Adults)** began enrollment in July 2003. This is the first adolescent protocol in the CTN. This study will be carried out at 5 CTP sites across 4 nodes. The targeted enrollment is 240 adolescent/young adult participants. All five sites are actively enrolling. Enrollment is at 13% of the targeted number.
- **Protocol CTN 0011 (A Feasibility Study of a Telephone Enhancement Procedure to Improve Participation in Continuing Care Activities)** has closed enrollment at all four sites, and is completing follow-ups.
- **Protocol CTN 0012 (HIV/AIDS, Hep C, and Infections Screening in Substance Abuse Treatment Programs)** was approved for implementation. This was initiated and data has begun to be collected.
- **Protocol CTN 0013 (Motivational Enhancement Therapy to Improve Treatment Utilization and Outcome in Pregnant Substance Abusers)** started enrollment in October 2003. This study will be carried out at 5 sites across 3 Nodes. The targeted enrollment is 200. The enrollment is at 5% of the total target. One site now has 7 randomized participants. Enrollment at the program is up over the last month at the highest amount in 11 years. Another site has 5 randomized participants. More sites are looking to begin recruitment of test cases shortly.
- **Protocol CTN 0021 (Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome for Spanish-Speaking Individuals Seeking Treatment for Substance Abuse)** began enrollment in November 2003. This is the first Spanish only protocol in the CTN. It will be conducted at 6 bi-lingual sites across 5 nodes and has a target enrollment of 480 patients.

Wave 3 Protocols: The third wave of protocols is progressing and some are already implemented.

- **Protocol CTN 0014 (Brief Strategic Family Therapy for Adolescent Drug Abusers (BSFT))** has been approved by NIDA. Therapist training and implementation will take place in waves. The first wave of sites has finished protocol training. Pilot family cases are completed at two sites and being recruited for therapist training at four additional sites. BSFT will be implemented at 14 sites across 10 nodes plus Puerto Rico. The Puerto Rico site is actively participating on the conference calls and is scheduled for a site visit. This intervention is the first CTN study to target adolescents and their families. Enrollment is expected to begin in the third quarter of 2004.
- **Protocol CTN 0015 (Women's Treatment for Trauma and Substance Use Disorder: A Randomized Clinical Trial)** began implementation in March 2004. This study will be carried out at 8 sites across 7 Nodes. The targeted enrollment is 480. This study began enrollment in January of this year. By March, all but one site had begun. As of March 30th, a total of 29 participants had been randomized. The weekly implementation calls have been instrumental in helping sites to brainstorm solutions for a variety of issues (such as boosting recruitment, or scheduling weekly assessments). Interestingly, the rate of sub-threshold PTSD among the population of women screened is turning out to be about near 9%, which is just under the percentage predicted by the protocol.
- **Protocol CTN 0016 (Patient Feedback: A Performance Improvement in Outpatient Settings)** began in January 2004. This is a feasibility study being conducted at 6 sites across 5 Nodes. Data is currently being collected at all sites. The study is on target for data collection to end during the summer of this year.
- Three HIV **protocols CTN 0017 (HIV and HCV Risk Reduction Intervention in Drug Detoxification and Treatment Settings), CTN 0018 (HIV/STD Safer Sex Skills Groups for Men in Methadone Maintenance or Drug Free Outpatient Programs), and CTN 0019 (HIV/STD Safer Sex Skills Groups for Women in Methadone Maintenance or Drug Free Outpatient Programs)** are being

finalized. They will be carried out at numerous sites across the Network. It is expected that these will start enrolling in April or May 2004.

- **Protocol CTN 0020 (Job Seekers Training for Patients with Drug Dependence)** is conducting training for therapists at the present time. It is expected to begin recruitment by June 2004. This study will be carried out at 16 sites across 8 Nodes. The target enrollment is 1,200 participants.

Wave 4 Protocols: These are still being revised and approved.

- These protocols include: **CTN 0022 (Family Management Skills for Drug Involved Women in Treatment), CTN 0023 (12-Step Facilitation as an Intervention to Increase 12-Step Involvement and Improve Outcomes Among Substance Dependent Individuals), CTN 0024 (Reducing HIV Risk Behavior Among Adolescents in Community Based Substance Abuse Programs), CTN 0025 (Community Reinforcement and Family Training (CRAFT)),** and **CTN 0026 (Treatment of Depression in Adult Substance Abusers with Escitalopram).**
- A CTN genetics Special Interest Group has formed and Dr. Thomas Crowley from Rocky Mountain Node is the Chair. NIDA DNBR staff, Drs. Jonathan Pollack and Joni Rutter are the NIDA liaisons for these activities. A face-to-face meeting of this group has been scheduled for the May CTN Steering Committee meeting. It is anticipated this group should develop a strategic plan for how to use the CTN to expand NIDA's genetic research application.

NIDA's New and Competing Continuation Grants Awarded Since September 2003

Adinoff, Bryon H. -- University of Texas South West Medical Center/Dallas
Limbic Sensitivity In Cocaine Addiction

Alexander, James F. -- University of Utah
Mechanisms of Effective Family Change In High Risk Youth

Andrews, Judy A. -- Oregon Research Institute
Early Predictors of Child and Adolescent Substance Use

Barres, Ben A. -- Stanford University
Role of Glia In the Formation of Functional Synapses

Beals, Janette -- University of Colorado Health Sciences Center
Chronic Stressors and Drug Abuse In 2 Indian Populations

Belousov, Andrei B. -- Tulane University of Louisiana
Cholinergic Regulation In the Hypothalamus

Bernstein, Edward -- Boston Medical Center
Brief Intervention To Reduce STDs In ER Drug Users

Bourgois, Philippe -- University of California San Francisco
The Logics for HIV Risk Among Homeless Heroin Injectors

C'de Baca, Janet -- Behavioral Health Research Center-Southwest
Randomized Interventions With Substance-Using Kids

Caggiula, Anthony R. -- University of Pittsburgh at Pittsburgh
Effects of Self-Administered Versus Noncontigent Nicotine

Clatts, Michael C. -- National Development & Research Institutes
HIV Risk & Migration - Young Yi Minority - Sichuan China

Couceyro, Pastor R. -- Rosalind Franklin University of Medicine & Science
CART Peptide Modulation of Stimulant Reward

Cunradi, Carol B. -- Pacific Institute for Research and Evaluation
Neighborhoods, Drug Use & Violence

Davis, Thomas P. -- University of Arizona
Blood-To-CNS Drug Uptake In Pain/Rheumatoid Arthritis

Deutsch, Dale G. -- State University New York Stony Brook
Evidence Against An Anandamide Transporter

Drobes, David J. -- H. Lee Moffitt Cancer Center & Research Institute
Brief Intervention For Smokers: Cue Reactivity & Smoking

Eberwine, James H. -- University of Pennsylvania
Proteomics of Morphine Responses of the Basal Ganglia

Eddington, Natalie D. -- University of Maryland Baltimore Professional School
Benztropine Analogs, Cocaine Abuse Pharmacotherapies

Eipper, Elizabeth A. -- University of Connecticut School of Medicine and Dentistry
GDP/GTP Exchange Factors: Nucleus Accumbens Plasticity

Eisch, Amelia J. -- University of Texas Southwestern Medical Center, Dallas
Regulation of Adult Neurogenesis By Opiates

Farmer-Dougan, Valeri A. -- Illinois State University
Effects of DA D1 and D2 Agonists on Reward Sensitivity

Forrester, Janet E. -- Tufts University, Boston
Nutritional Status In HIV Hispanic Drug Abusers

Fricker, Lloyd D. -- Yeshiva University
Peptidomics of Cocaine and Amphetamine Abuse

Galea, Sandro -- New York Academy of Medicine
The Neighborhood Environment and Drug Use In NYC

Galloway, Matthew -- Wayne State University
High Field MRS Assessment of Stimulant Exposure In Rats

Gebhart, Gerald F. -- University of Iowa
Mediators and Modulation of Nociception

Grella, Christine E. -- University of California, Los Angeles
Gender Differences In A Follow-Up Of Opiate Users In California

Hammond, Donna L. -- University of Iowa
Opioid Mechanisms of Analgesia

Hawkins, J. David -- University of Washington
Substance Use and the Consolidation of Adult Roles

Heil, Sarah H. -- University of Vermont & State Agricultural College
Early Abstinence's Effect On Later Abstinence In Smokers

Ho, Wenzhe -- Children's Hospital of Philadelphia
Drug Abuse, Substance P and HIV

Johnson, Kenneth M. -- University of Texas Medical Branch, Galveston
Neurochemical Pharmacology of Phencyclidine

Kelley, Ann E. -- University of Wisconsin, Madison
Corticostriatal-Hypothalamic Circuitry and Food Reward

Ko, Jane L. -- Seton Hall University
Molecular Basis of Mu-Opioid Receptor Gene Regulation

Koob, George F. -- Scripps Research Institute
Neuronal Substrates of Cocaine Reward

Lauder, Jean M. -- University of North Carolina, Chapel Hill
Cannabinoids In Early Sea Urchin Development

Lester, Robin A. -- University of Alabama at Birmingham
Subunit-Specific Regulation/Neuronal Nicotinic Receptors

Levin, Edward D. -- Duke University
Adolescence: A Sensitive Period For Nicotine Addiction

Liu-Chen, Lee-Yuan -- Temple University
Cellular Pharmacology of Kappa Opioid Receptor

Mackie, Kenneth P. -- University of Washington
Neuronal Cannabinoid Receptor: Function and Regulation

Martin, Billy R. -- Virginia Commonwealth University

Inhalation of Drugs of Abuse

Mayes, Linda C. -- Yale University
Cocaine-Exposed Children & ERP Studies of Neurocognition

Mcfarland, Krista M. -- Medical University of South Carolina
Stress-Induced Reinstatement of Cocaine-Seeking Behavior

Miller, Gregory M. -- Harvard University (Medical School)
Trace Amine Receptors In Non Human Primates

Mintzer, Miriam Z. -- Johns Hopkins University
Benzodiazepine Use/Abuse: Effects On Memory Mechanisms

Mumford, Elizabeth A. -- Pacific Institute for Research and Evaluation
Smokeless Tobacco: Epidemiology and Policies

Mundel, Peter -- Yeshiva University
Synaptopodin: Biogenesis & Plasticity of Spine Apparatus

Mustard, Julie A. -- Ohio State University
D1-Like Dopamine Receptors In Learning and Behavior

Nader, Michael A. -- Wake Forest University Health Sciences
Chronic Stress and Cocaine Abuse In Female Monkeys

Parsons, Jeffrey T. -- Hunter College
Patterns and Contexts of Club Drug Abuse

Peterson, Phillip K. -- Minneapolis Medical Research Foundation, Inc.
Dynorphin and Glial Cell Immunomodulation

Pisacane, Kerry M. -- Johns Hopkins University
Gender Differences In Consequences of Teenage Drug Use

Quintero, Gilbert A. -- University of New Mexico, Albuquerque
The Social Context of Collegiate Prescription Drug Abuse

Ramsay, Douglas S. -- University of Washington
Nitrous Oxide, Individual Differences, and Conditioning

Razdan, Raj K. -- Organix, Inc.
Anandamide -- Structure/Activity Relationships

Richtand, Neil M. -- University of Cincinnati
Role of D3 Dopamine Receptor In Behavioral Sensitization

Rosenberg, Robert L. -- University of North Carolina, Chapel Hill
Agonist-Driven Conformational Changes In nAChRs

Rudnick, Gary -- Yale University
Neurotransmitter Transport

Selley, Dana E. -- Virginia Commonwealth University
Transduction Mechanisms of Opioid Agonist Efficacy

Sipe, Jack C. -- Scripps Research Institute
FAAH Gene Mutations: Risk Factors In Drug Use/Addiction

Smith, James E. -- Wake Forest University Health Sciences
Neurobiological Parameters of Cocaine Reinforcement

Song, Zhao-Hui -- University of Louisville
Structure and Function of CB2 Cannabinoid Receptor

Standifer, Kelly M. -- University of Houston
Cellular Mechanisms of Orl1 Regulation and Cross Talk

Stanger, Catherine -- University of Vermont & State Agricultural College
Preventing Problems Among Children of Substance Abusers

Sterk, Claire E. -- Emory University
Current Smokers: A Phenomenological Inquirt

Storr, Carla L. -- Johns Hopkins University
Drug Use & Latent Structure of Adolescent Mental Health

Thayer, Stanley A. -- University of Minnesota, Twin Cities
HIV Neurotoxicity-Mechanism & Modulation By Cannabinoids

Von Zastrow, Mark E. -- University of California, San Francisco
Membrane Trafficking of Opioid Receptors

Vuchinich, Rudy E. -- University of Alabama at Birmingham
Intertemporal Choice Dynamics In Drug Abuse Prevention

Wang, Jia B. -- University of Maryland Baltimore Professinal School
MOR Phosphorylation In Opioid Tolerance and Dependence

Waterhouse, Barry D. -- Drexel University College of Medicine
Locus Coeruleus Function and Methylphenidate Action

Watkins, Linda R. -- University of Colorado at Boulder
Methods Development For Studying Dorsal Spinal Cord Glia

Weinberg, Guy -- University of Illinois at Chicago
TZD Treatment of Cocaine Toxicity

Weiss, Friedbert -- Scripps Research Institute
Novel Treatments for Cocaine Dependence

Whitbeck, Leslie B. -- University of Nebraska, Lincoln
Shonga Ska: Sacred Horse Society Drug Prevention Program

Widom, Cathy S. -- University of Medical/Dental NJ, Newark
Child Abuse and Neglect, Chronic Stress, and Drug Abuse

Wiley, Jenny L. -- Virginia Commonwealth University
Developmental Pharmacology of Cannabinoids

Worley, Paul F. -- Johns Hopkins University
Analysis of a Novel Cocaine Induced Immediate Early Gene

Zhang, Heping -- Yale University
Statistical Methods In Genetic Studies of Substance Use

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Extramural Policy and Review Activities

Receipt, Referral, and Review

NIDA received 1,103 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 725 applications.

OEA arranged and managed 19 review meetings in which 271 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 6 contract proposal reviews, 12 Phase I and Phase II SBIR contract review meetings, and 8 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 six Special Emphasis Panels to review applications in conflict with the chartered committees. Special Emphasis Panels were also constituted for Centers applications, two Program Projects applications, Behavioral Science Track Award for Rapid Transition (B/START), Conference Grants, Cutting Edge Basic Research Awards (CEBRA) and Imaging Science Track Awards for Research Transition (I/START). Two Special Emphasis Panels reviewed RFA submissions.

OEA managed the following RFA reviews:

- DA 04-003: Centers For The Development Of Medications To Treat Drug Dependence
- DA 04-004: NIDA Neuroproteomics Research Centers (NIDA NPRCs)

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

- N01DA-4-1114: Technical Support for Constituency Outreach & Research Dissemination
- N01DA-4-1116: Blending Research and Practice
- N01DA-4-1117: NIDA Notes
- N01DA-4-1115: Communications Support
- N01DA-4-8844: Analytical Chemistry & Stability Testing of Treatment Drugs
- N01DA-4-8849: Animal Models of Methamphetamine-Induced Cognitive Impairment

Concept Reviews

- N01DA-4-7747: High-resolution Genome Scan for Drug Abuse Loci
- N01DA-4-7746: Production, Analysis & Distribution of Cannabis and Marijuana Cigarettes and related Compounds
- N01DA-4-9906: Taipei MDMA Usage Study
- N01DA-4-9907: Dopamine Neuron Study
- N01DA-4-9908: Washington University MDMA Study
- N01DA-4-8849: Animal Models of Methamphetamine-Induced Cognitive

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Impairment

- N01DA-4-8850: Compound Identification and Operations Support
- N01DA-4-9905: Neuroimaging Branch Support Services

The **CTN Data and Safety Monitoring Board** met March 18-19, 2004, in Gaithersburg, Maryland. The group reviewed Wave 4 protocols, focusing on their data and safety monitoring plans, and the need for interim analyses. The Board also reviewed updates and trial progress on four ongoing studies, and agreed to bringing in study LIs to report on trial enrollment status and targets at the next meeting.

Extramural Outreach

Dr. Mark Swieter, OEA, gave presentations on The Peer Review Process at NIH and on Funding Mechanisms at a Grant Writing Workshop at the Virginia Youth Tobacco Program meeting on March 23, 2004, in Richmond, VA.

Dr. Mark Swieter delivered a talk on the Grants Enterprise at NIH to the NIDA INVEST and Humphrey fellows on March 5, 2004.

Dr. Teri Levitin, Director, OEA, has continued to serve on the NIH Director's Pioneer Award committee. This initiative is one of the NIH Roadmap activities; it will provide support for 5-10 investigators of exceptional creativity up to $500,000 per year for five years.

Dr. Teri Levitin organized and co-chaired a plenary session on "Images of Addiction" and organized and chaired a special session on "Funding Opportunities and Review Procedures for Brain Research at NIH" at the 15th Annual Spring Brain Conference in March 2004.

Dr. Teri Levitin organized and chaired an invited symposium for the Conference on Human Development meeting held in April 2004, in Washington, D.C. on "Funding Opportunities at NIH for Human Development Research".

Dr. Khursheed Asghar, OEA, presented a talk entitled "Review Process for NIDA MIDARP" at the April 13, 2004 NIDA sponsored meeting "Special Populations Research Development Series on Minority Institutions Drug Abuse Research Program (MIDARP)".

Staff Training and Development

The OEA Symposium Series, a forum for staff training and sharing of ideas and information, continued through the fall and winter. Topics addressed have included electronic Research Administration (eRA), the module for program staff in IMPAC II, a 5-year retrospective of NIDA's Career Development Award Program, Conference Grants, Cooperative Agreements, staff roles in promoting progress in the field, and staff management of active grants. The symposium series is organized and hosted by Dr. Mark Swieter.

Other Activities

Mr. Lyle Furr, OEA, attended the National Human Research Subjects Protections Conference in Orlando, FL, March 31, to April 2, 2004.

Mr. Richard Harrison, OEA, served on the Health Disparities Group and the Special Populations Minority Consortium and participated in the review of minority supplements in March 2004.

Ms. Pamela Stokes and Dr. Rita Liu, both of OEA, initiated an electronic system for referral of grant applications to the Institute's Divisions and program officials. The new system, developed in coordination with the Institute's budget office, Division and IT representatives, eliminates the need to send paper copies of grant applications around the Institute and streamlines the process for capturing program class codes assigned to applications.

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Congressional Affairs (Prepared April 12, 2004)

The President's Proposed FY 2005 Budget

For the National Institutes of Health, the FY 2005 President's budget proposes $28.8 billion, an increase of $729 million, or 2.6 percent. For NIDA, the FY 2005 budget request is $1.02 billion, an increase of $28.27 million over the FY 2004 conference level of $990.79 million comparable for transfers proposed in the President's request for an increase of 2.9 percent.

Hearings of Interest

On March 30, 2004, the House Government Reform Subcommittee on Criminal Justice, Drug Policy and Human Resources (Representative Mark Souder [R-IN], Chairman) held a hearing on measuring the effectiveness of addiction treatment to consider how to make the U.S. treatment system more effective. Federal witnesses included Dr. Nora Volkow, Director, NIDA, and Charles Curie, Administrator, SAMHSA. Dr. Volkow's formal testimony is posted on the NIDA website.

Dr. Volkow told the Subcommittee that scientific advances supported by NIDA are coming at an extraordinary rate and are significantly influencing the way this Nation approaches drug abuse and addiction. She stressed that understanding addiction as a chronic relapsing disease that involves the brain, behavior, the environment in which an individual is raised, along with genetic factors, is critical since it frames how we must ultimately develop strategies to treat this disease. Addiction also is a developmental disorder and NIDA is initiating a number of activities to get pediatricians and other primary care physicians more knowledgeable about drug abuse screening and treatments. She said that research shows addiction is similar to other chronic diseases such as type II diabetes, hypertension, cardiovascular disease, and many forms of cancer with respect to its onset, course, and response to treatment. Like these other chronic diseases, drug addiction can be effectively treated and managed over its course, but this requires treatments to be readily available and adhered to. Addiction treatment has also been shown to be an effective way to prevent the spread of diseases, such as HIV/AIDS and hepatitis. Participation in treatment also presents opportunities for screening, counseling, and referral for additional services, which can all help to reduce the spread of diseases to the general population. Numerous studies have shown that addiction treatments are comparable in effectiveness to treatments for other chronic illnesses.

On April 1, 2004, the Senate Appropriations Subcommittee on Labor, HHS, and Education (Senator Arlen Specter [R-PA], Chairman) held a hearing on the Fiscal Year 2005 NIH budget. Dr. Elias Zerhouni, Director, NIH, provided the NIH Overview, accompanied by the NIH IC Directors. Dr. Volkow's formal statement is posted on the NIDA website.

On April 1, 2004, the House Government Reform Subcommittee on Criminal Justice, Drug Policy and Human Resources (Representative Mark Souder [R-IN], Chairman) held a hearing entitled, "Marijuana and Medicine: The Need for a Science-Based Approach." Dr. Nora Volkow, Director of NIDA, testified. Dr. Volkow's formal statement is posted on the NIDA website.

Key Points from the Testimony:

- While there have been reports of marijuana having medicinal properties, numerous deleterious health consequences are associated with its short and long-term use, including the possibility of becoming addicted. During

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the period of intoxication, marijuana disrupts short-term memory, attention, judgment, as well as other cognitive functions.

- New research is showing that marijuana can affect almost every organ in the body, from the central nervous system to the cardiovascular, endocrine, respiratory/pulmonary and immune systems. Because it is typically smoked, it has been shown to impact the respiratory system and increases the likelihood of some cancers. Animal studies show that THC can impair the immune system's ability to fight infectious disease, thus increasing the likelihood of adverse health consequences.
- Marijuana is a Schedule I drug, which means it has a high potential for abuse and there is no current accepted medical use in the United States. However, based on early studies that found marijuana to relieve the nausea and vomiting accompanying cancer chemotherapy, the main active ingredient in marijuana, THC, has led to the FDA approval of a synthetic form of oral THC for nausea associated with cancer chemotherapy. In addition, its ability to increase appetite has resulted in oral THC being approved for the treatment of AIDS wasting.
- In 1997, the NIH convened a panel of non-federal experts in fields such as cancer treatment, infectious diseases, neurology and ophthalmology to examine the research on medical uses of marijuana. In 1999, the Institute of Medicine (IOM) published an exhaustive study, "Marijuana and Medicine: Assessing the Science Base." Both efforts found that too few scientific studies have been conducted to determine marijuana's therapeutic utility, but research is justified into the use of marijuana for certain conditions or diseases including pain, neurological and movement disorders, nausea in patients who are undergoing chemotherapy for cancer, and loss of appetite and weight related to AIDS. The reports noted there is greater promise in purifying the active constituents of marijuana, such as THC, and developing alternate delivery systems, such as inhalers, rather than smoked marijuana. The reports also noted that FDA-approved medications already exist for the treatment of the majority of proposed uses of smoked marijuana.
- NIH continues to accept proposals to investigate potential therapeutic uses of marijuana. Since the Reports by IOM and NIH were written, there have been two studies supported by NIH. One looked at the effects of smoked marijuana on HIV levels and appetite and reducing weight loss associated with HIV-related wasting syndrome. Another ongoing study is looking at the effects of THC in individuals who have the HIV infection with unintended weight loss. In addition to studying food intake and body composition, this study examines mood and physical symptoms, psychomotor task performance and sleep to determine the drug effects on food intake in relation to other behaviors.
- The Center for Medicinal Cannabis Research at the University of California in San Diego, a state funded research center, is currently conducting 17 pre-clinical or clinical studies that cover topics including cannabis for spasticity/tremors in multiple sclerosis patients, sleep disorders, CD4 immunity in AIDS and neuropathic pain.
- Marijuana is not a benign drug. It is illegal and its use has significant adverse health and social consequences. While studies are showing the development of useful cannabinoid-based medicines is an important area of investigation that could prove fruitful for a variety of health conditions, the use of smoked marijuana as a medicine is problematic due to its adverse health consequences and the inherent difficulties with respect to accurate dosing and purity of the formulation. Approval of the use of any drug must show substantial evidence of effectiveness and show the product is safe under the conditions of use proposed. Safe, in this context, means that the benefits of the drug appear to outweigh its risks.

On April 29, 2004, the House Appropriations Subcommittee on Labor, HHS, Education (Representative Ralph Regula [R-OH], Chairman) scheduled a theme hearing on "Substance Abuse and Mental Health" and asked that NIAAA, NIDA, and NIMH appear together with other agencies funded by the Subcommittee, to present their FY2005 budgets. Drs. T. K. Li, Director of NIAAA, Nora Volkow, Director of NIDA, and Thomas Insel, Director of NIMH, testified. Charles G. Curie, Administrator of SAMHSA and Deborah A. Price, Director, Office of Safe and Drugfree Schools, Department of Education also testified.

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]

HR 3866, the "Anabolic Steroid Control Act of 2004," was introduced March 1, 2004 by Representative James Sensenbrenner (R-WI). HR 3866 would crack down on steroid-like drugs and performance-enhancing supplements. The bill would expand the federal classification of anabolic steroids to include any supplement that is "chemically and pharmacologically related to testosterone," including products made with any of more than 50 specific substances. It also would double the permitted fine for selling or intending to distribute an anabolic steroid within 1,000 feet of a sports facility. HR 3866 would require the secretary of Health and Human Services and the attorney general to report to Congress on the health risks associated with dietary supplements that are not explicitly covered by the bill but contain similar substances. HR 3866 was approved by the House Judiciary Committee; it was also referred to the House Energy and Commerce Committee. Related bills: S 2195.

HR 3922, the "Drug-Impaired Driving Enforcement Act of 2004," introduced by Representative Sensenbrenner (R-WI). The bill would provide assistance and guidance to states to address the growing problem of drug-impaired driving, including offering model legislation and grants to states to enforce the law. The bill calls on the U.S. Secretary of Transportation to develop a model state drug impaired driving law that would in part call for evaluation, counseling, treatment, and supervision for persons convicted; enhance training of police; fund research to develop field tests to identify drug-impaired drivers. The bill was referred to the House Committee on Transportation and Committee on Judiciary.

S 1780, the "Anabolic Steroid Control Act of 2003," is a bill to amend the Controlled Substances Act to clarify the definition of anabolic steroids and to provide for research and education activities relating to steroids and steroid precursors. It was introduced October 23, 2003, by Senator Joseph Biden (D-DE). The bill was referred to the Senate Judiciary Committee. Related measures, HR 3866 and S 2195.

S 2195, the "Anabolic Steroid Control Act of 2004," introduced by Senator Joseph Biden (D-DE) on March 11, 2004, is a companion bill to HR 3866. It closely resembles HR 3866 but would authorize $15 million in grants annually from fiscal 2005 through 2010 to bolster programs in elementary and secondary schools educating children on harmful effects of anabolic steroids. The Senate adopted a resolution (S Res 335) in April 2004 condemning the used of steroids among baseball players and calling on the major leagues to follow other professional sports and tighten their testing program.

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International Activities

International Honors

Pavlov Medical University Rector Dr. Nicolai Yaitsky has been named an Academician of the **Russian Academy of Science**, the highest scientific honor in Russia. Membership is based on an individual's contributions to scientific research, development, education, and innovation. Among Dr. Yaitsky's accomplishments was the 1996 Exchange of Letters between Pavlov Medical University and NIDA that established the two institutions' binational collaboration on biomedical and behavioral research related to drug abuse and drug-related consequences. That agreement has resulted in NIDA support for a number of successful research projects, fellowships and professional development opportunities for Russian scientists, scientific exchanges between Russian and U.S. researchers, and binational and international research symposia.

NIDA-Supported Meetings

NIDA and the **American Society of Addiction Medicine** (ASAM) co-sponsored a day-long seminar at the society's 35th Annual Medical-Scientific Conference in collaboration with the International Society of Addiction Medicine (ISAM). Dorynne Czechowicz, M.D., DTR&D, chaired the seminar organizing committee and served as NIDA liaison to the ASAM conference program committee. DTR&D Director Francis Vocci, Ph.D.; Peter Geerlings, M.D., De Jellinek, Amsterdam, Netherlands; and David A. Fiellin, M.D., Yale, co-chaired the buprenorphine seminar. Other members of the seminar organizing committee included Marc Galanter, M.D., New York University and the following NIDA staff: IP Director Steven W. Gust, Ph.D.; Ivan Montoya, M.D., DTR&D; Robert Walsh, R.A.C., DTR&D; Betty Tai, Ph.D., Director, CCTN; and Ling Chin, M.D., M.P.H., CCTN. The seminar provided: 1) science-based information regarding the use of buprenorphine in different countries for detoxification and maintenance treatment of opioid addiction; 2) data from NIDA-supported research on the use of buprenorphine in office-based practices, and from the buprenorphine studies in the National Clinical Trials Network; 3) updates on treating opioid-dependent pregnant women and adolescents; and 4) issues related to the medical, clinical management, and integration of behavioral therapies to improve adherence to pharmacotherapy and enhance treatment outcomes. NIDA supported the participation of five international speakers: Nicholas Lintzeris, MBBS, Ph.D., Kings College, London, England; Marc Auriacombe, M.D., Universite Victor Segalen, Bordeaux, France; Antti Holopainen, M.D., Jarvenpaa Addiction Hospital, Haarajoki, Finland; Gabriele Fischer, M.D., University of Vienna, Austria, and Dr. Geerlings. The ASAM meeting was held April 22-25, 2004 in Washington, D.C.

NIDA contributed to the **22nd World Federation of Therapeutic Communities' World Conference** by supporting the participation of two NIDA staff members, Jack Stein, Ph.D., DESPR, and M. Patricia Needle, Ph.D., IP, and seven grantees who served as speakers: Sam Ball, Ph.D., Yale; Paul Roman, Ph.D., University of Georgia; James Sorensen, Ph.D., University of California at San Francisco; and Harry Wexler, Ph.D., Joann Sacks, Ph.D., Nancy Jainchill, Ph.D., and Stanley Sacks, Ph.D., all of National Development and Research Institutes, New York. Dr. Stein presented "Transferring Research to Practice through Partnerships" at the opening plenary session on behalf of NIDA Director Dr. Nora Volkow. Dr. Needle moderated a panel of international drug abuse treatment experts from Spain, Colombia, Ukraine, Algeria, and Switzerland who addressed challenges to international research in drug abuse. The panel included two former Hubert H. Humphrey Drug Abuse Research Fellows, Dr. Sergey Dvorak, Ukraine, and Dr. Malika Ait-Saada, Algeria. Drs. Stein and Needle also

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served as members of the scientific committee for the conference, which was held April 13-17, 2004 in Palma de Mallorca, Spain, and organized by the Spanish substance abuse treatment and prevention nongovernmental organization Proyecto Hombre in honor of its 20th anniversary.

NIDA co-sponsored an international symposium, **Developing Global Strategies for Identifying, Prosecuting, and Treating Drug-Impaired Drivers**, with the Office of National Drug Control Policy, the Counterdrug Technology Assessment Center, The International Association of Forensic Toxicologists [TIAFT], and the International Council on Alcohol, Drugs, and Traffic Safety [ICADTS]. The multidisciplinary program, held February 23-24, 2004 in Tampa, Florida, assembled researchers, police officers, prosecutors, judges, and treatment providers from North America, Europe, and Australia to improve understanding of existing limitations on identifying, prosecuting, and treating drugged drivers, to reduce drugged driving by developing strategies that combine drug detection technology with legal penalties for driving under the influence, and to identify priorities for future research relating to drugged driving in the fields of epidemiology, treatment, education and prevention efforts, and new technologies. The NIDA International Program supported the participation of speakers, rapporteurs, panelists, and participants from nine nations. NIDA-supported speakers and rapporteurs included: Johan de Gier, Ph.D., President, International Council on Alcohol, Drugs, and Traffic Safety, Oosterhout, Netherlands; Olaf Drummer, Ph.D., Head Scientific Services, Victorian Institute of Forensic Medicine, Australia; Alain Verstraete, Ph.D., University of Ghent, Ghent, Belgium; and Michel Willekens, Chief Inspector, Belgian Police, Ravels, Belgium. NIDA-supported panelists included: Pascal Kintz, Ph.D., Associate Director, Institut de Medecine Legal, Strasbourg, France; Manfred Moeller, Ph.D., and Miran Scheers, Institute of Legal Medicine, University of the Saarland, Homburg/Saar, Germany; Asbjorg Christophersen, Ph.D., and Jorg Morland, M.D., Norwegian Institute of Public Health, Oslo, Norway; Nele Samyn, Ph.D., Institut National de Criminalistique et Criminologie, Brussels, Belgium; Evan Graham, Royal Canadian Mounted Police, Vancouver, Canada; and Phillip Swann, Ph.D., VicRoads and Swinburne University, Australia. NIDA-supported participants included: Dr. Gert De Boeck, NICC, Belgium; Teemu Gunnar and Pirjo Lillsunde, National Public Health Institute, Helsinki, Finland; Manuel Lopez-Rivadulla and Angelines Cruz, University of Santiago de Compostela, Spain; Heikki Seppa, Helsingin Poliisilaitos, Helsinki, Finland; Marion Villain, Institut de Medecine Legal, Strasbourg, France; Karin Hammer, University of the Saarland, Homburg/Saar, Germany; Viviane Maes, Academic Hospital, University of Brussels, Brussels, Belgium; and Hans-Jurgen Maurer, Saarland Police, Saarland, Germany.

Fellowships and Professional Development Activities

Richard E. Isralowitz, Ph.D., Israel, has received a NIDA Distinguished International Scientist Collaboration Award to support his research visit to S. Lala Straussner, D.S.W., New York University, and Andrew Rosenblum, Ph.D., National Development and Research Institutes, New York. The scientists will identify appropriate methodology and data collection instruments that can be translated into Russian, conduct focus groups with treatment agency staff and substance-abusing U.S. immigrants from the Former Soviet Union, and begin preparing a NIDA grant proposal for a study of the psychosocial factors associated with drug abuse among Israeli immigrants from the Former Soviet Union. Dr. Isralowitz directs the Regional Alcohol and Drug Abuse Resources Center at Ben Gurion University, where he is responsible for the Israeli contributions to a drug abuse research program that promotes cooperation among Israeli, Palestinian, Egyptian, and U.S. drug abuse experts. The Integrated Substance Abuse Programs, University of California, Los Angeles coordinates that program with support from the U.S. Agency for International Development.

Two scientists have been selected as the 2004 WHO/NIDA/CPDD International Traveling Fellows: Aviv Weinstein, Ph.D., Israel, and Ignatius Praptoraharjo, M.S., Indonesia. The fellowships are co-sponsored by NIDA, the World Health Organization, and the College on Problems of Drug Dependence (CPDD) to support the participation of international researchers in the NIDA International Forum and the CPDD Annual Scientific Meeting. The Fellowship also supports brief research visits by the Fellows with NIDA grantees in the United States. Dr. Weinstein directs the PET/SPECT neuropsychiatric brain-imaging laboratory at Sourasky Medical Center, Tel Aviv University, where he studies the effects of chronic ecstasy use on motor coordination and the brain's dopaminergic system and the effects of recreational marijuana use on orientation, coordination, and brain metabolism. Dr. Weinstein will use the WHO/NIDA/CPDD Fellowship to collaborate with David Gastfriend, M.D., Harvard University, on translating and prospectively testing the American Society of Addiction

Medicine Patient Placement Criteria for use by drug and alcohol treatment facilities in Israel. Mr. Praptoraharjo conducts ethnographic research into the high-risk practices of Indonesian injection drug users as part of HIV/AIDS interventions conducted by the University of Illinois at Chicago (UIC). Mr. Praptoraharjo will use the WHO/NIDA/CPDD Fellowship to discuss potential collaborative research with Wayne Wiebel, Ph.D., and his colleagues at UIC, receive additional training from the AIDS International Training Research Program at UIC, and develop a grant proposal to adapt the Indigenous Leader Outreach Model for use in the different cultural and drug-using contexts of Indonesia.

Former NIDA Distinguished International Scientist and Hubert H. Humphrey Drug Abuse Research Fellow, Petra Exnerova, M.D., Czech Republic, presented an **update on the delivery of substance abuse treatment services in the Czech Republic** at the February 23, 2004 DESPR Seminar Series. She met with NIDA staff in the Services Research and Prevention Research Branches, DESPR, to discuss Czech research projects on which she might collaborate with NIDA grantees. Dr. Exnerova also attended the February 24, 2004 SAMHSA meeting for CSAT Adolescent Portfolio Grantees in Baltimore.

In March 2004, NIDA hosted an orientation program for the current NIDA Distinguished International Scientist, INVEST Research Fellows, and Hubert H. Humphrey Drug Abuse Research Fellows. The fellows visited the IRP on Thursday, March 4, meeting with Kenzie Preston, Ph.D.; Stephen Heishman, Ph.D.; Wallace Pickworth, Ph.D.; Marilyn Huestis, Ph.D.; David Epstein, Ph.D.; Eric Moolchan, M.D.; Alane Kimes, Ph.D.; and Elliot Stein, Ph.D. On Friday, March 5, Steven W. Gust, Ph.D., and M. Patricia Needle, Ph.D., IP, welcomed the attendees to NIDA headquarters and discussed the International Program's activities. The following NIDA staff summarized the Institute's research mission: Frank Vocci, Ph.D., DTR&D; David Shurtleff, Ph.D., DNBR; Jacques Normand, Ph.D., CAMCODA; Peter Delaney, Ph.D., DESPR; and Ling Chin, M.D., M.P.H., CCTN. A seminar, Introduction to the NIH Research Grant Process, featured presentations by Mark Swieter, Ph.D., Office of Extramural Affairs; David Thomas, Ph.D., DNBR; and Natalie Tomitch, M.P.H., M.B.A., Fogarty International Center. Attendees who summarized their NIDA-supported research efforts included Distinguished International Scientist Richard Isralowitz, Ph.D., Israel; and INVEST Fellows Lan Zhang, M.D., China; Pajulo Marjaterttu, M.D., Ph.D., Finland; and Yufeng Chen, Ph.D., China. Participating Humphrey Fellows included: Ana Djordjevic, M.D., Serbia and Montenegro; Mariano Hembra, M.D., Philippines; Raminder Kaur, MBBS, M.P.M., Malaysia; Boris Lobodov, M.D., Russia; David Otiashvili, M.D., Georgia; Riza Sarasvita, Magister Sains, Indonesia; Vladimir Stempliuk, M.S., Brazil; Cheng-Hua Tian, M.D., China; and Tomas Zabransky, MUDr. Ph.D., Czech Republic.

Travel Support

NIDA supported two international researchers who participated in the **Society for Prevention Research** 12th Annual Meeting, "Crossing Borders: Linking Prevention Science, Policy and Practice," May 25-28, 2004 in Quebec City, Canada. The NIDA-supported researchers were Amador Calafat, M.D., IREFREA (Research Institute on Child and Youth Risk Factors), Palma de Mallorca, Spain; and Lisa Wegner, M.Sc. O.T., University of the Western Cape, South Africa.

International Visitors

A group from the Mentor Foundation visited NIDA on March 3, 2004. The Mentor Foundation works in several countries to identify best practices in the prevention of drug abuse. Visitors included Jeff Lee, MEd., United Kingdom, Ken Winters, Ph.D., University of Minnesota, Diana Cer—n Otoya, Colombia, Maria Christina Garcia, Colombia, and Richard MacKenzie, Ph.D., UCLA. Steve Gust, Ph.D., International Program, Shakeh Kaftarian, Ph.D and Eve Reider, Ph.D., DESPR met the group.

Visiting NIDA from Brazil on March 9, 2004 were Judge Cristina Olimpio and Cristina Werner. The purpose of the visit was to find out about NIDA's drug abuse prevention research, with particular emphasis on the prevention services research as it relates to young offenders. Speaking with the visitors from DESPR were Shakeh Kaftarian, Ph.D. and Redonna Chandler, Ph.D.

Other Activities

Before coming to NIDA, M. Patricia Needle, Ph.D., IP, was Director, China Center, University of Minnesota, for 13 years. During January she returned to Minneapolis as an honored guest at ceremonies marking the **25th anniversary of the China Center** and celebrating the history and achievement of the exchanges supported

through the Center. While in the Twin Cities, Dr. Needle also visited with NIDA grantees and made a presentation to the staff of Addiction Medicine on the theme of "Current Status of the Epidemic of HIV Among Injection Drug Users: A Global Perspective."

Dr. Shakeh Kaftarian of DESPR has been convening meetings and conference calls with Dr. Irina Pervova of Russia and US research teams to assist in the establishment of collaborative research linkages between US prevention researchers and their Russian counterparts.

Dr. Jack Stein, DESPR, presented the keynote address at the World Federation of Therapeutic Communities Conference, Palma de Mallorca, Spain, April 13-17, 2004.

Peter Hartsock, Ph.D., participated in a Center for Strategic and International Studies symposium to establish a cooperative consortium dealing with prevention/intervention of HIV/AIDS in the former Soviet Union, March 5, 2004, Washington, D.C.

Peter Hartsock, Ph.D., participated in meetings at the Uniformed Services University of the Health Sciences dealing with increased research cooperation between the U.S. and Russia in dealing with HIV/AIDS, March 8, 2004, Bethesda, MD.

Dr. Iv‡n Montoya, DTR&D, presented at a workshop entitled "Pharmacotherapies for Drug Addiction" at the First Ibero-American Congress on Addictions, in Santiago de Compostela, Spain. The title of his presentation was "Pharmacotherapy for Cocaine Dependence."

Dr. Steven Goldberg, Chief, Preclinical Pharmacology Section, Behavioral Neuroscience Branch was invited to meet with Dr. Patrizia Popoli and colleagues, Pharmacology Department, Istituto Superiore di Sanita, Rome, Italy, on March 15-17, 2004 and March 21-22, 2004, to give a presentation entitled, "Cross talk between cannabinoid and opioid systems" and to review data collected as part of a highly productive, ongoing, collaborative research program with NIDA, IRP, on adenosinergic mechanisms underlying the behavioral effects of caffeine and other psychostimulants. Dr. Goldberg was also invited to visit Prof. Vincenzo Di Marzo of the Istituto di Chimica Biolecolare, Consiglio Nazionale delle Ricerche, in Naples, Italy, March 19-20, 2004, to present his findings on cross talk between cannabinoid and opioid systems and to review new data on the potential role the proposed new cannabinoid CB3 receptors and the vanilloid VR1 receptors play in the actions of THC and the endogenous cannabinoid anandamide. A start was made in designing a future collaborative research program between NIDA, IRP, and their institute for investigation of endogenous cannabinoid and vanilloid ligands.

Dr. Marilyn Huestis of the Chemistry and Drug Metabolism Section, IRP, recently hosted scientists from the Japanese Association of Forensic Toxicology. The Society is trying to establish quality assurance programs for toxicology laboratories throughout the country. These laboratories are responsible for post-mortem, emergency, clinical, and analytical toxicology in Japan. This includes drug treatment, driving under the influence of drugs, in utero drug exposure, and drug toxicity applications.

Dr. Marilyn Huestis, IRP, recently attended a multinational conference on "Developing Global Strategies for Identifying, Prosecuting, and Treating Drug-Impaired Drivers" held in Tampa, FL. There is strong international interest in improving public safety by removing drivers who are operating motor vehicles while under the influence of drugs from our roads. In addition, identification of the drugged driver is seen as an opportunity for treatment interventions. As the number of alcohol impaired drivers decreases, the number of drug-impaired drivers is increasing significantly. The meeting was sponsored by NIDA, the Office of the National Drug Control Policy, and the National Highway Traffic Safety Administration.

Dr. Marilyn Huestis serves on the US Anti-doping Research Advisory Board, which oversees research projects and grants on new analytical methods, ethics in sport, and establishment of anti-doping policy. Each year the US Anti-doping Agency has an international meeting on different aspects of anti-doping in sports. Representatives of most of the International Olympic Committee certified laboratories and from the different sporting societies, as well as experts in hematology, diagnostics, the World Anti-doping Agency and the Research Advisory Board attended this congress. This meeting focused on "Oxygen Transport Enhancing Agents and Methods" and included detection of recombinant erythropoetin, darbopoetin, blood transfusions, high altitude training, blood substitutes, and establishment of normal group ranges and individual normal ranges.

Dr. Marilyn Huestis chaired the Neuropsychopharmacology of Cannabinoids in Humans

symposium at the International Brain Research Organization's 6th World Congress of Neuroscience in Prague, Czech Republic. This symposium addressed the pharmacology of the CB1-cannabinoid receptor antagonist rimonabant and its potential therapeutic indications for obesity, nicotine cessation and as a treatment adjunct for alcohol, cocaine and cannabis dependence. Dr. Huestis also gave a presentation on the Effects of Cannabis on Human Performance and Behavior at the Medical School of Charles University, Prague. Many of the public health and safety concerns about cannabis use during operation of a car or machinery were addressed.

Dr. Marilyn Huestis addressed the Canadian Society of Forensic Sciences on the pharmacodynamics and pharmacokinetics of cannabis in Vancouver, Canada. In addition, she was asked to brief the US Consulate General and his senior staff on the same topic. High potency cannabis grown in British Columbia has become a major issue for the US Consulate in Vancouver.

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Meetings/Conferences

NIDA and the American Psychiatric Association (APA) organized and co-sponsored a special research-based program track entitled **Integrating the Science of Addiction Into Psychiatric Practice** during the 157th APA Annual Meeting held May 1-6, 2004. The nearly 30 sessions featured in this track, including 7 major lectures by some of the world's leading drug abuse and addiction researchers, addressed a wide array of topics linked to mental illness and drug abuse. Some of the topics built into the series included stress, trauma, and drug abuse; obesity and addiction; smoking and comorbid mental disorders; and attention deficit hyperactivity disorder (ADHD) and drug abuse. NIDA also highlighted a number of other sessions from the APA program based on scientific content that complements the series theme. The goal of this special track was to raise awareness of new and emerging issues in addiction and psychiatry and provide important information related to best practices and treatment strategies.

On February 26 and 27, 2004, NIDA sponsored a science meeting entitled **Identifying the Mechanisms of Action of Behavioral Treatments: Setting the Stage for Dissemination**. The meeting was organized and co-chaired by Drs. Melissa Racioppo and Lisa Onken. This meeting brought together experts in behavioral treatment research to discuss the challenges to identifying how behavioral treatments work, including the key ingredients, mediators, moderators, and mechanisms of treatment. This meeting was designed to highlight an area necessary for successful dissemination of efficacious treatments to community settings, and is part of NIDA's ongoing efforts to bridge the gap between clinical science and practice.

A NIDA-sponsored science meeting on **Enhancing Addictions Assessment, Behavioral Treatment, and Provider Training Using Information Technology** organized and co-chaired by Dr. Cece McNamara and Dr. Lisa Onken, DTR&D, was held on March 4-5, 2004 in Gaithersburg, MD.

On March 23-24, 2004, a meeting entitled **Long-Term Follow-Up of Prenatal Drug Exposure: Advances, Challenges, and Opportunities** was held in Bethesda, MD. The meeting was co-sponsored by NIDA, NICHD, and ORWH, NIH. Twenty-three longitudinal cohort studies were represented, and a total of more than 100 individuals attended the meeting. In addition to reports on progress and directions for all ongoing studies, there were sessions on neuroimaging in the cohort studies, genetic analyses, and relevant toxicological procedures. Group discussions addressed issues of measurement (e.g., risk and resiliency factors, substance abuse vulnerability), methodological considerations in longitudinal data analyses, and biological and social/environmental mechanisms underlying associations between prenatal exposure and developmental outcomes. The meeting was organized and co-chaired by Drs. Vincent Smeriglio (NIDA), Rosemary Higgins (NICHD), and Loretta Finnegan (ORWH). Other NIDA members involved in the meeting were Drs. Marilyn Huestis and Joni Rutter, both of whom made presentations, and Drs. Jonathan Pollock, Laurence Stanford, and Cora Lee Wetherington, each of whom chaired sessions.

A workshop on **Transcranial Magnetic Stimulation in the Treatment of Drug Abuse and Other Brain Disorders**, organized and chaired by Dr. Maria Majewska, DTR&D, was held on March 16, 2004 in Bethesda, Maryland. The theme of the workshop was the review and evaluation of Transcranial Magnetic Stimulation (TMS) technology in the treatment of neuropsychiatric disorders, with a discussion emphasis on TMS potential in the treatment of substance use disorders.

The **CTN Data and Safety Monitoring Board** met March 18-19, 2004, in

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Gaithersburg, Maryland. The group reviewed progress on several ongoing studies, discussed criteria for requiring interim analyses in CTN trials, and reviewed the data and safety monitoring plans for new protocols.

An **ASI Train the Facilitators Workshop** was held April 13-15, 2004 at Duke Clinical Research Institute in the North Carolina Node.

NIDA's CCTN coordinated a meeting between the National Cancer Institute's Community Oncology and Prevention Trials Research Group and NIDA's Clinical Trials Network to discuss smoking cessation. Nine NIDA researchers and seven NIDA staff (including Bill Corrigall) were joined by ten NCI researchers and six NCI staffers on March 23, 2004, at the Bethesda Marriott Suites. After introductions, Lori Minasian, MD, of the NCI, presented an overview of the NCI Community Oncology & Prevention Trials Research Group, and then described completed trials on smoking cessation, trials on smoking cessation currently in progress, and smoking cessation concepts being considered for future protocol development. In turn, Betty Tai, Ph.D., gave an overview of the NIDA Clinical Trials Network, and then described the trial on smoking cessation currently in progress, and the smoking cessation concepts being considered for future protocol development. Afterward, Richard Hurt, MD, a researcher from the NCI Trials Research Group, and James Sorensen, Ph.D., a researcher from the NIDA Clinical Trials Network, jointly led a group discussion of the feasibility of NCI and NIDA working together. The group discussed critical elements for collaboration; the possibilities and challenges of running one protocol over two networks versus two protocols over two networks; data management and data sharing; and cohorts and settings. There was enough enthusiasm and positive expectations for collaboration that Lori Minasian, MD and Betty Tai, Ph.D. decided to continue the discussion and preliminary planning at a second meeting to be held this summer.

The **CTN Concept and Protocol Review Subcommittee** met April 20-21, 2004 in Gaithersburg, Maryland, to review the Wave 5 protocol concepts. A total of 42 new protocol concepts have been received and were reviewed by a panel of experts from within the CTN. The submitted concepts span a broad range of research areas, with particular emphases on buprenorphine/ naloxone, smoking cessation, marijuana treatment, adolescents, psychiatric co-morbidity, and HIV and HCV interventions.

The inaugural **Hand-Off Meeting for the CTN's Motivational Interviewing Protocol** (Dr. Kathleen Carroll, P.I.) was held on May 17 -18, 2004 in Bethesda, MD. This meeting served to present the results of the protocol and how it can address critical needs in the treatment field via dissemination product(s). Dr. Suman Rao, OSPC, organized this meeting, designed to discuss dissemination strategies for a specific target audience.

The **CTN Dissemination Subcommittee Face-to-Face Meeting** was held on May 13 - 14, 2004 in Gaithersburg, MD. This meeting focused on creating a strategy to disseminate training materials of completed protocols within the CTN and interfacing with existing Blending Teams that are responsible for dissemination to the outside community. Dr. Suman Rao, OSPC, coordinated this meeting with the Dissemination Subcommittee Workgroup leaders.

Dr. Nemeth-Coslett, DTR&D and Drs. Appel and Thomas, DNBR, co-chaired a one-day symposium on February 24, 2004 hosted by NIDA entitled **Virtual Reality: Opportunities for the NIH**. Multidisciplinary experts highlighted the latest scientific findings on the current and potential roles for virtual reality technologies in medicine. Discussion included description of the theory and applications of virtual reality, emphasizing how this technology is being used in prevention and treatment therapies for drug abuse, post-traumatic stress disorder, eating disorders, phobias, and pain.

Jacques Normand, Ph.D., and Elizabeth Lambert, M.Sc., of the Population-Based Health Intervention Unit of NIDA's CAMCODA organized a Workshop on **New Dynamics of HIV Risk Among Drug-Using Men Who Have Sex With Men** on March 1-2, 2004 in Bethesda, MD. The workshop brought together 15 NIDA researchers and experts to review information and findings from their currently-funded NIDA grants on HIV/AIDS and drug-using men who have sex with other men (MSM). Discussion sessions, led by Ron Stall, Ph.D. and Sevgi Aral, Ph.D., of the Centers for Disease Control and Prevention, focused on the research findings and on public health surveillance data that show the incidence of HIV and other sexually transmitted infections is increasing among drug-using MSM. The meeting concluded with recommendations to help NIDA facilitate a program of research on new dynamics of HIV risks among drug using MSM and prevention strategies to address them. The presentations and discussions of the participants are now being prepared as manuscripts for publication in a special issue of a peer-reviewed journal, expected to

be available in the spring/summer of 2005.

On March 5, 2004, NIDA invited several speakers to inform Staff on the state of knowledge about dextromethorphan (DXM) abuse, which has recently been highlighted by the media. Dr. Edward Boyer, University of Massachusetts Medical School of Emergency Medicine, and Bob D'Alessandro, Center for Prevention Research and Resource Development presented information on the extent of reported use based on data from poison control centers and emergency rooms. Dr. Jerry Frankenheim discussed the mechanisms of action of DXM in the brain.

On February, 11, 2004, the Bioethics Task Force, a subcommittee of the National Advisory Council on Drug Abuse, met to discuss the development of guidelines for drug abuse research in children and adolescents. Drs. Ken Winters, University of Minnesota, Thomas Kelley, University of Kentucky, and Kathleen Merikangas and Daniel Pine of the National Institute of Mental Health (NIMH) Intramural Program were invited to the meeting to discuss their experiences and views regarding research with children and adolescents. General issues that were discussed included the implementation of the federal regulations on research with children, consent/assent, confidentiality, compensation and coercion. Unique issues related to specific types of studies including surveys, genetics, and treatment research were also discussed. As a follow-up to this meeting, Drs. Dorothy Hatsukami, chairperson of the Bioethics Taskforce, Susan Weiss, and Gayathri Jeyarasasingam, OSPC, met with Dr. David Wendler, Department of Clinical Bioethics NIH, to further discuss these issues and with Dr. Monique Ernst of the NIMH Intramural Program who provided an overview of the specific issues related to neuroimaging research in children. As a result of these meetings, the Bioethics Task Force is in the process of drafting preliminary guidelines for drug abuse research in children.

In the recent Society for Research on Adolescence Biennial Meeting in Baltimore, MD, March 11 - 14, 2004, NIDA participated in two sessions and a NIDA exhibit booth was on site. The sessions included a poster and a discussion hour focusing on child and adolescent research support at NIDA. Drs. Jessica Campbell, Kathy Etz, and Kevin Conway participated in the planning of the events and represented NIDA at the meeting, along with a number of members from the Child and Adolescent Workgroup.

NIDA co-sponsored-in collaboration with AHRQ, NIMH, NIAAA, and NCI-a day-long workshop entitled, **Participation in Government Health Services Research Grants**, Washington, DC, April 21, 2004.

Dr. Timothy P. Condon, Deputy Director, NIDA, discussed NIDA's research priorities with the Drug Strategies Board of Directors at The Americas Society in Manhattan, New York on November 13, 2003.

Dr. Timothy P. Condon presented "NIDA/ATTC Collaboration" at the CTN External Affairs Coordinating Committee in Tucson, Arizona on January 27, 2004.

Dr. Timothy P. Condon gave the opening remarks at a workshop on Identifying Mechanisms of Actions of Behavioral Treatments for Substance Abuse: Setting the Stages for Dissemination on February 26, 2004 in Gaithersburg, Maryland.

Dr. Timothy P. Condon gave the opening remarks at the Targeted Lipidomics: Signaling Lipids & Drugs of Abuse workshop on April 15, 2004 in Bethesda, Maryland.

Dr. Timothy P. Condon presented "Addiction as a Brain Disease: Implications for Blending Research and Practice" at the Second Annual Andrew C. McInvale Memorial Symposium: Dealing with Drug Abuse: Addiction, Relapse, and Remediation at Tulane University on April 16, 2004 in New Orleans, Louisiana.

Dr. Timothy P. Condon participated in the 13th World Conference on Tobacco or Health Stakeholders Caucus on April 27, 2004 in Chicago, Illinois.

Dr. Cindy Miner, Deputy Director, OSPC, presented "Crystal Meth Usage in the Lesbian, Gay, Bisexual, Transgender (LGBT) Community" as part of LGBT Health Awareness Week on March 18, 2004 in Baltimore, Maryland.

Dr. Cindy Miner, Deputy Director, OSPC, participated in the APA Research Colloquium for Junior Investigators at the American Psychiatric Association (APA) Annual Meeting on May 2, 2004 in New York, NY.

Dr. Cindy Miner, Deputy Director, OSPC, chaired a workshop entitled "Obtaining Research Funding From NIH: Keys to Successful Grant Writing" at the American Psychiatric Association (APA) Annual Meeting on May 3, 2004 in New York, NY.

Dr. Cindy Miner, Deputy Director, OSPC, presented "Abuse for Teens: The Science Behind Drug Abuse" at the National Institute of Health's 5th Annual Share the Health Exposition on April 24, 2004 in Silver Spring, Maryland.

Dr. Cindy Miner, Deputy Director, OSPC, presented the Keynote Address at the Chief Resident Immersion Training Program (CRIT) on May 20, 2004 in Chatham, Massachusetts.

On January 20, 2004 David Anderson, OSPC, Jackie Kaftarian, DESPR, and Caryn Blitz of the Community Antidrug Coalitions of America, presented a four-hour panel at CADCA's annual Leadership Council. The panel sought to clarify and expand dialogue between researchers and community prevention practitioners by focusing on very practical questions in the nexus between research and practice. According to the format, community coalition leaders from three cities (Deacon Dzerziewski, Gwen Wilson, Harry Kressler) presented questions, concerns, challenges and suggestions to three leading prevention researchers (David Hawkins, Harold Holder, Paul Florin). After the researchers' responses and a round of follow-up discussion, the audience was invited to participate. The topics discussed included the usefulness of research-based practices both for improving program effectiveness and for its persuasive value with communities and funders, and recognition that coalitions' dedication and ingenuity are vital both for adapting research to their communities' needs and for acting in areas where research has not yet provided clear guidance. The panel will be the basis for an article in an upcoming issue of Science & Practice Perspectives.

Sheryl Massaro, PILB, OSPC, coordinated NIDA's participation in the National Inhalants and Poisons Awareness Week event with SAMHSA and the National Inhalants Prevention Coalition (NIPC). NIDA helped to distribute NIPC's Community Action Kits nationwide, updated the English and Spanish NIDA InfoFacts fact sheets on Inhalants, revised NIDA's Research Report Series on Inhalants, and coordinated the participation of Dr. Nora D. Volkow in the press conference held on March 18, 2004 at the National Press Club.

Sheryl Massaro coordinated the participation of Dr. Nora D. Volkow in the webcast entitled "Addiction by Prescription". This was the first of a series of webcasts produced by SAMHSA as part of National Recovery Month, which is in September. However these webcasts will air throughout the year. "Addiction by Prescription" aired on March 3, 2004.

On February 5, 2004, Drs. David Shurtleff and Paul Schnur, DNBR, met with representatives of the Association for the American Veterinary Medical Colleges to discuss research and research training opportunities available to veterinarians and students of veterinary medicine at the National Institute on Drug Abuse.

Dr. David Shurtleff, Director, DNBR, presented "How To Write a Fundable Grant" with Dr. Abraham Bautista (NIDA) and Dr. Barbara Bayer (Georgetown University) at the Society on NeuroImmune Pharmacology (SNIP) in Santa Fe, NM on March 26, 2005.

Dr. William Corrigall, DNBR, gave the opening plenary titled Tobacco Addiction Research at NIDA: A Brain Research Perspective at the annual meeting of the Society for Research on Nicotine and Tobacco Europe meeting in Scottsdale AZ, February 2004.

Dr. William Corrigall gave a presentation titled NIDA's Agenda for Nicotine Research at the Bluegrass Chapter of the Society for Neuroscience Spring Neuroscience Day in Lexington KY, March 2004.

Dr. Dave Thomas, DNBR, chaired a session titled, "Virtual Reality and Addictions," at the Cybertherapy, 2004 meeting in San Diego, CA, January 2004.

Dr. Cora Lee Wetherington, NIDA's Women's Health Issues Coordinator and DNBR, gave a talk, "NIH Grant-Writing Strategies," at the workshop, Funding Your Research: Tips from the Experts, at the University of Michigan on March 12, 2004. The workshop was sponsored by the University of Michigan's Institute for Research on Women and Gender.

Dr. Cora Lee Wetherington gave the keynote address, "Gender-Based Approaches to Drug Abuse," at the Third Annual Conference on Women and Mental Health, Baltimore, MD, May 17, 2004.

Dr. Cora Lee Wetherington served on the organizing meeting for the 2nd World Congress on Women's Mental Health held March 17-20, 2004 in Washington, DC, and represented NIDA at the meeting.

Dr. Minda Lynch, BCSRB, DNBR, co-chaired a workshop at the Winter Brain Research Conference, Copper Mountain, Colorado, in January 2004 on "Nucleus Accumbens, Glutamate and Addiction". Drs. Christopher Pierce, David Self, Krista McFarland and Patricia DiCiano discussed their recent research on the role of central glutamatergic systems, receptors and cellular mechanisms in an animal model of relapse to addiction.

Dr. Susan Volman, DNBR, gave a talk on "Funding Opportunities at NIDA" for a workshop on the NIH grants process at the Spring Brain meeting in Sedona, AZ, on March 13, 2004.

Dr. Joni Rutter, DNBR, represented NIDA at the Society for Women's Health Research (SAGE Conference 2004), held in North Carolina, March 25-28, 2004.

Dr. Rutter and Dr. Riddle, DNBR, represented the Genetics and Molecular Neurobiology Branch and Dr. Rutter presented at the Long-Term Follow-Up of Prenatal Drug Exposure Advances, Challenges, and Opportunities, Bethesda, March 23-25, 2004.

Dr. Christine Colvis, DNBR, represented NIDA at the 2004 Association of Biomolecular Resource Facilities meeting in Portland, OR.

Dr. Lula Beatty, Chief, Special Populations Office, participated as a distinguished lecturer at the 61st Annual Meeting of the National Institute of Science on March 25, 2004 in Houston, Texas. Her presentation was entitled "Improving Health Through Addiction Research."

Dr. Lula Beatty organized a professional development workshop on women psychologists in research for the mid-winter meeting of the Society for the Psychology of Women, American Psychological Association on February 5, 2004 in Washington, DC.

Dr. Lula Beatty presented a talk entitled "Lost in the System: Meeting the Drug Abuse Needs of Racial/Ethnic Minority Populations" on March 17, 2004 for NIDA's Science for the Layman Series.

Dr. Lula Beatty presented a lecture entitled "Eliminating Discrimination Against Marginalized Populations in Health Research" on February 25, 2004 for the Ethics Seminar Program at Washington University, St. Louis, MO.

Dr. Lula Beatty participated in a planning meeting of the Emerging Scholars Interdisciplinary Network at the University of Pennsylvania, April 2-4, 2004 in Philadelphia, PA.

Dr. Lula Beatty participated in the Lonnie E. Mitchell HBCU Substance Abuse conference held March 31-April 2, 2004 in Baltimore, MD.

Dr. Lula Beatty presented a session on research opportunities at NIDA for the NIH Extramural Associates Program on February 9, 2004 in Bethesda, Maryland.

Ana Anders, Senior Advisor on Special Populations, SPO, co-chaired a meeting of the Steering Committee of the National Hispanic Science Network in Miami, on April 18-20, 2004.

Ana Anders participated in a meeting of the Federal Employee Coalition of Hispanic Association held in Washington D.C. April 6, 2004.

Ana Anders participated in NIDA's MIDARP meeting April 13 and 14, 2004 in Rockville, MD.

Flair Lindsey, Special Populations Office, presented information on the Summer Research with NIDA program and other research opportunities to students during the Department of Psychology's 10th Annual Career Day at Southern University on February 17, 2004 in Baton Rouge, LA.

Flair Lindsey presented information on the Summer Research with NIDA program to students at the Science, Technology, and Research Training Conference at Prince George's Community College on March 18, 2004 in Largo, MD.

Flair Lindsey presented information on the Summer Research with NIDA program to the Psychology Collegian Members of the Prince George's Community College on March 25, 2004 in Largo, MD.

Dr. Frank Vocci, Director, DTR&D, attended the annual meeting of the Society for

Research on Nicotine and Tobacco in Phoenix, February 18-20, 2004. At the meeting he met with grantees and pharmaceutical groups.

Dr. Frank Vocci attended the Methods and Biomarkers to Assess Reduction of Tobacco Toxin Exposure on February 26-27, 2004 in Washington, DC. The meeting was co-sponsored by NIDA, NCI, NIAAA, and CDC.

Drs. Frank Vocci, Jane Acri, and David McCann, all of DTR&D, traveled to Horsham, England on March 4-5, 2004 to meet with Novartis Pharmaceuticals.

Drs. Frank Vocci, Ahmed Elkashef, Ann Anderson, Richard Hawks and Ms. Liza Gorgon and Robert Walsh, all of DTR&D, met with Somerset Pharmaceuticals on March 17, 2004. On March 18-19, 2004 the same DTR&D group attended a protocol development meeting, co-chaired by Drs. Gerry Friedland and Walter Ling. The objective of that meeting was to discuss issues relating to the concurrent treatment of HIV+ opiate dependent patients for both opiate dependence (with buprenorphine) and HIV disease with Highly Active Anti-Retroviral Therapy (HAART).

Drs. Frank Vocci, Ahmed Elkashef, Roberta Kahn, and Ivan Montoya and Mr. Jurij Mojsiak site visited UCLA on April 14, 2004. On April 15-16, 2004 the DTR&D group met with UCLA Data and Safety Monitoring Board to review multiple study results.

Dr. Frank Vocci spoke at the Buprenorphine Mentors meeting in New Orleans on April 17, 2004.

Drs. Ivan Montoya, and Frank Vocci co-chaired and other DTR&D personnel attended the Medications Development for Cannabis Dependence meeting in Rockville on April 18-19, 2004.

Drs. Jamie Biswas, Ann Anderson, and Ahmed Elkashef were session chairs. The purpose of the meeting was to get advice on strategies to develop medications for the treatment of cannabis dependence and scientifically sound implementation methodologies.

Dr. Frank Vocci attended the American Psychiatric Association meeting on May 1-4, 2004. He organized and co-chaired a workshop on development of medications for the treatment of stimulant dependence.

Dr. Frank Vocci and DTR&D branch chiefs spoke at a Medications Program Review held at the NSC on May 17-18, 2004. Dr Peter Kalivas chaired the NIDA Council sub-committee that is reviewing the program.

Dr. Joseph Frascella, DTR&D, participated in a Special Populations Research Development Series Workshop on the Minority Institutions Drug Abuse Research Program (MIDARP) April 13-14, 2004 in Bethesda, MD.

Dr. Steven Grant chaired a symposium titled Substance Abuse: A Disorder of Cognition and Brain at the annual meeting of the Cognitive Neuroscience Society, April 19 - 22, 2004 in San Francisco, California. The symposium addressed the emerging view that dysfunction of brain circuits involved in fundamental cognitive processes make critical contributions to the clinical features of substance abuse disorders. Four young investigators funded through a NIDA RFA on Cognitive Aspects of Substance Abuse presented: Dr. Hugh Garavan, Medical College of Wisconsin, Dr. Julie Fiez, University of Pittsburgh, Dr. Kevin LaBar, Duke University and Dr. Julie Stout, Indiana University.

Dr. Steven Grant chaired a symposium entitled Drugs and Other Addictions: Does One Size Fit All? at the annual meeting of the American Psychiatric Association, May 1-6, 2004 in New York, NY. The symposium focused on similarities and differences in the diagnosis, epidemiology, treatment, and brain function across these disorders, with an emphasis on co-morbidity with both other addictive disorders and other psychiatric illnesses by. The participants in the symposium were: Dr. Marc Potenza, Yale School of Medicine, Dr. Nathan Shipira, University of Florida, Dr. Nancy Petry, University of Connecticut, and Dr. Linda Cottler, Washington University.

Dr. Steven Grant presented a talk on April 22, 2004 entitled Decisions & Addictions: A Cognitive Approach to Substance Abuse at the "Exploring the Mind: Multiple Perspectives on Decision-Making" Conference held at the Center for Mind and Brain, at the University of California, Davis, Davis, CA.

Dr. Steven Grant represented NIDA at the annual meeting of the Society for Biological Psychiatry, April 29-May, 2004 in New York, NY.

Dr. Laurence Stanford served as the chair of a session on the application of neuroimaging techniques in the Long-Term Follow-Up of Prenatal Drug Exposure: Advances, Challenges, and Opportunities Meeting held in March of 2004 in Bethesda, MD.

Drs. Laurence Stanford and Joseph Frascella participated in the 11th Annual Undergraduate and Graduate Research Symposium at Morgan State University on April 15, 2004 in Baltimore, MD.

Drs. Laurence Stanford and Joseph Frascella participated in a planning meeting to develop science exhibits on drug abuse and development to be displayed at the Arizona Science Center. The planning meeting was held April 26-27, 2004 in Boston, MA.

Dr. Joseph Frascella chaired a symposium entitled Obesity: Lessons Learned from Addiction at the annual meeting of the American Psychiatric Association in New York City, May 1-6, 2004.

Dr. Wilson Compton, DESPR Director, attended and participated in workgroup discussions at the NIH/American Psychiatric Association Cooperative Agreement meeting: The Future of Psychiatric Diagnosis, Refining the Research Agenda: Launch and Methods Conference, February 19-20, 2004, Bethesda, Maryland.

Dr. Wilson Compton presented on Epidemiology of Substance Use Disorders as part of the Wisconsin Bureau of Substance Abuse Services Teleconference Series, February 26, 2004.

Drs. Wilson Compton, Timothy Condon and Nora Volkow conducted a site visit to the Chicago Cook County Jail and criminal courts on March 2-3, 2004. The visit was coordinated by Illinois TASC and included visits with all major components of the criminal justice system in Cook County, including a women's treatment program in the jail. Following the visit to the Cook County facilities, the team also site visited the Haymarket Center in Chicago and the NIDA-funded Chestnut Health Systems/Lighthouse Institute research programs conducted in that facility.

Dr. Wilson Compton presented Research Efforts to Improve Addiction Services, at the NIMH Outreach Partnership conference, March 8, 2004.

Dr. Wilson Compton conducted a site visit to the College of Health and Urban Affairs of the Florida International University, Miami, Florida, March 15, 2004. This visit was hosted by Dean Ronald Berkman and included a formal presentation to provide an Update from the National Institute on Drug Abuse, as well as informal consultation/discussion sessions regarding development of research programs.

Dr. Bennett Fletcher, DESPR, chaired the Meeting on Treatment and Recovery Processes, January 15 -16, 2004 in Bethesda, Maryland. The meeting reviewed the state of the science on treatment processes to provide suggestions for future developments in the field.

On January 21, 2004, Drs. Elizabeth Robertson and Wilson Compton chaired a symposium titled "Science-Based Community Friendly Prevention Tools" at the CADCA Leadership Forum XIV. Presenters included: Drs. Linda Dusenbury, Susanna Nemes, and Christopher Williams.

Dr. Jack Stein, Chief, Services Research Branch (SRB), DESPR, chaired a half-day symposium at the TCA Winter Meeting about the Updates on Therapeutic Communities Research, featuring several NIDA grantees, Tucson, Arizona, January 10-13, 2004.

Dr. Eve Reider, DESPR, represented NIDA at an NIMH roundtable held February 25, 2004 at the Neuroscience Center, Bethesda, Maryland. The roundtable was: Preventing Child and Adolescent Mental Disorders: Research Roundtable on Economic Burden and Cost Effectiveness.

Dr. Elizabeth Robertson, DESPR, is serving on the NIH interagency to address the House Appropriations Committee's request for a 2005 appropriations report on "Underage Rural Drinking and Other Risky Behaviors Such As Illegal Drug Use Among 9 to 15 Year Old Children."

Dr. Elizabeth Robertson is serving on the Complex Interventions Planning Group, being coordinated by the NIH Office of Behavioral and Social Science Research. The first of two meetings, From Clinical Trials to the Community, was held in January 2004; the second planned for May 2004 will address alternate methodologies for

conducting research in community settings.

On March 11, 2004, Elizabeth Robertson, Ph.D. made a presentation to the CSAP Staff College titled "Preventing Drug Use among Children and Adolescents: An Update."

Dr. Elizabeth Robertson presented a poster symposium at the Society for Research on Adolescence in Baltimore, MD on March 13, 2004. The title of her presentation was "Multi-problem Adolescents: A Research Priority."

Drs. Redonna Chandler and Jack Stein, both of SRB, DESPR, presented Community: The Vital Link Between Public Health and Public Safety at the CADCA National Leadership Forum, Washington, DC, January 23, 2004.

Dr. Jerry Flanzer, SRB, DESPR, gave discussant comments for Drug Abuse, HIV and Medical and Social Consequences, a symposium at the Society for Social Work Conference, New Orleans, LA, January 16, 2004.

Dr. Jerry Flanzer presented at Advancing Social Work Research in Addictions and HIV, a conference sponsored by the George Warren Brown School of Social Work, Washington University, St. Louis, MO, April 15-16, 2004.

Dr. Thomas Hilton, SRB, DESPR, presented The Nuts and Bolts of Obtaining External Research Funding, at the Annual Society for Industrial and Organizational Psychology, Chicago, IL, April 2, 2004.

Dr. Thomas Hilton chaired a symposium entitled, Lessons Learned: Strategies and Pitfalls in Workplace Intervention Studies, at the conference on Workplace Strategies and Interventions for Improving Health and Well-Being, Washington, DC, April 12-15, 2004.

Dr. Leslie Cooper, ERB, DESPR, attended and served as a moderator for the trans-NIH initiative, "NIH Extramural Associates Program 25th Anniversary and Biennial Update Conference", held in Rockville, MD, February 23 - 24, 2004.

Jag Khalsa, Ph.D., of CAMCODA presented a Symposium on Issues in the Medical Management of HIV/HCV co-infection in IVDUs, April 22, 2004, Washington, DC, at the 35th Annual Conference of the American Society of Addiction Medicine. At this symposium, an international panel of clinicians and scientists discussed current issues and medical management practices for patients with HIV/HCV co-infection and drug abuse. The proceedings will be published as a supplement in Clinical Infectious Diseases.

Nicolette Borek, Ph.D., CAMCODA, participated as a scientific staff collaborator in the Network Meeting of the Adolescent Trials Network for HIV/AIDS Interventions in Washington, DC, April 14-16, 2004. The ATN is a collaborative network cosponsored by NICHD, NIDA, NIMH, and NIAAA.

Nicolette Borek, Ph.D., CAMCODA, was a participant in the Invited Discussion Hour "Support for Research on Adolescence at the National Institute on Drug Abuse" at the Society for Research on Adolescence Biennial Meeting in Baltimore, Maryland, March 11-14, 2004.

Peter Hartsock, Ph.D., CAMCODA, participated in the conference, "Leveraging the Power of Industry: Strategies to Fight HIV/AIDS," March 12, 2004, Washington, D.C. The conference was sponsored and co-chaired by U.S. Department of Commerce Secretary Donald Evans, DHHS Secretary Tommy Thompson, U.S. Department of State Global AIDS Coordinator and Ambassador Randall Tobias, and Global Business Coalition on HIV/AIDS President Ambassador Richard Holbrooke. Dr. Hartsock presented on NIDA's program of advanced mathematical applications to studying the transmission dynamics of HIV/AIDS and assessing the public health impact and cost effectiveness of AIDS interventions.

Peter Hartsock, Ph.D., participated in a meeting of the Health and Security Senior Working Group of the Chemical and Biological Arms Control Institute dealing with responding to the challenge of biological weapons (January 29, 2004, Washington, D.C.). Dr. Hartsock presented on NIDA's program of advanced mathematical applications to studying the transmission dynamics of HIV/AIDS and assessing the public health impact and cost effectiveness of AIDS interventions. This program is already contributing to national security, both in dealing with HIV/AIDS and applications of the program's methodologies to understanding the transmission dynamics of and intervention in, smallpox and anthrax.

Jag Khalsa, Ph.D., CAMCODA, and Phillip Peterson of University of Minnesota presented a mini-symposium on "Tuberculosis and Drug Abuse" at the Annual Meeting of the Society on NeuroImmune Pharmacology, Santa Fe, NM, March 27, 2004. Dr. Keith McAdams, Professor of Tropical and Infectious Disease, London School of Hygiene and Tropical Medicine gave an excellent global overview of TB; Dr. Andrea Howard of Montefiore presented the impact of drug abuse on TB; Dr. Molitor of the University of Minnesota described the pig model of TB; and Dr. Vivek Kapur of the University of Minnesota discussed the current proteomics/genetic techniques used in the study of infections. A white paper is planned for publication in Journal of Infectious Diseases.

Dr. Jean Lud Cadet, IRP, gave a talk at NIH to Outreach Partners on March 9, 2004 entitled, "Molecular Neuropsychiatry Research Section: Basic and Clinical Research Updates."

Dr. Jean Lud Cadet, IRP, gave a talk at the Lonnie Mitchell Conference on April 1, 2004 entitled, "Neuropsychiatric and Neurovascular Effects of Drugs of Abuse: Cocaine and Marijuana in Focus."

Dr. Amy Newman, IRP, was invited to present a seminar to the HHMI-NIH Research Scholars and the NIH Clinical Research Training Program, Bethesda, MD, February 2004.

Dr. Amy Newman was invited to present a seminar to the Department of Chemistry & Environmental Science, New Jersey Institute of Technology, Newark, NJ, February 2004.

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Media and Education Activities

Press Releases

December 12, 2003 - **NIDA NewsScan #27**

- Research Yields New Insights into Molecular Markers of Addiction
- The Value of Vouchers May Not Be as Relevant as the Timing
- Long-Term Treatment Yields Greatest Drug-Use Reductions
- Cocaine Use May Cause Alterations in Brain Regions Involved in Decision Making
- Natural Fat Compound May Be Basis For New Class of Drug Targeting Obesity and Other Compulsive Disorders, Including Addiction
- Study Investigates Short-Term Effects of Marijuana Use on HIV+ Patients
- Scientists Seek To Identify Patterns in Injection Drug Users

December 19, 2003 - **Teen Drug Abuse Declines Across Wide Front**. HHS Secretary Tommy G. Thompson and John P. Walters, Director of National Drug Control Policy, released the results of the 2003 Monitoring the Future survey, showing an 11 percent decline in drug use by 8th, 10th, and 12th grade students over the past two years. The finding translates into 400,000 fewer teen drug users over two years.

January 5, 2004 - **New Study Suggests Methamphetamine Withdrawal is Associated with Brain Changes Similar to Those Seen in Depression and Anxiety**. Results of a new study indicate that people who have recently stopped abusing the powerfully addictive drug methamphetamine may have brain abnormalities similar to those seen in people with mood disorders. The findings suggest practitioners could improve success rates for methamphetamine users receiving addiction treatment by also providing therapy for depression and anxiety in appropriate individuals. The study was published in the January 2004 issue of the *journal Archives of General Psychiatry*.

January 13, 2004 - **Timothy P. Condon Named Deputy Director of the National Institute on Drug Abuse**. Dr. Timothy Condon has been named Deputy Director of the National Institute on Drug Abuse (NIDA), a component of the National Institutes of Health. Dr. Condon will assist in developing, implementing, and managing NIDA's programs, priorities, resources, policies and research dissemination efforts. In addition, he will continue to serve as director of the Institute's Office of Science Policy and Communications.

January 22, 2004 - **NIDA NewsScan #28**

- Animal Models of Adolescent Drug Abuse: Integrative Studies of Brain and Behavioral Development
- Behavioral and Cognitive Processes Related to Adolescent Drug Use
- Prevention Research for the Transition to Adulthood
- Medications Development for Cannabis-Related Disorders
- HIV/AIDS, Severe Mental Illness, and Homelessness
- National Cooperative Drug Discovery Groups for the Treatment of Mood Disorders or Nicotine Addiction
- Ruth L. Kirschstein National Research Service Awards for Individual

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Predoctoral Fellows

February 19, 2004 - "**Virtual Reality: Opportunities for the NIH**". Virtual reality technologies are proving to be an important new tool in medical science. The National Institute on Drug Abuse, National Institutes of Health, hosted the symposium "*Virtual Reality: Opportunities for the NIH*" to highlight the latest scientific findings on the current and potential roles for virtual reality technologies in medicine.

March 1, 2004 - **NIDA Study Finds Alcohol Treatment Medication, Behavioral Therapy Effective for Treating Cocaine Addiction**. Results of a study funded by the National Institute on Drug Abuse (NIDA), National Institutes of Health, suggest that disulfiram, a medication used to treat alcohol addiction, is effective in combating cocaine abuse. The researchers also conclude in the same study that combining disulfiram with behavioral therapy provides more positive results in treating cocaine dependence than disulfiram in combination with another form of therapy. The research was published in the March 2004 issue of the *Archives of General Psychiatry*.

July 11, 2003 - **NIDA NewsScan #24**
Special Issue of NewsScan Focuses on NIDA Funding News

- NIDA to Fund Medication Development Units
- NIDA Seeks New Funding Solicitations for Proteomics Research
- Behavioral Therapies Program (PA-03-126)
- Women Gender Differences and Drug Abuse (PA-03-139)
- Cutting Edge Basic Research Awards (PAR-03-017)

March 17, 2004 - **NIDA NewsScan #29**

- Novelty-Seeking Teens May Be More Easily Influenced by Tobacco Advertisements
- Behavioral Symptoms May Indicate Increased Smoking Risk Among Adolescents
- Prevention Program Curbs Drug Abuse Among Middle-School Youth
- Long-Lasting Medication Shows Promise for Treatment of Heroin Addiction
- Buprenorphine May Help Those Addicted to Heroin and Cocaine
- Scientists Use Visual Attention Tool To Help Explain How Smoking Cues Affect Smokers

March 23, 2004 - **Detroit to be Site of NIDA Blending Meeting**. NIDA will host "Blending Clinical Practice & Research: Forging Partnerships in the Great Lakes States to Enhance Drug Addiction Treatment" at the Renaissance Marriott in Detroit, Michigan September 27-28, 2004. This 2-day conference will provide an opportunity for clinicians and researchers to examine cutting-edge findings about drug use and addiction and their application to clinical practice.

Dr. Nemeth-Coslett, DTR&D, continues to co-chair the Translationally Oriented Approaches, Devices and Strategies (TOADS) work-group. Two years of efforts to attract new-to-NIDA investigators have been substantially rewarded with more than two dozen applications for Phase I/Phase II SBIR grants and/or contracts, Cutting Edge Basic Research Awards (CEBRAs), and various R-type grants focusing on virtual reality. This NIDA Program has received a good bit of media attention from the AP, local TV broadcasts, a feature article in the Washingtonian (April 2004) and by JAMA.

Articles of Interest

December 25, 2003, *JAMA*- "Addiction Treatment Strives for Legitimacy" - Interview with Frank Vocci, Ph.D.

March 1, 2004, *Washingtonian Magazine*-"What Are You Afraid Of?" - Interview with David A. Thomas, Ph.D.

Exhibits/Conferences

Lonnie E. Mitchell Historic Black Colleges And Universities Substance Abuse Conference (HBCU): March 30 - April 2, 2004
American Counseling Association Annual Convention: March 31 - April 4, 2004
Association of Minority Health Professions Schools: April 7-9, 2004
Experimental Biology: April 17-21, 2004
American Society of Addiction Medicine: April 23-25, 2004

American Psychiatric Association: May 5-6, 2004
American Psychological Society: May 27-30, 2004
National Association of State Alcohol and Drug Abuse Directors/National Prevention Network: June 5-9, 2004
American Nurses Association: June 25-29, 2004
National Congress of Parents and Teachers: June 26-28, 2004
Association of Higher Education and Disability: July 13-17, 2004
American Psychological AssociationJuly 28 - August 1, 2004

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Planned Meetings

NIDA will host a two-day conference **Blending Clinical Practice and Research: Forging Partnerships in the Great Lakes States to Enhance Drug Addiction Treatment** at the Marriott Renaissance, Detroit, Michigan on September 27-28, 2004. This conference will bring together clinicians and researchers to examine cutting-edge scientific findings about drug abuse and addiction and their application to clinical practice.

Drs. Timothy Condon and Susan Weiss will chair a symposium entitled **Aging and Substance Abuse: What Problems Lie Ahead?** at the 2004 College on Problems of Drug Dependence (CPDD) Annual Conference to be held June 12-17, 2004 in San Juan, Puerto Rico The goal of the symposium is to stimulate interest in this area of research in order to prevent and/or ameliorate the medical, social, and financial consequences of continued or emerging substance abuse in aging baby boomers. Participants in this symposium will include Drs. Wilson Compton, Frederic Blow, Thomas Patterson, and David Oslin.

NIDA will hold a **Grant Writing Workshop at the 2004 College on Problems of Drug Dependence (CPDD) Conference** in San Juan, Puerto Rico. Approximately 50 early-career scientists will participate in learning how to apply for grants and the grant process at NIDA. Drs. Timothy Condon, Cindy Miner, David Shurtleff, and Mark Green from NIDA, and Dr. Scott Lukas, McLean Hospital, Harvard Medical School, will present. Dr. Suman Rao, OSPC, is chairing and coordinating this event.

NIDA will hold a **Tutorials Workshop prior to the 2004 College on Problems of Drug Dependence (CPDD) Conference** in San Juan, Puerto Rico. The presentations this year will be on (1) "Cultural Sensitivity, Human Subject Protection, Community Requirements, and Data Quality in Addictions Research" by Dr. Arlene Stiffman, (2) "Anti-Craving Medications: A Potential Target for Medication Development" by Dr. Charles O'Brien, (3) "Behavioral Pharmacology (pre-clinical and clinical)" by Dr. Linda Dykstra" and (4) "Effects of Drugs of Abuse on the Immune System, Including HIV Expression" by Dr. Jean Bidlack. Approximately 30 NIDA Director's Travel Awards will be issued to current NIDA fellows and trainees. Dr. Suman Rao, OSPC, is coordinating this annual workshop.

On the evening of June 13, 2004, Drs. David McCann, Jane Acri and Rik Kline will chair a CPDD workshop entitled: **Integration of Toxicology- and PK-Related Testing into Early Medications Discovery: A Workshop for NIDA Medicinal Chemists**. The specific aims of the workshop are to: (1) provide NIDA grantee chemists and their pharmacologist colleagues with a clear understanding of the methods used in NIDA's contract-based predictive toxicity testing and (2) to address important questions related to data interpretation. Speakers and the titles of their talks will be as follows: Dr. Arthur M. Brown (Chan Test, Inc.), "*In Vitro* Assays to Predict QT Prolongation"; Dr. Arthur Weissman (NovaScreen Biosciences Corp.), "*In Vitro* CYP Assays to Predict Potential for Drug-Drug Interactions"; Dr. James Terrill (NIDA DTR&D), "*In Vitro* Assays for the Early Assessment of Mutagenic Potential"; and Dr. Edwin J. Matthews (FDA, Center for Drug Evaluation Research), "*In Silico* Prediction of Drug Toxicity."

A NIDA sponsored meeting is planned for Fall 2004 entitled **Cognitive and Affective Science Findings: Translation to New Behavioral Treatments for Drug Addiction**. The objective of this meeting is to bring together researchers in the basic sciences and in behavioral treatment development in an effort to understand the mechanisms underlying basic behavioral, cognitive and affective processing in the

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context of drug addiction, and to identify methods for translating this knowledge into innovative and novel approaches for drug addiction treatment. The meeting is being organized and co-chaired by Drs. Mary Ann Stephens, Lisa Onken, and Joe Frascella, all of DTR&D.

Dr. Steven Grant, DTR&D, is participating in the organization of a meeting of the economics of substance abuse, tentatively entitled **Drugs at Any Cost** to be held in October 2004 in Bethesda, MD. Dr. Grant will be chairing a session on neuroeconomics.

Dr. Laurence Stanford, with colleagues from the NINDS, NIMH, NICHD, and NIBIB, is organizing a meeting to explore the potential of functional neuroimaging in understanding the development of the human brain and brain-behavior relationships. The meeting, entitled, **Pediatric Functional Neuroimaging: a Trans-NIH Workshop**, will be held on May 24th through 26th, 2004 in Bethesda.

On October 22, 2004, during the NIDA Mini-Convention that precedes the Society for Neuroscience Annual Meeting, Drs. Thomas Aigner (DNBR), Steven Grant (DTR&D), and Nathan Appel (DTR&D) will co-chair a symposium entitled **Creative Directions in Imaging Drug Effects in Animals**. The goal of this session is to present outstanding, state-of-the-art, examples of imaging research in animals that are now possible using Positron Emission Tomography (PET), Magnetic Resonance Imaging and Microscopy (MRI/MRM), and optical methods, since there has been a such remarkable evolution of functional biomedical imaging methods that may be applied to drug abuse research. The scheduled speakers are Drs. Susan Andersen (McLean Hospital), G. Allan Johnson (Duke University), Helene Benveniste (Brookhaven National Laboratories), and Mark Schnitzer (Stanford University).

National CTN Steering Committee Meetings are planned for the following dates and locations: July 22-23 in Washington, DC; and September 27-29 in Detroit, Michigan.

The **CTN Data and Safety Monitoring Board** will meet July 15-16, 2004 and November 16-17, 2004 in Gaithersburg, Maryland. The group will review the continuing progress of the CTN's protocols.

A **Nicotine Dependence Workshop** will be held October 1, 2004, in Detroit, Michigan.

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Publications

NIDA Publications

Problems of Drug Dependence, 2003: Proceedings of the 65th Annual Scientific Meeting,
The College on Problems of Drug Dependence, Inc.
NIH Pub. No. 04-5492
This publication is the result of an annual meeting, and is comprised of comprehensive, up-to-date reviews of research in progress from many disciplines in drug abuse and drug dependence.

Research Report Series: Inhalant Abuse (Revised)
NIH Pub. No. 04-3818
This report is based on research on the use and prevalence of inhalants and presents information on the types of inhalants, the consequences of their use, who is abusing inhalants, and how to recognize inhalant abuse.

NIDA NOTES

NIDA NOTES, Volume 18, Issue No. 5
NIH No. 04-4378
The Director's Column addresses the challenge of comorbid substance abuse and mental disorders and the need for a better understanding of the origins and progression of comorbidity. NIDA and the National Institute of Mental Health are supporting research to increase fundamental knowledge of these dual disorders, advance efforts to prevent their destructive combination, and treat those already afflicted. The lead story notes that stress in the absence of drug taking can trigger changes in dopamine-releasing cells in the brain's ventral tegmental area similar to those caused by addictive drugs, suggesting that stress may increase vulnerability to addiction. Other research findings report that hard-to-treat smokers may benefit from a medication that acts on dopamine and is used to treat Parkinson's disease. Other topics include a report on last year's Blending Conference, and a synopsis of the latest Science & Practice Perspectives.

NIDA NOTES, Volume 18, Issue No. 6
NIH 04-4378
The Director's Column in this issue notes that the medical consequences of drug abuse and addiction extend beyond the chemical pathways of the brain. Some of drugs' destructive impact is temporary, and patients' health improves after they receive treatment and stop using drugs. Whether the destruction is short-lived or chronic, however, the growing list of recognized health consequences of abuse and addiction underscores the fact that drug abuse is not just a brain disease that exists in medical isolation. Rather, its harm is evident throughout the body and requires the comprehensive attention of the medical community. This issue also examines research linking cocaine use with a compromised immune system response and could help explain the high incidence of infectious disease among drug abusers. Another article presents research findings that use of ecstasy (MDMA) may increase users' risk for cardiac valve disease.

NIDA INVEST Letter - April 2004 - This edition of the quarterly newsletter announces the agreement to collaborate on binational drug abuse research that was signed by NIDA, the Spanish National Plan on Drugs (PNSD), and the Spanish National Institute of Drug Research and Training (INIFD) at the U.S.-Spain Binational Workshop on Drug Abuse and Addiction Research held October 23-24, 2003, in Washington, D.C. The issue also features remarks by NIH Director Elias Zerhouni,

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M.D., calling for more international research collaboration on global health issues; a profile of NIDA Hubert H. Humphrey Drug Abuse Research Fellow Dr. Sergey Dvoryak, Ukraine; and a "From the Field" report by NIDA grantee Dr. Deni Carise, Treatment Research Institute, Philadelphia, Pennsylvania, discussing international collaboration on a new version of the Addiction Severity Index.

Revised Application Forms - NIDA INVEST Drug Abuse Research Fellowship - These forms have been updated to correspond with the most recent revisions to the Public Health Service Grant Application (Form 398), and are now available online in two formats: Adobe Acrobat PDF and MS Word. Access the forms on the NIDA web page (www.drugabuse.gov) by selecting "International" from the "Researchers and Health Professionals" menu, then following the links to "Fellowships and Other Research Opportunities," and "INVEST Research Fellowship."

During the months January - April, eight editions of the **CTN Bulletin Board** were distributed. The Bulletin Board is an electronic report on the progress of the protocols, committees, and node activity in the CTN.

Two brochures for CTN Protocol - Job Seekers Training for Patients with Drug Dependence (CTN-0020) were approved for distribution throughout the CTN and published.

A patient recruitment brochure was approved for CTN Protocol - Reducing HIV/STD Risk Behaviors: A Research Study for Men in Drug Abuse Treatment (CTN-0018) and printed for distribution.

A patient recruitment brochure was approved for CTN Protocol - Reducing HIV/STD Risk Behaviors: A Research Study for Women in Drug Abuse Treatment (CTN-0019) and printed for distribution.

Two patient brochures for the CTN Protocol - Suboxone (Buprenorphine/Naloxone) Taper: A Comparison of Taper Schedules (CTN-0003) were translated into Spanish and distributed throughout the Network.

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Dr. Arnaldo R. Quinones, CCTN Medical Officer, is co-author of the publication: "The NEAT Study: A 48 Week Open-Label Study to Compare the Antiviral Efficacy and Safety of GW433908 Versus Nelfinavir in Antiretroviral Therapy-Na•ve HIV-1 Infected Patients," Journal of Acquired Immune Deficiency Syndrome, 35(1), pp. 22-32, January 1, 2004.

A Special Issue of Prevention Science (Vol. 5, No.1, March 2004) titled "Blending Research and Practice in Schools" was edited by Drs. Shakeh Kaftarian, Elizabeth Robertson and Wilson Compton of DESPR. This Special Issue includes a variety of articles by NIDA grantees, which were presented at a conference in April of 2003 titled "What Do Schools Really Think About Prevention Research? Blending Research and Reality" sponsored by DESPR. Articles explore the: 1) necessity for innovative research designs and methodologies which could have direct bearing on the value and applicability of research-based practices; 2) importance of building the capacity of practitioners for a successful implementation of research-based programs in real-life settings; and 3) dynamic tension between fidelity of implementation and program adaptation.

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Staff Highlights

Honors and Awards

CAPT Leslie Cooper, ERB, DESPR, was deployed (March 17 -19, 2004) as part of the United States Public Health Services Commissioned Corps Readiness Force. The Washington, DC Department of Health (DC DOH) requested Centers for Disease Control and Prevention (CDC) assistance in responding to reports of elevated lead levels in residential tap water. The DC Emergency Medical System Administration was activated and requested assistance from Vice Admiral, Richard Carmona, United States Surgeon General to deploy officers from the United States Public Health Service Commissioned Corps (USPHSCC) to respond to this public health crisis. Captain Cooper served both as an epidemiologist and a nurse doing data collection and venipunctures during this deployment.

Dr. Nemeth-Coslett, DTR&D, has accepted the nomination as the Vice President of Education for the Executive Toastmasters Club, 2004-2005.

In March 2004, **CAPT Steve Oversby**, DTR&D, was awarded a Certificate of Recognition from Donald Rumsfeld, Secretary of Defense, and also received a Letter of Commendation from the President of the U.S. Naval War College, upon completion of the Joint Maritime Operational Warfare graduate course.

Dr. Dorota Zolkowska, IRP, Visiting Fellow in the Integrative Neuroscience Section, Behavioral Neuroscience Branch, NIDA/IRP, was a recipient of the 2004 FARE Award for presentation of her research entitled: "Prevention of the Neurotoxic Effect of Dynorphin by Use of a Targeted Proteomics Approach" at the Annual Society for Neuroscience Meeting in New Orleans, LA.

Dr. Mu-Fa Zou, IRP, Medicinal Chemistry Section, Medications Discovery Branch was promoted to Staff Scientist in January 2004.

Staff Changes

Helen Cesari, M.Sc., Associate Director, CAMCODA, has been on assignment detail with the Office of the Director as Special Assistant to the Deputy Director since February 10, 2004.

Thomas Kresina, Ph.D, Deputy Director, CAMCODA, has been on assignment detail with Center for Substance Abuse Treatment (CSAT) SAMHSA since April 5, 2004.

Azeekat Abu joined OPRM's Grants Management Branch as a Grants Management Specialist on March 21, 2004.

Veronica Holland-Lawrence, CAMCODA, accepted a new position with NIDDK, April 19, 2004.

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Grantee Honors

Dr. Renee Cunningham-Williams received an Honorable Mention, Young Investigator Award, at the Institute for Research on Pathological Gambling and related Disorders, Harvard University Division on Addictions. December 7-9, 2003.

In January 2003, **Dr. Renee Cunningham-Williams** was promoted to Research Associate Professor at Washington University in St. Louis, MO.

Dr. Ernest Drucker received a 2004 Soros Justice Fellowship to support his research and development of a public health paradigm for understanding the effects of high rates of incarceration in the US. The 18 month fellowship will help support his current research and allow him to work more closely with groups interested in the application of these findings to public education, litigation, and advocacy efforts.

Dr. Marion Forgatch of the Oregon Social Learning Center received the "Friend of Early Career Prevention Network Mentoring Award" from the Society of Prevention Research, in 2003.

Dr. Lori Holleran of the University of Texas at Austin School of Social Work received an "Outstanding Investigator Award" from the Center for Health Promotion & Disease Prevention Research in Underserved Populations, The University of Texas School of Nursing, February, 2004.

On March 30, 2004, **Dr. Hendree Jones** of Johns Hopkins University testified before the U.S. Congress on the topic of drug treatment effectiveness.

Dr. Danica Knight was awarded a Presentation Award for: "Is the Treatment Process Different for Women in Residential Treatment?" at the annual meeting of the American Psychological Association, Toronto, Canada.

The American Psychopathological Association (APPA) awarded NIDA grantee, **Dr. John W. Olney** with the 2003 Joseph Zubin Award. The APPA established this award in 1992 to honor individuals who have made seminal contributions to psychopathology research. It honors a person who has contributed to our knowledge base and has stimulated others. In connection with the Zubin award, Dr. Olney wrote a review article, "Neuroapoptosis During Synaptogenesis: A Final Common Path to Neurodevelopmental Disturbances," that will be published in a book based on the proceedings of the APPA meeting.

Dr. Carolyn Webster Stratton of the University of Washington School of Nursing was selected as a fellow in the American Psychological Association, February 2004.

Dr. Roger Weiss, Northern New England Node's Principal Investigator, was recently promoted to Professor of Psychiatry at Harvard Medical School and honored as a Distinguished Fellow of the American Psychiatric Association.

Dr. Ken C. Winters, Associate Professor at the University of Minnesota, has been appointed as Associate Editor of *Psychology of Addictive Behaviors*, and as Chair of the Technical Advisory Network, Mentor Foundation (international drug abuse prevention).

Operation PAR, one of the CTN's Community Treatment Programs in the Florida Node, was featured in the President's National Drug Control Strategy report. The agency's nationally known gender specific treatment for women and children is listed as an effective treatment program in the document. The article includes a comprehensive interview by the Chief Executive officer, Nancy L. Hamilton, MPS, CAP,

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