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

Research Findings - Basic Research

Amphetamine, LSD and PCP Act through a Common Signaling Pathway

It has been established that drugs of abuse affect the regulation of DARPP-32 (32 kD dopamine and cAMP-regulated phosphoprotein) phosphorylation. In this publication, the researchers examined the molecular effects of D-amphetamine, LSD and PCP on phosphorylation of DARPP-32 and three of its downstream effector molecules. The researchers created three strains of mutant mice, each with a DARPP-32 phosphorylation site that had been mutated to an alanine, which prevented phosphorylation at key sites, threonine (Thr) 34, Thr 75 and Serine (Ser) 130. In the Thr 34 and Ser 130 mutant animals, they found psychotomimetic-induced increases of downstream effector molecules, were reduced in frontal cortex and striatum compared to wild-type and the ability of the psychotomimetics to increase c-fos mRNA in cingulated cortex and in the paraventricular region of striatum was reduced in the Thr 34 and Ser 130 mutant animals. Looking at the effects of amphetamine, LSD and PCP on prepulse inhibition (PPI) and repetitive movements, researchers observed attenuation of both behavioral parameters with each drug in the Thr 34 mutant animals. Both behaviors were also attenuated in the Ser 130 mutant animals except for PCP/PPI effect. By eliminating single phosphorylation sites on DARPP-32, these researchers were able to demonstrate a decrease in behavioral effects of psychotomimetics, revealing the critical role that this molecule has in both molecular and behavioral drug response. Svenningsson, P., Tzavara, E.T., Carruthers, R., Rachleff, I., Wattler, S., Nehls, M., McKinzie, D.L., Fienberg, A.A., Nomikos, G.G. and Greengard, P. Diverse Psychotomimetics Act Through a Common Signaling Pathway. Science. 302(5649), pp. 1412-1415, November 21, 2003.

Marijuana and Pregnancy

Earlier studies from Dr. S.K. Dey's laboratory has shown that in a mouse model, anandamide, an endogenous cannabinoid ligand, and its receptors play an important regulatory role in the establishment of normal pregnancy and these effects are dose and stage-specific as lower levels of endocannabinoids and CB receptors were found to be beneficial for implantation while higher concentrations were detrimental to this process. In a recent paper, they demonstrate that anandamide within a very narrow range regulates blastocyst function and implantation by differentially modulating mitogen-activated protein kinase (MAPK) signaling and Ca++ channel activity via CB1 receptors. Anandamide at a low concentration induces extracellular regulated kinase (ERK) phosphorylation and nuclear translocation in trophectoderm cells without influencing Ca++ channels, and renders the blastocyst competent for implantation in the receptive uterus. In contrast, anandamide at a higher concentration inhibits Ca++ channel activity and blastocyst competency for implantation without influencing MAPK signaling. These studies utilized genetic, pharmacological and physiological approaches to uncovering a potentially important regulatory mechanism for synchronizing blastocyst and uterine competency to implantation. This observation in addition to advancing our basic knowledge has high clinical relevance as elevated levels of anandamide could induce spontaneous early pregnancy losses in women who smoke marijuana. Wang, H., Matsumoto, H., Guo, Y., Paria, B.C., Roberts, R.L. and Dey, S.K. Differential G-protein Coupled Cannabinoid Receptor Signaling by Anandamide Directs Blastocyst Activation for Implantation. Proc Natl Acad Sci., pp. 14914-14919, 2003.

Extended Access to Nicotine Self-administration in Rats Does Not Lead to Gradual Escalationin Intake

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Researchers at the Scripps Research Institute in La Jolla previously reported that groups of rats given extended access to self-administer cocaine or heroin showed a gradual escalation in drug intake compared to groups of animals that had a more restricted access to these drugs. Dr. Athina Markou and her colleagues sought to broaden these findings to the study of nicotine self-administration in rats. Using the same experimental design of the earlier studies, groups of rats were given access to nicotine one hour a day for five days a week, one hour a day seven days a week, or six hours a day seven days a week. A fourth group of animals had no access to the experimental chamber. All animals were observed for somatic signs of nicotine withdrawal on day 25 of nicotine self-administration, 17 hours after the end of the previous session. On day 31 of nicotine access, the animals were challenged with the nicotinic receptor antagonist mecamylamine for somatic signs of withdrawal and subsequently for effects on nicotine self-administration. The investigators found that extended access to nicotine self-administration resulted in the development of nicotine dependence for periods lasting up to four weeks, but did not lead to higher rates of drug intake; these results differed from the earlier findings for cocaine and heroin. The authors propose that these results parallel those in humans, where nicotine addicts show long-lasting stable rates of intake following an initial increase in intake during the acquisition phase of dependence and cocaine addicts who have a propensity to escalate drug intake. Patterson, N.E. and Markou, A. Prolonged Nicotine Dependence Associated with Extended Access to Nicotine Self-administration in Rats. Psychopharmacology OnLine, Jan. 8, 2004.

Placebo Effects of Tobacco Smoking and Other Nicotine Intake

In this review, Perkins et al. discuss common terms and methods of placebo research, especially the balanced-placebo design. Also included was discussion of the limited research directly assessing placebo effects of smoking and other nicotine intake, namely studies that manipulated instructions to subjects about the drug content of an ingested substance. Finally, other studies relevant to gauging the likely magnitude of placebo smoking effects were examined. In an effort to encourage more research on these placebo effects, substantial attention is paid to future directions. Among recommendations are testing the utility of the balanced-placebo design and other rigorously controlled designs, and including multiple measures of placebo effects in addition to self-report. Future research also should explore the moderating influences of the environmental context and of individual difference factors on placebo effects of smoking and other nicotine intake. Perkins, K.A., Sayette, M., Conklin, C. and Cagguila, A.R. Nicotine & Tobacco Research 5(5), pp. 695-709, 2003.

Altered Integration between Dopamine, Glutamate and Norepinephrine in Midbrain Dopamine Neurons May Account for Individuals' Tendency to Seek Psychostimulants

In a majority of the midbrain dopamine neurons, the afferent signaling that activates the glutamate receptor shifts the regular spontaneous discharge pattern of activity to burst firing, represented by a transient pause of the discharge due to the metabotropic glutamate-induced hyperpolarization. The burst firing results in a phasic release of dopamine and may be important in the neural processing of reward, including both natural rewards and those signaled by conditioned visual and auditory cues. Dr. John Williams showed that spontaneous bursting activity could not be detected in slices of midbrain because they lacked afferent input. Similarly, bursting activity occurred *In vivo* in dopamine-deficient animals only in the presence of the dopamine precursor, L-dopa. This work suggests that the integrity of the endogenous dopamine system, regulated by network feedback mechanisms, is critical in the generation of the burst firing pattern of the dopamine neurons. He also showed that amphetamine enhanced the burst firing rate of these neurons by shortening the pause phase of the discharges (reduction of the mGlu receptor-mediated hyperpolarizing outward current). This effect occurred through activation of the alpha-1 adrenergic receptors as the effect of amphetamine was mimicked by an adrenergic agonist and was attenuated by an antagonist. In addition, the enhancement of burst firing in these dopamine neurons normally induced by alpha-1 receptor activation was reduced in animals that actively sought cocaine (self-administering) but not in the yoked controls. The consequences of this adaptation would be a lower burst discharge and a reduced dopamine release at target loci. It suggests that individuals' tendency to seek psychostimulants may involve impaired integration among dopamine, glutamate and norepinephrine in midbrain dopamine neurons. The altered burst discharge may underlie changes in synaptic plasticity and could encode information for reward-related learning. Paladini, C. A., Robinson, S., Morikawa, H., Williams, J. T. & Palmiter, R. Dopamine Controls the Firing Pattern of Dopamine Neurons Via a Network Feedback Mechanism. Proc Natl Acad. Sci. 100, pp. 2866-2871, 2003; Morikawa, H.,

Khodakhah, K. and Williams, J.T. Two Intracellular Pathways Mediate Metabotropic Glutamate Receptor-Induced Calcium Mobilization in Dopamine Neurons. J. Neurosci. 23, pp. 149-157, 2003.

Simulation of Neuronal Encoding for Memory Task as a Simple Model for Assessment of Drugs' Effect on Behavior Performance

The firing pattern of a single neuron or ensembles of neurons varies in response to changing external or internal environments of the organism. What information does it encode and what is its functional significance? In many labs, interpretations of the electrophysiological data are at the level of altered excitation/inhibition of neurons or in brain circuits. Dr. Deadwyler's group employs a simple model to assess the "behavioral effect" on functionally relevant synaptic events and records neuronal activity in the memory circuits of the hippocampus. Their study is unique in that activity in the hippocampal cells was evoked with trains of electrical pulses that mimicked firing patterns of these neurons recorded *In vivo* when animals traversed place fields or when they were performing a short-term memory task. The simulation of neuronal encoding of a particular behavior task provides a simple experimental model that facilitated assessment of behavioral impact in a brain circuit of interest and assessed how cognitive encoding or consequences may be affected when homeostasis of the brain is altered, such as under the influence of drugs. The model allowed Dr. Deadwyler to conclude that under normal synaptic feedback control mechanisms, the phenomenon of depolarization-induced suppression of inhibition (disinhibition) mediated by the endocannabinoid system in the hippocampus, was not involved in the short-term memory process. Hampson, R.E., Zhuang, S-Y., Weiner, J.L. and Deadwyler, S.A. J. Neurophysiol., 90, pp. 55-64, 2003.

5-Butylthevinone: Sterochemistry of the Diels-Alder Reaction of 5-butylthebaine with 3-buten-2-one

In this paper the authors have reported on the X-ray analysis of 5-butylthevinone (7∀-acetyl-4,5-∀-epoxy-3,6-dimethoxy-5-∃-butyl-17-methyl-6∀,14∀-ethenoisomermorphinan), $C_{27}H_{35}N_{O4}$. This compound belongs to an important class of opioids, known as orvinols (highly potent analgesics), and is the sole product of a Diels Alder reaction of 5-butylthebaine with 3-buten-2-one, through attack of the dienophile on the ∃-face of diene, even though it has been suggested that the introduction of 5∃-substituents tends to hinder attack from the ∃face, and leads to the production of exo-etheno adducts through attack from the ∀-face. Chen, W., Metcalf, M.D., Coop, A., Flippen-Anderson, J.L. and Deschamps, J.R. Acta Cryst. E59, 0114-0016, 2003.

Nicotinic Ligand Transport

There is a continuing research interest in developing chemical agents with a structural similarity to nicotine, which could be therapeutically delivered as smoking-cessation agents, without the identified risks associated with smoking cigarettes. One such class of compounds, developed by Dr. Linda Dwoskin and her collaborators, are known as N-alkylnicotinium analogs, which chemically consist of the nicotine molecule alkylated on the pyridine ring nitrogen by alkyl groups of varying length. The resulting compounds have been shown capable of inhibiting the release of dopamine which nicotine induces, particularly for alkyl groups of carbon length seven to twelve. The inhibition produced can be in the low micromolar to nanomolar range, in terms of IC50 inhibitory values. One of the most promising of these compounds is NONI, or N-octyl nicotinium iodide, which appears to function as a competitive antagonist with nicotine, as judged by its ability to inhibit nicotine binding, and its potent inhibition of dopamine overflow from rat striatal slices preloaded with tritiated dopamine, using Scatchard analysis of the results. NONI shows moderate binding to the neuronal nicotinic receptor subtypes containing the beta 2 subunit (i.e., alpha4beta2 and alpha3beta2), but not the alpha7 subunit. Because NONI is a salt carrying a cationic positive charge on the nicotine moiety, it would be expected to exhibit low permeability across the brain brain barrier (BBB), and present an inherent drug delivery problem. However, in a recent in-situ rat brain infusion study, Dr. Dwoskin has reported that tritiated NONI has a permeability comparable to that of tritiated choline. Furthermore, NONI has a Ki of 49 microM in inhibiting the transport of of tritiated choline, whereas nicotine was largely ineffective in this regard. Because both choline (5000 microM) and NONI (250 microM) could significantly inhibit the uptake of tritiated choline, it was concluded that NONI is transferred across the BBB at least in part by active transport by the choline transporter. This work suggests the utilization of the choline transporter as a delivery system for charged nicotinic ligands. Allen, D.D., Lockman, P.R., Roder, K.E., Dwoskin, L.P., and Crooks, P.A. The Journal of Pharmacology and Experimental Therapeutics, 304(3), pp. 1268-1274, 2003.

Syntaxin 1A Interacts Directly with the GABA Transporter to Inhibit GABA Efflux and Exchange in Rat Brain

GABA is the primary inhibitory transmitter in the brain. GABA transporters control the extracellular levels of GABA by coupling transmitter uptake to the sodium and chloride cotransport. These GABA transporter (GAT1), in turn, are regulated by interactions with syntaxin 1A, a protein involved in vesicle docking and in the regulation of ion channels and transporters. Dr. Quick and his group had previously shown that syntaxin 1A decreases the transport of GABA and its associated ions through interactions with the aspartic acid residue in the N-terminal tail of the transporter. However, the reduction in uptake could be the result of many steps in the transport cycle, including substrate binding, substrate flux or efflux, or reorientation of transporters that did not bind GABA. Dr. Quick's group mutated the aspartic acid residues of the transporter and showed that the syntaxin 1A-mediated reduction in GABA flux and efflux was mimicked by mutations in GAT1 at the syntaxin 1A binding site. This suggested that syntaxin 1A exerts its effects through interactions with GAT1's N-terminal tail and that the inhibition occurs after substrate binding and involves both unidirectional transport and transmitter exchange. Wang, D., Decken, S.L., Whitworth, T.L. and Quick, M.W. Molecular Pharmacology, 64, pp. 905-913, 2003.

A Spatial Focusing Model for G Protein Signals: Regulator of G protein Signaling (RGS) Protein-Mediated Kinetic Scaffolding

Regulators of G protein signaling (RGS) are GTPase-accelerating proteins (GAPs), which can inhibit heterotrimeric G protein pathways. In this study, Drs. Neubig and Traynor and their colleagues at the University of Michigan provide experimental and theoretical evidence that high concentrations of receptors (as at a synapse) can lead to saturation of GDP-GTP exchange making GTP hydrolysis rate-limiting. This results in local depletion of inactive heterotrimeric G-GDP, which is reversed by RGS GAP activity. Thus, RGS enhances receptor-mediated G protein activation even as it deactivates the G protein. Evidence supporting this model includes a GTP-dependent enhancement of guanosine 5'-3-O-(thio)triphosphate (GTPgammaS) binding to G(i) by RGS. The RGS domain of RGS4 is sufficient for this, not requiring the NH(2)- or COOH-terminal extensions. Furthermore, a kinetic model including only the GAP activity of RGS replicates the GTP-dependent enhancement of GTPgammaS binding observed experimentally. Finally in a Monte Carlo model, this mechanism results in a dramatic "spatial focusing" of active G protein. Near the receptor, G protein activity is maintained even with RGS due to the ability of RGS to reduce depletion of local Galpha-GDP levels permitting rapid recoupling to receptor and maintained G protein activation near the receptor. In contrast, distant signals are suppressed by the RGS, since Galpha-GDP is not depleted there. Thus, a novel RGS-mediated "kinetic scaffolding" mechanism is proposed which narrows the spatial range of active G protein around a cluster of receptors limiting the spill-over of G protein signals to more distant effector molecules, thus enhancing the specificity of G(i) protein signals. Zhong, H., Wade, S.M., Woolf, P.J., Linderman, J.J., Traynor, J.R. and Neubig, R.R. A Spatial Focusing Model for G protein Signals. Regulator of G Protein Signaling (RGS) Protein-Mediated Kinetic Scaffolding. J Biol Chem. 278(9), pp. 7278-7284, February 28, 2003. Epub November 21, 2002.

The Role of GABAB Receptors in the Discriminative Stimulus Effects of Gamma-Hydroxybutyrate in Rats: Time Course and Antagonism Studies

Gamma-Hydroxybutyrate (GHB) is a neurotransmitter in brain and an emerging drug of abuse, although its mechanism of action is poorly understood. Dr. Charles France and his research team at the University of Texas Health Science Center characterized the role of GABA(A), GABA(B), and other receptors in the discriminative stimulus effects of GHB. Eight rats reliably discriminated 200 mg/kg GHB from saline after a median of 35 (range: 23-41) training sessions. GHB, a metabolic precursor 1,4-butanediol (1,4-BDL), and the GABA(B) agonist (+/-)baclofen all occasioned greater than 83% responding on the GHB lever. The onset of action was similar for GHB and 1,4-BDL; however, 1,4-BDL exhibited a longer duration of action than GHB. The GHB precursor gamma-butyrolactone, the benzodiazepine diazepam, the neuroactive steroid pregnanolone, the opioid agonist morphine, and the N-methyl-d-aspartate antagonist ketamine elicited substantial GHB-appropriate responding, although none occasioned greater than 66% drug-lever responding. The barbiturate pentobarbital and the GABA(A) receptor agonist muscimol did not occasion greater than 17% drug-lever responding at any dose tested. The benzodiazepine antagonist flumazenil attenuated GHB-lever responding occasioned by diazepam, but not GHB. The GABA(B) receptor antagonist CGP 35348 antagonized GHB-lever responding

occasioned by baclofen or GHB. Small doses of the purported GHB receptor antagonist (2E)-(5-hydroxy-5,7,8,9-tetrahydro-6H-benzo[a][7]annulen-6-ylidene ethanoic acid (NCS-382) attenuated partially the effects of GHB, whereas larger doses of NCS-382 alone occasioned partial GHB-lever responding. These results implicate GABA(B) mechanisms in the discriminative stimulus effects of GHB and further suggest that the effects of 1,4-BDL under these conditions result from its conversion to GHB. That NCS-382 shares effects with GHB could explain the lack of antagonism reported for NCS-382 in some studies. Carter, L.P., Flores, L.R., Wu, H., Chen, W., Unzeitig, A.W., Coop, A. and France, C.P. The Role of GABAB Receptors in the Discriminative Stimulus Effects of Gamma-Hydroxybutyrate in Rats: Time Course and Antagonism Studies. J Pharmacol Exp Ther., 305(2), pp. 668-674, May 2003. Epub February 11, 2003.

Immunity and Drugs of Abuse: Opioids and Immunity

Various opioids have been shown to inhibit immune function. Dr. Loh has shown the cooperativity of the delta and mu systems. There is even a negative cooperativity in which the absence of the mu system reduces the effects of delta agonists. They focus on the inhibition of phagocytosis by macrophages. Studies with selective opioid agonists show that mu- and delta(2)-opioid receptors, but not kappa, are involved in opioid inhibition of phagocytosis in elicited murine macrophages. All mu and delta(2) agonists tested had similar maximal effects on phagocytosis, and all dose-response curves suggest positive cooperativity. In addition, mu and delta antagonists antagonized the effect of both mu and delta agonists. Furthermore, in mu-opioid receptor knockout mice (MORKO), Dr. Loh observed a decrease in potency and maximal effect for a delta agonist. These data suggest that mu and delta receptors are not only involved in the modulation of phagocytosis in macrophages, but they also affect each other's activity by an unknown cooperative mechanism. Tomassini, N., Renaud, F.L., Roy, S. and Loh, H.H. Mu and Delta Receptors Mediate Morphine Effects on Phagocytosis by Murine Peritoneal Macrophages. J Neuroimmun., 136, pp. 9-16, 2003.

Opioid Mechanisms of Immune Modulation

Dr. Sharp and his group have probed the biochemical and molecular pathways whereby DORs (delta opioid receptors) affect the activation of phosphotidylinositol-3 kinase (PI3 kinase) and thereby modulate T-cell IL-2 gene expression and protein production in thymocytes. In addition to these upstream signaling studies, they measured the effects of these signaling pathways on the activation of transcription factors involved in IL-2 gene transcription. These basic studies are providing a clearer understanding of how opioids effect immune modulation. Opioid receptors (DORs) modulate thymocyte (TCR) signaling through the mitogen-activated protein kinases (MAPKs), ERKs 1 and 2. These studies determined whether a DOR agonist alone ([D-Ala(2)-D-Leu(5)]enkephalin; DADLE) affects phosphorylation of the activating transcription factor (ATF-2) and its interaction with the MAPK, c-Jun NH2-terminal kinase (JNK). DOR expression was induced on murine splenocytes by anti-CD3 and then quiescent cells were treated with DADLE. DADLE, itself, dose-dependently induced maximal phosphorylation of ATF-2 within 5-10 min; naltrindole, a specific antagonist, abolished this. Anti-ATF-2 immunoprecipitates from control and DADLE-treated splenocytes showed a dominant 59 kDa phosphorylated band and a 71 kDa band. DADLE stimulated phosphorylation of both bands, although the 71 kDa band was selectively immunoprecipitated by anti-JNK. Thus, DADLE stimulated phosphorylation of 71kDa ATF-2 and its association with JNK, suggesting that JNK is activated through DORs. Along with previous observations, these studies suggest that lymphocyte DORs can affect the activation of MAPKs by TCR-independent stimulation (e.g., JNK) or indirectly by modulating TCR-dependent stimulation (e.g., ERK). Shahabi, N.A., McAllen, K. and Sharp, B.M. Phosphorylation of Activating Transcription Factor in Murine Splenocytes through Delta Opioid Receptors. Cell Immunol., 221, pp. 121-127, 2003.

Morphine Enhances HCV Replication

There is currently little information related to opioids' actions on hepatitis C virus (HCV) infections. Recently, morphine was demonstrated to increase the replication of HCV in liver cells. Thus, as with HIV, morphine causes enhanced infectivity by this virus and may be of concern in individuals with hepatitis. Little information is available regarding whether substance abuse enhances hepatitis C virus (HCV) replication and promotes HCV disease progression. Dr. Wenzhe Ho investigated whether morphine alters HCV mRNA expression in HCV replicon-containing liver cells. Morphine significantly increased HCV mRNA expression, an effect which could be abolished by either of the opioid receptor antagonists, naltrexone or beta-funaltrexamine. Investigation of the mechanism responsible for this enhancement of

HCV replicon expression demonstrated that morphine activated NF-KB promoter and that caffeic acid phenethyl ester, a specific inhibitor of the activation of NF-kappaB, blocked morphine-activated HCV RNA expression. In addition, morphine compromised the anti-HCV effect of interferon alpha (IFN-alpha). Dr. Ho's *in vitro* data indicate that morphine may play an important role as a positive regulator of HCV replication in human hepatic cells and may compromise IFN-alpha therapy. Li, Y., Zhang, T., Douglas, S.D., Lai, J.P., Xiao, W.D., Pleasure, D.E. and Ho, W.Z. Morphine Enhances Hepatitis C Virus (HCV) Replicon Expression. Amer J Path., 163, pp. 1167-1175, 2003.

Cannabinoids and Immunity

Most studies have shown that an opioid or cannabinoid receptor mediates the immune modulation by different drugs. Dr. Norbert Kaminski has shown that the calcium ionophore (PMA/Io)-stimulated interleukin-2 production was blocked but the cannabinoid-induced inhibition of PMA/Io-stimulated interleukin-2 was not blocked by cannabiniod type 1 or type 2 antagonists. This shows that there are apparently two different systems at work in lymphocytes. Cannabinoids exhibit immunosuppressive actions that include inhibition of interleukin-2 production in response to a variety of T cell activation stimuli. Traditionally, the effects of these compounds have been attributed to cannabinoid receptors CB1 and CB2, both of which are expressed in mouse splenocytes. Therefore, a CB1 antagonist and a CB2 antagonist were used to investigate the role of cannabinoid receptors in the cannabinoid-induced inhibition of phorbol ester plus calcium ionophore (PMA/Io)-stimulated interleukin-2 production by mouse splenocytes. PMA/Io-stimulated interleukin-2 production was inhibited by cannabinol, cannabidiol, and both WIN 55212-2. Cannabinoid-induced inhibition of PMA/Io-stimulated interleukin-2 was not attenuated by the presence of both SR144528 and SR141716A. Using pertussis toxin to address the role of G protein-coupled receptors in this response, it was determined that pertussis toxin treatment did not attenuate cannabinol-induced inhibition of PMA/Io-stimulated interleukin-2. With the demonstration that cannabinoid-induced inhibition of PMA/Iostimulated interleukin-2 was not mediated via CB1 or CB2, alternative targets of cannabinoids in T cells were examined. Specifically, it was demonstrated that cannabinoids elevated intracellular calcium concentration in resting splenocytes and that the cannabinol-induced elevation in intracellular calcium concentration was attenuated by treatment with both SR144528 and SR141716A. Interestingly, pretreatment of splenocytes with agents that elevate intracellular calcium concentration inhibited PMA/Io-stimulated interleukin-2 production, suggesting that an elevation in intracellular calcium concentration might be involved in the mechanism of interleukin-2 inhibition. These studies suggest that immune modulation produced by cannabinoids involves multiple mechanisms, which might be both cannabinoid receptor-dependent and-independent. Kaplan, B.L.F., Rockwell, C.E. and Kaminski, N.E. Evidence for Cannabinoid Receptor-Dependent and-Independent Mechanisms of Action in Leukocytes. J Pharm Exper Ther., 306, pp. 1077-1085, 2003.

Atrophin 2 Recruits Histone Deacetylase and is Required for the Function of Multiple Signaling Centers During Mouse Embryogenesis

This research identified a new transcription factor required for early forebrain development. By performing a genetic screen in mice, the Peterson group isolated a number of mutants, including open minded (OM). OM mice fail to close the anterior neural tube, and fuse the telencephalic with the optic vesicles by 9.5 days gestation. The gene mutated in OM mice has now been identified and characterized: it is Atrophin 2 (ATR2) and it is a transcriptional repressor that interacts with histone deacytlase 1. Its loss leads to the dysfunction of two important signaling centers in the forebrain: the anterior neural ridge and the prechordal mesoderm. This dysregulation is also apparent by the misexpression or loss of expression of the genes encoding the essential secreted proteins FGF8 and sonic hedgehog, respectively. This study provides essential insight into the molecular mechanism by which many forebrain regions are formed, including the cortex and the basal ganglia. Zoltewicz, J.S., Stewart, N.J., Leung, R. and Peterson, A.S. Development, 131, pp. 3-14. 2004.

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Research Findings - Behavioral Research

The Role of Sensory Cues in Craving and Smoking

The relative contribution of sensory and pharmacological variables in regulating craving and smoking remains unclear. Rapid smoking procedures and denicotinized cigarettes can be used to further disentangle these factors, and to explore the relationship between craving and smoking. The present study examined the role of nicotine and sensory cues in mediating craving and smoking, and the relationship between craving and smoking. Participants (n=15) engaged in one session each of rapid smoking (up to nine cigarettes with puffs taken every 6 s) and normal paced smoking with nicotinized and denicotinized cigarettes (total of four sessions). During the next 3 h, craving and withdrawal assessments and smoking opportunities were scheduled every 15 min. Plasma nicotine levels were measured at baseline, immediately and 15 min after the smoking interventions, and subsequently at the time when the participant first chose to smoke. Results showed that craving ratings were equally suppressed immediately after all conditions. After self-paced conditions, both types of cigarettes produced equivalent effects on latency to smoke. Latency to smoke was significantly longer after rapid smoking of nicotinized cigarettes compared to all other conditions. Finally, changes in craving were associated with choices to smoke. The sensory cues associated with smoking suppressed craving ratings regardless of the smoking pace or nicotine content. Only at high doses did nicotine levels play an additional role in acutely suppressing smoking behavior. Small elevations in craving ratings were associated with choices to smoke. Dallery, J., Houtsmuller, E.J., Pickworth, W.B. and Stitzer, M.L. Effects of Cigarette Nicotine Content and Smoking Pace on Subsequent Craving and Smoking. Psychopharmacology, 165(2), pp. 172-180, 2003.

Nicotine-Dependence Symptoms In Adolescent Smokers

Although many factors have been identified as related to adolescent smoking, few studies have examined the role of nicotine-dependence (ND) symptoms. The purpose of this study was to investigate the association between ND symptoms and smoking status among adolescents in the early stages of the smoking onset process. The McGill University Study on the Natural History of Nicotine Dependence is an ongoing 6-year prospective investigation of the natural history of ND among 1267 grade 7 students in ten Montreal high schools. The baseline response was 55.4%. Subjects for this cross-sectional analysis of baseline data, collected in 1999, included 241 past 3-month smokers (mean age [SD] =13.0+/-0.7 years at baseline). ND symptoms were measured in five indicators, including a measure based on the criteria for tobacco dependence in the International Classification of Diseases-10th Revision (ICD-10), the Hooked on Nicotine Checklist, and three symptom clusters (withdrawal, self-medication, and ND/cravings symptoms). The association between ND symptom indicators and each of sporadic, monthly, weekly, and daily smoking relative to less frequent smoking was investigated in multiple logistic regression analysis. Dr. Difranza and colleagues found that low cigarette exposure, 16.6% of past 3-month smokers were tobacco dependent. The proportion increased from 0%, 3.1% and 4.6% among triers, sporadic smokers, and monthly smokers, respectively, to 19.4% and 65.9% among weekly and daily smokers, respectively. ND/cravings consistently distinguished each smoking category from less frequent smokers. These data challenge current smoking onset models, which suggest that ND develops only after several years of heavy or daily smoking. ND symptoms are associated, at least cross-sectionally, with increased smoking in adolescents. To increase the likelihood of being effective, tobacco-control programs for children and adolescents will need to take early ND symptoms into account. O'Loughlin, J., DiFranza, J., Tyndale, R.F.,

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Meshefedjian, G., McMillan-Davey, E., Clarke, P.B.S., Hanley, J. and Paradis, G. Nicotine-Dependence Symptoms are Associated with Smoking Frequency in Adolescents. American Journal of Preventive Medicine, 25(3), pp. 219-225, 2003.

Altered Value of Carbohydrates for Females Withdrawn From Nicotine

Discontinuing nicotine intake usually results in weight gain partially due to heightened energy intake from between-meat snacks. This experiment tested the hypothesis that the reinforcing value of palatable carbohydrate-rich snacks increases for female smokers during nicotine deprivation. Eighteen smokers and 18 nonsmokers completed a concurrent-schedules operant computer task on two separate days. Smokers were bioverified abstinent at the second testing. The operant task allowed participants to earn points redeemable for either carbohydrate snacks or money on concurrent variable-ratio schedules of reinforcement. There were five different probabilities of earning points redeemable for snacks (8%, 16%, 25%, 50%, 75%), while the probability of earning points redeemable for money remained fixed at 25%. Reward value of snacks was measured by switch point: the reinforcement ratio at which the effort required to earn snacks exceeded their value to the respondent, as signified by a shift to working for money. Results showed that smokers undergoing nicotine deprivation persisted in working for snacks into leaner reinforcement schedules than nonsmokers ($p=.026$). Furthermore, nicotine deprivation increased smokers' allocation of effort to earn snack foods relative to their own behavior when smoking ($p=.006$). Variation in palatability or hunger did not explain these differences in snack reward value. Findings indicate that nicotine deprivation is associated with a heightened reward value of appealing snack foods for female smokers. Spring, B., Pagoto, S., McChargue, D., Hedeker, D. and Werth, J. Altered Reward Value of Carbohydrate Snacks for Female Smokers Withdrawn From Nicotine. Pharmacology, Biochemistry and Behavior, 76(2), pp. 351-360, 2003.

Reward Value of Cigarette Smoking Among Schizophrenic, Depressed, and Nonpatient Smokers

The study was designed to determine whether schizophrenic and depressed smokers perceive the reinforcement value of cigarette smoking differently from nonpsychiatric smokers who smoke as heavily. The authors assessed the preferences for smoking cigarettes versus engaging in other pleasant activities, the perceived advantages and disadvantages of smoking, and the amount of reinforcement that would be needed to attain smoking abstinence among 26 schizophrenic, 26 depressed, and 26 nonpsychiatric heavy smokers. Both schizophrenic and depressed participants chose smoking as their preferred activity more often than nonpsychiatric smokers, and they did not differ from each other. The patients also exceeded the comparison group in the benefits they ascribed to smoking and felt they would require more incentives to quit, but they attributed comparable drawbacks to smoking. Schizophrenic and depressed smokers recognize many drawbacks associated with smoking, but compared to nonpatients who smoke as heavily, they also perceive more benefits and find cigarettes more appealing than alternative rewards. Spring, B., Pingitore, R. and McChargue, D.E. Reward Value of Cigarette Smoking for Comparably Heavy Smoking Schizophrenic, Depressed, and Nonpatient Smokers. American Journal of Psychiatry, 160(2), pp. 316-322, 2003.

Separable Components of Satiation In Cigarette Smoking

To examine mechanisms underlying satiation in cigarette smoking, 18 smokers received intravenous (iv) nicotine, alone or in combination with denicotinized cigarette smoke. Nicotine was administered using programmed presentations of either pulsed injections or continuous infusions, with iv saline serving as a control. A high-nicotine cigarette smoke condition (usual brand) was also presented. During each of the six test sessions, subjects were allowed to puff on their usual brands of cigarette ad libitum while the programmed satiation conditions were in force. Administration of iv nicotine caused a small suppression of ad libitum smoking behavior; denicotinized smoke produced a significantly larger reduction, showing that short-term satiation is more dependent on the presentation of smoke than delivery of nicotine per se. However, denicotinized smoke alone did not have as much effect as puffs from the usual brands of cigarettes. The combination of iv nicotine and denicotinized smoke puffs produced equivalent satiation to that of the usual brand. Cigarette craving and negative affect were partially relieved by iv nicotine presentations as well as by denicotinized smoke, and again the combination of iv nicotine and denicotinized smoke approximated the effects of the usual brand. The results of this study underscore the importance of both sensorimotor aspects of smoking and the pharmacologic effects of nicotine in tobacco dependence. Rose, J.E., Behm, F.M., Westman, E.C., Bates, J.E. and Salley, A. Pharmacologic and Sensorimotor

Components of Satiation in Cigarette Smoking. Pharmacology, Biochemistry and Behavior, 76(2), pp. 243-250, 2003.

Nicotine Self-Administration In Adolescent and Adult Female Rats

A rat model was used to determine the impact of the age of onset on nicotine self-administration. In Experiment 1, nicotine self-administration of female Sprague-Dawley rats over a range of acute doses (0.01-0.08 mg/kg per infusion) was determined in adolescent (beginning at 54-62 days) versus adult (beginning at 84-90 days). In Experiment 2, chronic nicotine self-administration over 4 weeks from adolescence into adulthood was compared with the chronic self-administration beginning in adulthood. In Experiment 3, adolescent-adult differences in nicotine effects on body temperature and locomotor responses were determined. Adolescent-onset rats showed increased nicotine intake compared with adult-onset rats in an eight-fold range of acute unit doses/infusion. Significant age differences were also seen in the chronic level of nicotine self-administration. Over 4 weeks, the adolescent-onset group had nearly double the rate of nicotine self-administration of the benchmark nicotine dose (0.03 mg/kg per infusion) compared to the adult-onset group. This increased nicotine intake persisted into adulthood. Adolescent rats had a significantly greater response than adults to the hypothermic effects of nicotine, but had significantly less response than adults to the reduction in locomotor activity seen after nicotine. Thus, adolescent-onset nicotine self-administration in female rats was associated with significantly higher levels of nicotine self-administration versus rats that began nicotine self-administration in adulthood. This greater self-administration persists into adulthood and may underlie greater propensity of adolescents to nicotine addiction. Levin, E.D., Rezvani, A.H., Montoya, D., Rose, J.E. and Swartzwelder, H.S. Adolescent-Onset Nicotine Self-Administration Modeled In Female Rats. Psychopharmacology, 169(2), pp.141-149, 2003.

Facial Coding Analysis of Smoking Opportunity on Cue-Elicited Urge

The authors analyzed smokers' facial expressions using the Facial Action Coding System (P. Ekman & W. V. Friesen, 1978) under varying smoking opportunity conditions. In Experiment 1, smokers first were told that they either could (told-yes) or could not (told-no) smoke during the study. Told-yes smokers reported higher urges than did told-no smokers. Unexpectedly, told-yes smokers became increasingly likely to manifest expressions related to negative affect and less likely to evince expressions related to positive affect, compared with told-no smokers. In Experiment 2, smokers were more likely to show positive affect-related expressions if the delay was 15 s than if it was 60 s. Craving may be related to both a desire to use and an impatient desire to use immediately. Sayette, M.A., Wertz, J.A., Martin, C.S., Cohn, J.F., Perrott, M.A. and Hobel, J. Effects of Smoking Opportunity On Cue-Elicited Urge: A Facial Coding Analysis. Experimental and Clinical Psychopharmacology, 11(3), pp. 218-227, 2003.

Attentional Bias Predicts Outcome In Smoking Cessation

Most attempts to quit smoking end in failure, with many quitters relapsing in the first few days. Responses to smoking-related cues may precipitate relapse. A modified emotional Stroop task-which measures the extent to which smoking-related words disrupt performance on a reaction time (RT) task-was used to index the distracting effects of smoking-related cues. Smokers (N = 158) randomized to a high-dose nicotine patch (35 mg) or placebo patch completed the Stroop task on the 1st day of a quit attempt. Smokers using an active patch exhibited less attentional bias, making fewer errors on smoking-related words. Smokers who showed greater attentional bias (slowed RT on the first block of smoking words) were significantly more likely to lapse in the short-term, even when controlling for self-reported urges at the test session. Attentional bias measures may tap an important component of dependence. Waters, A.J., Shiffman, S., Sayette, M.A., Paty, J.A., Gwaltney, C.J. and Balabanis, M.H. Attentional Bias Predicts Outcome In Smoking Cessation. Health Psychology, 22(4), pp. 378-387, 2003.

Effects of Nicotine Deprivation on Craving Response Covariation In Smokers

Most models of craving propose that when cravings are strong, diverse responses-thought to index an underlying craving state-covary. Previous studies provided weak support for this hypothesis. The authors tested whether nicotine deprivation affects degree of covariation across multiple measures related to craving. Heavy and light smokers (N = 127) were exposed to smoking cues while either nicotine deprived or nondeprived. Measures included urge ratings, affective valence, a behavioral choice task assessing perceived reinforcement value of smoking, and smoking-related

judgment tasks. Results indicated higher correlations in the nicotine-deprived than in nondeprived group. The measures principally responsible for this effect loaded onto a single common Craving factor for nicotine-deprived but not nondeprived smokers. These findings suggest that, under certain conditions, measures of craving-related processes covary. Sayette, M.A., Martin, C.S., Hull, J.G., Wertz, J.M. and Perrott, M.A. Effects of Nicotine Deprivation On Craving Response Covariation In Smokers. Journal of Abnormal Psychology, 112(1), pp. 110-118, 2003.

Cigarette Smoking and Smoking-Related Beliefs After 2 Decades in a Community Sample

Rates of cigarette smoking and smoking-related beliefs in 1980 and 2001 among 7th-11th graders in a midwestern community were compared. Smoking was less prevalent in 2001 than in 1980, with the greatest declines in experimental smoking and a smaller drop in regular smoking. Beliefs about smoking generally became more negative. Adolescents (particularly nonsmokers) viewed smoking as more addictive and as having more negative social consequences in 2001 than in 1980 and had more negative attitudes toward smoking in 2001. These results were replicated among parent-child pairs in which parents were measured when they were adolescents between 1980 and 1983 and their children were measured in 2001. These beliefs and attitudes partially mediated the effects of time on smoking. Chassin, L., Presson, C.C., Sherman, S.J. and Kim, K. Historical Changes In Cigarette Smoking And Smoking-Related Beliefs After 2 Decades In A Midwestern Community. Health Psychology, 22(4), pp. 347-353, 2003.

Implicit and Explicit Attitudes Toward Cigarette Smoking

Two studies examined the effects of context and motivational state on two implicit measures of attitudes toward smoking (priming and the Implicit Association Test) as well as on explicit attitudes among nonsmokers and smokers. The priming measure was sensitive to changes in the salience of different aspects of smoking and to changes in motivational state (nicotine deprivation). There were only modest relations between explicit and implicit attitudes, and the two implicit measures were generally uncorrelated. These results have implications for the complexity and ambivalence of attitudes toward smoking held by smokers and for interventions that seek to change their attitudes and smoking behavior. Sherman, S.J., Rose, J.S. and Koch, K. Implicit and Explicit Attitudes Toward Cigarette Smoking: The Effects of Context and Motivation. Journal of Social and Clinical Psychology, 22(1), pp. 13-39, 2003.

Food Restriction Enhances Behavioral Sensitivity to Abused Drugs and Increases Dopamine Receptor Signaling

Chronic food restriction in rats is known to enhance sensitivity to the rewarding and motor-activating effects of abused drugs. Dr. Kenneth Carr and his colleagues have been investigating the neural mechanisms that account for this phenomenon. In the present study, they looked for evidence that food restriction produces increased dopamine (DA) receptor function in brain areas that are involved in the central substrates for reinforcement. In one experiment, they injected selective agonists for either the D1 or the D2/3 types of DA receptor and observed that both agonists produced greater motor activation in food-restricted animals. They also found higher levels of c-fos induction by these agonists in striatal (for the D1 agonist) and pallidal (for D2/3 agonist) areas. DA receptors are known to induce c-fos by activating cyclic AMP signaling. Therefore, in other experiments, they used neuronal membranes prepared from caudate-putamen and nucleus accumbens to investigate whether changes in signal transduction mechanisms downstream from DA receptors might be involved in the observed effects. Their results indicated that coupling between D2 receptors and the Gi protein was increased by food restriction. There was no change in adenylyl cyclase (AC) stimulation by the D1 agonist, but the results suggested a possible alteration in the AC isoform. The findings of these studies suggest that food restriction produces neuroadaptations in D1 and D2 receptor-bearing cells that, in turn, mediate augmented behavioral and transcriptional responses to DA agonists. These changes are therefore also likely to mediate an increased sensitivity to drugs of abuse seen under conditions of food deprivation. The exact nature of these neuroadaptations, however, remains to be fully elucidated. Carr, K.D., Tsimberg, Y., Berman, Y., and Yamamoto, N. Evidence of Increased Dopamine Receptor Signaling in Food-Restricted Rats. Neuroscience, 119, pp. 1157-1167, 2003.

Genetically Altered Mice with Higher Dopamine Levels "Want" but do not "Like" Sweet Reward More than Normal Mice

The mesolimbic dopamine system plays an important role in natural reward and drug

addiction, but the exact contribution of DA to reward is controversial. One hypothesis suggests that DA mediates the sensory pleasure, or hedonic value (the "liking") of rewards such as food and drugs. Under this hypothesis, addiction results from withdrawal-induced anhedonia caused by DA downregulation. A second hypothesis is that DA is primarily involved in reward learning, and that drug addiction results from aberrant neural learning processes, which cause exaggerated reward predictions or excessive drug-taking habits. Dr. Kent Berridge (with his colleague Dr. Terry Robinson) has been developing a third idea, the incentive salience hypothesis, which posits that DA systems modulate the perceived incentive value of reward stimuli so that rewards become more "wanted" without necessarily being more "liked." Their hypothesis suggests that addiction results from sensitization of mesolimbic systems, causing an excessive "wanting" to take drugs. In the current study, Berridge and colleagues used a genetic mutant approach to examine the consequences of elevated synaptic dopamine. The mutant mice have genetic knockdown of the dopamine transporter (DAT), which preserves only 10% of normal DAT and results in a 70% elevated level of synaptic dopamine. Behavioral observations were made on: (1) spontaneous food and water intake, (2) incentive motivation and learning to obtain a palatable sweet reward in a runway task, and (3) affective "liking" reactions (i.e., facial expressions) elicited by the taste of sucrose. The hyperdopaminergic DAT knockdown mice had higher food and water intake and maintained higher body weight, consistent with the obverse effect of DA deficiency (observed in other experiments), which reduces eating. In the runway task, the hyperdopaminergic mutant mice showed enhanced acquisition and greater incentive performance for a sweet reward compared to wild-type animals. Mutant mice left the start box more quickly, required fewer trials to learn, paused less often in the runway, resisted distractions better, and proceeded more directly to the goal. Those observations suggest that the hyperdopaminergic mice attribute greater incentive salience ("wanting") to a sweet reward, although they do not rule out the possibility that the mutant animals also have enhanced reward learning. In a third experimental procedure, the affective taste reactivity test, sucrose taste did not elicit higher orofacial "liking" reactions from mutant mice, and in fact, produced somewhat reduced "liking" at the highest concentrations. These results indicate that chronically elevated extracellular dopamine facilitates "wanting" and learning of an incentive motivation task for a sweet reward, but does not increase "liking" reactions to the hedonic impact of sweet tastes. Pecina, S., Cagniard, B., Berridge, K.C., Aldridge, J.W., and Zhuang, X. Hyperdopaminergic Mutant Mice have Higher "Wanting" but not "Liking" for Sweet Rewards. Journal of Neuroscience, 23, pp. 9395-9402, 2003.

Chronic Stress and Obesity: A New View of "Comfort Food"

Dr. Mary Dallman and her colleagues have, over many years, carried out studies in a rat model to understand the relationship between acute and chronic stress, feeding, and the hormones, neurotransmitters, and neural circuits that underlie behavior. In a recent paper, they proposed a new working model of the chronic effects of glucocorticoid (GC) function in the central nervous system that can help explain the altered eating patterns by humans who are chronically stressed, depressed, drug-addicted, or have eating disorders. The effects of adrenal corticosteroids on subsequent adrenocorticotropin secretion, and feedback regulation of these effects, are complex. Acutely (within hours), glucocorticoids (GCs) directly inhibit further activity in the hypothalamo-pituitary-adrenal axis, but the chronic actions (across days) of these steroids on brain are directly excitatory. Chronically high concentrations of GCs act in three ways that are functionally congruent: (i) GCs increase the expression of corticotropin-releasing factor (CRF) mRNA in the central nucleus of the amygdala, a critical node in the emotional brain. CRF enables recruitment of a chronic stress-response network. (ii) GCs increase the salience of pleasurable or compulsive activities (e.g. ingesting sucrose, fat, and drugs, or wheel running), which, in turn can motivate the ingestion of "comfort food." (iii) GCs act systemically to increase abdominal fat depots, which provide a negative feedback signal to inhibit catecholamines in the brainstem and CRF expression in hypothalamic neurons that regulate adrenocorticotropin. Chronic stress, together with high GC concentrations, usually decreases body weight gain in rats; by contrast, in stressed or depressed humans chronic stress induces either increased comfort food intake and body weight gain or decreased intake and body weight loss. Comfort food ingestion that specifically produces abdominal obesity also decreases CRF mRNA in the hypothalamus of rats. Depressed people who overeat have decreased cerebrospinal CRF, catecholamine concentrations, and hypothalamo-pituitary-adrenal activity. Integrating these observations into the model, Dr. Dallman proposes that people eat comfort food in an attempt to reduce activity in the chronic stress-response network and its attendant anxiety. These mechanisms, identified from research in animals, may help explain the obesity epidemic in our society. Dr. Dallman is currently using

this model in her research funded by NIDA to investigate whether chronic stress enhances the process whereby normally rewarding activities become "devalued" relative to supernormal drug rewards by drug abuse and addiction. Dallman, M.F., Pecoraro, N., Akana, S.F., La Fleur, S.E., Gomez, F., Houshyar, H., Bell, M.E., Bhatnagar, S., Laugero, K.D., and Manalo, S. Chronic Stress and Obesity: A New View of "Comfort Food." Proceedings of the National Academy of Sciences, USA 100, pp. 11696-11701, 2003.

Neurons in Nucleus Accumbens Remain Responsive to Drug-associated Cues after Prolonged Abstinence from Cocaine Self-administration

For abstinent drug users, exposure to stimuli associated with prior drug use can provoke craving and increase the risk of relapse. Thus, the neural representation of drug-predictive environmental stimuli is likely to be persistently salient. Dr. Mark West and his colleagues tested this hypothesis using single-unit recording in rats, to determine whether nucleus accumbens (NAcc) neurons exhibit responses to a discriminative stimulus ($S^{D,}$) tone previously paired with cocaine availability during cocaine self-administration. In behavioral testing, presentation of the tone after 3-4 weeks of abstinence resulted in cue-induced relapse of drug seeking under extinction conditions - i.e., with no cocaine provided for the animal's operant responses. NAcc neurons did not exhibit any tone-evoked activity before cocaine self-administration training, but during extinction, they showed significant SD tone-evoked activity. The researchers further examined whether the NAcc subdivisions, shell and core, had differential responses. Under extinction conditions, shell neurons exhibited significantly greater activity evoked by the SD tone than by a neutral tone that had never been paired with cocaine. In contrast, core neurons responded indiscriminately to the S^{D} and neutral tones. The onset of S^{D} tone-evoked activity occurred well before the earliest movements began (150 msec), although it often persisted beyond the onset of tone-evoked movements. Thus, the firing of these neurons appears to be most clearly related to the motivational significance of the tone, rather than to subsequent movements. These results indicate that NAcc shell neurons exhibit persistent processing of information about reward-related stimuli after prolonged drug abstinence. While the NAcc shell appears to be involved in discriminating the motivational value of such stimuli, the NAcc core does not. The results are also consistent with a growing body of experimental evidence indicating that stimulus-reward associations are not unlearned or forgotten during extinction. Rather, via an active process, animals and humans learn not to respond to certain cues under circumstances where the cue no longer predicts reward, but may relapse to cue-induced responding in environments that differ from the extinction context. Ghitza, U.E., Fabbricatore, A.T., Prokopenko, V., Pawlak, A.P., and West, M.O. Persistent Cue-evoked Activity of Accumbens Neurons after Prolonged Abstinence from Self-administered Cocaine. Journal of Neuroscience, 23, pp. 7239-7245, 2003.

Exposure to Amphetamine or Cocaine Limits the Ability of Later Environmental Enrichment to Promote Structural Plasticity in the Brain

Drugs of abuse and many other kinds of experiences share the ability to alter the morphology of neuronal dendrites and spines, the primary site of excitatory synapses in the brain. Dr. Terry Robinson, Dr. Brian Kolb and colleagues hypothesized that exposure to psychostimulant drugs might influence later experience-dependent structural plasticity. They treated rats repeatedly with amphetamine or cocaine and then housed them in either a complex environment or standard laboratory cages for 3-3_ mo. The brains were processed for Golgi-Cox staining, and the number of dendritic branches and density of dendritic spines on medium spiny neurons in the nucleus accumbens and pyramidal cells in the parietal cortex were quantified. On most measures, prior treatment with amphetamine or cocaine interfered with the ability of experience in a complex environment to increase dendritic arborization and spine density, which occurred in the untreated controls. Studies of humans who have used psychostimulants for long periods indicate that they have neuropsychological deficits that persist during abstinence. These deficits are usually attributed to either neurotoxic effects of the drugs or their ability to render specific brain areas dysfunctional. However, the data from the current study suggest an alternative way in which drug use might produce persistent behavioral and cognitive deficits, by impairing the ability of specific neural circuits to change as a result of experience. On a more positive note, if exposure to psychostimulant drugs can alter the effects of subsequent experience, then experience may be able to influence the later effects of drugs. In fact, there is evidence from animal studies that early environmental enrichment can be protective against the effects of psychostimulant drugs in adulthood. Kolb, B., Gorny, G., Li, Y., Samaha, A.N., and Robinson, T.E. Amphetamine or Cocaine Limits the Ability of Later Experience to Promote Structural

Plasticity in the Neocortex and Nucleus Accumbens. Proceedings of the National Academy of Sciences, USA, 100, pp. 10523-10528, 2003.

Activity in the Ventral Subiculum is Necessary for Reinstatement of Cocaine- or Cue-Induced Cocaine Seeking

Exposure to a drug-associated environment can provoke relapse to drug seeking in both humans and animals, even after prolonged periods of abstinence. For this to occur, information about the environment must have access to motivational circuitry in the brain. One likely route for such information is via the ventral subiculum (vSUB), an extension of ventral hippocampus known to play a role in goal-directed behavior. In this study, Dr. George Rebec and his associate Dr. WenLin Sun investigated the role of the ventral subiculum in cocaine- or cue-induced cocaine-seeking behavior in rats tested on a between-session reinstatement model. Rats were trained to self-administer cocaine in a lever-pressing operant task in a daily 2 hr session. Responding was reinforced contingent on a modified fixed-ratio 5 schedule. Reinstatement tests began after the lever-pressing behavior was extinguished in the absence of cocaine and conditioned cues (light and tone). Bilateral microinjections of lidocaine to transiently inactivate the vSUB decreased cocaine- or cue-induced reinstatement of cocaine-seeking behavior compared with saline microinjections into the same area in another group of rats. Lidocaine microinjections, however, had no effect on cocaine self-administration behavior or food-maintained or food-reinstated responding. Collectively, these results suggest that the vSUB plays an important role in cocaine-seeking behavior. Considering the role of this structure in context learning, these data suggest that the full expression of cocaine- or cue-induced reinstatement may depend on the context in which the cocaine experience occurs. Sun, W. and Rebec, G.V. Lidocaine Inactivation of Ventral Subiculum Attenuates Cocaine-Seeking Behavior in Rats. Journal of Neuroscience, 23, pp. 10258-10264, 2003.

Furthering Our Understanding of the Role of Dorsomedial Prefrontal Cortex in Conditioned-cue-induced Cocaine-seeking Behavior in Rats

It is well known that environmental cues (i.e., people, places and situations) previously paired with cocaine can induce craving in humans. Similarly, using an animal model of drug abuse relapse, environmental cues can reinstate cocaine-seeking behavior in laboratory rats. Over the past several years, neuroscientists have implicated several brain regions as possible substrates involved in environmental-cue associated drug craving and relapse, and two in particular: the amygdala and the prefrontal cortex (PFC). Dr. Ron See and his colleagues at the University of South Carolina explored in detail the role of PFC in an animal model of conditioned-cued-induced cocaine relapse. The PFC comprises several subdivisions in the brain including the: anterior cingulate (ACing), the prelimbic cortex (PL), and the infralimbic cortex (IL). Dr. See temporarily, and in-turn, systematically inactivated each of these brain regions and determined their role in conditioned-cued-induced cocaine-seeking behavior. From these inactivation studies, he and his colleagues determined that inactivation of the ACing, or the PL impaired the ability of environmental cues to induce cocaine seeking. In contrast, inactivation of the IL had no effect on conditioned-cued cocaine seeking. These results support a role for the involvement of some of the subdivisions of the dorsomedial PFC as part of the brain's circuitry involved in conditioned-cued-induced drug-seeking behavior. McLaughlin, J. and See R.E. Psychopharmacology, pp. 168, pp. 57-65, 2003.

Adolescent Sensitivity to Nicotine and Cross-sensitization to Cocaine Effects in Adulthood

In 2002, Dr. Sari Izenwasser reported that peri-adolescent rats were less sensitive to the development of behavioral sensitization with repeated cocaine administration than their adult counterparts. This was an important observation, as sensitization is believed to reflect an underlying change in the neurobiological substrate for reinforcing effects of drugs of abuse, and therefore may be involved in the addiction process. More recently, she has examined the behavioral and neurochemical effects of repeated nicotine treatments in this model. The study of nicotine mechanisms in adolescence is also an important area of investigation, since it has been reported that adolescents show a more rapid progression to dependence on smoking than do adults. Moreover, girls may show an even more precipitous course. In this study, adult and peri-adolescent rats (postnatal day 28 to 40) received 0.4mg/kg of nicotine/day via intra-peritoneal administration for 7 days. Matched age and sex control groups received vehicle instead. After each injection, locomotor activity was measured for one hour. On day 8, all rats were challenged with a cumulative dosing regimen of i.p. cocaine and their locomotor activity tested for 10-min after each injection to probe for cross-sensitization. This portion of the study design addresses

concerns that smoking or nicotine exposure may "prime" subsequent illicit drug abuse. Both developmental and gender differences were observed in acute effects of nicotine and in the development of sensitization to locomotor stimulation: The young male group had a higher activity count (and greater stereotypy) after the first nicotine injection than all other groups, and did not show a behavioral sensitization. All other groups (female adolescent, and both adult groups) sensitized to nicotine's behavioral activating and stereotypy effects. However, female adolescents showed a significant sensitized response after only one nicotine exposure (versus adults, who showed significant sensitization on day five for both behavioral measures). Unlike their response on locomotor measures, male adolescents did show a sensitized stereotypy that emerged on the fourth nicotine injection. When all groups were challenged with cocaine on day 8, adolescent males - who had not shown locomotor sensitization to repeated nicotine - were sensitized to all doses of cocaine tested (i.e., had higher activity counts than males treated with vehicle) and, in fact, showed greater cross-sensitization than their adult counterparts. By contrast, neither female group showed any greater response than their chronic vehicle controls after cocaine. These findings, in conjunction with previous reports of gender differences in rats treated acutely, or chronically, with behaviorally active doses of nicotine, highlight potential neurobiological differences in the substrates for addictive processes in adolescence. Thus, although methodological differences between these various studies must be considered (e.g., varied routes of administration and schedules), male adolescents may be initially more behaviorally responsive to nicotine, whereas females may show a more rapid neuroadaptation that gives rise to changing behavioral profiles. Collins, S.L. and Izenwasser, S. Chronic Nicotine Differentially Alters Cocaine-induced Locomotor Activity in Adolescent vs. Adult Male and Female Rats. Neuropharmacology, Available online December 10, 2003.

A Non-drug Reinforcer, Saccharin, Reduces Oral Self-administration of Phencyclidine (PCP) in Male and Female Rhesus Monkeys

Prior research with non-human primates and rats has clearly established that under a wide variety of conditions the availability of non-drug reinforcers can reduce the acquisition and/or maintenance of drug self-administration. Dr. Carroll has previously demonstrated the suppressive effects of concurrent saccharin on PCP oral self-administration in male monkeys and in a recent study sought to directly compare such effects in males and females. Seven male and seven female subjects responded for oral PCP under fixed-ratio (FR) schedules of 4, 8, 16, 32, 64 and 128 during concurrent availability of either saccharin or water. In both males and females, saccharin availability suppressed the number of operant responses for PCP and the number of PCP deliveries at low to intermediate FR values. Suppression in the number of deliveries was greater for females than males at FR values of 4, 8, 16, and 32. Saccharin produced suppression in the mg/kg consumption of PCP in both males and females with a sex difference in the degree of suppression occurring at FR 32, wherein the suppression seen was greater in females. These data extend to females the prior finding that saccharin can suppress PCP consumption, and further suggest that at certain parameters, suppression may be greater in females. These sex differences are of interest in view of prior work from Dr. Carroll's lab reporting that availability of wheel-running suppressed i.v. cocaine self-administration only in female rats (Cosgrove et al. 2002), and that females exhibited more suppression of i.v. cocaine self-administration than males in response to baclofen (Campbell et al., 2002) and to ketaconazole (Carroll et al, 2001). Such differences point to the need for both animal and human research to continue to examine to sex differences in studies aimed at strategies to reduce drug intake. Cosgrove, K.P. and Carroll, M.E. Effects of a Non-drug Reinforcer, Saccharin, on Oral Self-administration of Phencyclidine in Male and Female Rhesus Monkeys. Psychopharmacology, 170, pp. 9-16, 2003.

A Simulated Neural Model of the Midbrain Dopamine System, Embodied in a Robot, Provides Novel Insights into Reward Processing

Dr. Olaf Sporns was recently funded through NIDA's CEBRA program to extend his neural modeling studies of reward learning to drug abuse applications. A number of laboratories have developed computational models to understand the role of neuromodulatory systems in creating and maintaining stable and adaptive neuronal representations. A unique feature of Sporns' work, however, is that his model is imbedded in a physical robot that can interact with a real environment to investigate what happens under conditions of changing stimulus content and demands of the environment. In this paper, Sporns and his graduate student William Alexander describe a neural network model of the dopaminergic system based on observed anatomical and physiological properties of the primate midbrain. The model relies on value-dependent synaptic modifications to acquire temporal information about the

association between reward-related events and environmental stimuli. The model generates phasic "neuromodulatory" responses corresponding to prediction errors, which act as a value signal with positive and negative components, representing the unpredicted occurrence of rewarding stimuli or the omission of an expected reward, respectively. The value signal modulates widespread synaptic changes, including afferent connections of the value system itself. The model was embedded in an autonomous robot, and its behavior was tested as changes were made in the robot's motor characteristics and in the stimulus content of the environment. The robot (named "Monad") could move around in its environment and contact objects with a gripper arm. Neural units in the simulation triggered all actions of the robot, which could sense its environment with a camera and sensors on the inner surface of the gripper, defined as "appetitive taste" sensors. Initially, Monad was programmed to emit an "innate," unconditioned response of prolonged gripping of each object it encountered. After learning (essentially an instrumental conditioning paradigm), objects visually triggered a conditioned response consisting of immediate approach and gripping of the object. The researchers then observed the development of neural activity in the simulated nervous system as conditioning of reward-related behaviors occurred through the interaction between the robot and its surroundings. By using an embodied system, they were able to make unique observations about the pace of learning in various unpredictable environments, which cannot be done in pure simulations. For example, when many objects were in the environment, the objects became bunched as the robot handled them. Subsequently Monad was rewarded at a faster pace and the neural representation of reward prediction shifted to an earlier time. Results of this work show how the coupling of brain, body, and environment can affect ongoing plasticity in ways that are unexpected. The system provides a platform for understanding how real neuromodulatory systems control plasticity in natural environments, without external control over stimulus-response schedules. A deeper understanding of how neuromodulation operates in complex behavioral contexts may highlight how reward processing is altered in diseases such as addiction. Alexander, W.H. and Sporns, O. An Embodied Model of Learning, Plasticity, and Reward. Adaptive Behavior, 10, pp. 143-159, 2002.

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

Research Findings - Treatment Research and Development

Modafinil and Cocaine: A Double-blind, Placebo-controlled Drug Interaction Study

Modafinil is a novel compound that is approved for the treatment of narcolepsy. It is now being studied as a potential treatment for cocaine dependence. The neurotransmitter actions of modafinil are opposite to cocaine-induced neuroadaptations affecting dopamine and glutamate reward circuits. Since cocaine-dependent subjects might use cocaine during a clinical trial with modafinil, this study tested the safety of intravenous cocaine (30 mg) in combination with modafinil. Each of seven subjects received a baseline (open-label) cocaine infusion. Three subsequent cocaine infusions were administered after subjects received 4 days of low dose modafinil (200 mg/day), high dose modafinil (400 mg/day), or placebo in randomized double-blind sequences. One subject received placebo prior to all infusions. The results indicate that co-administering modafinil and a single dose of intravenous cocaine is not associated with medical risk in terms of blood pressure, pulse, temperature, or electrocardiogram measures. Dackis, C.A., Lynch, K.G., Yu, E., Samaha, F.F., Kampman, K.M., Cornish, J.W. et al. Drug Alcohol Depend., 70(1), pp. 9-37, 2003.

Tiagabine Increases Cocaine-Free Urines in Cocaine-Dependent Methadone-Treated Patients: Results of a Randomized Pilot Study

Dr. Gerardo Gonzalez and colleagues evaluated the safety and efficacy of the GABAergic agent tiagabine in reducing cocaine use among methadone-treated patients. A ten-week randomized double-blind placebo-controlled trial was conducted at the Opiate Treatment Research Program, Veteran's Affairs Connecticut Healthcare System in West Haven, Connecticut, USA. The participants were 45 cocaine-dependent methadone-treated patients who were predominately Caucasian (75.6%), male (77.8%) and never married (53%) with an average age of 38 years (SD = 6.5). Comparison groups received tiagabine 12 mg/day (n = 15), tiagabine 24 mg/day (n = 15) or placebo (n = 15). Treatment retention was over 80% for all treatment groups. The sample mean (+/- SE) of cocaine-free urines for the first week after study entry and before tiagabine was started was 1.16 (0.19) urines/week. During weeks 9 and 10 cocaine-free urines increased significantly from baseline by 33% with high-dose tiagabine (24 mg/day), by 14% with low-dose tiagabine (12 mg/day) and decreased by 10% with placebo (hierarchical linear model, $Z = 2.03$; $P < 0.05$). Self-reported cocaine use also decreased significantly more with active medications than with placebo. The results suggest that tiagabine at 24 mg/day was well tolerated among these methadone-treated patients with only one reporting headache and appears to be a promising GABAergic medication that moderately improves cocaine-free urines. Gonzalez, G., Sevarino, K., Sofuoglu, M., Poling, J., Oliveto, A., Gonsai, K. et al., Addiction, 98(11) pp. 1625-1632, 2003.

Effects of Triazolam Pretreatment on Behavioral and Physiological Effects of Cocaine in Humans

There is evidence to suggest that gamma-aminobutyric acid (GABA) agonists may attenuate the behavioral effects of cocaine and may be effective pharmacotherapies for cocaine abuse and dependence. Dr. Craig Rush and colleagues from the University of Kentucky examined the effect of triazolam (0 and 0.5 mg), a GABA (A) modulator, combined with oral cocaine (0 and 300 mg) in 10 individuals with recent histories of cocaine use. Volunteers received each of the four possible drug combinations in mixed order. Drug effects were assessed using a battery of subject-rated drug-effect

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questionnaires and physiological indices. Cocaine alone produced prototypical stimulant-like subject-rated drug effects (e.g., increased ratings of High, Like Drug, and Willing to Take Drug Again) and triazolam produced sedative-like effects. Triazolam pretreatment did not significantly attenuate the subject-rated effects of cocaine. Haga, J.L., Baker, R.W. and Rush, C.R. Behavioral and Physiological Effects of Cocaine in Humans Following Triazolam. Pharmacol Biochem Behav., 76(3-4), pp. 383-392, December 2003.

Deficiencies in Dietary Polyunsaturated Fatty (PUFA) Acids May Contribute to Aggression in Cocaine Addicts

Many substance abusers have poor dietary habits. Dr. Laure Buydens-Branchey and colleagues at the State University of New York examined the correlation of plasma fatty acids (FA) profiles with aggression in 24 cocaine-dependent patients admitted to an inpatient substance abuse unit. Six had a past history of aggression and 18 did not. A comparison of the FA levels of aggressive and non-aggressive patients performed 4 days after their admission did not reveal any significant difference in saturated FAs or monounsaturated FAs. Aggressive patients had significantly lower levels of the n-6 polyunsaturated fatty acid (PUFA) docosapentaenoic acid (DPA), of total n-3 PUFAs and of the n-3 PUFA docosahexaenoic acid (DHA), and a marginally significant increase in the ratio of n-6 to n-3 PUFAs. Measurements performed 18 days after admission showed that most FAs increased in both patient groups. Some PUFAs, especially those of the n-3 series, increased more sharply in the aggressive patients. These data suggest that the aggressive individuals might have been deficient in n-3 rich nutrients and support the evidence indicating a possible link between an n-3 deficiency and aggression in humans. Buydens-Branchey, L., Branchey, M., McMakin, D.L. and Hibbeln, J.R. Drug Alcohol Depend., 71(3), pp. 319-323, September 2003.

Plasma Polyunsaturated Fatty Acids May Play A Role In Relapse Rates of Cocaine Addicts

There is evidence to suggest that polyunsaturated fatty acids (PUFAs) may play a role in the pathophysiology of depressive and aggressive disorders. In animals, there is evidence that PUFAs could play a role in substance abuse through their action on central serotonergic and dopaminergic systems. Dr. Laure Buydens-Branchey and colleagues at the State University of New York examined the association of plasma PUFAs with relapse rates in 38 cocaine addicts discharged after a period of detoxification on an inpatient unit. PUFA status was assessed at baseline, shortly after admission. Resumption of substance use was assessed 3 months, 6 months and 1 year following discharge. Subjects who relapsed at 3 months had significantly lower baseline levels of total n-6 PUFAs, linoleic acid (LA, 18:2n-6), arachidonic acid (AA, 20:4n-6) and total n-3 PUFAs when compared to non-relapsers by ANCOVAs with age and weight as covariates. Lower baseline total n-6 PUFAs, LA and AA continued to predict relapse 6 months and 12 months following discharge. Age, marital status, educational level, cocaine use parameters or psychopathology did not differ between relapsers and non-relapsers. These data suggest the existence of a causal relationship between n-6 or n-3 status and relapse vulnerability in cocaine addicts, and provide a rationale for the exploration of possible relationships between relapse to addictive disorders and PUFA status in observational and interventional trials. Buydens-Branchey, L., Branchey, M., McMakin, D.L. and Hibbeln, J.R. Psychiatry Res. 120(1), pp. 29-35, August 2003.

Office-Based Treatment of Opiate Addiction with a Sublingual-Tablet Formulation of Buprenorphine and Naloxone

Dr. Paul Fudala and colleagues conducted a multi-center, randomized, placebo-controlled trial involving 326 opiate-addicted persons who were assigned to office-based treatment with sublingual tablets consisting of buprenorphine (16 mg) in combination with naloxone (4 mg), buprenorphine alone (16 mg), or placebo given daily for four weeks. The primary outcome measures were the percentage of urine samples negative for opiates and the subjects' self-reported craving for opiates. Safety data were obtained on 461 opiate-addicted persons who participated in an open-label study of buprenorphine and naloxone (at daily doses of up to 24 mg and 6 mg, respectively) and another 11 persons who received this combination only during the trial. The double-blind trial was terminated early because buprenorphine and naloxone in combination and buprenorphine alone were found to have greater efficacy than placebo. The proportion of urine samples that were negative for opiates was greater in the combined-treatment and buprenorphine groups (17.8 percent and 20.7 percent, respectively) than in the placebo group (5.8 percent, $P<0.001$ for both comparisons); the active-treatment groups also reported less opiate craving ($P<0.001$

for both comparisons with placebo). Rates of adverse events were similar in the active-treatment and placebo groups. During the open-label phase, the percentage of urine samples negative for opiates ranged from 35.2 percent to 67.4 percent. Results from the open-label follow-up study indicated that the combined treatment was safe and well tolerated. In conclusion, buprenorphine and naloxone in combination and buprenorphine alone are safe and reduce the use of opiates and the craving for opiates among opiate-addicted persons who receive these medications in an office-based setting. Fudala, P.J., Bridge, T.P., Herbert, S., Williford, W.O., Chiang, C.N., Jones, K. et al., N Engl J Med., 349(10) pp. 949-958, 2003. Transferring Methadone-Maintained Outpatients to the Buprenorphine Sublingual Tablet: A Preliminary Study There is no accepted algorithm to transfer opioid-dependent patients from methadone (METH) to its new alternative, buprenorphine (BUP). Five outpatients transferred (double blind, double dummy) from METH 60 mg/day (with one day at 45 mg) to BUP 8 mg s.l. tablet. Relative to METH maintenance, BUP decreased opioid agonist symptoms (transfer day 1) and increased withdrawal symptoms (days 1 and 2) and blood pressure (day 2). Self-reported heroin use did not increase from METH maintenance levels. It may be feasible to transfer outpatients on METH 60 mg/day to BUP 8 mg/day s.l. tablet, although this pilot protocol needs refinements to improve tolerability and clinical efficacy. Greenwald, M.K., Schuh, K.J. and Stine, S.M. Am J Addict, 12(4), pp. 365-374, 2003.

Protease Inhibitors Used for Treatment of HIV May Produce Opiate Withdrawal in Methadone-Maintained Patients

Dr. Elinore McCance-Katz and colleagues at the Medical College of Virginia examined the interactions between (1) lopinavir-ritonavir (L/R), a fixed combination of protease inhibitors used for the treatment of HIV infection, and (2) ritonavir alone at the same dosage as that in the L/R formulation, with methadone in opiate addicts. L/R was associated with significant reductions in the methadone area under the concentration-time curve, maximum concentration, and minimum concentration, as well as increased methadone oral clearance and increased opiate withdrawal symptoms, whereas ritonavir use alone modestly and non-significantly increased methadone concentrations. Because lopinavir is a potent inducer of methadone metabolism, treatment with L/R requires clinical monitoring and may require increased methadone doses in some patients, whereas ritonavir has no significant effect on methadone metabolism. McCance-Katz, E.F., Rainey, P.M., Friedland, G. and Jatlow, P. Clin Infect Dis., 37(4), pp. 476-482, August 2003.

Nicotine Withdrawal and Depressive Symptomatology During Short-Term Smoking Abstinence: A Comparison of Postmenopausal Women Using and Not Using Hormone Replacement Therapy

This study investigated whether taking medications for transdermal hormone replacement therapy (HRT) influenced smoking-cessation variables in postmenopausal women undergoing short-term abstinence from cigarettes. Women were recruited into two groups according to their pre-enrollment medication status--those currently on HRT (n = 17) or those not on HRT (n = 13). The HRT group had their previous medication replaced with a standard 0.1 mg estradiol transdermal system and 2.5 mg of Cycrin daily. After 2 weeks of medication adjustment, participants continued smoking as usual for 1 week, at which time baseline measurements were taken. Participants were then instructed to quit smoking for the remaining 2 weeks. They were provided with smoking-cessation counseling and monitored for abstinence. Data were collected during five clinic visits on all dependent measures: Minnesota Nicotine Withdrawal Scale, Beck Depression Inventory (BDI) scale, Profile of Mood States, Motor Speed Tasks, and Reaction Time Test. Contrary to the hypothesis, the exogenous hormone use did not have a differential effect on most of the dependent variables during the first 2 weeks of smoking abstinence. One exception was depressive symptomatology: the BDI change scores (week 2 - baseline) differed significantly for the HRT and non-HRT groups ($p = .045$), with women in the HRT group experiencing an increase in depressive symptomatology. This finding, though preliminary, may have clinical implications for postmenopausal women who attempt to quit smoking while on HRT, particularly since depressed mood following abstinence is associated with a relapse to smoking. Allen, S.S., Hatsukami, D.K. and Christianson, D. Nicotine Tob Res., 5(1), pp. 49-59, 2003.

A Preliminary Placebo-Controlled Trial of Selegiline Hydrochloride for Smoking Cessation

Dr. Tony George and colleagues studied the safety and efficacy of the monoamine oxidase B inhibitor selegiline hydrochloride compared with placebo for smoking cessation in nicotine-dependent cigarette smokers. Forty subjects with DSM-IV

nicotine dependence were randomized to: 1) selegiline hydrochloride (5 mg p.o. twice daily) or 2) placebo in an 8-week trial. Outcome measures included smoking cessation rates, treatment retention, and medication side effects. Selegiline hydrochloride increased trial end point (week 8) 7-day point prevalence smoking cessation rates (selegiline hydrochloride, 9/20 [45.0%]; placebo, 3/20 [15.0%], odds ratio = 4.64, 95% CI, 1.02-21.00, p <.05), and smoking cessation rates during the last 4 weeks of the trial (selegiline hydrochloride, 6/20 [30.0%]; placebo, 1/20 [5.0%], odds ratio = 8.14, 95% CI, 0.88-75.48, p =.07) in comparison with placebo. Six-month follow-up 7-day point prevalence smoking cessation rates were reduced compared with trial end point (selegiline hydrochloride, 4/20 [20.0%]; placebo, 1/20 [5.0%], odds ratio = 4.75, 95% CI, 0.48-46.91, p =.18). Treatment retention was similar between drug and placebo groups (p =.13), and selegiline hydrochloride was well tolerated in cigarette smokers. This preliminary study suggests that selegiline (10 mg/day) is safe for use and enhances smoking cessation rates compared with placebo in nicotine-dependent cigarette smokers. George, T.P., Vessicchio, J.C., Termine, A., Jatlow, P.I., Kosten, T.R. and O'Malley, S.S. Biol Psychiatry, 53(2), pp. 136-143, 2003.

Treatment of Adolescent Smokers with the Nicotine Patch

This study examined the effects of the nicotine patch on craving and withdrawal symptoms, safety, and compliance among adolescents. The secondary goal was to conduct a preliminary investigation of the effectiveness of the nicotine patch in helping adolescents quit smoking. The study design was a double-blind, placebo-controlled, randomized trial of the nicotine patch. The intervention also provided intensive cognitive-behavioral therapy and a contingency-management procedure. Participants (n=100) attended 10 treatment visits over 13 weeks. Compared with the placebo patch group, the active nicotine patch group experienced a significantly lower craving score and overall withdrawal symptom score (p=.011 and p=.025, respectively), as well as a time trend toward lower scores (p<.001) in craving only. Moreover, the nicotine patch appeared safe for adolescents to use. No differences by treatment group were found in experiencing adverse events, except that the participants in the placebo patch group reported more headaches than those in the active nicotine patch group. As another measure of safety, the overall mean salivary cotinine levels were significantly lower at 1, 6, 8, and 10 weeks post quit (all p<.05) compared with baseline levels, although these results were confounded by dropouts. Additionally, a significant number of participants were compliant with using the nicotine patch daily. Finally, point prevalence (7-day and 30-day abstinence rates) and survival analysis of participant abstinence indicated no significant differences between treatment groups. The results of this study suggest that the nicotine patch is a promising medication and a larger clinical trial of the nicotine patch among adolescents is warranted. Hanson, K., Allen, S., Jensen, S. and Hatsukami, D. Nicotine Tob Res., 5(4), pp. 515-526, 2003. Efficacy of Nicotine Patch in Smokers with a History of Alcoholism Smokers with a history of alcohol dependence may have more difficulty quitting, might relapse to alcohol use, and might especially benefit from nicotine replacement therapy for smoking cessation. One hundred fifteen smokers with a history of alcohol dependence (median of 5 years previously) were randomly assigned to either a 21-mg nicotine patch or placebo in a trial designed to be as similar as possible to a prior study that examined smokers with no history of alcoholism. Both studies were of heavy smokers with similar levels of nicotine dependence; thus, any differences in trials would be due to a history of alcohol problems per se. In the current trial, adjusted prolonged smoking abstinence in those with a history of alcohol dependence was higher in the active than the placebo group at end-of-treatment (28% vs. 11%; odds ratio, 3.2; p = 0.04) and at 6-month follow-up (24% vs. 6%; odds ratio, 4.9; p = 0.02). Among subjects not lost to follow-up, none reported drinking problems or increases in craving for alcohol. Smoking abstinence was not lower and the odds ratio for nicotine patch therapy was not greater in smokers with a history of alcohol dependence than in smokers with no such history. Heavy smokers with a history of alcoholism benefit from nicotine patch treatment. Hughes, J.R., Novy, P., Hatsukami, D.K., Jensen, J. and Callas, P.W. Alcohol Clin Exp Res., 27(6), pp. 946-954, 2003.

Maternal Vaccination Against Nicotine Reduces Nicotine Distribution to Fetal Brain in Rats

Vaccination of adult male rats against nicotine has been shown to reduce nicotine distribution to the brain. The current study examined whether vaccination of female rats before pregnancy would reduce the distribution to fetal brain of a single nicotine dose administered during gestation. Female rats immunized with a nicotine conjugate vaccine received a single dose of nicotine 0.03 mg/kg i.v. on gestational day 16 to 22. Five minutes later, vaccinated rats had substantially higher bound and lower unbound

serum nicotine concentration and lower brain nicotine concentration than controls. Fetal brain nicotine concentration was reduced by 43% in vaccinated rats, comparable to the reduction in the maternal brain nicotine concentration. The whole-fetus nicotine concentration was not altered by vaccination. A similar experiment was performed in which pregnant rats were passively immunized with rabbit nicotine-specific IgG 7 or 21 mg/kg just before nicotine dosing. The effects of passive immunization on nicotine distribution in the mother were IgG dose-related and the higher dose reduced nicotine distribution to fetal brain by 60%. These data suggest that vaccine effects on nicotine distribution to serum and brain are similar in pregnant female rats to those previously reported in adult males. Vaccination of female rats before pregnancy, or passive immunization during pregnancy, can reduce the exposure of fetal brain to a single dose of maternally administered nicotine. Keyler, D.E., Shoeman, D., LeSage, M.G., Calvin, A.D. and Pentel, P.R. J Pharmacol Exp Ther., 305(2) pp. 587-592, 2003.

A Preliminary Study on Effects of Intravenous Nicotine on Cerebral Glucose Metabolism

Nicotine, when self-administered by smoking tobacco products, is reported to enhance positive mood in seasoned smokers. NIDA-funded researchers posited that since most drugs of abuse have been shown to decrease regional cerebral metabolic rate(s) for glucose (rCMRglc), in humans, nicotine might similarly reduce rCMRglc. Positron emission tomography (PET) with [F-18]fluorodeoxyglucose was used to assess the effects of intravenous nicotine (1.5 mg) on cerebral glucose metabolism in six healthy male volunteers (21-38 years of age). PET scans during placebo and nicotine were performed, and measures of mood and 'feeling state' were self-reported. Data were analyzed using analysis of variance. Nicotine reduced global glucose metabolism by 9.51% compared to placebo control, with reductions in most of the 30 individual regions tested. Nine regions demonstrated statistically significant bilateral effects, although the statistical model did not separate these effects from a global effect. The subjects reported both positive and negative effects of nicotine on mood/feeling state. The widespread decreases in cerebral metabolism are consistent with the many effects of nicotine on cognition and mood. The findings indicate that nicotine resembles other drugs of abuse in reducing brain metabolism, perhaps by a common mechanism. Stapleton, J.M., Gilson, S.F., Wong, D.F, Villemagne, V. L., Dannals, R.F., Grayson, R.F., Henningfield, J.E and London, E.D. Intravenous Nicotine Reduces Cerebral Glucose Metabolism: A Preliminary Study. Neuropsychopharmacology, 28(4), pp. 765-772, April 2003.

rCBF Effects of Nicotine Versus Mecamylamine

The effects of acute nicotine and smoking on brain function were investigated in separate studies, with the primary goal of identifying neural systems that mediate these effects. In Study 1, 18 healthy volunteer cigarette smokers received a single session during which they smoked a nicotine-containing cigarette, smoked a de-nicotinized cigarette, and received i.v. nicotine injections in conjunction with smoking a de-nicotinized cigarette. In Study 2, 16 Ss smoked a nicotine-containing and de-nicotinized cigarette in each of two sessions two hours after receiving either the nicotinic antagonist, mecamylamine or placebo, orally. Regional cerebral blood flow (rCBF) was assessed, and subjective measures of smoking withdrawal symptoms were collected. A principal-components analysis identified 3 factors consisting of frontal, striatal, and reticular systems. Nicotine increased normalized rCBF in the left frontal region and decreased rCBF in the left amygdala. The rCBF in the right hemisphere reticular system was related to nicotine dose in an inverted-U-shaped pattern and was strongly related to both the self-reported craving for cigarettes and to the addiction scale of a smoking motivation questionnaire. The effects of mecamylamine on rCBF were generally opposite to those of nicotine. Rose, J.E., Behm, F.M., Westman, E.C., Mathew, R.J., London, E.D, Hawk, T.C., Turkington, T.G. and Coleman, R.E. PET Studies of the Influences of Nicotine on Neural Systems in Cigarette Smokers. American Journal of Psychiatry, 160(2), pp. 323-333, February 2003.

Comparison of EEG Tracing in Abstinent Methamphetamine Users and Normal Controls

Quantitative EEG has been used to characterize abnormalities in brain function in a number of disorders, including cocaine dependence, but has not been used to characterize abnormalities associated with methamphetamine dependence. Methamphetamine exposure is associated with long-lasting reductions in markers for DA neurons in preclinical models and probably in humans. Researchers at UCLA studied 11 methamphetamine-dependent subjects and 11 non-drug using volunteers to test the hypothesis. Methamphetamine-dependent subjects were hospitalized for

four days to document abstinence while the non-drug using volunteers were studied as outpatients. EEG power was log-transformed prior to analysis. Conventional EEG tracings were interpreted by a qualified electroencephalographer, who was blinded to the subjects' identity. The four-day abstinent, methamphetamine-dependent volunteers had increased EEG power in the delta and theta bands. Power in the alpha and beta bands did not differ between the groups. Within the methamphetamine-dependent group, a majority of the conventional EEGs were abnormal (64%) compared to 18% in the no drug controls. Abstinent methamphetamine-dependent subjects have also been shown to demonstrate qEEG abnormalities that are consistent with a generalized encephalopathy. Newton, T.F, Cook, I.A, Kalechstein, A.D., Duran, S., Monroy, F, Ling, W. and Leuchter, A.F. Quantitative EEG Abnormalities in Recently Abstinent Methamphetamine Dependent Individuals. Clinical Neurophysiology, 114(3), pp. 410-415, March 2003.

Cingulate Hypoactivity in Cocaine Users During a GO-NOGO Task as Revealed by Event-Related Functional Magnetic Resonance Imaging

Dr. Hugh Garavan and colleagues at the Medical College of Wisconsin used functional magnetic resonance imaging to investigate whether chronic cocaine use leads to a neural dysfunction resulting in an inability to withhold pre-potent responses. Chronic cocaine abusers and normal comparison subjects were scanned while performing a GO-NOGO task in which successful performance required prepotent behaviors to be inhibited. Chronic cocaine abusers exhibited significantly less task-related activation in the cingulate, pre-supplementary motor and insula cortex. This hypoactivity was observed for both successful NOGOs and errors of commission in chronic cocaine users relative to cocaine-naive controls. This attenuated response, in the presence of comparable activation levels in other task-related cortical areas, suggests cortical and psychological specificity in the locus of drug abuse-related cognitive dysfunction. The results suggest that addiction may be accompanied by a disruption of brain structures critical for the higher-order, cognitive control of behavior. Kaufman, J.N., Ross, T.J., Stein, E.A., Garavan, H. Journal of Neuroscience, 23(21), pp. 7839-7843, 2003.

Increased Activation in the Right Insula during Risk-Taking Decision Making Is Related to Harm Avoidance and Neuroticism

Dr. Martin Paulus and colleagues at University of California, San Diego used functional magnetic resonance imaging (fMRI) to investigate the role of the insula in risk-taking and decision making in normal human subjects. They hypothesized that the degree of risk-taking is related to the degree of activation in the insular cortex. Seventeen healthy, right-handed subjects performed a risk-taking decision-making task during functional magnetic resonance imaging (fMRI) using a fast event-related design. This investigation yielded three main findings. First, right insula (BA 13) activation was significantly stronger when subjects selected a "risky" response versus selecting a "safe" response. Second, the degree of insula activation was related to the probability of selecting a "safe" response following a punished response. Third, the degree of insula activation was related to the subjects' degree of harm avoidance and neuroticism as measured by the TCI and NEO personality questionnaires, respectively. These results are consistent with the hypothesis that insula activation serves as a critical neural substrate to instantiate aversive somatic markers that guide risk-taking decision-making behavior. Paulus, M.P., Rogalsky, C., Simmons, A., Feinstein, J.S. and Stein, M.B. Increased Activation in the Right Insula During Risk-Taking Decision Making is Related to Harm Avoidance and Neuroticism. NeuroImage, 19(4), pp. 1439-1448, August 2003.

Exploring the Neurological Substrate of Emotional and Social Intelligence

Dr. Antoine Bechara and colleagues at the University of Iowa investigated whether deficits in poor judgment in decision-making, especially in the personal and social realms was related to measures of emotional intelligence. Emotional intelligence has been defined as an array of emotional and social abilities, competencies and skills that enable individuals to cope with daily demands and be more effective in their personal and social life. Patients with lesions to the ventromedial (VM) prefrontal cortex, insula cortex or amygdala have defective somatic markers and tend to exercise poor judgment in decision-making. The subjects in this study were twelve patients with focal, stable bilateral lesions of the VM cortex or amygdala or the right insular cortices, and 11 patients with focal, stable lesions in structures outside the neural circuitry thought to mediate somatic state activation and decision-making. Subjects were tested on the Emotional Quotient Inventory (EQ-I), a standardized psychometric measure of various aspects of emotional and social intelligence. Subjects were also tested on various other procedures designed to measure decision-making (the Gambling Task), social functioning, as well as personality changes and

psychopathology; standardized neuropsychological tests were applied to assess their cognitive intelligence, executive functioning, perception and memory as well. Patients with lesions in the somatic marker circuitry had significantly lower emotional intelligence and poorer judgment in decision-making compared to the other patients with brain lesions. The patients with lesions in the somatic marker circuitry also had disturbances in social functioning, in spite of normal levels of cognitive intelligence (IQ) and the absence of psychopathology based on DSM-IV criteria. The findings provide preliminary evidence suggesting that emotional and social intelligence is different from cognitive intelligence. They suggest, moreover, that the neural systems supporting somatic state activation and personal judgment in decision-making may overlap with critical components of a neural circuitry subserving emotional and social intelligence, and is independent of the neural system supporting cognitive intelligence. Bar-On, R., Tranel, D., Denburg, N.L. and Bechara, A. Exploring the Neurological Substrate of Emotional and Social Intelligence. Brain, 126, pp. 1790-1800, 2003.

Human Striatal Response to Salient Non-rewarding Stimuli

Dr. Gregory Berns and colleagues at Emory University used functional magnetic resonance imaging to investigate whether activation of the striatum in normal human subjects is related specifically to reward-related stimuli or processes salient events, regardless of their reward value. Saliency refers to an event that both is unexpected and elicits an attentional-behavioral switch (i.e., arousing). Flickering visual distractors presented in the background of an ongoing task were used as the salient events. Distractor salience was manipulated by altering the frequency of distractor occurrence with infrequently presented distractors that were considered more salient. In the first experiment (19 subjects), the distractors were made behaviorally relevant by defining a subset of them as targets requiring a button press. In the second experiment (17 subjects), the distractors were not behaviorally relevant (i.e., they did not require any response). The fMRI results revealed increased activation in the nucleus accumbens after infrequent (high salience) relative to frequent (low salience) presentation of distractors in both experiments. Caudate activity increased only when the distractors were behaviorally relevant. These results demonstrate a role of the striatum in coding non-rewarding salient events. In addition, a functional subdivision of the striatum according to the behavioral relevance of the stimuli is suggested. Zink, C.F., Pagnoni, G., Martin, M., Dhamala, M. and Berns, G.S. Human Striatal Response to Salient Non-Rewarding Stimuli. Journal of Neuroscience, 23(22), pp. 8092-8097, 2003.

Psychosocial Stress and the Duration of Cocaine Use in Non-treatment-Seeking Individuals with Cocaine Dependence

Dr. Igor Elman and colleagues at McLean Hospital investigated whether there was link between psychosocial stress and cocaine dependence. Thirty-six non-treatment-seeking individuals were administered computerized multidimensional instruments, including the Profile of Mood States (POMS) and Speilberger State-Trait Anxiety Inventory (STAI), the Addiction Severity Index (ASI) and the Hamilton Rating Scale for Depression (HRSD). Based on the median POMS tension-anxiety scale score the entire sample was divided into two groups, those with high and low levels of stress. The two groups (n = 16 and 20) were similar in terms of age, gender distribution, and severity of addiction. Compared with the low stress group, high-stress individuals displayed significantly longer duration of cocaine use, greater POMS, STAI-state, STAI-Trait, and HRSD scores. These results extend prior reports implicating stress in the course of cocaine dependence to non-treatment-seekers and suggest that the stress-cocaine link may be generalizable to psychosocial stress and negative affective states. Karlsgodt, K.H., Lukas S.E., and Elman I. Psychosocial Stress and the Duration of Cocaine Use in Non-treatment Seeking Individuals with Cocaine Dependence. American Journal of Drug and Alcohol Abuse, 29(3), pp. 539-551, August 2003.

Multiple Neuronal Networks Mediate Sustained Attention

Dr. Hugh Garavan and colleagues at the Medical College of Wisconsin used functional magnetic resonance imaging to determine the neural substrates of sustained attention (vigilance). Twenty five normal subjects were scanned while performing a rapid visual information processing (RVIP) task. Performance of the RVIP task activated a network of frontal, parietal, occipital, thalamic, and cerebellar regions, whereas deactivations were seen in the anterior and posterior cingulate, insula, and the left temporal and parahippocampal gyrus. Good task performance, as defined by better detection of target stimuli, was correlated with enhanced activation in predominantly right fronto-parietal regions and with decreased activation in predominantly left temporo-limbic and cingulate areas. Factor analysis revealed that

these performance-correlated regions were grouped into two separate networks comprised of positively activated and negatively activated intercorrelated regions. Poor performers failed to significantly activate or deactivate these networks, whereas good performers either activated the positive or deactivated the negative network, or did both. The fact that both increased activation of task-specific areas and increased deactivation of task-irrelevant areas mediate cognitive functions underlying good RVIP task performance suggests two independent circuits, presumably reflecting different cognitive strategies, can be recruited to perform this vigilance task. These results provide a basis for investigating brain mechanisms of sustained attention deficits in substance abusers. Lawrence, N.S., Ross, T.J., Hoffmann, R., Garavan, H. and Stein, E.A. Multiple Neuronal Networks Mediate Sustained Attention. Journal of Cognitive Neuroscience, 15, pp. 1028-1038, 2003.

Preliminary Evidence of Hippocampal Dysfunction in Adolescent MDMA (Ecstasy) Users

Dr. Leslie Jacobsen and colleagues published the results of an exploratory study designed to assess the potential cognitive and neurobiological effects of the use of MDMA in adolescence. Six adolescent MDMA users and six non-using adolescents that were matched on age, gender, IQ, and other drug use were asked to perform a series of tasks that tested their attentional and memory capabilities. In tests that measured performance on simple, selective, and divided attention tasks, MDMA users were found to have significantly longer reaction times, but no differences in accuracy. Adolescent MDMA users were found to differ in hippocampal activation pattern during working memory tasks from non-using adolescents, but this difference was only present at the most difficult level of the tasks, and was also found to be greatest among those individuals that had most recently used MDMA. This study is the first to demonstrate these differences among adolescent MDMA users that, when compared with the majority of users studied as adults, have comparatively little lifetime exposure to the drug. Jacobsen, L.K., Mencl, E.W., Pugh, K.R., Skudlarski, P. and Krystal, J.H. Preliminary Evidence of Hippocampal Dysfunction in Adolescent MDMA ("ecstasy") Users: Possible Relationship to Neurotoxic Effects. Psychopharmacology, DOI: 10.1007/s00213-003-1679-4, November 28, 2003.

Magnetic Resonance Spectroscopy of Neurotransmitters in the Human Brain

Dr. Edward Novotny and colleagues published a review of recent advances in magnetic resonance spectroscopy (MRS) that included an overview of the application of advanced MRS techniques to children and adolescents. Novotny, E.J., Fulbright, R.K., Pearl, P.L., Gibson, K.M. and Rothman, D.L. Magnetic Resonance Spectroscopy of Neurotransmitters in Human Brain. Ann Neurol. 54, Suppl 6:S25-31, 2003.

Enzymatic Assay for Perfluoro-tagged Metabolites of L-DOPA Using Crude Lysate from E. coli Transformed with pKKAADCII

Dr. Sherry Dingman and colleagues have developed isomers of L-DOPA tagged with multiple fluorine atoms and have demonstrated that the tagged isomers are converted by the enzyme L-aromatic acid decarboxylase, a naturally occurring enzyme in dopaminergic neurons, into molecules of fluorine-tagged dopamine. This finding suggests that these isomers have the potential to follow the native neuronal pathway for dopamine synthesis and may thus be useful in magnetic resonance studies of dopamine function in the brain. Moreover, the assays used provide a new tool for the screening of new compounds for use in fluorine imaging of neural pathways. Dingman S., Snyder-Leiby T., Mack D.J., Thomas R. and Guo C. Applied Microbiology and Biotechnology, DOI: 10.1007/s00253-003-1485-2, November 21, 2003.

Variable-Density Spiral 3D Tailored RF Pulses

Dr. V. Andrew Stenger and colleagues reported the development of a new protocol that allows for functional magnetic resonance imaging of neural activity using an excitation pulse of shortened duration. The shortened duration results in a decrease in susceptibility artifacts, which hinder our ability to image many brain structures that lie in close proximity to air-bone interfaces (i.e., the sinuses of the skull). Stenger, V.A., Boada, F.E., and Noll, D.C. Variable-Density Spiral 3D Tailored RF Pulses. Magnetic Resonance in Medicine, 50(5), pp. 1100-1106, 2003.

Reduced Cortical Gray Matter Density in Human MDMA (Ecstasy) Users: A Voxel-based Morphometry Study

In a preliminary study to determine if MDMA (Ecstasy) use resulted in morphological alterations in the brain, a team of NIDA-supported scientists employed voxel-based

morphometric techniques to compare the concentration of gray and white matter in the brain of MDMA polydrug users to polydrug users that had never used MDMA. Their results demonstrated that a number of areas of the cerebral cortex, as well as cerebellum and midline brainstem, had reduced gray matter concentrations. These alterations in brain structure may underlie or contribute to reported neuropsychiatric impairments in MDMA users. Cowan, R.L., Lyoo, I.K., Sung, S.M., Ahn, K.H., Kim, M.J., Hwang, J., Haga, E., Vimal, R.L., Lukas, S.E. and Renshaw, P.F. Reduced Cortical Gray Matter Density in Human MDMA (Ecstasy) Users: A Voxel-Based Morphometry Study. Drug and Alcohol Dependence, 72(3), pp. 225-235, 2003.

Specific and Somatotopic Functional Magnetic Resonance Imaging Activation in the Trigeminal Ganglion by Brush and Noxious Heat

In an investigation of the utility of functional magnetic resonance imaging in elucidating the peripheral processing of pain information, Dr. David Borsook and colleagues used fMRI to measure activation in the trigeminal ganglion to noxious and innocuous stimuli. They found that the activation patterns were somatotopically organized, with the signal localized to the areas of the ganglion that corresponded to the known anatomical segregation of the ophthalmic, maxillary and mandibular divisions of the trigeminal nerve. They further found that the two stimulus types produced opposite activation patterns, with noxious stimuli producing an increase and innocuous stimuli producing a decrease in the fMRI signal. These findings are the first demonstration that MRI can detect functional changes in the trigeminal ganglion and illustrate that fMRI can be used to detect changes at the peripheral stages of neural processing in response to pain and other somatosensory modalities, providing evidence that functional neuroimaging may be useful in evaluating the effects of pain therapies. Borsook, D., DaSilva, A.F., Ploghaus, A., and Becerra, L. Specific and Somatotopic Functional Magnetic Resonance Imaging Activation in the Trigeminal Ganglion by Brush and Noxious Heat. J. Neurosci., 23(21), pp. 7897-7903, 2003.

Neural Circuitry Underlying Pain Modulation: Expectation, Hypnosis, Placebo

Borsook and colleagues reviewed their own and other previous studies on the cognitive aspects of the perception of pain. This review underscores the fact that the context in which pain is experienced, for instance, whether the pain is expected or not, greatly affects the specific areas of the brain that are activated in functional neuroimaging studies and, importantly, also affects how painful a stimulus is judged to be. As an example, if a painful stimulus is always preceded by a specific cue, activation increases in the rostral anterior cingulate cortex and in the insula when the cue is presented, and the magnitude of the pain, as assessed by the subject, is less than if the same stimulus were delivered without the preceding cue. If, however, an ambiguous signal is presented, activation occurs in the ventromedial prefrontal cortex and the mid-cingulate cortex. Under these conditions, the stimulus is reported to be more painful than if no cue is given. These data demonstrate that the perception of pain is strongly modulated by psychological factors and, by associating such factors with specific regions of the brain, may point the way toward more effective therapies and means of assessing their efficacy. Ploghaus, A., Becerra, L., Borras, C. and Borsook, D. Neural Circuitry Underlying Pain Modulation: Expectation, Hypnosis, Placebo. Trends in Cognitive Science, 7(5), pp. 197-200, 2003.

Family Transmission for Use, Abuse, and Dependence of Marijuana

Researchers in the program project of Thomas Crowley, University of Colorado, have shown family transmission of three levels of marijuana use, abuse, and dependence in a clinic-referred sample of adolescents. This study expands the literature that had previously only focused on use in adolescents or abuse and dependence in adults. Risk ratios ranged from 1.5 to 3.3; spousal correlations ranged from .33 to .70; parent-offspring correlations ranged from .17 to .30, and sibling correlations ranged from .34 to .44. The proportion of variance attributed to parent transmission ranged between 25% and 44%. These results document the not surprising observation of significant risk of transmission from parents, environmental influence from siblings, and assertive mating for all 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(7), pp. 834-841, 2003.

Limbic Activation by Procaine in Female Cocaine-addicted Subjects Produces a Different Pattern of rCBF than Males

In a study in which procaine-a limbic system activator-was administered to female cocaine patients, there was a muted activation response in comparison to a matched

comparison group. While this was unexpected because it was hypothesized that the limbic system would be sensitized in cocaine-addicted subjects, this result was nevertheless similar to that found with males. But other patterns of activation, and inactivation, did not follow the pattern of male addicted subjects. In particular, there were differences in the orbitofrontal cortex where females showed little change compared to controls following either saline or procaine while males did show changes. Specifically, decreased activation following saline was seen in males but not in females. Conversely, increased activation in this same region was seen in males following procaine but there was no increase in females relative to controls. Other sex pattern differences were observed suggesting that cocaine had differential effects on the neuronal structures of men and women. Since the hypothesized activation due to sensitization did not occur in either male or female addicted subjects, it is now suggested that these findings reflect changes in the cholinergic and/or the serotonergic 3 receptors. Adinoff, B., Devous, M.D., Sr., Best, S.E., Harris, T.S., Chandler, P., Frock, S.D., and Williams, M.J. Regional Cerebral Blood Flow in Female Cocaine-Addicted Subjects Following Limbic Activation. Drug and Alcohol Dependence, 71, pp. 255-268, 2003.

Failure to Find an Association for Haplotypes of the Mu Opioid Receptor in Severe Opioid Dependence

The mu opioid receptor has several polymorphisms and is the molecular target for both endogenous opioid peptides and exogenous opioids that make it an excellent candidate for study in comparison of opioid dependent individuals. However, Ashwin Patkar, Wade Berrettini and associates analyzed five SNPs (T-1793A, -1699t insertion, A-1320G, C+17T, AND A+118G) and showed no frequency differences between index cases of severe opioid dependence and a careful comparison group. However, there were significant differences in allele frequencies of these polymorphisms between European and African Americans. Crowley, J.J., Oslin, D.W., Patkar, A.A., Gottheil, E., DeMaria, P.A., Jr., O'Brien, C.P., Berrettini, W.H., and Grice, D.E. A Genetic Association Study of the Mu Opioid Receptor and Severe Opioid Dependence. Psychiatric Genetics, 13, pp. 169-173, 2003.

Stress Induced by Imagery Increases Cocaine Craving in Cocaine-dependent Individuals

Sinha and colleagues at Yale University and collaborators induced stress in cocaine-dependent individuals by imagery recall of a stressful event and assessed physiological and cognitive responses compared to imagery of a neutral experience. Increases were seen on a cocaine craving scale, anxiety scale, heart rate, blood pressure, and plasma levels of cortisol, prolactin and epinephrine. Similar increases were seen for induced craving by imagery of drug paraphernalia. These data suggest both stress and drug-related cues activate the HPA axis as well as the noradrenergic/sympatho-adreno-medullary system. Accordingly stress may play an important role in drug-taking and relapse. Sinha, R., Talih, M., Malison, R., Cooney, N., Anderson, G.M. and Kreek, M.J. Hypothalamic-Pituitary-Adrenal Axis and Sympatho-Adreno-Medullary Responses During Stress-Induced and Drug Cue-Induced Cocaine Craving States. Psychopharmacology, 170, pp. 62-72, 2003.

Induced Craving in Cocaine Dependent Subjects Produces Distinctive Electrocortical Profiles as Assessed by qEEG

Reid, Prichep and colleagues at NYU School of Medicine induced craving by paraphernalia handling, video viewing, and guided imagery relevant to cocaine environment of the subjects. Distinctive EEG patterns were observed for the two eyes-open situations (paraphernalia and video) that manifested as increased beta activity and decreased delta in the frontal cortex and an increased beta in the occipital cortex. Guided imagery (eyes closed) induced an increase in delta and theta in the frontal cortex and an increase in beta in the occipital cortex. Some of the behavioral measures (e.g., increased anxiety) correlated with these electrocortical measures. These data support other studies of cerebral blood flow and demonstrate that cocaine craving may be topographically mapped and subsequently analyzed for functional relevance. Reid, M.S., Prichep, L.S., Ciplet, D., O'Leary, S., Tom, M.L., Howard, B., Rotrose, J., and John, E.R. Quantitative Electroencephalographic Studies of Cue-Induced Cocaine Craving. Clinical Electroencephalography, 34(3), pp. 110-123, 2003.

PTSD Symptom Severity as a Predictor of Cue-Elicited Drug Craving in Victims of Violent Crime

Dr. Michael Saladin and colleagues at the Medical University of South Carolina,

examined posttraumatic stress disorder (PTSD) symptom severity as a predictor of cue-elicited craving among alcohol-and cocaine-dependent individuals with a history of a least one physical and/or sexual assault. Approximately half of the sample had current PTSD. Severity of PTSD symptoms was measured via the Impact of Events Scale-Revised (IES-R) total severity score. Subjects listened to four trials of a brief narrative imagery script followed by the presentation of an *In vivo* cue. The script presentation consisted of a description of either the subject's worst traumatic event or a neutral scene. The *In vivo* cues consisted of the presentation of either the subject's preferred drug or neutral cues. Craving was measured in response to both the script and *In vivo* cues. Results indicated a high degree of correlation between self-report craving and 1) PTSD symptom severity, 2) type of substance use disorder (SUD) (alcohol dependence vs. cocaine dependence), and 3) sex and race of participant. A series of stepwise multiple regressions indicated that PTSD severity was significantly predictive of trauma cue-elicited craving and drug cue-elicited craving. Saladin, M.E., Drobes, D.J., Coffey, S.F., Dansky, B.S., Brady, K.T. and Kilpatrick, D.G. Addictive Behaviors, 28, pp. 1611-1629, 2003.

"Who Gets In?": Recruitment and Screening Processes of Outpatient Substance Abuse Trials

In this study Dr. Shelly Sayre and colleagues at the University of Texas in Houston conducted a brief telephone screening interview with 1759 callers seeking treatment at the Treatment Research Clinic over a 16 month period in order to examine the effectiveness of various recruitment methods in attracting eligible participants and to identify screening variables that characterized eligible and ineligible callers. Callers referred by friends and family were more likely to be eligible than callers from other referral sources. Callers seeking treatment for cocaine abuse who reported more severe alcohol/substance abuse problems were more likely to be eligible for treatment protocols, while those with severe problems in other psychosocial areas (legal, medical, and psychiatric) were often excluded. Alcohol and nicotine dependent callers reporting severe alcohol problems were more likely to be eligible but otherwise were not different from callers who were ineligible. The effectiveness of recruitment methods may not be the same for different types of substance use disorders. This study underscores the importance of having a sensitive screening assessment for recruiting a homogeneous yet representative sample for outpatient substance abuse clinical trials. Sayre, S.L., Evans, M., Hokanson, P.S., Schmitz, J.M., Stotts, A.L., Averill, P. and Grabowski, J. Addictive Behaviors, 29, pp. 389-398, 2004.

Cross Cultural Evaluation of Smokers Risk for Panic and Anxiety Pathology: A Test in a Russian Epidemiological Sample

Dr. Michael Zvolensky and colleagues evaluated the main and interactive effects of level of smoking (cigarettes per day) and anxiety sensitivity (fear of anxiety and anxiety related sensations) in predicting panic and anxiety variables in an epidemiologically-defined sample of smokers from Moscow (n=95). The combination of high levels of anxiety sensitivity and smoking predicted agoraphobic avoidance, but not frequency of panic attacks during the past week. These findings suggest anxiety sensitivity may moderate the relation between level of smoking and prototypical panic psychopathology variables (panic attacks and agoraphobic avoidance) even after controlling for the theoretically-relevant factors of alcohol abuse and negative affect. Zvolensky, M.J., Kotov, R., Antipova, A.V., and Schmidt, N.B. Behaviour Research and Therapy, 41(10), pp. 1199-1215, October 2003.

Pretreatment Task Persistence Predicts Smoking Cessation Outcome

Dr. Thomas Brandon and colleagues at the University of South Florida, conducted a study to test whether persistence on difficult tasks is associated with nicotine dependence and independently predictive of success at smoking cessation. This study was based on R. Eisenberger's (1992) learned industriousness theory that states that individuals display differing degrees of persistence depending on their history of reinforcement for effortful behavior. These differences may influence the development, maintenance, and cessation of addictive behaviors. In the present study, a pretreatment measure of task persistence (mirror tracing) completed by 144 smokers predicted sustained abstinence through 12 months of follow-up. Moreover, persistence predicted outcome independent of other significant predictors: gender, nicotine dependence, negative affect, and self-efficacy. Brandon, T.H., Juliano, L.M., Irvin, J.E., Lazev, A.B. and Simmons, V.N. Journal of Abnormal Psychology, 112, pp. 448-456, 2003.

Sex Differences in the Effects of Stressful Life Events on Changes in Smoking Status

Dr. Sherry McKee and colleagues associated with the Yale TTURC examined stressful life events associated with substance use to determine if there are sex-specific responses to stress resulting in changes in smoking status. A community-based sample of ever smokers from the Americans' Changing Lives study was used to examine the interactive effects of sex and stressful life events on the likelihood of two outcomes; relapse among former smokers and failure to quit among current smokers. Results indicated that stressful life events appear to have a greater deleterious effect on continued abstinence and the ability to quit smoking for women when compared to men. In particular, health and financial events are important risk factors for women and tobacco use. McKee, S.A., Maciejewski, P.K., Falba, T., and Mazure, C.M. Addiction, 98, pp. 847-855, 2003.

Perceived Barriers to Quitting Smoking Among Alcohol Dependent Patients in Treatment

Researchers at Brown University investigated the perceived barriers to smoking among alcohol-dependent smokers (n=96) in an inner-city residential substance abuse treatment program. Information on barriers to smoking is important in order to design effective intervention programs addressing the concerns of alcoholic patients. The majority of respondents to the questionnaire reported withdrawal-related barriers such as expecting to feel irritable, anxious, restless, and about half expected intolerable urges to smoke if they were to quit smoking. However, concerns about effects on sobriety and needing cigarettes to cope with feeling down were also endorsed by almost half of the patients. Providing corrective feedback about these barriers could be useful when addressing smoking with patients who have alcohol abuse or dependence. Asher, M.K., Martin, R.A., Rohsenow, D.J., MacKinnon, S.V., Traficante, R., and Monti, P.M. Journal of Substance Abuse Treatment, 24, pp. 169-174, 2003.

Past Alcohol Problems Do Not Predict Worse Smoking Cessation Outcomes

Smokers with a past history (PH) of alcohol problems are heavier smokers and more nicotine dependent than smokers with no history of alcohol problems (NH). To test the hypothesis that PH smokers are less likely to be able to quit smoking than NH smokers, Dr. Hughes and colleagues at the University of Vermont conducted a secondary analysis of PH vs. NH smokers, all of whom were highly nicotine dependent (> 30 cigs/day). The findings indicate that heavy PH smokers are not less able to quit on a given attempt compared to heavy NH smokers. Thus a past history of alcohol problems (independent of nicotine dependence) does not predict a worse outcome on a given quit attempt. Hughes, J.R. and Callas, P.W. Drug and Alcohol Dependence, 71, pp. 269-273, 2003.

The Relationship Between Cocaine Craving, Psychosocial Treatment, and Subsequent Cocaine Use

A three-item craving questionnaire was administered weekly to 449 patients in the NIDA Collaborative Cocaine Treatment Study, to see whether it predicted cocaine use in the ensuing week. The results showed that a higher composite score on the craving questionnaire was associated with greater likelihood of cocaine use in the subsequent week; each 1-point increase on the composite score of the craving questionnaire increased the likelihood of cocaine use in the ensuing week by 10%. However, among patients who received individual plus group drug counseling, the treatment condition with the best overall cocaine use outcome, increased craving scores were not associated with greater likelihood of cocaine use in the subsequent week. The relationship between craving and subsequent cocaine use varied by treatment condition, suggesting that the most effective treatment in the study might have weakened the link between craving and subsequent use by helping patients abstain despite high craving. Weiss, R.D., Griffin, M.L., Mazurick, C., Berkman, B., Gastfriend, D.R., Frank, A., Barber, J.P., Blaine, J., Salloum, I. and Moras, K. American Journal of Psychiatry, 160, pp. 1320-1325, 2003.

Community Reinforcement Therapy (CRA) Contributes to Outcome in CRA Plus Vouchers Studies

Dr. Steven Higgins and colleagues at the University of Vermont examined differences in treatment outcome between individuals receiving Community Reinforcement Approach therapy (CRA) plus voucher incentives contingent on abstinence and those receiving Vouchers alone. Study participants included 100 cocaine dependent adults randomly assigned to one of the two conditions. Voucher therapy lasted 12 weeks and the CRA therapy lasted 24 weeks and included monitored disulfiram therapy for those eligible and willing to take it. Previous research has demonstrated an effect of

voucher incentives on retention. In this study, those receiving CRA with voucher incentives showed better treatment retention rates, used cocaine at a lower frequency during treatment, and reported a lower frequency of alcohol intoxication both during treatment and at 2 year follow-up. CRA plus vouchers condition also improved employment outcomes. Overall researchers concluded that CRA with vouchers provides an additional benefit over and above voucher incentives alone, particularly in terms of retention, reduced cocaine use during treatment, reduced drinking to intoxication, and employment. Higgins, S.T., Sigmon, S.C., Wong, C.J., Heil, S.H., Badger, G.J., Donham, R., Dantona, R.L. and Anthony, S. Journal of the Archives of General Psychiatry, 60(10), pp. 1043-1052, October, 2003.

New Treatment for Incarcerated Women with Post-Traumatic Stress Disorder (PTSD) and Substance Use Disorders (SUDs)

Dr. Caron Zlotnick and colleagues at Brown University and Harvard Medical School piloted a cognitive behavioral therapy, Seeking Safety with 17 incarcerated women with PTSD and SUDs as an adjunct to usual treatment provided by the prison. Of those receiving the treatment 53% no longer met criteria for PTSD at the end of treatment and 3 months following treatment 46% still no longer met criteria for PTSD. Although 35% reporting the use of illicit substances within three months of release from prison, overall results show a significant decrease in drug use from baseline. Measures of client satisfaction suggest the treatment is appealing to women and has the potential to be beneficial especially for PTSD symptoms. These results must be considered preliminary given the uncontrolled nature of the trial and the small number of participants. Zlotnick, C., Najavits, L.M., Rohsenow, D.J. and Johnson, D.M. Journal of Substance Abuse Treatment, 25(2), pp. 99-105, September, 2003.

Single or Dual Drug Targets are Equally Effective in a Brief Abstinent Test Procedure

Dr. Maxine Stitzer and colleagues at Johns Hopkins University compared response of methadone maintained cocaine and opioid users to voucher incentives when receipt of $200.00 in incentives was contingent on abstinence from either a single target, cocaine, or two targets, cocaine and opioids during a four day abstinence test. Participants were equally likely to initiate and maintain abstinence from cocaine in both conditions but they were more likely to initiate and maintain abstinence from heroin in the dual target condition. This research refutes the notion that adding a second target might interfere with participant's ability to initiate cocaine abstinence and suggests that it may facilitate abstinence from multiple drugs. Correia, C.J., Dallery, J., Katz, E.C., Silverman, K., Bigelow, G. and Stitzer, M.L. Experimental and Clinical Psychopharmacology, 11(4), pp. 302-308, November, 2003.

Client Commitment Language During Motivational Interviewing Predicts Drug Use Outcomes

Dr. William R. Miller and colleagues at the University of New Mexico coded tapes of motivational interviewing sessions for strength of utterances related to motivation, desire, commitment, need, readiness, and reasons to change. Participants could be divided into three groups based on proportion of days abstinent (PDA) before and after treatment, those with High PDA, before and after (maintainers), those with Low PDA before and High PDA after treatment (changers) and Low PDA before and after (stragglers). Commitment strength (CS) during the client evaluation of a change plan predicted PDA outcome group. Although strength of desire, need, and reasons to change each predicted CS, CS itself was more predictive of PDA outcome suggesting that CS may be a pathway through which these other variables influence behavior. Amrhein, P.C., Miller, W.R., Yahne, C.E., Palmer, M. and Fulcher, L. Journal of Consulting and Clinical Psychology, 71(5), pp. 862-878, October 2003.

Gambling Urges in Pathological Gambling: A Functional Magnetic Resonance Imaging Study

Gambling urges in Pathological Gambling (PG) often immediately precede engagement in self-destructive gambling behavior. Drs. Marc Potenza, Bruce Rounsaville and colleagues conducted a study of the neural correlates of gambling urges underlying PG to help direct research into effective treatments. Echoplanar functional magnetic resonance imaging was used to assess brain function during viewing of videotaped scenarios with gambling, happy, or sad content. Participants rated the quality and magnitude of their emotional and motivational responses. Men with PG (n = 10) reported mean +/- SD greater gambling urges after viewing gambling scenarios vs. control subjects (n = 11) (5.20 +/- 3.43 vs. 0.32 +/- 0.60;

chi2 1,19 = 21.71; P<.001). The groups did not differ significantly in their subjective responses to the happy (P =.56) or sad (P =.81) videotapes. The most pronounced between-group differences in neural activities were observed during the initial period of viewing of the gambling scenarios: PG subjects displayed relatively decreased activity in frontal and orbitofrontal cortex, caudate/basal ganglia, and thalamus compared with controls. Distinct patterns of regional brain activity were observed in specific temporal epochs of videotape viewing. For example, differences localized to the ventral anterior cingulate during the final period of gambling videotape viewing, corresponding to the presentation of the most provocative gambling stimuli. Although group differences in brain activity were observed during viewing of the sad and happy scenarios, they were distinct from those corresponding to the gambling scenarios. In men with PG, gambling cue presentation elicits gambling urges and leads to a temporally dynamic pattern of brain activity changes in frontal, paralimbic, and limbic brain structures. When viewing gambling cues, PG subjects demonstrate relatively decreased activity in brain regions implicated in impulse regulation compared with controls. Potenza, M.N. Steinberg, M.A., Skudlarski, P., Fulbright, R.K., Lacadie, C.M., Wilber, M.K., Rounsaville, B.J., Gore, J.C., and Wexler, B.E. Archives of General Psychiatry, 60(8), pp. 828-836, August 2003.

Prevalence of Alcohol and Drug Use in an Adolescent Training Facility

Dr. Lyn Stein and colleagues at the NIDA-funded Center for Alcohol and Addiction, Brown University, conducted a study of the substance use and crime histories of incarcerated male adolescents. Chart reviews of 186 adolescents indicated that drug use was highly prevalent, with 88.7% using alcohol and 95.7% using marijuana. Ethnic differences in drug use were found, with Caucasian, non-Hispanic adolescents significantly more likely to use cocaine, hallucinogens, and heroin than were adolescents of other ethnicities. Among the crimes committed, possession of a controlled substance was the most prevalent, with 31.8% of adolescents involved. These results provide important guidance for developing targeted behavioral treatments to reduce incarcerated adolescents' use of drugs and involvement in drug-related crimes. Lebeau-Craven, R., Stein, L., Barnett, N., Colby, S.M., Smith, J.L.and Canto, A.L. Substance Use & Misuse, 38(7), pp. 825-834, June 2003.

Participation in 12-Step-Based Fellowships Among Dually-Diagnosed Persons

Dr. Magura and colleagues of the National Development and Research Institutes and the Mental Health Empowerment Project, New York, investigated dually-diagnosed participants' involvement in traditional and targeted 12-Step groups. A total of 277 participants recruited from targeted 12-Step groups comprised of dually-diagnosed substance abusers with mental health problems (Double Trouble Recovery, DTR) were interviewed about their involvement in 12-Step groups, and the role of these groups in recovery. Participants reported extensive 12-Step involvement, with 85% reporting at least weekly attendance, and 46% reporting "Always sharing" at meetings. Most participants (83%) rated attendance at DTR as very important to their recovery, and 76% rated other group members as very important to recovery. Respondents with a diagnosis of schizophrenia were more likely to attend DTR than were respondents with other mental health diagnoses. Barriers cited to attending 12-Step meetings included lack of meeting availability (often because of discharge from programs where meetings took place), and logistics such as transportation. This study suggests that participants view targeted 12-Step groups as beneficial to recovery, and identifies issues to consider in developing targeted groups. Laudet, A.B., Magura, S., Vogel, H.S. and Knight, E.L. Alcoholism Treatment Quarterly, 21(2), pp. 19-39, 2003.

Psychiatric and Substance Dependence Comorbidities, Sexually Transmitted Diseases, and Risk Behaviors among Methamphetamine-Dependent Gay and Bisexual Men Seeking Outpatient Drug Abuse Treatment

Findings regarding psychiatric and substance dependence comorbidities, lifetime rates of infectious disease, and high-risk sexual behaviors are reported from a large sample of urban gay and bisexual men seeking outpatient behavioral drug abuse treatment in L.A. Over one-quarter of participants met criteria for lifetime anxiety disorder and over one-half of the sample met criteria for lifetime depressive disorders. Compared to those without psychiatric diagnoses, significant differences were observed in lifetime prevalence of sexually transmitted infections among those who have generalized anxiety disorder, specific phobia and major depressive disorder, social phobia, and bipolar disorder. Differences in infectious disease prevalence did not correspond to significantly different rates of high-risk sexual behaviors. Findings indicate that gay and bisexual men seeking outpatient treatment for methamphetamine dependence are likely to experience psychiatric comorbidity and to have high rates of infectious disease, including HIV, syphilis and gonorrhea. Shoptaw,

S., Peck, J., Reback C.J., and Rotheram-Fuller, E. Journal of Psychoactive Drugs, 35, pp. 161-168, 2003.

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

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

Proteins Made by HIV-1 Block an Enzyme That Normally Destroys Viral Genomes: A Potential for Therapeutic Intervention

HIV/AIDS treatments in part rely on a cocktail of protease inhibitors to stop the enzymes needed for viral replication in infected individuals. One of the major issues in HIV/AIDS therapy is that people discontinue or inconsistently take the medication when the viral load becomes below detectable levels, leading them to believe that they are cured. HIV-1 is notorious for mutating its genome to circumvent the line of defense the medications offer when the medication is not used properly, sometimes rendering the medication useless when the virus resurges. It is imperative, therefore, for researchers to identify new targets for HIV/AIDS therapy. One other barrier in studying HIV/AIDS is the use of animal models because HIV-1 is human specific and using other viruses in other animals makes it difficult to extrapolate any findings to the human condition. Thus understanding the mechanisms behind the species specificity may contribute to the generation of better animal models and better therapeutic options. To this end, researchers have identified an mRNA editing enzyme, called APOBEC3G, which incorporates into the virus upon infection and mutates the viral genome so that the virus is unable to propagate and infect additional cells. HIV-1 encodes a protein called the virion infectivity factor (Vif) and it is required for the production of infectious virions. These researchers discovered that Vif specifically binds to human APOBEC3G and prevents its incorporation into the virus, allowing the virus to propagate at will. These important experiments suggest that therapeutic interventions that either induced APOBEC3G or that blocked the binding of Vif to APOBEC3G so that APOBEC3G incorporation into the virus is restored could be clinically beneficial. Mariani, R., Chen, D., Schrofelbauer, B., Navarro, F., Konig, R., Bollman, B., Munk, C., Nymark-McMahon, H., and Landau, N. Species-Specific Exclusion of APOBEC3G from HIV-1 Virions by Vif. Cell, 114, pp. 21-31, 2003.

A Cross-Border HIV Prevention Intervention for IDUs in China and Vietnam

In this paper, researchers describe the background and early implementation of a peer-based HIV prevention intervention involving social marketing of sterile needles and syringes for injection drug users (IDUs) in a border region of northern Vietnam and southern China. Peer educators collect and safely dispose of used needles and syringes and provide IDUs with a choice of new needles/ syringes or vouchers redeemable in pharmacies and clinics for new needles/syringes. The project arose from a pattern of changing drug use and increasing HIV infection in the region but its development took 4 years and faced many challenges. Implementation of the intervention posed a new set of challenges for the participating health departments, police, peer educators, pharmacists, injection drug users, and the communities at large. Early implementation of the project has revealed successful multi-sectoral collaboration, and broad acceptance by IDUs of pharmacy vouchers and distribution of new needles/syringes. However, IDUs' persistent fear of the police, particularly in Vietnam, has required reliance on separate collection by peer educators of used needles/syringes and distribution of pharmacy vouchers and new needles. In China, new needles/syringes and vouchers are largely being provided through exchange. Understanding the development and implementation challenges and the strategies that were successful in overcoming them (including the importance of being flexible and adaptable to contextual factors) may be useful to those interested in launching similar, much-needed interventions in other parts of the world. Hammett, T., Des Jarlais, D., Liu, W., Ngu, D., Tung, N., Hoang, T., et al. Development and Implementation of a Cross-Border HIV Prevention Intervention for Injection Drug

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Users in Ning Ming County (Guangxi Province), China and Lang Son Province, Vietnam. Internat J Drug Policy, 14 (5-6), pp. 389-398, 2003.

Boundary-Crossing and Drug Use Among Young Adults in a Low-Income, Minority, Urban Neighborhood

In this paper, researchers examined the relationship between boundary-crossing sexual partnerships (i.e., those between partners who are 5 or more years older, of a different race or ethnicity, or live in a different neighborhood or borough) and use of crack or injected drugs among young adults in Bushwick, Brooklyn. Women who smoked crack or injected drugs were more likely to have a sexual partner who was older, of a different race/ethnicity, or from a different borough than were women who did not use these drugs; men who used these drugs were more likely to have older sex partners than men who did not. Young people who use these drugs are known to be at higher risk of having HIV and a number of other sexually-transmittable infections such as hepatitis B, genital herpes, and syphilis. These results imply that this risk may be even higher for people who cross these boundaries. In addition, if these young people become infected, they may be particularly likely to serve as a gateway for spreading infection to other social groups. Flom, P., Friedman, S., Neaigus, A. and Sandoval, M. Boundary-Crossing and Drug Use Among Young Adults in a Low-Income, Minority, Urban Neighborhood. Connections, 25 (2), pp. 77-87, 2003.

Cognitive-Behavioral Intervention to Reduce HIV Risks in Crack Users and IDUs

This paper presents the results of a study evaluating the efficacy of a theory-based cognitive-behavioral intervention to reduce HIV risk among street-based crack and injection drug users not currently in drug treatment in Long Beach, California. A nine-session, 4-month enhanced intervention (including HIV counseling and testing) was compared to a two-session standard counseling and testing intervention developed by NIDA in terms of their efficacy for reducing drug- and sex-related risk behaviors. The theory-based enhanced intervention rarely was found to be different from NIDA's standard counseling and testing intervention in reducing both drug- and sex-related risks, as indicated by cessation and/or reduction of drug use (measured by urine test and self-report), entry into drug treatment, and increased frequency of condom use. One of the few significant effects was that the enhanced intervention significantly increased injecting drug users' use of their own injection equipment. On the other hand, for both interventions, most risk behaviors were significantly reduced. It is concluded that the theory-based cognitive-behavioral intervention has limited advantage over the standard intervention in terms of both magnitude and frequency of HIV risk reduction achieved by high-risk, active drug users. Hershberger, S.L., Wood, M.M. and Fisher, D. A Cognitive-Behavioral Intervention to Reduce HIV Risks in Crack Users and IDUs. AIDS Behav., 7(3), pp. 229-243, 2003.

Drug Use, Incarceration Rates, and Prison-Associated HIV Risks in Thailand

Incarceration is a known risk for HIV infection in Thai drug users. Through the 1990s, incarceration rates for drug-related offenses rose sharply, whereas HIV prevention and drug treatment in prisons remained limited. In this study, researchers assessed HIV and incarceration risks for injection drug users (IDU) and non-IDU in a large treatment center cohort in northern Thailand to investigate HIV and prison risks in this period. Thai Bureau of Corrections data were used to assess incarceration and prevention funds in prisons, 1992-2000. They found that, among 1,865 drug users in the treatment cohort, 503 (27.0%) had ever been jailed. Men (OR 3.3, 95% CI 2.1, 5.2), IDU (OR 6.3, 95% CI 5.1, 7.9), and MSM (OR 3.4, 95% CI 1.8, 6.3) were more likely to have been jailed. Among male IDUs who had ever been jailed (N = 272), 15.8% had used drugs in prison. In a multivariate model, incarceration and ever IDU remained independently associated with HIV infection; IDU, MSM behaviors, and harmful traditional practices remained independently associated with having been jailed. From 1992 to 2000, overall alleged narcotics offenses increased from 117,000 to 276,000/year. The number of persons incarcerated for narcotics offenses increased fivefold from 1992 to 1999, from 12,860 to 67,440. For FY 2000, narcotics treatment accounted for 0.06% of the Thai corrections budget, whereas HIV programs in prisons were 0.017%. These findings suggest that incarceration rates for narcotics offenses have increased sharply in Thailand, whereas prevention has lagged. Having been jailed is an important independent risk for HIV infection among Thai male drug users, especially IDU and MSM, demonstrating the urgent need for HIV prevention and drug treatment in Thai prisons. Beyrer, C., Jittiwutikarn, J., Teokul, W., Razak, M., Suriyanon, V., Srirak, N., et al. Drug Use, Increasing Incarceration Rates, and Prison-Associated HIV Risks in Thailand. AIDS and Behavior, 7(2), pp. 153-161, June 2003.

Effector Cell Mediated Cytotoxicity in HIV Infected Subjects

CD8+ cytotoxic T lymphocyte (CTL) activity is currently believed to be one of the key immunologic mechanisms responsible for the prevention or attenuation of HIV-1 infection. The induction of CD8+ T cell activation may also result in the production of soluble or non-classical lytic factors that are associated with protection from infection or slower disease progression. Traditionally, CD8+ CTL responses have been measured by the classic chromium release assay, monitoring the ability of T cells (Effector cells) to lyse radiolabelled HLA - matched "target cells" that express the appropriate antigen-MHC complex. This method is not only labor intensive, semi quantitative assay at best, but also needs fresh, non-cryopreserved cells. Recently, cytokine specific ELISPOT assays or tetrameric MHC-I/ peptide complexes have been utilized to directly quantitate circulating CD8+ effector cells, and these assays are more sensitive, quantitative and reproducible than the traditional CTL lysis assay and can also be performed on cryopreserved cells. Although these are reproducible assays for the assessment of soluble antiviral activity secreted by activated T cell populations they can be extremely expensive to perform. Authors have used FACS Analysis to measure Granzyme B release as a function of cell mediated cytotoxicity. This method helped quantitate the CTL activity and also identified the phenotype of the cells elucidating this immune response. The method described not only monitors immunological response but is also simple to perform, precise and extremely time efficient and is ideal for screening a large number of samples. Mahajan, S.D., Aalinkeel, R., Schwartz, S.A., Chawda, R.P. and Nair, M.P. Effector Cell Mediated Cytotoxicity Measured by Intracellular Granzyme B release in HIV Infected Subjects. Biol Proced Onlin., 5, pp. 182-188, 2003.

Elevated C-Reactive Protein Levels are Associated with Endothelial Dysfunction in Chronic Cocaine Users

To examine the relationship of the serum C-reactive protein (CRP, a marker for inflammation) and endothelial function and their associations with coronary artery calcification, lipid profile and cardiac changes, researchers performed analyses of serum lipids and CRP, echocardiography, spiral computed tomography scans and endothelial function assays in 53 participants with a history of chronic cocaine use. They found no statistically significant differences in demographic characteristics and drug use between CRP normal (<1.9 mg/l) and abnormal groups. The brachial artery diameter percentage changes in the third scan (immediately after deflation of cuff) and the fourth scan (90 s after deflation of cuff) were significantly associated with the CRP levels (the third: beta=-0.054, S.E.=0.027; P=0.028; the fourth: beta=-0.065, S.E.=0.026; P=0.016). The multiple regression models showed that CRP was the only significant predictor of artery diameter changes (%) in these two scans. The CRP abnormal group had more coronary artery calcification (calcium scores >5, 16.7 vs. 0%; P=0.036) and more cardiac diastolic dysfunction expressed as deceleration time >240 ms (16.7 vs. 0%; P=0.036). They concluded that elevated serum CRP levels are associated with endothelial dysfunction, coronary artery calcification and cardiac diastolic dysfunction in chronic cocaine users. Meng, Q., Lima, J.A., Lai, H., Vlahov, D., Celentano, D.D., Margolick, J.B. and Lai, S. Elevated C-Reactive Protein Levels are Associated with Endothelial Dysfunction in Chronic Cocaine Users. Int J Cardiol., 88(2-3), pp. 191-198, 2003.

Factors Associated with Accelerated Atherosclerosis in HIV-1-Infected Persons Treated with Protease Inhibitors

Recent evidence suggests that as a group protease inhibitors (PIs) may accelerate certain factors associated with atherosclerosis. The objective of this study was to evaluate the effect of individual PIs (indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir) on certain factors associated with atherosclerosis. Persons who took saquinavir and/or ritonavir were compared with those on other PIs. Between May 2000 and July 2001, the lipid profiles, C-reactive protein (CRP) levels, coronary artery calcium (CAC) scores, and blood cell morphologic parameters were measured in 98 black adult participants aged 25 to 45 years with HIV-1 infection in Baltimore, MD. Among these 98, there were 55 (56.1%) taking PIs. Students' t-test and chi2 test were used to detect the between-group differences. Study participants in both the PI and non-PI groups were similar in age, sex, body mass index, blood pressure, red and white blood cell counts, time since HIV diagnosis, and duration on anti-retroviral therapy. Compared with those who took non-PI regimens, those who took indinavir, nelfinavir, or saquinavir had significantly higher levels of mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH). Those taking any PI had significantly higher total cholesterol and low-density lipoprotein. Those taking nelfinavir, ritonavir, or saquinavir were more likely to have a higher CAC score (>5) than those on non-PI

regimens. There were no differences in the lipid profiles, MCV, MCH, CRP, and CAC between those taking saquinavir and/or ritonavir and those taking other PIs. Overall, the changes noted might lead to anticipation of clinical changes linked to accelerated atherosclerosis in patients on PIs. Lai, S., Lai, H., Celentano, D.D., Vlahov, D., Ren, S., et al. Factors Associated with Accelerated Atherosclerosis in HIV-1-Infected Persons Treated with Protease Inhibitors. AIDS Patient Care STDs,17(5), pp. 211-219, 2003.

Gene Cluster Influences HIV-1 Transmission

MCP-1 (CCL2), MCP-3 (CCL7), and eotaxin (CCL11) are genes for CC chemokines clustered on the long arm of chromosome 17. Previous studies have implicated these chemokines in monocyte recruitment, viral replication, and anti-HIV cytotoxic T cell responses. An epidemiological analysis identified genetic variants influencing HIV-1 transmission and disease progression. In this study, genomic DNA from over 3000 participants enrolled in 5 natural history cohorts in the U.S. were analyzed. Nine single nucleotide polymorphisms (SNP) covering 33 kb containing these 3 genes were genotyped using the polymerase chain reaction. Distortions in allele, genotype, and haplotype frequencies were assessed with respect to HIV-1 transmission and rates of disease progression using categorical and survival analyses. Results indicate that extensive linkage disequilibrium was present. Three SNP (-2136T located in the MCP-1 promoter region, 767G in intron 1 of MCP-1, and -1385A in the Eotaxin promoter) were nearly always found together on a 31 kb haplotype (H7) containing the 3 genes. Frequencies of the 3 variants and the H7 haplotype were significantly elevated (OR, 0.6; P = 0.005-0.01) in uninfected European-Americans repeatedly exposed to HIV-1 through high-risk sexual behavior or contaminated blood products. The findings suggest that although the extensive linkage disequilibrium precludes positive identification of the causal variant, genetic variation in the H7 region influences susceptibility to HIV-1 infection. Since these chemokines do not bind the primary HIV-1 coreceptors CCR5 or CXCR4, the observed influence on transmission may result from activation of the immune system in response to infection rather than receptor blockage. Modi, W., Goedert, J., Strathdee, S., Buchbinder, S., Detels, R., Donfield, S., O'Brien, S. and Winkler, C. MCP-1-MCP-3-Eotaxin Gene Cluster Influences HIV-1 Transmission. AIDS, 17(16), pp. 2357-2365, 2003.

HCV/HIV Co-Infection Associated Hepatocyte Apoptosis Via an "Innocent Bystander Mechanism"

Hepatitis C virus (HCV) infects approximately 40% of HIV patients, and the resulting hepatic dysfunction is the primary cause of death in patients with co-infection. Groopman and his colleagues at Harvard hypothesize that hepatocytes exposed to hepatitis C virus (HCV) and human immunodeficiency virus (HIV) might be injured via an "innocent bystander" mechanism due to cell-surface binding of viral proteins. To assess this, they studied the effects of HCV envelope protein E2 and T-tropic HIV envelope glycoprotein gp120 on hepatocytes and saw potent apoptosis. Either viral protein alone did not induce this effect. HCV E2 and M-tropic HIV gp120 also induced significant apoptosis. Blocking the CXCR4 receptor led to a reduction in apoptosis. HCV E2 and HIV gp120 acted collaboratively to trigger a specific set of downstream signaling events, including up-regulation of the FAS ligand and dephosphorylation of the anti-apoptotic molecule AKT (Munshi et al. 2003a). The investigators (Balasubramanian et al. 2003b) also report that expression of the pro-inflammatory chemokine IL-8, induced by HCV-E2 and HIV-gp120, may be mediated through p38 MAP kinase and SHP2 in an NF-kappa B-independent manner, albeit through AP-1-driven processes. This research suggests that hepatic injury may occur in HCV/HIV co-infection through the induction of novel downstream signaling pathways and provide a rationale for therapeutic interventions that interfere with specific receptors and signaling molecules. Munshi, N., Balasubramanian, A., Koziel, M., Ganju, R.K. and Groopman, J.E. Hepatitis C and Human Immunodeficiency Virus Envelope Proteins Cooperatively Induce Hepatocytic Apoptosis Via an Innocent Bystander Mechanism. J Infect Dis., 188(8), pp. 1192-1204, October 15, 2003; and Balasubramanian, A., Ganju, R.K. and Groopman, J.E. Hepatitis C Virus and HIV Envelope Proteins Collaboratively Mediate Interleukin-8 Secretion through Activation of p38 MAP Kinase and SHP2 in Hepatocytes. J Biol Chem., 278(37), pp. 35755-35766, 2003.

Hepatitis C Virus Infection and Incident Type II Diabetes

Although hepatitis C virus (HCV) infection is more common among adults with type II diabetes, it is uncertain whether HCV precedes the development of diabetes. The investigators performed a prospective (case-cohort) analysis to examine if persons that acquired type II diabetes were more likely to have had antecedent HCV infection when enrolled in a community-based cohort of men and women between the ages of

44 and 65 in the United States (Atherosclerosis Risk in Communities Study [ARIC]). Among 1,084 adults free of diabetes at baseline, 548 had developed diabetes over 9 years of follow-up evaluation. Incident cases of diabetes were identified by using fasting glucose and medical history and HCV antibodies at baseline. A priori persons were categorized as low-risk or high-risk for diabetes based on their age and body mass index, factors that appeared to modify the type II diabetes-HCV infection incidence estimates. The overall prevalence of HCV in this population was 0.8%. Among those at high risk for diabetes, persons with HCV infection were more than 11 times as likely as those without HCV infection to develop diabetes (relative hazard, 11.58; 95% CI 1.39-96.6). Among those at low risk, no increased incidence of diabetes was detected among HCV-infected persons (relative hazard, 0.48; 95% CI 0.05-4.40). In conclusion, pre-existing HCV infection may increase the risk for type II diabetes in persons with recognized diabetes risk factors. Additional larger prospective evaluations are needed to confirm these preliminary findings. Mehta, S.H., Brancati, F.L., Strathdee, S.A., Pankow, J.S., Netski, D., Coresh, J., Szklo, M. and Thomas, D.L. Hepatitis C Virus Infection and Incident Type II Diabetes. Hepatology, 38(1), pp. 50-56, 2003; and Mehta, S.H., Moore, R.D., Thomas, D.L., Chaisson, R.E. and Sulkowski, M.S. The Effect of HAART and HCV Infection on the Development of Hyperglycemia Among HIV-infected Persons. J Acquir Immune Defic Syndr., 33(5), pp. 577-584, 2003.

HIV Infection, HPA Axis, Cytokines and Cognition

Immediately after infection, HIV-1 enters the central nervous system (CNS) and is localized in highest concentration in the hippocampus and basal ganglia. Since these areas are associated with HPA axis and autonomic activities as well as cognition, it has been hypothesized that these functions will be impacted adversely in HIV-1 infection. In the treatment of HIV infection, although the highly potent antiretroviral (HAART) drugs have been effective in reducing peripheral viral load and prolonging life expectancy, these drugs do not cross the blood-brain barrier in therapeutic concentrations. Therefore, it has been proposed that the beneficial effects of HAART on the CNS will be limited. Investigations among seropositive individuals, showing hypo-reactivity of the autonomic system and HPA axis activity, suggest that HIV-1 infection is a model of chronic stress. Furthermore, an elevated baseline TNF-alpha level as well as its increased reactivity to an alpha-adrenergic challenge among HIV-1+ individuals, may lead to additional neurodegeneration. It is proposed that the effects of HIV-1 infection on the brain will have implications for neurocognitive and mental health functioning in seropositive individuals even in patients undergoing HAART therapy. These outcomes may result in the need to develop facilities for long term "care-giving." Kumar, M., Kumar, A.M., Waldrop, D., Antoni, M.H. and Eisdorfer, C. HIV-1 Infection and Its Impact on the HPA Axis, Cytokines, and Cognition. Stress, 6(3), pp. 167-172, 2003.

HIV Prevention Among Drug Users: Outcome of a Network-Oriented Peer Outreach Intervention

A network-oriented HIV prevention intervention based on social identity theory and peer outreach was implemented for HIV positive and negative drug users. A community sample of 250 were randomly assigned to an equal-attention control condition or a multi-session, small-group experimental condition, which encouraged peer outreach; 94% of participants were African American, and 66% used cocaine or opiates. At follow-up, 92% of participants returned, and experimental compared with control group participants were 3 times more likely to report reduction of injection risk behaviors and 4 times more likely to report increased condom use with casual sex partners. Results suggest that psychosocial intervention emphasizing prosocial roles and social identity, and incorporating peer outreach strategies, can reduce HIV risk in low-income, drug-using communities. Latkin, C.A., Sherman, S. and Knowlton, A. HIV Prevention Among Drug Users: Outcome of a Network-Oriented Peer Outreach Intervention. Health Psychol. 22(4), pp. 332-339, 2003.

HIV Treatments Influence Unsafe Sexual and Injection Practices Among IDUs

Researchers sought to determine if HIV treatment-related attitudes are associated with unprotected sex and needle sharing among HIV-seropositive and -seronegative IDUs in Baltimore, Maryland. IDUs participating in a cohort study between December 2000 and July 2001 completed an interviewer-administered questionnaire on attitudes toward HIV treatment and risk behaviors (593 HIV-seronegative, 338 HIV-seropositive), including: perceived HIV transmissibility through unprotected sex and needle sharing, and safer sex and injection fatigue. Logistic regression was used to examine the role of attitudinal factors on needle sharing and unsafe sex. Results

indicate that almost two-thirds of sexually active participants engaged in unprotected sex and approximately half of those injecting drugs shared needles. Among HIV-seropositive IDUs, perception of reduced HIV transmissibility through unprotected sex was significantly associated with unprotected sex (AOR, 3.33; 95% confidence interval (CI), 1.05-10.55). Safer injection fatigue was independently associated with needle sharing among HIV-seropositive IDUs (AOR, 6.55; 95% CI, 1.69-25.39). Among HIV-seronegative IDUs, safer sex fatigue and safer injection fatigue were independently associated with unprotected sex (AOR, 3.12; 95% CI, 1.17-8.35) and needle sharing (AOR, 5.15; 95% CI, 2.33-11.37), respectively. These findings suggest that, among HIV-seropositive IDUs, perceiving that HIV treatments reduce HIV transmission was significantly associated with unprotected sex. Risk reduction fatigue was strongly associated with unsafe sexual and injection behaviors among HIV-seronegative individuals. HIV prevention interventions must consider the unintended impact of HIV treatments on attitudes and risk behaviors among IDUs. Tun, W., Celentano, D., Vlahov, D. and Strathdee, S. Attitudes Toward HIV Treatments Influence Unsafe Sexual and Injection Practices Among Injecting Drug Users. AIDS, 17(13), pp. 1953-1962, September 5, 2003.

HIV 1 Pharmacogenomics in Clinical Practice: Relevance of HIV-1 Drug Resistance Testing

Throughout most of the past century, physicians could offer patients no treatments for infections caused by viruses. The experience with treatment of infection by human immunodeficiency virus (HIV) has changed the way healthcare workers deal with viral infections and has triggered a growing rate of discovery and use of antiviral agents, the first fruits of the expanding genomics revolution. HIV treatment also provides an informative paradigm for pharmacogenomics because control of infection and its consequences is limited by the development of viral drug resistance and by host factors. This report summarizes studies published to date on the significance of testing of HIV-1 resistance to antiretroviral drugs. The only Food and Drug Administration-approved kit is commercially available through Visible Genetics, Inc., for HIV drug resistance testing by genotypic sequencing. Genotypic sequencing alone is most likely an adequate test to assist in the therapeutic decision-making process in cases of previous regimen failure, treatment-naive patients in areas of high prevalence of transmitted resistant virus, and pregnant women. However, in exceptional cases of highly complex mutation patterns and extensive cross-resistance, it may be useful to obtain a phenotype test, because that result may more easily identify drugs to which the virus is least resistant. There are no published clinical trial results on the usefulness of the so-called virtual phenotype over genotypic sequencing alone. The paradigm of viral pharmacogenomics in the form of HIV genotypic sequencing has been not only useful to the treatment of other viral diseases but also important to the real-life implementation of the growing discipline of genomics or molecular medicine. The application of this paradigm to the thousands of potential therapeutic targets that have become available through the various human genome projects will likely change the landscape of diagnosis and management of many diseases, including cancer. Patarca, R., Isava, A., Campo, R., Rodriguez, N.J., Nunez, E., Alter, M., Marchette, M., et al. HIV Pharmacogenomics in Clinical Practice: Relevance of HIV-1 Drug Resistance Testing (Part 2). J Environ Pathology Toxic Oncolo. 22(4), pp. 235-279, 2003.

Impact of Expanding Syringe Access on Sources of Syringes for IDUs in New York City

Beginning in January 2001, it became legal for pharmacies, health care facilities and certain health care providers in New York State (NYS) to sell or provide syringes (10 maximum) without prescription. Cross-sectional survey data from three research projects recruiting active injection drug users (IDUs) in Harlem and the South Bronx (N=682) were analyzed by calendar quarter, from January 2001 through September 2002, to assist in an evaluation of the impact of the program, the Expanded Syringe Access Demonstration Program (ESAP). The outcome variable examined was having used a pharmacy as the source of the last injection syringe. The percent of IDUs who knew that it was legal to buy a syringe from a pharmacy increased over time (25-54%, $P<0.001$). Pharmacy as the source of the last injection syringe increased to approximately 20%, and syringe exchange programs (SEPs) remained the most common source (approximately 50%). In a multiple logistic regression analysis, IDUs who knew it was legal were more likely to have purchased their last syringe from a pharmacy (AOR =4.65, CI =2.58-8.36). Pharmacies were more likely to be used by those who were younger (AOR =0.96, CI =0.93-0.99) and those who were White (AOR =2.55, CI =1.30-5.00), and calendar quarter was a significant independent predictor of pharmacy use (AOR =1.22, CI =1.06-1.40). Overall, these data indicate

that: (a) knowledge about the option of purchasing syringes from a pharmacy has increased, but enhanced dissemination efforts to IDUs, especially particular sub-groups, are needed; and (b) pharmacies were becoming a supplemental source of syringes for active IDUs (in communities served by SEPs). Deren, S., Fuller, C., Pouget, E., Blaney, S., Tortu, S., Kang, S-Y., McMahon, J., et al. Impact of Expanding Syringe Access in New York on Sources of Syringes for Injection Drug Users in Harlem and the Bronx, NYC, USA. Internat J Drug Policy, 14(5-6), pp. 373-379, 2003.

Iron-deficiency Anemia and the Cycle of Poverty Among HIV-Infected Women in the Inner City

The prevalence of iron-deficiency anemia appears to be extremely high among female injection drug users in the inner city who have HIV and/or HCV infections. Iron deficiency and its associated anemia may contribute to reduced energetic efficiency, lower aerobic capacity, decreased endurance, and fatigue. In practical terms, the functional limitations of iron deficiency and iron-deficiency anemia may affect the ability of women to participate in work, school, social, and family activities. Iron deficiency may contribute to the cycle of poverty in the inner city by limiting the ability of women to work, earn money, and afford iron-rich sources of food. Although iron supplementation may prevent or treat iron deficiency, the use of iron supplements needs to be approached with caution in women with HIV and HCV infections. Semba, R. Iron-Deficiency Anemia and the Cycle of Poverty Among Human Immunodeficiency Virus-Infected Women in the Inner City. Clin Infect Dis.,37 Suppl 2: S105-111, 2003.

Longitudinal Patterns of Drug Injection Behavior in the ALIVE Study Cohort, 1988-2000

The objective of this study was to characterize longitudinal patterns of drug injection behavior for individuals and to identify their early determinants. Participants were 1,339 IDUs recruited into the AIDS Link to Intravenous Experience (ALIVE) Study in Baltimore, Maryland, through community outreach efforts. The study was initiated in 1988, and follow-up continued through 2000, with semiannual visits. Patterns of self-reported drug injection (yes/no) were defined for each participant, based on the number of drug-use transitions. The effect of baseline factors was assessed using multinomial logistic regression models. Over the 12-year study period, four patterns were noted: 29% of participants remained persistent drug injectors, 20% ceased injection, 14% relapsed once, and 37% had multiple transitions. Persistent injectors had the shortest follow-up and the highest mortality. For persons who changed their behavior, 3.4 years elapsed before their first cessation attempt, on average. Factors differentiating the groups included history of incarceration, young age, participation in drug treatment programs, recent overdose, and commercial sex. The observed long-term injection patterns are consistent with the view of drug addiction as a chronic disease. This view emphasizes the need for prolonged efforts to sustain cessation and to prevent adverse health and social outcomes among injection drug users. Galai, N., Safaeian, M., Vlahov, D., Bolotin, A. and Celentano, D., ALIVE Study. Longitudinal Patterns of Drug Injection Behavior in the ALIVE Study Cohort, 1988-2000: Description and Determinants. Am J Epidemiol., 158(7), pp. 695-704, 2003.

Opiate Drug Use: A Potential Contributor to the Endocrine and Metabolic Complications in Human Immunodeficiency Viral Disease

Dobs and her colleagues (Cooper et al., Johns Hopkins) report that endocrine and metabolic abnormalities are common in HIV disease and have been attributed to both the disease and its treatment. Other risk factors and behaviors are also important, however. Approximately 28% of new HIV infections occur in users of injection drugs, such as opiates. This paper focuses on the effects of opiates on metabolic and endocrine systems and their potential to contribute to the metabolic and endocrine problems in HIV. Opiate use has been associated with hypogonadism, adrenal dysfunction, reduced bone mineral density and growth-hormone abnormalities. In addition, some studies have suggested abnormalities in glucose and lipid metabolism among opiate users. Although evidence should be viewed as preliminary, these potential abnormalities should be kept in mind when treating opiate-dependent patients infected with HIV. Cooper, O.B., Brown, T.T. and Dobs A. Opiate Drug Use: A Potential Contributor to the Endocrine and Metabolic Complications in HIV Disease. Clin Infect Dis., 37, S132-136, 2003.

Pilot Study to Enhance HIV Care Using Needle Exchange-Based Health Services for Out of Treatment Injecting Drug Users

Out-of-drug treatment active heroin injectors infected with human immunodeficiency

virus (HIV) were recruited to receive HIV therapy by accessing a Community Health Care Van (CHCV) at sites of needle exchange. Subjects were willing to initiate, but were not receiving, recommended HIV therapy and were not interested in formal drug treatment. Antiretroviral therapy regimens were selected and linked to heroin injection timing. Weekly visits were scheduled by CHCV staff to assess adverse side effects and encourage adherence. Of the 13 participants, the mean baseline HIV-1 RNA level and CD4 lymphocyte count were 162,369 (log 5.21) copies per milliliter and 265 cells per milliliter, respectively. By 6 months, the proportion whose HIV-1 RNA was below the limits of detection (<400 copies/mL) was 85% (N = 11); 77% (N = 10) had nondetectable levels by 9 months. By 12 months, 54% (N = 7) had a persistently nondetectable viral load, and the net increase in CD4 lymphocyte count was 150 cells per milliliter. As an additional and unintended benefit of this pilot project, 9 (69%) subjects chose to enter drug treatment after achieving a nondetectable viral load. Entry into drug treatment was associated with durability of viral suppression. This small pilot study suggests that health services based on needle exchange may enhance access to HAART among out-of-treatment HIV-infected IDUs. In addition, it demonstrates that this population can benefit from this therapy with the support of a nontraditional, community-based health intervention. The research results have important implications for the development of strategic community-based programs that address the complex medical needs of out-of-treatment IDUs with HIV disease. They also suggest that when services are organized in a way that is acceptable to drug users, they will utilize them and derive clinical benefit. Altice, F.L., Springer, S., Buitrago, M., Hunt, D.P., and Friedland, G.H. Pilot Study to Enhance HIV Care Using Needle Exchange-Based Health Services for Out-of-Treatment Injecting Drug Users. J Urban Health, 80(3), pp. 416-427, Sept 2003.

Potential Hidden Source Of Hepatitis C Infection Among Non-Injecting Drug Users

Despite a growing awareness of the routes of HCV transmission, a substantial proportion of HCV cases have no identifiable source of infection, especially among non-injection drug users. One explanation is that past and present HCV risk exposures may go unreported in epidemiological surveys. Underreporting of injection drug use, often a stigmatized behavior, may occur due to respondent misrepresentation, inaccurate recall of injection-related behavior, or inadequate questionnaire methodology. Whereas most of the epidemiological studies that have examined non-injection drug use risk factors have focused on potential intranasal routes of HCV transmission (with far less attention paid to possible oral transmission), the opposite is true of biological studies. Virological evidence related to potential oral transmission of HCV is extensive, whereas similar research into potential intranasal transmission is virtually nonexistent. Current evidence neither confirms nor invalidates the existence of oral or intranasal drug-related HCV transmission. Resolution of this question has significant implications for HCV prevention, drug treatment and harm reduction programs, and blood donor screening policies. Although inconclusive, current epidemiological and virological evidence warrants the support of further research in this area. McMahon, J. M. and Tortu, S. A Potential Hidden Source of Hepatitis C Infection Among Non-Injecting Drug Users. Journal of Psychoactive Drugs, 35(4), pp. 455-460, 2003.

Predictors of Sharing Drugs Among IDUs in the South Bronx: Implications for HIV Transmission

HIV may be transmitted in the process of sharing injected drugs, even if all participants have their own syringes. In an effort to gain understanding of the extent and predictors of drug sharing, data were obtained via personal interviews with 1,024 injection drug users from four neighborhoods in the South Bronx. The relationship between drug-sharing and demographic, sexual, and drug-related variables was first examined in a bivariate analysis, and then via multiple logistic regression. Individuals who split drugs were more likely to be female, have had sex with a casual partner, exchanged sex for drugs or other needs, recently smoked crack cocaine, and shared needles. They were less likely to live or inject at their own home or have used a new needle the last time they injected. In a final logistic model, correlates of drug sharing included trading sex, injecting outside one's home, and using borrowed, rented or shared needles. Despite the lack of significance for gender in the final logistic model, females were at high risk of drug sharing because they constituted the great majority of those who exchanged sex. Continuing research is needed to understand how drug-sharing contributes to the spread of HIV and other infections, as are studies of approaches to reducing drug sharing. Prevention strategists and outreach organizations should be aware of the HIV risks inherent in the widespread practice of drug sharing. Fernando, D., Schilling, R.F., Fontdevila, J., El-Bassel, N. Predictors of

Sharing Drugs Among Injection Drug Users in the South Bronx: Implications for HIV Transmission. J Psychoactive Drugs, 35(2), pp. 227-236, April-June 2003.

Prevalence and Risk Factors for HIV Among Sniffers, Short-Term Injectors, and Long-Term Injectors of Heroin

The prevalence of HIV and associated risk behaviors were assessed among three groups of heroin users: long term injection drug users (LTIDUs), new injection drug users (NIDUs), and heroin sniffers (HSs) with no history of injection. HIV seroprevalance was similar among NIDUs (13.3%) and HSs (12.7%). LTIDUs had almost twice as high a level of HIV infection (24.7%). After including drug use and sex behavior variables in logistic regression models, both drug and sexual risk factors remained in the models. Attributable risk percent (APR) from injection for HIV infection among injection drug users was estimated to be 55.7% for LTIDUs and 5.8% for NIDUs. High-risk sex behavior plays an important role in the prevalence of HIV among drug users and accounts for nearly all the infection among NIDUs. Both injection and sexual risk behaviors need to be stressed in HIV prevention and intervention programs aimed at drug users. Chitwood, D.D., Comerford, M. and Sanchez, J. Prevalence and Risk Factors for HIV Among Sniffers, Short-Term Injectors, and Long-Term Injectors of Heroin. J Psychoactive Drugs, 35(4), pp. 445-454, 2003.

Prevalence of Mental Disorders, Psychological Distress, and Mental Health Services Use Among Lesbian, Gay and Bisexual Adults in the United States

Recent estimates of mental health morbidity among adults reporting same-gender sexual partners suggest that lesbians, gay men, and bisexual individuals may experience excess risk for some mental disorders as compared with heterosexual individuals. However, sexual orientation has not been measured directly. Using data from a nationally representative survey of 2,917 midlife adults, the authors examined possible sexual orientation-related differences in morbidity, distress, and mental health services use. Results indicate that gay-bisexual men evidenced higher prevalence of depression, panic attacks, and psychological distress than heterosexual men. Lesbian-bisexual women showed greater prevalence of generalized anxiety disorder than heterosexual women. Services use was more frequent among those of minority sexual orientation. Findings support the existence of sexual orientation differences in patterns of morbidity and treatment use. Cochran, S.D., Sullivan, J.G. and Mays, V.M. Prevalence of Mental Disorders, Psychological Distress, and Mental Health Services Use among Lesbian, Gay, and Bisexual Adults in the United States. J Consulting Clinical Psych., 71(1), pp. 53-61, 2003.

Psychological Distress and Progression to AIDS in a Cohort of IDUs

Researchers investigated whether distress was independently associated with more rapid progression to AIDS among HIV-infected injection drug users (IDUs). A cohort study of IDUs in Baltimore was followed from 1988 through 1999. A total of 451 IDUs met the eligibility criteria of being HIV-seropositive but were AIDS-free at baseline. Cox proportional hazards models were used to investigate progression to AIDS within 2 years of baseline, controlling for CD4 lymphocyte count, HIV-1 viral load, and oral thrush. Of the 451 participants, 76.3% were male and 95.8% were African-American; the median age at enrollment was 34 years. The cumulative incidence of AIDS within 2 years of baseline was 7.1%. In multiple regression analysis, distress was associated with more rapid time to AIDS (adjusted relative hazard [RH] = 2.39; 95% CI: 1.16-4.90). The strongest association was observed among IDUs with the lowest (<200 x 10 /L) CD4 counts (adjusted RH = 4.94; 95% CI: 1.30-18.77). Psychological distress was independently associated with shorter time to AIDS among HIV-infected IDUs, especially among those with the lowest CD4 cell counts, but was not predictive of mortality in this cohort. Further study of the effects of psychological distress on AIDS progression within this population is warranted. Golub, E.T., Astemborski, J.A., Hoover, D.R., Anthony, J.C., Vlahov, D. and Strathdee, S.A. Psychological Distress and Progression to AIDS in a Cohort of IDUs. J Acquir Immune Defic Syndr., 32(4), pp. 429-434, 2003.

Qualitative Evaluation of a Volunteer AIDS Outreach Intervention

Qualitative research can play an important role in explaining outcomes of behavioral interventions and constitutes a largely unrealized potential of ethnographic methods in AIDS research. The Self Help in Eliminating Life Threatening Diseases (SHIELD) intervention trained African American injection drug users to conduct outreach among their drug-using peers and sexual partners. Though the intervention was not targeting adolescents, some participants chose to conduct outreach with youth fortuitously

found on the street. Still others spoke to groups of youth in their homes. This paper seeks to understand the dynamics of outreach encounters between older, drug-using outreach workers and adolescents. Contextual features that were important in determining the quality of outreach encounters with youth included the setting (on the street or in the home), characteristics of the outreach worker such as gender, content of the outreach message, and style of interpersonal communication. Dickson-Gomez, J., Knowlton, A. and Latkin, C. Hoppers and Oldheads: Qualitative Evaluation of a Volunteer AIDS Outreach Intervention. AIDS Behav., 7(3), pp. 303-315, 2003.

Referring Drug Users from an NEP to Treatment with a Mobile Van and LAAM

Researchers evaluated program entry, retention, and early treatment response of needle exchange program (NEP) attenders referred to a drug treatment program using levomethadyl acetate hydrochloride (LAAM). Of 163 referrals, 114 (70%) entered the program, and 84% were retained for at least 90 days. Comparing baseline and follow-up visits after 1 month, there were significant reductions in the Addiction Severity Index subscale scores for drug and alcohol use and legal situation. A 31% and 22% reduction in heroin- and cocaine-positive urine tests was observed, respectively ($p < .0001$). Although LAAM is no longer considered a first line treatment for heroin addiction, these results demonstrate the feasibility of utilizing long-acting agonist therapies such as LAAM to treat opioid dependence among NEP attenders. Kuo, I., Brady, J., Butler, C., Schwartz, R., Brooner, R., Vlahov, D. and Strathdee, S. Feasibility of Referring Drug Users from a Needle Exchange Program into an Addiction Treatment Program: Experience with a Mobile Treatment Van and LAAM Maintenance. J Subst Abuse Treat., 24(1), pp. 67-74, 2003.

Readiness for Cessation of Drug Use Among NEP Attenders and Non-Attenders

Needle exchange programs (NEPs) represent a bridge to drug abuse treatment. NEP attenders tend to have more severe drug problems, however, and may be less ready to reduce their drug use than other drug users. This study investigated the relationship between NEP attendance and readiness for cessation of drug use. Since the period from 1988 through 1989, a community-based sample of IDUs in Baltimore has undergone semiannual interview-administered questionnaires and HIV testing. A total of 288 IDUs completed a questionnaire on readiness for cessation of drug use. Readiness for drug use cessation was assessed from a 28-item validated scale of problem drug use and intention to quit, based on the "stages of change" model. Logistic regression was used to determine factors associated with readiness for cessation of drug use, including socio-demographics, drug use behaviors, and NEP attendance. Thirty percent of respondents attended the NEP in the past month. Stage of change in readiness for cessation of drug use did not differ between NEP attenders and nonattenders (OR= 0.9; 95% CI: 0.5-1.6). Similar proportions of persons recently attending and not attending the NEP were classified as ready to stop drug use (about 30%). In multivariate analysis, readiness for cessation of drug use was associated with speedball injection and previous enrollment in drug treatment but not with NEP attendance. NEP attenders, although exhibiting characteristics consistent with more severe drug dependence, were as motivated for cessation of drug use as were nonattenders. These findings suggest that formal collaboration between NEPs and drug treatment programs could increase the proportion of IDUs in treatment. Henderson, L.A., Vlahov, D., Celentano, D.D. and Strathdee, S. Readiness for Cessation of Drug Use Among Recent Attenders and Non-Attenders of a Needle Exchange Program. J Acquir Immune Defic Syndr., 32(2), pp. 229-237, 2003.

Recruitment of Heterosexual Couples in Public Health Research: A Study Protocol

Public health research involving social or kin groups (such as sexual partners or family members), rather than samples of unrelated individuals, has become more widespread in response to social ecological approaches to disease treatment and prevention. This approach requires the development of innovative sampling, recruitment and screening methodologies tailored to the study of related individuals. In this paper, researchers examine and describe a set of sampling, recruitment and screening protocols developed to enlist urban, drug-using, heterosexual couples into a public health research study. This population is especially hard to reach because they are engaged in illegal and/or stigmatized behaviors. The protocols were designed to integrate adaptive sampling, street-and referral-based recruitment, and screening procedures to verify study eligibility and relationship status. Recruitment of heterosexual couples through one partner, preferably the female, can be an effective enlistment technique. Verification of relationship status is an important component of dyadic research. Comparison of parallel questionnaires administered to each member

of a dyad can aid in the assessment of relationship status. However, multiple independent sources of information should be used to verify relationship status when available. Adaptive sampling techniques are effective in reaching drug-using heterosexual couples in an urban setting, and the application of these methods to other groups of related individuals in clinical and public health research may prove to be useful. However, care must be taken to consider potential sources of sampling bias when interpreting and generalizing study results. McMahon, J., Tortu, S., Torres, L., Pouget, E. and Hamid, R. Recruitment of Heterosexual Couples in Public Health Research: A Study Protocol. BMC Med Res Methodol., 3(1), 24, 2003.

Safer Injection Sites in NYC: A Utilization Survey of IDUs

HIV, HBV, HCV, drug overdose, and other drug-related health problems still pose significant health risks to IDUs and their sex partners, indicating the need for further development of innovative public health interventions. A relatively new intervention implemented in many municipalities throughout the world is the "safer injection site" (SIS). An SIS is a legal facility that allows people to prepare and inject pre-obtained drugs in a hygienic, anxiety-free atmosphere under the supervision of health personnel. In this paper, researchers examine the responses of a sample of IDUs in New York City to whether they would use an SIS should one be implemented in mid-town Manhattan. The SIS would be part of a comprehensive effort to offer needle-exchange, street outreach, testing and counseling, support groups, referral services including drug treatment, and on-site primary and dental services. The results of this study indicate that a large majority of the IDUs sampled would utilize an SIS should one be implemented, and that those most likely to use it are IDUs at the highest risk for contracting or spreading blood-borne diseases such as HIV and hepatitis, and for experiencing a drug overdose. Broadhead, R., Borch, C., Van Hulst, Y., Farrell, J., Villemez, W. and Altice, F. Safer Injection Sites in New York City: A Utilization Survey of Injection Drug Users. J Drug Issues, 22(3), pp. 733-750, 2003.

Secondary Syringe Exchange Among Injection Drug Users

Syringe-exchange programs (SEPs) have proven to prevent the spread of blood-borne pathogens, primarily HIV, among IDUs. In the U.S., only about 7% of IDUs have access to and use SEPs. Some IDUs engage in secondary syringe exchange (SSE), meaning that one IDU (a "provider") obtains syringes at an SEP to distribute to other IDUs ("recipients"). This formative qualitative research was conducted to understand why and how IDUs engage in SSE to aid in the development of a large-scale peer HIV prevention intervention. Interviews with 47 IDUs in Oakland and Richmond, California, indicated that SSE was embedded in existing social networks, which provided natural opportunities for peer education. SSE providers reported a desire to help other IDUs as their primary motivation, while recipients reported convenience as their primary reason for using SSE. Building SSE into SEP structures can facilitate an effective provision of risk reduction supplies and information to IDUs who do not access SEPs directly. Snead, J., Downing, M., Lorvick, J., Garcia, B., Thawley, R., Kegeles, S. and Edlin, B. Secondary Syringe Exchange Among Injection Drug Users. J Urban Health, 80(2), pp. 330-348, 2003.

Study Demonstrates the Risk of Sexual Transmission of HCV is Low

In this study, the risk of sexual transmission of HCV within a sexually active population was measured and found to be low. Sexual behaviors and HCV antibody status were measured in persons seeking repeat HIV testing in San Francisco from October 1997 through March 2000. Among 981 repeat testers, the prevalence of HCV antibody was 2.5%. Among men who have sex with men who denied intravenous drug use (n=746), factors associated with HCV antibody positivity included age greater than 50 years (odds ratio [OR], 8.5; 95% confidence interval [CI], 2.6-27.7), HIV infection (OR, 5.7; 95% CI, 1.6-20.6), and being nonwhite (OR, 3.3; 95% CI, 1.1-10.0). HCV antibody positivity was not associated with sexual risk behaviors. In 576.6 person-years of observation, no new HCV seroconversions occurred (incidence=0 per 100 person-year; 95% CI, 0-.6), whereas 6 new herpes simplex virus-2 infections (2.8 per 100 person-years) and 10 new HIV infections (1.8 per 100 person-years) occurred. Hammer, G.P., Kellogg, T.A., McFarland, W.C., Wong, E., Louie, B., Williams, I., et al. Low Incidence and Prevalence of Hepatitis C Virus Infection Among Sexually Active Non-Intravenous Drug-Using Adults, San Francisco, 1997-2000. Sex Trans Dis., 30, pp. 919-924, 2003.

Substance Use and High-Risk Sex among People with HIV: A Comparison Across Exposure Groups

Substance use is associated with increased risk for HIV transmission by HIV-positive

people to uninfected partners through sexual contact. The largest risk groups for infection, men who have sex with men (MSM) and injecting drug users (IDUs), have high rates of substance use, but little is known about their substance use post-HIV diagnosis. Researchers compared the prevalence of substance use between these two groups and a third group, heterosexual men and women, and tested for differential associations between substance use and sexual behaviors across exposure groups in a national sample of patients in treatment for HIV. Substance use was most prevalent among MSM. Substance use and current dependence were associated with being sexually active among MSM but not IDUs; marijuana, alcohol, and hard drug use were most strongly associated with being sexually active among MSM. Whereas substance use predicted high-risk sex, there were few differences among exposure groups in these associations. Beckett, M., Burnam, A., Collins, R.L., Kanouse, D.E., Beckman, R. Substance Use and High-Risk Sex Among People with HIV: A Comparison Across Exposure Groups. AIDS Behav. 7(2), pp. 209-219, 2003.

Self-Report Data and the Correlates of HIV Status: Conditional and Marginal Approaches

Researchers examined whether relationships between individual characteristics and HIV status can be identified when self-report data are used as a proxy for HIV serostatus results. The analyses use data obtained from HIV serostatus and face-to-face interviews with 7,256 out-of-treatment drug users in 10 sites from 1992 to 1998. Relationships among 17 individual characteristics were determined by comparing and evaluating the fit of both standard and nonstandard loglinear models and evaluating the fit of marginal homogeneity models. The loglinear analyses showed that HIV was related to individual characteristics in 38% of the relationships. In most cases, the strength of the relationships between HIV status and individual characteristics did not differ when HIV status was measured as self-report data. Rindskopf, D., Strauss, S., Falkin, G. and Deren, S. Assessing the Consequences of Using Self-Report Data to Determine the Correlates of HIV Status: Conditional and Marginal Approaches. Multivariate Behav Research, 38(3), pp. 325-352, 2003.

The Impact of Needle-Exchange Programs on the Spread of HIV Among IDUs: A Simulation Study

Researchers sought to determine the impact of the implementation of a needle-exchange program (NEP) on the spread of HIV in an IDU community. They conducted a Monte Carlo simulation study of a theoretical population of 10,000 IDUs. The population was followed monthly from 1984 to 2000. HIV was assumed to be transmitted only by needle sharing. The NEP was introduced in 1989 and evaluated over a period of 11 years. The impacts of the proportion of the population attending the NEP, the risk level of IDUs attending the NEP, the reduction in needle-sharing frequency, and the number of new needle-sharing partners acquired at the NEP on prevalence and incidence of HIV were determined. Increasing the proportion of the population who always attend the NEP and eliminating needle-sharing incidents among IDUs who always attended the NEP were the most effective ways of reducing the spread of HIV. Attracting high-risk users instead of lower risk users to the NEP also reduced the spread of HIV, but to a lesser extent. NEPs are effective at reducing the spread of HIV; even under the worst case scenario of low risk users more likely to attend the NEP, one additional partner per month as a result of attending the NEP, and poor NEP attendance, the estimated prevalence was still less than that from the scenario without an NEP. Under our model, NEPs were shown to reduce the spread of HIV significantly. Efforts should be focused on getting as many IDUs as possible to become regular NEP attenders and stop sharing needles rather than partially reducing the frequency of sharing by a larger number of IDUs. Raboud, J.M., Boily, M.C., Rajeswaran, J., O'Shaughnessy, M.V., and Schechter, M.T. The Impact of Needle-Exchange Programs on the Spread of HIV Among IDUs: A Simulation Study. J Urban Health, 80(2), pp. 302-320, 2003.

The PRECEDE Model for Predicting HIV Risks in Puerto Rican IDUs

The PRECEDE model for health promotion proposes three types of influences on health behaviors: Predisposing, Enabling, and Reinforcing factors. This model was used to examine a range of influences on HIV risk behaviors (sharing syringes and other injection-related paraphernalia) among Puerto Rican injection drug users (IDUs). A total of 698 IDUs were interviewed (438 in East Harlem, New York, and 260 in Bayam, Puerto Rico). Both types of risk behaviors were more prevalent in Puerto Rico. Similarities in influences on syringe sharing behaviors were found in the two sites and included self-efficacy (for reducing injection-related sharing) and norms. Influences on the sharing of other injection-related paraphernalia were primarily enabling factors in both communities, and purchasing drugs with others was the

strongest predictor of paraphernalia sharing. These findings underscore the importance of addressing risks associated with joint drug purchasing in both locations and enhancing efforts to reduce risks among IDUs in Puerto Rico. Deren, S., Kang, S-Y., Rapkin, B., Robles, R.R., Andia, J.F. and Colón, H.. The Utility of the PRECEDE Model in Predicting HIV Risk Behaviors Among Puerto Rican Injection Drug Users. AIDS and Behavior, 7(4), pp. 405-412, 2003.

Women's Drug Injection Practices in the High-Risk Community of East Harlem

This study examined the most recent injection events of injection-drug-using women, determined the prevalence of HIV, hepatitis B (HBV), and hepatitis C (HCV), and identified significant predictors of injection-related risk behaviors. After validation of drug use, 185 street-recruited women participated in structured interviews and were offered HIV, HBV, and HCV testing and counseling. Interview topics included (1) demographic characteristics, (2) characteristics of injection partners (IPs), and (3) relevant situation-specific factors. Prevalence was 28% for HIV infection, 80% for HBV, and 70% for HCV. Injection events were either solitary (n=110) or social (n=75). Most were safe, and 75% of syringes used were obtained from a syringe exchange. Inferential analyses identified two variables that independently predicted unsafe events: (1) respondent had injected previously with her IP, and (2) her IP was her spouse or primary heterosexual partner. Two trends were identified: Injection events in which women felt "very close" to their IP or reported lack of control over injection practices tended to be unsafe. Although most events were safe, safe practices were not adhered to with spouses or primary partners. These findings suggest that syringe exchanges should be supported and may be an ideal setting for interventions targeted to drug-injecting couples. Tortu, S., McMahon, J., Hamid, R. and Neaigus, A. Women's Drug Injection Practices in East Harlem: An Event Analysis in a High-Risk Community. AIDS and Behavior, 7(3), pp. 317-328, 2003.

Zinc Status in Human Immunodeficiency Virus Type 1 Infection and Illicit Drug Use

Zinc deficiency is the most prevalent micronutrient abnormality seen in HIV infection. Low levels of plasma zinc predict a 3-fold increase in HIV-related mortality, whereas normalization has been associated with significantly slower disease progression and a decrease in the rate of opportunistic infections. Studies in Miami, Florida, indicated that HIV-positive users of illicit drugs are at risk for developing zinc deficiency, at least partially because of their poor dietary intake. Zinc deficiency characterized by low plasma zinc levels over time enhances HIV-associated disease progression, and low dietary zinc intake is an independent predictor of mortality in HIV-infected drug users. The amount of zinc supplementation in HIV infection appears to be critical, because deficiency, as well as excessive dietary intake of zinc, has been linked with declining CD4 cell counts and reduced survival. More research is needed to determine the optimal zinc supplementation level in HIV-infected patients, to prevent further burden on an already compromised immune system. Baum, M.K., Campa, A., Lai, S., Lai, H. and Page, J.B. Zinc Status in HIV Type 1 Infection and Illicit Drug Use. Clin Infect Dis., 37, Suppl 2:S117-123, 2003.

Contextual Factors and Other Correlates of Sexual Risk of HIV Among African-American Crack-Abusing Women

This study examined differences in contextual factors, substance use, sexual risk behaviors, and comorbid histories between African-American, out-of-treatment, crack-abusing women who had either a single sexual partner or multiple partners. Bivariate analysis indicated that women with multiple partners were more likely than women with a single partner to be homeless, financially dependent, and to have histories of sexual, physical, and emotional abuse. Women with multiple partners reported higher levels of depression, anxiety, and more symptoms of posttraumatic stress disorder (PTSD). In multiple logistic regression analysis, being unemployed, difficult childhood, and number of days of crack use in the previous 30 days, longer crack runs, and more frequent unprotected fellatio were associated with increased odds of having multiple sexual partners. Being married or living as married was associated with decreased odds of having multiple sexual partners. The importance of assessing contextual and historical factors and implications for future research is discussed. Roberts, A.C., Wechsberg, W.M., Zule, W. and Burroughs, A.R. Addictive Behaviors, 28, pp. 523-536, 2003.

Spiritual Beliefs, World Assumptions, and HIV Risk Behavior Among Heroin and Cocaine Users

Dr. Arthur Margolin and colleagues examined the relationship between spirituality and HIV risk behavior in a sample of 34 inner-city cocaine-using methadone-maintained patients. Spirituality was operationally defined in terms of "life meaningfulness" and included the Santa Clara Strength of Religious Faith (T. G. Plante & M. T. Boccaccini, 1997b) and the World Assumptions Scale (R. Janoff-Bulman, 1989; assessing benevolence, meaningfulness, and worthiness of the self). Hierarchical multiple regression analyses of self-reported drug- and sex-related risk behavior were conducted with sex and race entered as control variables. The full models accounted for 23% and 42% of the variance in drug- and sex-related risk behavior, respectively. Strength of spiritual/religious faith (B = .37) and belief in a benevolent (beta = .50) and meaningful (beta = .46) world were independent predictors of sex-related, but not drug-related, HIV preventive behavior. Avants, S.K., Marcotte, D., Arnold, R., and Margolin A. Psychology of Addictive Behaviors, 17(2), pp. 159-162, June 2003.

A Randomized Clinical Trial of a Manual-Guided Risk Reduction Intervention for HIV-positive Injection Drug Users

Dr. Arthur Margolin and colleagues randomized 90 HIV-seropositive, methadone-maintained injection drug users (IDUs) to an HIV Harm Reduction Program (HHRP+) or to an active control that included harm reduction components recommended by the National AIDS Demonstration Research Project. The treatment phase lasted 6 months, with follow-ups at 6 and 9 months after treatment entry. Patients in both treatments showed reductions in risk behaviors. However, patients assigned to HHRP+ were less likely to use illicit opiates and were more likely to adhere to antiretroviral medications during treatment; at follow-up, they had lower addiction severity scores and were less likely to have engaged in high risk behavior. Findings suggest that enhancing methadone maintenance with an intervention targeting HIV-seropositive IDUs increases both harm reduction and health promotion behaviors. Margolin, A., Avants, S.K., Warburton, L.A., Hawkins, K.A., and Shi. J. Health Psychology, 22(2), pp. 223-228, March 2003.

Methamphetamine Abuse as a Barrier to HIV Medication Adherence Among Gay and Bisexual Men

This paper is a qualitative analysis of HIV-medication adherence from an interview conducted with 23 HIV-infected participants who entered a 16-week behavioral drug treatment program for gay and bisexual male methamphetamine abusers. Participants discussed the effects of their methamphetamine use on their medication adherence. Methamphetamine use as a barrier to adherence was coded into two main themes: (1) planned non-adherence and (2) unplanned non-adherence. Planned non-adherence was a strategy for coping with demanding HIV medication schedules, or was linked to sexual behaviors while using methamphetamine or to fears of interaction effects from mixing methamphetaime with HIV medications. Participants did not define their medication regimen adjustments as non-adherence but as a way to achieve a sense of control over their lives. Unplanned non-adherence was linked to methamphetamine-related disruptions in food and sleep schedules. Medication adherence among persons with HIV infection is important not only because of the effect of non-adherence on an individual's health but also because non-adherence can lead to medication-resistant viral strains. The findings reported here are helpful in designing culturally specific HIV medication adherence interventions for this population. Reback, C.J., Larkins, S., and Shoptaw, S. AIDS Care, 15, pp. 775-785, 2003.

HIV Risk-Reduction Strategies for Substance Abusers: Effecting Behavior Change

Substance abuse has a strong link to HIV/AIDS in the United States. Use and abuse of alcohol and other drugs often reduce inhibitions and encourage engagement in high-risk sexual behaviors that can ultimately result in HIV and AIDS. The HIV/AIDS epidemic in the United States has disproportionately affected minorities with African Americans being the group hardest hit. This article presents some of the behavioral, social, and psychological factors that influence the risk for drug use. It highlights and assesses the effectiveness of HIV risk-reduction strategies developed for drug-using populations and makes recommendations for a more holistic and integrated approach utilizing multiple interventions at multiple levels. Jones, D.J. Journal of Black Psychology, 30(1), pp. 59-77, February 2004.

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

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

Prenatal Drug Exposure and Auditory Brain Response in Infancy

Results from the multi-site Maternal Lifestyle Study (MLS) indicate that prenatal cocaine and/or opiate exposure affects neural transmission in one-month old infants. Auditory brain stem response (ABR) was measured as an indicator of the functional integrity of the central nervous system in 477 exposed and 554 comparison infants matched for race, sex, and gestational age. Study sites were located in Detroit, Memphis, Miami, and Providence. Analyses were conducted for exposed and comparison groups and for level of prenatal cocaine exposure, with adjustment for covariates (alcohol, marijuana, tobacco, gestational age at birth, social class, and site). Heavy prenatal cocaine exposure (³3 days per week, first trimester) was associated with an increase in the I-III, I-V, and III-V interpeak latencies, indicating prolongation of neural transmission. The I-V interpeak latency represents central brain stem conduction time from acoustic nerve to inferior colliculus in the midbrain, and may reflect delayed brainstem maturation. Heavy cocaine exposure was also related to a shorter latency to peak I, possibly indicating hypersensitivity to auditory stimuli. Hypersensitivity, or excitability, has been reported previously for cocaine-exposed infants. Infants with prenatal opiate exposure showed a longer latency to Peak V and a longer III-V interpeak latency, supporting previous findings in small samples of opiate-exposed infants. Lester, B.M., LaGasse, L., Seifer, R., et al. The Maternal Lifestyle Study (MLS): Effects of Prenatal Cocaine and/or Opiate Exposure on Auditory Brain Response at One Month. J Pediatrics, 142, pp. 279-285, 2003.

Cumulative Risk and Parenting Stress for Mothers of Drug-Exposed Infants

This study examined the relationship between cumulative environmental risks, parenting attitudes (parenting stress and potential for child abuse and neglect), and child development in a subgroup of 161 mothers and their drug-exposed infants who were part of a randomized longitudinal study of a home-based early intervention. Mothers with five or more environmental risk factors reported higher parenting stress than women with four or fewer risks and greater potential for child abuse and neglect than women with two or fewer risks at 6 and 18-month visits. Risks included depression, domestic violence, non-domestic violence, family size, homelessness, incarceration, absence of significant other in home, negative life events, psychiatric symptoms, and severity of drug use. Amount of risk was not related to children's mental, motor, or language development at 6, 12, or 18 months of age. Nair, P., Schuler, M.E., Black, M.M., Kettinger, L., and Harrington, D. Cumulative Environmental Risk in Substance Abusing Women: Early Intervention, Parenting Stress, Child Abuse Potential and Child Development. Child Abuse and Neglect, 27, pp. 997-1017, 2003.

Drug-Exposed Infants, Early Home Intervention, and Developmental Outcomes

Researchers at the University of Maryland have reported on effects of a home intervention program for prenatally drug-exposed infants and their families. Biological mother-infant dyads were randomly assigned to a control (n=54) or intervention (n=54) group at 2 weeks postpartum. Control families received brief monthly tracking visits. Intervention families received a developmentally-oriented home intervention, weekly through 6 months, and bi-weekly from 6 to 18 months. Developmental assessments were carried out at 6, 12, and 18 months of age, as were assessments of ongoing maternal drug use. During the 18-month period under study, there were

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no significant group differences in entry into drug treatment, or in reported ongoing use of cocaine and/or heroin, alcohol, or marijuana. Ongoing cocaine and/or heroin use was associated with lower infant mental development scores, and infant mental scores declined over the first 18 months post partum in this inner-city, low socioeconomic status sample. Nonetheless, infants in the intervention group had higher mental and motor development scores than did control infants. The investigators note the importance of including a drug treatment component in future interventions. Schuler, M.E., Nair, P. and Kettinger, L. Drug-Exposed Infants and Developmental Outcome. Archives of Pediatric and Adolescent Medicine, 157, pp. 133-138, 2003.

Amantadine Does Not Modulate Reinforcing, Subjective, or Cardiovascular Effects of Cocaine in Humans

Data from several clinical studies have suggested that amantadine, which has dopaminergic agonist and glutamatergic antagonist effects, may be useful for the treatment of cocaine dependence. The interaction between amantadine and smoked cocaine was examined in 10 cocaine smokers (7 men, 3 women), who participated in a 26-day inpatient study. Participants were maintained on amantadine (0 and 100 mg bid) for 5 days prior to laboratory testing, using a double-blind crossover design. Under each medication condition, participants smoked a sample dose of cocaine base (0, 12, 25, and 50 mg) once, and were subsequently given five choice opportunities, 14 min apart, to self-administer that dose of cocaine or receive a merchandise voucher ($5.00). Each cocaine dose was tested twice under each medication condition, and the order of medication condition and cocaine dose varied systematically. Cocaine produced stimulant-like reinforcing, subjective, and physiological effects. Amantadine maintenance did not modify the choice to self-administer smoked cocaine. The investigators stated that these findings, taken together with the decidedly mixed literature, suggest that amantadine (100 mg bid) will not have a role in the treatment of cocaine dependence. Collins, E.D., Vosburg, S.K., Hart, C.L., Haney, M. and Foltin, R.W. Amantadine Does Not Modulate Reinforcing, Subjective, or Cardiovascular Effects of Cocaine in Humans. *Pharmacol Biochem Behav.*, 76(3-4), pp. 401-407, 2003.

Chronic Drug Use and Reproductive Health Care among Low Income Women in Miami, Florida: A Comparative Study of Access, Need and Utilization

Interviews of low-income women in Miami, FL, addressed reproductive health issues in a stratified, network-referred sample of chronic drug users (CDUs) and socially and ethnically similar women who were not CDUs. Women who were not CDUs were significantly more likely to report a regular source of health care than CDUs. About one third of each group reported experiencing reproductive health problems (other than pregnancy) in the 12 months preceding their interview. Chronic drug users were twice as likely to report that these problems remained untreated. Measures of use of preventive services (physical exam, breast exam, pelvic exam, family planning visit) consistently showed lower use by CDUs. A higher proportion of women who were not CDUs reported pregnancies in the 12 months preceding interview. The 32 pregnant CDUs were much less likely to have received prenatal care than the 42 pregnant women who were not CDUs. For women who reported a pregnancy in the year preceding interview, logistic regression analysis showed a strong and robust negative effect of being a CDU on receiving prenatal care even when the effects of having a usual source of care and having third-party coverage were controlled. Crandall, L.A., Metsch, L.R., McCoy, C.B., Chitwood, D.D. and Tobias, H. Chronic Drug Use and Reproductive Health Care among Low Income Women in Miami, Florida: A Comparative Study of Access, Need and Utilization. J Behav Health Serv and Res., 30(3), pp. 321-331, 2003.

Relapse in Outpatient Treatment for Marijuana Dependence

The current study provides an initial examination of lapse and relapse to marijuana use among 82 individuals who achieved at least 2 weeks of abstinence during outpatient treatment for marijuana dependence. Seventy-one percent used marijuana at least once (i.e., lapsed) within 6 months of initial abstinence, averaging 73 days (SD = 50) till lapsing. Similarly, 71% of those who lapsed, relapsed to heavier use defined as at least 4 days of marijuana use in any 7-day period. Early lapses were more strongly associated with consequent relapse. Previous studies have noted that marijuana-dependent outpatients experience difficulty initiating abstinence from marijuana much as do those dependent on other substances. The present data suggest that these similarities extend to difficulty maintaining abstinence. Moore, B.A. and Budney, A.J. Relapse in Outpatient Treatment for Marijuana Dependence. J Subst Abuse Treat., 25(2), pp. 85-89, 2003.

The Time Course and Significance of Cannabis Withdrawal

Researchers at Vermont University report that withdrawal symptoms following cannabis cessation are comparable to tobacco and other withdrawal syndromes. Withdrawal symptoms following cessation of heavy cannabis (marijuana) use have been reported, yet their time course and clinical importance have not been established. A 50-day outpatient study assessed 18 marijuana users during a 5-day smoking-as-usual phase followed by a 45-day abstinence phase. Parallel assessment of 12 ex-users was obtained. A withdrawal pattern was observed for aggression, anger, anxiety, appetite, decreased body weight, irritability, restlessness, shakiness, sleep problems, and stomach pain. Onset occurred between days 1-3, peak effects between days 2-6, and most effects lasted 4-14 days. The magnitude and time course of these effects appeared comparable to tobacco and other withdrawal syndromes. These effects likely contribute to the development of dependence and difficulty stopping use. DSM criteria for "cannabis withdrawal" are proposed. Budney, A.J., Moore, B.A., Vandrey, R.G., Hughes, J.R., et al. The Time Course and Significance of Cannabis Withdrawal. J Abnormal Psych., 112(3), pp. 393-402, 2003.

Treatment of Marijuana Dependence: A Review of the Literature

Until recently, relatively little research has focused on the treatment of marijuana abuse or dependence; however, marijuana use disorders are now receiving increased attention. This paper reviews the initial clinical trials evaluating the efficacy of outpatient treatments for adult marijuana dependence. Findings from five controlled trials of psychotherapeutic interventions suggest that this disorder appears responsive to the same types of treatment as other substance dependencies. Moreover, these initial studies suggest that many patients do not show a positive treatment response, indicating that marijuana dependence is not easily treated. Strengths and weaknesses of the data are presented. Preliminary data from less controlled studies relevant to the treatment of marijuana dependence are discussed to suggest future research areas. Although very few studies on treatment for marijuana abuse and dependence have been completed, the initial reports identify promising treatment approaches and demonstrate a need for more research on the development of effective interventions. McRae, A., Budney, A. and Brady, K. Treatment of Marijuana Dependence: A Review of the Literature. J Subst Abuse Treat., 24(4), pp. 369-376, 2003.

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

Research Findings - Epidemiology and Etiology Research

Predictors of Adolescent Substance Use in Children with ADHD

This study followed up 142 subjects who had been assessed and treated for attention deficit/hyperactivity disorder (ADHD) in childhood, to assess risk for substance use in adolescence (ages 13-18) compared with matched adolescent controls without ADHD. As noted by the authors, previous studies of the risks associated with ADHD have resulted in discrepant findings, particularly when conduct problems, often associated with ADHD, are taken into account. To help address these issues, this study assessed the roles of two key components of ADHD, inattention and impulsivity-hyperactivity, separately, as well as the roles of persistence of ADHD and of the development of conduct disorder in adolescence. Several important findings emerged. First, in this sample, childhood ADHD was associated with greater use and abuse of alcohol, and heavier and earlier use of tobacco and other drugs. Second, childhood inattention was a significant predictor of most categories of adolescent substance use even when controlling for childhood impulsivity-hyperactivity and oppositional-conduct disorder symptoms (ODD/CD), although the latter predicted illicit drug use. Third, while those ADHD subjects who developed conduct disorder showed the highest levels of substance use and related problems, those with persistent ADHD without conduct disorder also showed significantly elevated levels of substance use. Thus, this study suggests that ADHD may pose a risk for substance use problems separately from its relationship to conduct disorder, and points to particular features, namely severe inattention problems and persistence of ADHD symptoms into adolescence, that may identify those at elevated risk. Molina, B.S.G., and Pelham, W.E. Childhood Predictors of Adolescent Substance Use in a Longitudinal Study of Children with ADHD. J Abnorm Psychol, 112, pp. 497-507, 2003.

Prevalence and Development of Psychiatric and Substance Use Disorders in Childhood and Adolescence

The authors used longitudinal data from a representative community sample of 1420 nine through sixteen year olds, to describe the prevalence and continuity of psychiatric disorders over time. Several significant findings were reported. By age 16, over a third (36.7%) of subjects met DSM-IV criteria for one or more disorders, and those with one disorder were 3 times more likely to have the same or another diagnosis at later waves. Rates of comorbidity were high, with one quarter (25.5%) diagnosed with 2 or more disorders at one time. Almost all disorders showed significant rates of continuity over time. Continuity from one diagnosis to another was significant between anxiety and depressive disorders, and from anxiety and conduct disorder to substance abuse, in girls. Substance use disorders increased with age and were more prevalent in boys than girls. The sample, while representative, does not represent the American population, but prevalence rates were comparable to those in several other studies. The notable points from this study relate particularly to the findings regarding continuity: that in a representative sample, only anxiety and conduct disorders predicted substance use disorders, and only in girls. This has important implications for improving our understanding of the etiology of adolescent drug abuse, for identifying those children at particular risk, and for developing and testing effective childhood interventions to prevent later drug abuse. Costello, E.J., Mustillo, S., Erkanli, A., Keeler, G., and Angold, A. Prevalence and Development of Psychiatric Disorders in Childhood and Adolescence. Arch Gen Psychiatry, 60, pp. 837-844, 2003.

Poverty Influences Some Forms of Child Psychopathology

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The authors took advantage of a natural experiment to test the role of social selection vs. social causation of childhood psychopathology. During the course of their longitudinal study, the opening of a casino on an Indian reservation provided an income supplement to a subsample that moved 14% of the study families out of poverty. The findings confirmed previous reports of an inverse relationship between family income and child psychiatric diagnoses and symptoms, in both Indian and non-Indian children. Those children whose families moved out of poverty with the income supplement demonstrated drops in their psychiatric symptoms to the low levels of children who were never poor, while those whose families remained poor continued to have the high levels of symptoms seen in other poor children. These findings applied specifically to conduct and oppositional defiant disorders; anxiety and depressive disordered showed no significant change. Findings were replicated in non-Indian children whose families moved out of poverty during the same period. Given that this income supplement was not the result of family characteristics, the findings support a social causation theory for behavioral disorders in children. Because conduct and oppositional defiant disorders are strongly associated with risk for drug abuse, this study has significant implications for understanding drug abuse etiology and targeted interventions. Costello, E.J., Compton, S.N., Keeler, G. and Angold, A. Relationships Between Poverty and Psychopathology. JAMA, 290, pp. 2023-2029, 2003.

Genetic and Environmental Risk Factors in Men and Women

The authors used data on psychiatric syndromes from interviews with 5600 male-male and female-female twin pairs from a population-based registry to study patterns of comorbidity. They sought to gain better understanding of the contributions of genetic and environmental risk factors to etiology of internalizing and externalizing disorders, and to test for gender differences in these patterns and contributions. Model-fitting identified two genetic factors, one for externalizing disorders (alcohol and drug dependence, antisocial and conduct disorders) and one for internalizing disorders (major depression, generalized anxiety disorder, and phobia). Among internalizing disorders, one genetic factor loaded heavily for major depression and generalized anxiety, the other for phobia. Of the ten syndromes studied, alcohol dependence and drug abuse/dependence appear to be influenced by specific genes. Shared environmental factors were strongest for conduct disorder and antisocial behavior. Of note, all of the models showed no sex differences. Thus, genetic factors appear to underlie the tendency toward psychiatric comorbidity, and development of specific disorders may be related to individual experiences; however, for the drug use disorders, there appear to be specific genes as well, and the strongest psychiatric risk factors (conduct and antisocial disorders) are the most influenced by shared environmental influences. These findings support both genetic and environmental approaches to understanding and intervening with drug abuse vulnerability. Kendler, K.S., Prescott, C.A., Myers, J. and Neale, M. The Structure of Genetic and Environmental Risk Factors for Common Psychiatric and Substance Use Disorders in Men and Women. Arch Gen Psychiatry, 60, pp. 929-937, 2003.

Co-Occurrence of Alcohol, Drug, and Psychiatric Disorders Among U.S. Residents of Mexican Origin

This study examined comorbidity in Mexican immigrants and US-born Mexican-Americans, an ethnic group who comprise 66% of the Latino population of the US. Subjects were selected from urban and rural areas of Fresno County, CA; and the weighted sample was composed of 60% immigrants and 40% US-born and had 46.6% females and 53.4% males. Comorbidity refers to co-occurrence of any two diagnoses; whereas the term dual diagnoses refers to co-occurrence of a substance abuse disorder (alcohol or drug) and non-substance use psychiatric disorder. The dominant pattern observed was dual diagnoses of a non-substance use psychiatric disorder with alcohol abuse or dependence. Co-occurring lifetime rates of alcohol or other drug disorders with non-substance use psychiatric disorders, or both, were 8.3% for men and 5.5% for women and were 12.3% for the US born and 3.5% for immigrants. Alcohol abuse or dependence with co-occurring psychiatric disorders is a primary disorder among Mexican-origin adult males (7.5% lifetime prevalence). Mexican-origin females have negligible rates of alcohol or drug abuse and dependence disorders. US-born men and women are almost equally likely to have co-occurring disorders involving substances. Among all sex and nativity subgroups, individuals with drug abuse or dependence disorders have very high comorbidity rates. Comorbidity is expected to increase in the Mexican-origin population owing to acculturation effects; therefore, early preventive interventions and culturally competent treatment services for low-income youth and adults are needed. Vega, W.A., Sribney, W.M. and Achara-Abrahams, I. Co-Occurring Alcohol, Drug, and Other Psychiatric Disorders Among Mexican-Origin People in the United States. Am J Public Health, 93(7), pp. 1057-

1064, 2003.

An Enumeration Approach for Prevalence Estimates of Cocaine and Heroin Users and Operatives

Better estimates of crack, powder cocaine and heroin using and/or selling populations are needed to provide appropriate levels of services to these hidden populations. The prevalence of crack, powder cocaine, and heroin users and operatives (drug dealers and others involved in drug sales and distribution activities) was estimated in the Central Harlem area of New York City using an enumeration method. Central Harlem was divided into 45 primary sampling units (PSUs), and two years of police department data on drug-related allegations were used to classify the PSUs as having high, middle, and low levels of allegations. In 9 randomly selected PSUs (three from each level), interviewers used chain referral sampling procedures that were steered by using a nomination technique. Within sampled PSUs, 657 respondents nominated 5756 others for a total of 6413. Seven indicators identified 1007 unique individuals among 2835 nominated by two or more respondents, totaling to 4585 unique persons. These drug users and operatives were divided by the total number of persons in these PSUs according to the 1990 census to estimate the number of drug users and distributors in the 36 PSUs not sampled and for all 98725 residents of Central Harlem. Approximately 13.4% of Central Harlem residents were estimated to be users of crack, powder cocaine and/or heroin with no roles in drug distribution. Approximately 6.7% of Central Harlem residents were estimated to be operatives of these drugs, some of whom may also have been users. This study demonstrates that enumeration techniques can used to project prevalence estimates for crack, powder cocaine, and heroin users and operatives in a large urban geographic area. Rees Davis, W., Johnson, B.D., Randolph, D., and Liberty, H.J. An Enumeration Method of Determining the Prevalence of Users and Operatives of Cocaine and Heroin in Central Harlem. Drug Alcohol Depend, 72(1), pp. 45-58, 2003.

Comorbid Substance Use and Psychiatric Disorders Among Juvenile Detainees

To estimate the prevalence of comorbid psychiatric disorders in the past 6 months, the Diagnostic Interview Schedule for Children Version 2.3 was administered to 1,829 randomly selected detainees (1172 males, 657 females, aged 10-18) in the Cook County Juvenile Temporary Detention Center. Overall, more than 10 percent of males and almost 14 percent of females had a substance abuse disorder and a major mental disorder, such as psychosis, manic episode, or major depressive episode. Approximately 600 of these 1,829 young people had substance abuse disorders and behavioral disorders. In the subset of 305 youth with major mental disorders, more than 50 percent of females and nearly 75 percent of males also reported a substance abuse disorder. When the subset of 874 youth with substance abuse disorders was examined, 30 percent of the females and 21.4 percent of the males were found to also have a major mental disorder. About 25 percent of juvenile justice system detainees with major mental disorders reported that their psychiatric problem preceded their substance abuse disorder by more than 1 year. Almost 67 percent of females and more than 54 percent of males developed their mental and drug abuse disorders within the same year. Overall, these findings point to the need for assessment and treatment of juvenile detainees with comorbid substance abuse and mental health disorders. Abram, K.M., Teplin, L.A., McClelland, G.M. and Dulcan, M.K. Comorbid Psychiatric Disorders in Youth in Juvenile Detention. Arch Gen Psychiatry, 60(11), pp. 1097-1108, 2003.

Executive Functioning and Temperament in Adolescent Females with Substance Use Disorders

This study was designed to assess the role of temperament in the association between executive functioning (EF) and adolescent females substance use disorders (SUD). The sample included 340 drug using females between 14 and 18 years of age. This included 240 adolescent females with SUD diagnoses. Results suggest that temperament mediates the association between EF and adolescent females' drug use. Furthermore, EF and temperament interact to account for unique variance in drug use involvement, above and beyond the main effects of age, EF, and temperament. Interestingly, the investigators found that low EF was only significantly related to increased drug use involvement for participants with a "good" temperament and not for those with a difficult temperament. Participants with a difficult temperament exhibited significantly greater drug use involvement than those with a good temperament. In conclusion, these findings suggest that a difficult temperament may be a more important risk factor for adolescent females' drug use than low EF. Giancola, P.R. and Mezzich, A.C. Executive Functioning, Temperament, and Drug Use

Involvement in Adolescent Females with a Substance Use Disorder. J Child Psychol Psychiatry, 44(6), pp. 857-866, 2003.

Predictive Value of Mild Disorders: Implications for DSM-V

High prevalence estimates in epidemiological surveys have led to concerns that the DSM system is overly inclusive and that mild cases should be excluded from future DSM editions. The purpose of this study is to demonstrate that the DSM-III-R disorders in the baseline National Comorbidity Survey (NCS) can be placed on a severity gradient that has a dose-response relationship with outcomes assessed a decade later in the NCS follow-up survey (NCS-2) and that no inflection point exists at the mild severity level. The NCS was a nationally representative household survey of DSM-III-R disorders in the 3-year time span 1990-1992. The NCS-2 is a follow-up survey of 4375 NCS respondents (76.6% conditional response rate) reinterviewed in 2000 through 2002. The NCS-2 outcomes include hospitalization for mental health or substance disorders, work disability due to these disorders, suicide attempts, and serious mental illness. Twelve-month NCS/DSM-III-R disorders were disaggregated into 3.2% severe, 3.2% serious, 8.7% moderate, and 16.0% mild case categories. Results indicated that all 4 case categories were associated with statistically significantly elevated risk of the NCS-2 outcomes compared with baseline noncases, with odds ratios of any outcome ranging monotonically from 2.4 to 15.1 for mild to severe cases. This graded association between mental illness severity and later clinical outcomes suggests that the retention of mild cases in the DSM is important to represent the fact that mental disorders vary in severity, and that cost-effectiveness analysis should include recognition that treatment of mild cases might prevent a substantial proportion of future serious cases. Kessler, R.C., Merikangas, K.R., Berglund, P., Eaton, W.W., Koretz, D.S., and Walters, E.E. Mild Disorders Should Not Be Eliminated From the DSM-V. Arch Gen Psychiatry, 60, pp. 1117-1122, 2003.

Liability to Substance Use Disorders: An Overview

Variation in the risk for and severity of substance use disorders (SUD) in the population is caused by multiple organismic (genetic, biochemical, psychological) and environmental factors. Whereas drug- or drug-class-specific liability mechanisms exist, a substantial proportion of variance in the risk is shared between specific liabilities, reflecting mechanisms that determine common liability to SUD. Data from epidemiologic, clinical, psychological, physiological, biochemical, and family and genetic studies reviewed in this paper indicate the existence of mechanisms and characteristics shared in common by liabilities to SUD related to different drugs. These mechanisms can be conceptualized as common liability to SUD, a latent trait accounting for a substantial portion of variation in SUD risk and severity and determined by all factors influencing the probability of SUD development. Vanyukov, M.M., Tarter, R.E., Kirisci, L., Kirillova, G.P., Maher, B.S., Clark, D.B. Liability to Substance Use Disorders: 1. Common Mechanisms and Manifestations. Neurosci Biobehav Rev, 27, pp. 507-515, 2003.

Liability to Substance Use Disorders: A Quantitative Approach

Liabilities to complex disorders present difficulties in measurement related to the arbitrariness of diagnostic threshold definitions and problems with discrimination between trait values, especially within the 'normal' individuals. The inability to quantitatively estimate the risk for a disorder, such as substance use disorders (SUD), is an obstacle for studying etiological (e.g. genetic) mechanisms and developing efficient prevention and treatment measures. Based on the concept of common liability to SUD, this paper delineates an application of the longitudinal family/high-risk design and item response theory to the development of a continuous index of liability. The method has been tested in both simulation study and empirical data. The approach described affords the opportunity to quantitatively estimate the risk for SUD at an early age and before any drug exposure. This method is also applicable to measuring liabilities to other complex disorders, especially those with relatively late onset. Vanyukov, M.M., Kirisci, L., Tarter, R.E., Simkevitz, H.F., Kirillova, G.P., Maher, B.S. and Clark, D.B. Liability to Substance Use Disorders: 2. A Measurement Approach. Neurosci Biobehav., Rev 27, pp. 517-526, 2003.

Cortisol, Personality, and Aggressive Behavior in Adolescent Males

This study tested the hypothesis that low resting salivary cortisol concentration in preadolescent boys would be associated with aggressive behavior later in adolescence. It also tested whether personality traits mediate this relation. Resting salivary cortisol concentrations from 314 boys (10-12 years of age) were assayed. When the boys reached 15 to 17 years of age these concentrations were analyzed in

the context of personality traits, measured with the Multidimensional Personality Questionnaire, and aggressive behavior, measured with the Youth Self-Report inventory. Low cortisol in preadolescence was associated with low harm avoidance, low self-control, and more aggressive behavior 5 years later, during middle adolescence. Low self-control was identified as the primary personality mediator of the relation between low cortisol and later aggressive behavior. Results suggest that low resting cortisol concentrations in adolescent males are predictive of clinically important personality factors. Shoal, G.D., Giancola, P.R. and Kirillova, G.P. Salivary Cortisol, Personality, and Aggressive Behavior in Adolescent Boys: A 5-Year Longitudinal Study. J Am Acad Child Adolesc Psychiatry, 42, pp. 1101-1107, 2003.

Meta-Analysis of Models of Comorbidity using Family Study Data

Knowledge regarding the causes of comorbidity between two disorders has a significant impact on research regarding the classification, treatment, and etiology of the disorders. Two main analytic methods have been used to test alternative explanations for the causes of comorbidity in family studies: biometric model fitting and family prevalence analyses. Unfortunately, the conclusions of family studies using these two methods have been conflicting. This meta-analysis of 42 family studies examined the validity of family prevalence analyses in testing alternative comorbidity models: the alternate forms model, the correlated liabilities model, and the three independent disorders model. Results suggest that some analyses may be valid tests of the alternate forms model (i.e., two disorders are alternate manifestations of a single liability), but that none of the analyses are valid tests of the correlated liabilities model (i.e., a significant correlation between the risk factors for the two disorders) or the three independent disorders model (i.e., the comorbid disorder is a third, independent disorder). Findings suggest that family studies using family prevalence analyses may have made incorrect conclusions regarding the etiology of comorbidity between disorders. Rhee, S.H., Hewitt, J.K., Corley, R.P., and Stallings, M.C. The Validity of Analyses Testing the Etiology of Comorbidity Between Two Disorders: A Review of Family Studies. J Child Psychol Psychiatry, 44, pp. 612-636, 2003.

Perceived Temptation to Use Drugs and Actual Drug Use Among Women

Perceived level of temptation to use drugs under specified circumstances has received little or no attention. Data from this study of 125 adult women drug users residing in the Atlanta, Georgia metropolitan area are derived from Project FAST - an intergenerational study of drug use among 250 women conducted between 1997 and 2000 that examined substance use, psychological and psychosocial functioning, and a variety of HIV-related risk behaviors among women and their adult daughters. Four dyad groups were identified with approximately equal numbers of women being recruited for each dyad group: (1) drug-using mothers who had drug-using daughters; (2) drug-using mothers with non-using daughters; (3) drug-using daughters with non-using mothers; and (4) non-using mothers who had non-using daughters. The study described here examined 16 specific items assessing temptations to use drugs and compared perceptions to actual drug use behaviors. Marital status was the only statistically significant predictor of women's drug use. Women's age, race, educational attainment, childhood maltreatment history, psychosocial profiles, exposure to substance abusers, and interpersonal relationships had no significant impact upon the amount of drugs used, once the effects of their levels of temptation to use drugs and marital status were known and taken into account. It may be that the effects of women's temptations to use drugs under specified circumstances may be related more closely to the actual contexts in which they find themselves having to make decisions about whether or not to use drugs than other variables that could also affect such decisions. Items assessing their temptation level are more salient to their drug use process than whether or not they belonged to a particular racial/ethnic group and whether or not they have strong interpersonal support networks. Five key findings have specific implications for substance abuse prevention and treatment programs: (1) women who were married or living as married reported nearly twice the amount of drug use as women whose marital status was other-than-married; (2) greater drug use was reported by people who said that they would be tempted to use drugs if they were hanging around in their neighborhood; (3) greater drug use was reported by women who said that they would be tempted to use drugs when they were celebrating and feeling happy; (4) women who said that they would be tempted to use drugs when they were waking up and facing a difficult day reported more drug use than those who said that they would not be tempted to use drugs under such a circumstance; and (5) the greatest drug use was reported by women who felt that they would be tempted to use drugs if they found themselves in a place where everyone else was using drugs. These findings

suggest that there is a close relationship between temptations to use drugs in specific circumstances and actual drug usage. Women who reported the greatest amounts of drug use tended to have the greatest need for training/education to help them to acquire the skills to avoid using drugs in various situations. Klein, H., Elifson, K.W., and Sterk, C.E. Perceived Temptation to Use Drugs and Actual Drug Use Among Women, J Drug Issues, Winter, pp. 161-191, 2003.

Religiosity and Drug Use Disorders

This study sought to clarify the dimensions of religiosity and relate these dimensions to risk for psychiatric and substance use disorders, using a population-based sample. Factor analysis of 78 questionnaire items on religiosity revealed seven underlying factors. Social religiosity and thankfulness were associated with reduced risk for both internalizing and externalizing and drug use disorders. General religiosity, belief in an involved God, forgiveness, and viewing God as a judge were all associated with reduced risk for externalizing (including drug use) disorders, and unvengefulness was associated with reduced risk for internalizing disorders. Of note, these findings, in a population-based sample, conform with previous reports that high levels of religious involvement are associated with reduced risk for drug use disorders. While this study cannot illuminate the possible causal relationships between these characteristics, it lays groundwork for further exploration. Kendler, K.S., Liu, X., Gardner, C.O., McCullough, M.E., Larson, D., and Prescott, C.A. Dimensions of Religiosity and Their Relationship to Lifetime Psychiatric and Substance Use Disorders. Am J Psychiatry, 160, pp. 496-503, 2003.

Recanting of Substance Use Reports In a Longitudinal Prevention Study

This study analyzed recanting of substance use reports for lifetime use of alcohol, alcohol to get drunk, cigarettes, marijuana and cocaine in an 8-wave panel study designed to evaluate the Drug Abuse Resistance Education (DARE) program in the state of Illinois. Although this phenomenon has been identified elsewhere, the current analysis of recanting is a unique attempt to track this behavior over the entire course of adolescence. Overall, rates of recanting for specific drugs was extremely high, ranging from 45% for lifetime reports of alcohol use to 81% for lifetime reports of cocaine use. Most recanting occurred in the wave immediately following the wave of first disclosure. Paralleling results from other studies, race/ethnicity was an important correlate of recanting in both bivariate and multivariate analyses. African American respondents had higher rates of recanting than White subjects. Even after controlling for the number of follow-up waves, the later the wave of first disclosed lifetime drug use, the lower the probability that drug use would be recanted ever (for all substances) or in the wave immediately following first disclosure (for reports of ever having been drunk or for lifetime marijuana or cocaine use). One important limitation of this study is that it is focused on a sample attending schools in one particular state (Illinois) in the United States during one particular time period. Fendrich, M. and Rosenbaum D.P. Recanting of Substance Use Reports in a Longitudinal Prevention Study. Drug Alcohol Depend, 20, pp. 241-253, 2003.

Marijuana Use Affects Completion of High School

Cross-sectional research has shown a link between adolescent substance use and educational motivation. The purpose of the current study was to examine this link in a longitudinal sample of African American youth. The study examined the interrelationships between alcohol and both marijuana use and school motivation over the high school years and their effect on graduation in 681 African American adolescents (50.8% female). School motivation was shown to relate to subsequent alcohol use throughout high school and marijuana use early in high school. School motivation did not affect graduation status, but alcohol and marijuana use were related to a lower likelihood of graduating from high school. Some gender differences and differences among those who had tried alcohol or marijuana at the first wave as opposed to those who had not tried each substance were found. The findings support a systems model where school experiences can affect substance use, which, in turn, can affect the completion of high school. Zimmerman, M.A., Schmeelk-Cone, K.H. A Longitudinal Analysis of Adolescent Substance Use and School Motivation Among African American Youth. J Res Adolesc, 13(2), pp. 185-210, 2003.

Tryptophan Ratio Related to Suicidal Behavior in Prospective Study

A lower ratio of tryptophan to other amino acids in serum (tryptophan ratio), established as an index of serotonin precursor available to the brain, has been shown to be associated with increased suicidal behavior in cross-sectional studies. The purpose of this study was to conduct the first prospective examination of the utility of

the tryptophan ratio along with clinical variables in predicting suicidal behavior in high-risk and reference adolescents. Adolescents with alcohol use disorders (AUDs) and prior suicidal attempts (n=20), adolescents with AUDs without suicide attempts (n=20), and community controls with neither of these characteristics (n=20) were matched on demographic variables. These groups were not significantly different on the tryptophan ratio at baseline. Of 56 subjects who completed follow-up assessments, six had suicidal behavior in the follow-up period. The tryptophan ratio, along with demographic and clinical variables, was examined using Cox regression with a backward stepwise variable elimination procedure. In the final model, the tryptophan ratio and major depressive disorder both significantly contributed to the prediction of suicidal behavior. This finding suggests that the tryptophan ratio may improve the identification of adolescents at high risk for suicidal behavior. Clark, D.B. Serum Tryptophan Ratio and Suicidal Behavior in Adolescents: A Prospective Study. Psychiatry Res, 119(3), pp. 199-204, 2003.

Physical and Sexual Abuse, Depression and Alcohol Use Disorders in Adolescents: Onsets and Outcomes

This study examined the relationships among physical and sexual abuse (PS Abuse), major depressive disorder (MDD), and alcohol use disorders (AUD) in adolescence, as well as related young adult outcomes. Adolescents (mean age: 16.4 years; range: 14-18 years) were recruited from clinical and community sources and classified into four groups: (1) AUD+PS Abuse (n=154), (2) AUD only (n=255), (3) PS Abuse only (n=74), and (4) Controls (n=268). Subjects were longitudinally assessed through young adulthood (age 19 years or older). Measures included interview assessments of DSM-IV AUD and MDD, classified as "primary" or "secondary", and questionnaire measures of alcohol consumption and depression. Primary MDD preceded AUD whereas secondary MDD had a later onset than AUD. PS Abuse accelerated the onsets of primary MDD, secondary MDD and AUD. While affected adolescents had typically improved in both alcohol consumption and depression at the young adult assessment, the majority of those with adolescent AUD had AUDs in young adulthood, and MDD remained common in those with a history of PS Abuse. These results indicate that MDD among adolescents with AUD may be partly attributable to PS Abuse. Clark, D.B., DeBellis, M.D., Lynch, K.G., Cornelius, J.R and Martin, C.S. Physical and Sexual Abuse, Depression and Alcohol Use Disorders in Adolescents: Onsets and Outcomes. Drug Alcohol Depend, 69(1) pp. 51-60, 2003.

Racial/Ethnic Differences in Smoking Accounted for, in Part, by Social Influence

Using data from a longitudinal panel of nearly 3000 adolescents to predict current smoking among young adults, this study tested whether considering variables that tap prior social bonds and influences eliminates race/ethnicity as a significant predictor of current smoking. At age 23, African Americans and Asians exhibited substantially lower rates of current smoking than Whites and Hispanics. Controlling for social influences during high school, particularly exposure to siblings and friends who smoked plus parental disapproval of smoking, accounted for these differences. Social bonding variables, in contrast, had a limited effect on these differences. Interventions aimed at decreasing adolescent vulnerability to prosmoking influences, reducing overall levels of peer cigarette use, and helping parents better convey their disapproval of smoking should help curb young adult smoking and diminish racial/ethnic differences in tobacco use. Ellickson, P.L., Perlman, M. and Klein, D.J. Explaining Racial/Ethnic Differences in Smoking During the Transition to Adulthood. Addict Behav., 28(5), pp. 915-931, 2003.

Role Models and Psychosocial Outcomes Among African American Adolescents

The authors examined who 679 African American ninth-graders (aged 14-17 yrs) from urban environments look up to and how their role model choices relate to substance use, delinquency, academic engagement, and psychological well-being. Male adolescents without male role models and females identifying brothers as role models reported the most problem behavior. Adolescents with paternal male role models had the most positive school outcomes, no differences were found in psychological well-being among adolescents in terms of their male role models. The presence of female role models, in contrast, was associated with psychological well-being such that adolescents with maternal role models reported the least distress. Adolescents without female role models had the lowest grades and most negative school attitudes. These findings remained when parental support, family conflict, and father presence in the household were controlled, suggesting role model effects are separate from parenting effects. Findings support and expand on the notion that having someone to

look up to is critical for African American youths' development. Bryant, A.L. and Zimmerman, M.A. Role Models and Psychosocial Outcomes Among African American Adolescents. J Adolesc Res., 18(1), pp. 36-67, 2003.

Predictors of the Transition to Regular Smoking

This study identified predictors of the transition from experimentation to regular smoking in middle adolescence, late adolescence, and young adulthood. Students completed self-report surveys assessing the following potential predictors of the transition to regular smoking from grades 8 to 10, grades 10 to 12, and grades 12 to age 23 years: demographic characteristics, smoking-related attitudes, behaviors and environment, other problem behaviors; academic orientation; parental bonding; and mental health. Regression techniques which adjust for weighting and clustering of observations were used to determine the independent associations of the predictor variables on subsequent smoking status. Risk factors for the transition to regular smoking during middle adolescence included being white, prosmoking attitudes, friend smoking, weak academic orientation, and less parental support. During late adolescence, being African-American was protective, whereas risk factors included prosmoking attitude, drinking, non-intact nuclear family, and less parental support. Risk factors in young adulthood include younger age and prosmoking attitudes. Results point to several smoking-related attitudes, social influences, and behaviors that prevention efforts may target to curb the escalation of smoking. Tucker, J.S., Ellickson, P.L., and Klein, D.J. Predictors of the Transition to Regular Smoking During Adolescence and Young Adulthood, J Adolesc Health, 32(4), pp. 314-324, 2003.

Protective Factors Against Serious Violent Behavior in Adolescence

This study used data from the Seattle Social Development Project to examine factors in adolescence that affect the probability of violent behavior at age 18 among youths who received high teacher ratings of aggression at age 10. The study found a lower probability of violence among youths at age 18 was associated with attendance at religious services, good family management by parents, and bonding to school at age 15. A higher probability of later violence was associated with living in a disorganized neighborhood and having the opportunity for and involvement with antisocial peers at age 15. The likelihood of violence at age 18 among aggressive youths was reduced when they were exposed to multiple protective factors at age 15, even for those simultaneously exposed to risk factors. Herrenkohl, T.I., Hill, K.G., Chung, I.J., Guo, J., Abbott, R. and Hawkins, J.D. Protective Factors Against Serious Violent Behavior in Adolescence: A Prospective Study of Aggressive Children. Soc Work Res., 27(3), pp. 179-191, 2003.

Stress Related to Anxiety, Depression and Antisocial Behavior in African American Youth

Few researchers have studied trajectories of stress over time in relation to psychosocial outcomes and behaviors among adolescents. A sample of African American adolescents were assessed longitudinally on perceived stress, psychological well-being, support, antisocial behaviors, and academic success. Patterns of stress over 4 time points were developed using a cluster-analytic approach. Differences among the trajectory clusters were examined using psychosocial outcomes and behaviors. Adolescents with chronic levels of stress reported more anxiety and depression, engaged in antisocial behaviors, and reported less active coping than youth in other trajectories. Adolescents with low levels of stress over time reported fewer psychological problems, perceived more social support, and were more likely to graduate from high school than those with higher stress levels over time. The study also found that an increase in stress coincided with a lack of support and more psychological problems over time. Schmeelk-Cone, K.H. and Zimmerman, M.A. A Longitudinal Analysis of Stress in African American Youth: Predictors and Outcomes of Stress Trajectories. J Youth Adolesc., 32(6), pp. 419-430, 2003.

Racial Identity and Academic Attainment Among African American Adolescents

This study explored the relationships between racial identity and academic outcomes for African American adolescents. In examining race beliefs, the study differentiated among (a) importance of race (centrality), (b) group affect (private regard), and (c) perceptions of societal beliefs (public regard) among 606 African American 17-year-old adolescents. Using cluster analysis, profiles of racial identity variables were created (labeled buffering/defensive, low connectedness/high affinity, idealized, and alienated), and these profile groups were related to educational beliefs, performance, and later attainment (high school completion and college attendance). The alienated

group showed the lowest percentage of individuals attending post-secondary education, while the buffering-defensive group showed the highest college attendance. Also, the relationships between academic attitudes and academic attainment differed across groups. The paper discusses the need to consider variation in how minority youth think about group membership in order to better understand academic development. Chavous, T.M., Bernat, D. H. Schmeelk-Cone, K., Caldwell, C.H., Kohn-Wood, L. and Zimmerman, M.A. Racial Identity and Academic Attainment Among African American Adolescents, Child Dev., 74(4), pp. 1076-1090, 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.

Preventing Tobacco and Alcohol Use Among Elementary School Students

The present study examined the effectiveness of a substance abuse prevention program in preventing tobacco and alcohol use among elementary school students in grades 3 through 6. The prevention program teaches social resistance skills and general personal and social competence skills. Rates of substance use behavior, attitudes, knowledge, normative expectations, and related variables were examined among students (N = 1090) from 20 schools that were randomly assigned to either receive the prevention program (9 schools, n = 426) or serve as a control group (11 schools, n = 664). Data were analyzed at both the individual-level and school-level. Individual-level analyses controlling for gender, race, and family structure showed that intervention students reported less smoking in the past year, higher anti-drinking attitudes, increased substance use knowledge and skills-related knowledge, lower normative expectations for smoking and alcohol use, and higher self-esteem at the posttest assessment, relative to control students. School-level analyses showed that the annual prevalence rate was 61% lower for smoking and 25% lower for alcohol use at the posttest assessment in schools that received the prevention program when compared with control schools. In addition, mean self-esteem scores were higher in intervention schools at the posttest assessment relative to control schools. Findings indicate that a school-based substance abuse prevention approach previously found to be effective among middle school students is also effective for elementary school students. Botvin, G.J., Griffin, K.W., Paul, E. and Macaulay, A.P. Preventing Tobacco and Alcohol Use Among Elementary School Students through Life Skills Training. Journal of Child & Adolescent Substance Abuse, 12, pp. 1-17, 2003.

Stress Exposure Among Young Adults

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, authors 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 Avison, W.R. Status Variations in Stress Exposure Among Young Adults: Implications for the Interpretation of Prior Research. Journal of Health and Social Behavior, 44, pp. 488-505, 2003.

Sports Participation and Substance Abuse In Young Adults

The widely held notion that sports participation reduces subsequent risk of substance use is evaluated with longitudinal data of a representative sample of 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. 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. The implications of these results are discussed. Eitle, D., Turner, R.J. and Eitle, T.M. The Deterrence Hypothesis Reexamined: Sports Participation and Substance Abuse Young Adults. Journal of Drug Issues, 33, pp. 193-222, 2003.

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

Research Findings - Prevention Research

Children's Proactive and Reactive Aggressive Behaviors Can be Manipulated

Reactive aggression includes hostile, "hot-blooded" and defensive behavior, generally directed at someone or something perceived as a threat. Proactive aggression is generally goal related, involves unemotional and "cold-blooded" behavior that is oriented toward power or dominance, and involves little physiological arousal. This study assessed the effectiveness of two behavior manipulations for the purpose of differentially lowering reactive and proactive aggression in children. Fifty males between the ages of 10 and 12 were selected to play pinball in competition for points against an unknown peer whose responses were actually controlled by the experimenter. Participants could exhibit different levels of aggression towards the unknown peer by : 1) sending an annoying noise; 2) interfering with the opponent's game; or 3) offering a pro-social behavior. After playing five rounds, participants were randomly assigned to two groups: 1) reactive anger manipulation group, where trained instructors helped participants to practice distraction and relaxation techniques and alternative behaviors to aggression; or 2) positive instrumental manipulation group, where trained instructors provided rewards and reinforcement for not using proactive aggression, emphasizing the importance of team-work, taking turns, and noninterference. Then the participants played pinball for another five rounds. Results indicate that positive instrumental manipulation significantly lowered aggressive responses for both reactive and proactive behavior in children. Reactive anger manipulation did not produce similar effects. Phillips, N.C., and Lochman, J.E. Experimentally Manipulated Change in Children's Proactive and Reactive Aggressive Behavior. Aggressive Behavior, 29, pp. 215-227, 2003.

Large-Scale Trial of Revised Project ALERT

Project ALERT was originally designed to use interactive teaching methods to motivate middle-school students against using drugs, and to give them the skills they need to translate that motivation into effective resistance behavior. The initial evaluation of Project ALERT found that the program effectively prevented or reduced both cigarette and marijuana use among eighth-grade students, although committed cigarette smokers did not reduce or stop smoking. Project ALERT also had a modest initial impact on alcohol use, but this disappeared by 8th grade. In an effort to improve the program's effectiveness and generalizability, Project ALERT was revised to focus primarily on smoking cessation and alcohol use, and involve parents in substance-use prevention. The revised version of this program was tested in a randomized trial including a wide variety of schools in urban, small-town, and rural Midwestern communities. The revised version of the curriculum produced the following effects: 1) significant reductions in cigarette initiation (ever use), current use (use in past month), and regular use (weekly use); 2) significant reduction in marijuana initiation, and moderate but nonsignificant reductions in current and regular marijuana use; and 3) nonsignificant reductions on alcohol initiation and current use. Ellickson, P. L., Daniel F., McCaffrey, Ghosh-Dastidar, B. and Longshore, D.L. New Inroads in Preventing Adolescent Drug Use: Results from a Large-Scale Trial of Project ALERT in Middle Schools. American Journal of Public Health, 93(11), pp. 1830-1836, 2003.

Extent of National Awareness for Principles of School Prevention Effectiveness

The U.S. Department of Education's Principles of Effectiveness require recipients of Safe and Drug-Free Schools and Community Act funds to: 1) base drug and violence prevention programming on needs assessment data; 2) develop measurable program

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goals and objectives; 3) implement programs for which there is research evidence of effectiveness; and 4) periodically evaluate programs relative to their goals and objectives. A survey of school personnel showed that levels of awareness of these principles were relatively low at both school district (59.6% or 95% CI = 56.7%-62.5%) and individual school (22.3% or 95% CI = 20.2% - 24.4%) levels. Therefore greater communication about these principles to school districts is needed, and in turn, this should increase communication between school districts and school-level substance use and prevention staff. Simmons-Rudolph, A.P., Ennett, S.T., Ringwalt, C.L., Rohrback, L.A., and Vincus, A.A. The Principles of Effectiveness: Early Awareness and Plans for Implementation in a National Sample of Public Schools and Their Districts. Journal of School Health, 73, pp. 181-185, 2003.

Factors Associated with Teachers' Adherence to Prevention Curricula

Teachers' fidelity in implementing substance use prevention curricula is widely considered desirable, and is linked empirically to prevention effectiveness. Factors pertinent to teachers' adherence to curriculum guides were explored using data from a nationally representative sample of 1905 substance use prevention teachers in the nation's public and private schools. Results suggest that about one-fifth of the teachers did not use a curriculum guide at all; while only 15% reported that they followed one very closely. Adherence was positively associated with: 1) teachers' discretion in their coverage of prevention lessons; 2) beliefs concerning the effectiveness of the most recent training they received and the curricula they taught; and 3) their principal's level of support for substance use prevention. The authors conclude that some degree of curriculum adaptation is inevitable, but adherence to curriculum guides may be improved through teacher training. Ringwalt, C.L., Ennett, S.T., Johnson, R., Rohrbach, L.A., Simons-Rudolph, A. P., Vincus, A.A. and Thorne, J. Factors Associated with Fidelity to Substance Use Prevention Curriculum Guides. Health Education and Behavior, 30, pp. 375-391, 2003.

Relevant Biological Background Knowledge Enables Children to Learn About the Mechanisms of Drug Action

To prevent early drug and alcohol experimentation, experts suggest that prevention efforts should be initiated in elementary school. However, there has been little systematic assessment of the knowledge that elementary school-aged children need in order to understand the risks associated with substance abuse. This study sought to determine whether children are better able to learn about the physiological mechanisms of drug action if they have relevant biological background knowledge than if they do not. The participants were 363 third- to sixth-grade students from 24 classrooms in four Catholic schools in an ethnically diverse metropolitan area who were enrolled in a study of the efficacy of a drug-education curriculum designed to teach a causally coherent explanation of how alcohol and cocaine effect behavior. All children took pre- and posttests designed to measure knowledge about alcohol and cocaine, attitudes and intentions toward their use, and knowledge of the brain and circulatory system. The children were randomly assigned to four small groups within same-grade groupings, and one researcher was randomly assigned to oversee each group. The groups received one of four curricula: (1) basic theory of drug action, (2) biologically enhanced version of the theory, (3) version confronting smoking myths, or (4) control group. Results indicated that biological knowledge was greater among older students, but on the whole, elementary school-aged children may not have sufficient grasp of general biological information to apply it to a specific case like the circulation of drugs. Nevertheless, biological knowledge, especially knowledge of the brain's controlling functions, was positively associated with greater endorsement of central theories of drug action. Most importantly, the hypothesis that relevant biological knowledge would be associated with both concurrent drug knowledge and gains in drug knowledge following exposure to a drug and alcohol education curriculum was supported. Sigelman, C.K., Bridges, L.J., Sorongon, A.G., Rinehart, C.S., Brewster, A.B., and Wirtz, P. Biological Background Knowledge and Learning From a Drug and Alcohol Education Program. The Journal of Genetic Psychology, 164(2), pp. 133-152, 2003.

Prevention Program Slows Increases in Drug Use and Delinquency

This is a study of outcomes of the Preparing for the Drug Free Years Program (PDFY), a universal family-based prevention intervention proven to be effective in previous studies. This study extends prior research on the program, which has predominantly addressed process outcomes and intervention efficacy with regard to specific substances, by examining growth over time in polysubstance use and non-drug delinquency. Latent growth curve modeling was used to analyze 5 waves of data collected from 429 rural adolescents. Results showed that adolescents assigned to the

PDFY condition had a slower rate of linear increase over time in both substance use and delinquency compared with adolescents assigned to the control condition. Moreover, pretest level of delinquency was a reliable, positive predictor of growth in substance use, whereas pretest level of substance use did not predict growth in delinquency. Mason, W.A., Kosterman, R., Hawkins, J.D., Haggerty, K.P., and Spoth, R.L. Reducing Adolescents' Growth in Substance Use and Delinquency: Randomized Trial Effects of a Parent-Training Prevention Intervention. Prevention Science, 4(3), pp. 203-212, 2003.

Both Physiological and Social-Cognitive Processes Should be Addressed in Clinical Interventions with Aggressive Boys

Physiological and social-cognitive correlates of aggression were examined in an *In vivo* laboratory provocation situation. Fifty-one male participants (age 9 to 13) were selected based on teacher aggression screening, ranging from normative to high levels. A provocation was induced by the experimenter communicating a threat from an unseen "peer" in the laboratory. Bivariate linear regression analyses showed that aggression significantly predicted heart rate at both pre- and post-induction, and aggression significantly predicted attributions of intent following the provocation. Results indicated that aggression was a significant predictor of changes in hostile attribution and heart rate following the threat induction. A positive correlation was also found between heart rate change and attribution change. The findings suggest that both physiological and social-cognitive processes should be addressed in clinical interventions with aggressive children. Williams, S.C. and Lochman, J.E. Aggressive and Nonaggressive Boys' Physiological and Cognitive Processes in Response to Peer Provocations. Journal of Clinical Child and Adolescent Psychology, 32(4), pp. 568-576, 2003.

Curriculum Found To Be Effective, Culturally Grounded Approach to Prevention

The authors present findings from an effectiveness study of a school-base drug abuse prevention intervention developed for culturally diverse, urban middle school students. The 'keepin' it R.E.A.L.' curriculum consists of 10 lessons promoting antidrug norms and teaching resistance skills and other social skills, reinforced by booster activities and a media campaign. Three versions of the intervention were delivered: Mexican American, combined African American and European American, and Multicultural. The investigators hypothesized that: 1) the three culturally-grounded interventions would influence anti-drug attitudes and reduce drug use compared to the standard or existing intervention and 2) the greater the cultural matching between student background and intervention condition, the stronger the effect of the program (cultural matching hypothesis). Thirty-five middle schools were randomly assigned to 1 of the 3 versions or to the control group. A total of 6,035 students completed baseline and follow-up interviews over a two-year period. Analyses utilizing a generalized estimating equations approach suggest that the intervention was effective, with significant effects on gateway drug use as well as norms, attitudes, and resistance strategies. There was little support for the cultural matching hypothesis. Contrasts suggested that the Mexican American and Multicultural versions impacted the most outcomes. Hecht, M.L., Marsiglia, F.F., Elek, E., Wagstaff, D.A., Kulis, S., Dustman, P., and Miller-Day, M. Culturally Grounded Substance Use Prevention: An Evaluation of the keepin' it R.E.A.L. Curriculum. Prevention Science, 4(4), pp. 233-248, 2003.

Pairing Aggressive and Nonaggressive Children in Strategic Peer Affiliation is Effective

During a 6-week summer school program 118 second graders participated in a program that incorporated strategic peer affiliation (a "buddy system") to assess the impact of pairing moderately aggressive children (the targets of the intervention) and nonaggressive children. All participants were observed playing foosball with their buddies and with aggressive and nonaggressive non-buddies as teammates. Aggressive children had lower levels of disruptive behavior when their teammate was nonaggressive, regardless of whether the teammate was a buddy. Nonaggressive children showed elevated disruptive behavior when playing with an aggressive non-buddy, but not when playing with an aggressive buddy. The highest level of aggressive behavior was seen in pairs of aggressive teammates who were friends. One year later, no increase in peer-rated aggressive behavior was found in either group. Results suggest that unidirectional peer influence is possible and that strategic peer affiliation can be an effective intervention that does not put nonaggressive children at risk for acquiring undesired behaviors. Hektner, J.M., August, G.J., and Realmuto, G.M. Effects of Pairing Aggressive and Nonaggressive Children in Strategic

Peer Affiliation. Journal of Abnormal Child Psychology, 31(4), pp. 399-412, 2003.

Gateway Communications are Ineffective in Anti-Marijuana Campaigns

Successful anti-marijuana messages can be hypothesized to have two types of effects: persuasion effects that result in change in people's beliefs about using marijuana, and priming effects, that strengthen the correlation between beliefs and associated variables such as attitude toward and intention to use a drug. This study examined different sets of anti-drug advertisements for persuasion and priming effects focusing on the effectiveness of the gateway argument in anti-marijuana interventions. The belief that marijuana is a gateway to other drugs was selected since it often is endorsed by campaign planning officials and health educators. A sample of 418 middle and high school students was randomly assigned to a control video or one of three intervention conditions two of which included the gateway message in either an explicit or implicit way. Results did not support the use of the gateway belief in anti-marijuana interventions. No clear persuasion or priming effects were found for any of the ad sequences. In fact, in comparison to the control condition, adolescents in the explicit gateway condition tended to agree less with the gateway message and displayed weaker correlations between anti-marijuana beliefs and their attitude toward marijuana use. For most youth there was no room for the ads to lower intentions to use marijuana since they did not intend to use. For higher risk youth many of whom presumably had used marijuana but had not gone on to use other drugs, the gateway message runs counter to their experience and is rejected. These results suggest that the gateway message should not be used in anti-drug interventions. Yzer, M.C., Cappella, J.N, Fishbein, M., Hornik R. and Ahern, R.K. The Effectiveness of Gateway Communications in Anti-Marijuana Campaigns. Journal of Health Communication, 8(2), pp. 129-143, 2003.

Predictors of Early Sexual Risk in High Risk Youth

This longitudinal study assessed the characteristics that predicted the timing of first sexual intercourse in a high-risk sample of adolescents between the ages of 11 and 14. A high-risk community sample was recruited through advertisement and a telephone interview with parents, who were asked to reported on their child's current risk factors, such as low grades, suspected drug use, and aggression. Youth were eligible to participate in the study if parents reported the presence of at least four risk factors. Following recruitment, families participated in a 2-3 hour assessment involving questionnaires, structured interviews, and a family assessment task. Following the assessment, participants were administered brief telephone interviews. The analyses were conducted with 162 adolescents who were virgins at baseline and for whom it was possible to determine the date of first sexual intercourse. The modal age of first intercourse was 14. Pubertal status, externalizing ratings, delinquency, substance use, monitoring, and deviant-peer involvement were univariate predictors of age of first sexual intercourse, whereas deviant-peer involvement was the sole predictor in the multivariate analysis. These results suggest that precocious sexual initiation can be understood using models of the etiology of other problem behavior and that deviant-peer involvement is a particularly salient dimension of this trajectory. French, D. and Dishion, T.J. Predictors of Early Initiation of Sexual Intercourse Among High-Risk Adolescents. Journal of Early Adolescence, 23(3), pp. 295-315, 2003.

The Potential Role of Deviant Talk in Adolescent Antisocial Behavior

Deviant talk in adolescent friendships has been previously found to predict escalation in substance use, delinquency, and violence. The current paper extends past work on deviant talk by examining its dynamic, self-organizing properties. From the direct observations of peer interactions, a simple measure was developed that indicated whether, as an interaction unfolded, deviant talk bouts became longer in duration, indicating an "attractor state" according to dynamic systems principles. Participants included 102 high-risk adolescents and their friends. A time series of the duration of each successive deviant talk bout over the course of an interaction was created for all dyads. Slope values were derived from the time-series and used as an index of attractor strength. As hypothesized, the attractor index predicted serious authority conflict (arrests, school expulsion) and drug abuse three years later, after controlling for problem behavior, family coercion, and deviant peer associations. The findings suggest that the process by which adolescents become increasingly absorbed in deviant talk is an important underlying mechanism in the development of serious antisocial behavior. Granic, I. and Dishion, T.J. Deviant Talk in Adolescent Friendships: A Step Toward Measuring a Pathogenic Attractor Process. Social Development, 12(3), pp. 314-334, 2003.

Predictors of Smoking Among Rural Adolescents

This study investigated a model of social and cognitive cross-sectional predictors of smoking, with a focus on rural adolescents. Gender-specific differences in etiology were examined by testing the same model separately for boys and girls. Seventh graders (N=1,673) residing in northeastern Iowa self-reported smoking, peer smoking norms, adult smoking norms, drug refusal assertiveness, drug refusal techniques, life skills, prosmoking attitudes, risk-taking tendency, and family management practices. Data were collected during a class period in 36 junior high schools. Peer smoking norms, adult smoking norms, drug refusal assertiveness, drug refusal techniques, prosmoking attitudes, and risk-taking tendency were associated with smoking. Notably, family management skills and life skills were associated with current smoking for girls only. Based on the results of the present study and on previous research, smoking prevention programs for rural adolescents should incorporate normative education, drug refusal training, parent skills training, and competence enhancement skills training, strategies that have been successful with urban and suburban populations. Epstein, J.A., Botvin, G.J., and Spoth, R. Predicting Smoking among Rural Adolescents: Social and Cognitive Processes. Nicotine and Tobacco Research, 5, pp. 485-491, 2003.

Cognitive Predictors of Children's Attitudes Toward Alcohol and Cocaine

Using a multi-ethnic sample of 217 elementary school children, this study looked at age-related differences in attitudes and intentions regarding alcohol and cocaine use. It also examined possible cognitive underpinnings of these attitudes and intentions, such as basic familiarity with each substance, expectancies about short-term psychological and behavioral effects, beliefs about long-term health effects, and causal understanding of drug action. Findings revealed that as they get older, children increasingly report familiarity with alcohol and cocaine and they understand that their effects are in large part brain-mediated rather than due to a drug's direct effects on peripheral parts of the body. Although older children were more likely than younger children to endorse positive expectancy statements about alcohol and cocaine, negative expectancies prevailed at all ages and did not weaken with age. The knowledge, belief, and understanding variables examined in this study were associated with attitudes toward cocaine use, but not alcohol. Structural equation modeling involving these variables revealed that cognitive predictors had no significant indirect associations with cocaine use intentions through attitudes. Instead, cognitions predicted attitudes and attitudes, in turn, predicted intentions of cocaine use. Whereas most studies have emphasized associations between expectancies and attitudes toward drug use, this study suggests that other sorts of cognitions deserve further exploration. The findings also suggest that it may be beneficial to supplement drug prevention efforts with an approach that targets general knowledge about drugs, knowledge of drugs' long-term effects, and causal understanding of how drugs alter brain functioning. Bridges, L.J., Sigelman, C.K., Brewster, A.B., Leach, D.B., Mack, K.L., Rinehart, C.S., and Sorongon, A.G. Cognitive Predictors of Children's Attitudes Toward Alcohol and Cocaine. Journal of Child and Adolescent Substance Abuse, 12(3), pp. 19-44, 2003.

Young Adults with Attention-Deficit/Hyperactivity Disorder and Conduct Disorder are at Unique Risk for Drug Dependence

Prior research examining relations among attention-deficit/hyperactivity disorder (ADHD), conduct disorder (CD), and substance abuse has suggested that CD fully accounts for relationships between ADHD and substance abuse. This study tested an alternate theory that ADHD and CD interact to produce substance use problems. The 481 participants were part of a 10- to 12-year longitudinal study of the etiological pathways to substance use and psychopathology. Results indicated that college aged youth with a history of a greater number of symptoms of both hyperactivity-impulsivity-inattention (HIA) and conduct problems (CP) when they were younger had the highest rates of marijuana and hard drug use dependence symptoms. Interestingly, youth with higher HIA and lower CP symptoms often had the lowest rates of substance use and dependence symptoms, suggesting that HIA, in the absence of CP, may serve as a protective factor. This subtype is often characterized by relatively low levels of impulsivity and an anxious, shy or socially withdrawn personality style, which could account for the low levels of substance use. The only substance to which HIA was uniquely related after controlling for the overlap between ADHD and CD was tobacco. Since stimulant medications are the most effective medical treatment for reducing symptoms of HIA, the authors speculate that individuals with HIA may use the socially acceptable stimulant drug nicotine as a way to decrease their HIA symptoms. As a whole, these study findings support the

hypothesis that there may be unique characteristics, such as impulsivity, executive deficits or peer rejection, that are associated with HIA-CP that impose a particularly high risk for antisocial behavior, substance use and dependence. Flory, K., Milich, R., Lynam, D.R., Leukefeld, C., and Clayton, R. Relation Between Childhood Disruptive Behavior Disorders and Substance Use and Dependence Symptoms in Young Adulthood: Individuals With Symptoms of Attention-Deficit/Hyperactivity Disorder and Conduct Disorder Are Uniquely at Risk. Psychology of Addictive Behaviors, 17(2), pp. 151-158, 2003.

The Associations of Social Self-Control, Personality Disorders, and Demographics With Drug Use Among High-Risk Youth

A 10-item self-report measure of social self-control was examined for its association with substance use, controlling for its associations with 12 personality disorder indices and 4 demographic variables among a sample of 1,050 high-risk youth. Social self-control was found to be associated with 30-day cigarette smoking, alcohol use, marijuana use, and hard drug use, controlling for these other variables. The most consistent concurrent predictors of substance use were male gender, antisocial personality disorder, and social self-control. These results highlight the importance of social self-control as a unique concurrent predictor of substance use and suggest that social self-control skill training is relevant in substance abuse prevention programming. Sussman, S., McCuller, W.J., and Dent, C.W. Implications for Social Self-Control Training. Addictive Behaviors, 28(6), pp. 1159-1166, 2003.

Callous/Unemotional Traits are Related to Social-Cognitive Problems in Adjudicated Youths

Callous/unemotional (C/U) and impulsivity/conduct problems (I/CP) in youth may be associated with psychopathic traits. This study sought to clarify the nature of these two factors, and examine their relation with social-cognitive problems in incarcerated adolescents. Self-report measures and archival data were collected from one hundred sixty- nine male and female adjudicated youth to assess their psychopathic traits, emotional distress, behavioral dysregulation, social-cognitive processes, and delinquency severity. Analyses demonstrated that the I/CP factor is associated with increased levels of dysregulated behavior, while the C/U dimension is related to deficits in empathy. Also, C/U traits were associated with an increased focus on the positive aspects of aggression and a decreased focus on the negative aspects of hostile acts. Findings remained after controlling for demographic characteristics, abuse history, intellectual abilities, and delinquency severity. Results provide support for the two-dimensional nature of psychopathology in youth and suggest that C/U traits are associated with lower emotional distress and a specific social information-processing pattern. Pardini, D.A., Lochman, J.E., and Frick, P.J. Callous/Unemotional Traits and Social Cognitive Processes in Adjudicated Youth. Journal of American Academy of Child and Adolescent Psychiatry, 42, pp. 364-371, 2003.

Flexibility in Parent Child Interactions Peaks During the Adolescent Transition

This family research study (n=149) was designed to test how parent-child interaction trajectories, measured through observation, changed over three periods of time: 1) preadolescence (ages 9-12), the adolescent transition (13-14), and after the adolescent transition (ages 15-18). The authors hypothesized that preadolescent parent-child interactions would be very stable in nature and would become much more unstable during the transition period. These unstable patterns were expected to restabilize after the transition period. Patterns were documented and analyzed using a new dynamic systems methodology called "state space grids." Participants in the study were a subsample of boys involved in the Oregon Youth Study who completed all five waves of data collection in that study. The boy and one or two parents were videotaped engaging in problem solving discussions over two high conflict family issues. The problem solving sessions were coded using the Family Process Code to categorize behavior into 1 of 25 content codes and 1 of 6 valance or affect codes. This analysis focused on the valance codes, which were collapsed into four groups. The findings strongly supported the hypothesis that the early adolescent transition involves increased behavioral flexibility in interaction style between these boys and their parents. Granic, I., Hollenstein, T., Dishion, T.J., and Patterson, G.R. Longitudinal Analysis of Flexibility and Reorganization in Early Adolescence: A Dynamic Systems Study of Family Interactions. Developmental Psychology, 39(3), pp. 606-617, 2003.

Longitudinal Relations Among Depression, Stress, And Coping In High Risk Youth

The structural relationships among risk and protective factors were examined in a sample of 646 continuation high school students. Depression predicted more perceived stress but was not a unique predictor of anger coping, seeking social support, or substance use. Perceived stress increased seeking social support, which subsequently decreased the use of anger coping. This suggests that social support may be a means of prevention for adolescents. Anger coping behaviors were significant in sustaining depression and perceived stress, and in increasing hard drug use over time. Analyses of moderators of this effect indicated that there was no difference in the stress-coping depression relationship between Latinos and Caucasians. However, the relationship among perceived stress, anger coping, and depression was stronger for female than for male adolescents. Galaif, E.R., Sussman, S., Chou, C.P., and Wills, T.A., Longitudinal Relations Among Depression, Stress, and Coping in High Risk Youth. Journal of Youth and Adolescence, 32(4), pp. 243-258, 2003.

Mixed Outcomes after 3 Years of a Multifaceted Prevention Program for Disruptive Elementary School Children

This study examined predictors and outcomes of attendance in two standard components of a multifaceted preventive intervention aimed at children with early-onset disruptive behavior after 3 years of intervention. Mean rate of attendance in the Family Program, but not the Summer School Program, differed by level of child disruptiveness (i.e., the grouping variable). Predictors of attendance (SES, single-parent status, child IQ) did not differ across high- and low-disruptive groups. However, level of child disruptiveness moderated academic achievement and aggression outcomes, but not social competence. Higher attendance in the Summer Program was associated with higher child social competence at Year 3 for all children. For academic achievement, higher attendance in the Summer Program was associated with higher scores for mild/moderately disruptive children and lower scores for highly disruptive children in Year 3. Higher attendance in the Family Program was associated with lower aggression scores for mild/moderately disruptive children. Findings highlight the importance of matching intervention components to the assessed or expressed needs of client subgroups. August, G.J., Egan, E.A., Realmuto, G.M., and Hektner, J.M. Parceling Component Effects of a Multifaceted Prevention Program for Disruptive Elementary School Children. Journal of Abnormal Child Psychology, 31(5), pp. 515-527, 2003.

Project Towards No Drug Abuse: Two-Year Outcomes of a Trial That Compares Health Educator Delivery To Self-Instruction

This paper describes the 2-year follow-up of a 12-session version of an indicated drug abuse prevention program, Project Towards No Drug Abuse (TND). Self-instruction programming often is used to help youth who are at high risk for dropout and drug abuse to complete their high school education. However, a health educator-led program is much more interactive. In this study the effects of self-instruction versus health educator-led versions of this curriculum were examined. Eighteen schools were randomly assigned by block to one of three conditions-standard care (control), health educator-led classroom program, and self-instruction classroom program. Subjects were followed up 1 and 2 years later. Two-year results are reported here. Results showed that the self-instruction program produced no behavioral effects relative to the standard care control condition. The 2-year follow-up results indicated maintenance of program effects on cigarette smoking and hard drug use in the health educator-led version. It was concluded that Project TND shows maintenance of effects on some drugs 2 years after program implementation, when most youth were young adults. More work is needed to learn how to maintain effects across substances. Continued exploration of modalities of implementation may be helpful. Sussman, S., Sun, P., McCuller, W.J., and Dent, C.W. Preventive Medicine, 37(2), pp. 155-162, 2003.

Family-Based Interventions for Substance Use and Misuse Prevention

Because "substance abuse" is a "family disease" of lifestyle, including both genetic and family environmental causes, effective family strengthening prevention programs should be included in all comprehensive substance abuse prevention activities. This article presents reviews of causal models of substance use and evidence-based practices. National searches by the authors suggest that there is sufficient research evidence to support broad dissemination of five highly effective family strengthening approaches (e.g. behavioral parent training, family skills training, in-home family support, brief family therapy, and family education). Additionally, family approaches have average effect sizes two to nine times larger than child-only prevention approaches. Comprehensive prevention programs combining both approaches

produced much larger effect sizes. Kumpfer, K.L., Alvarado, R., and Whiteside, H.O. Family-based Interventions for Substance Use and Misuse Prevention. Substance Abuse and Misuse, 38(11-13), pp. 1759-1787, 2003.

The Development of the Driver's Angry Thoughts Questionnaire

Angry, aggressive drivers are a significant psychological and health hazard on the road. This study was undertaken to develop a measure of angry thinking while driving and to provide initial reliability and validity data. The questionnaire under evaluation, the Driver's Angry Thoughts Questionnaire (DATQ), includes 88 thoughts people have when angry while driving, generated from 248 college students. Investigators also measured the propensity to become angry when driving, expression of anger behind the wheel, driving habits, hostile automatic thoughts, and trait anger. Factor analysis identified five forms of driving-related angry cognitions: Judgmental/Disbelieving Thinking, Pejorative Labeling/Verbally Aggressive Thinking, Revenge/Retaliatory Thinking, Physically Aggressive Thinking, and Coping Self-Instruction. Pejorative labeling/verbally aggressive, physically aggressive, and revengeful/retaliatory thinking correlated positively with each other and with driving anger, expressing driving anger, aggression on the road, and risky driving behavior. Coping self-instruction tended to correlate negatively with these variables. Judgmental/disbelieving thinking correlated positively with other forms of angry thinking but correlated only somewhat with other variables (e.g., expression of anger). Driving-related angry thoughts, except coping self-instruction, correlated positively with general hostile automatic thoughts. The analyses supported the validity of the measure. Deffenbacher, J.L., Petrilli, R.T., Lynch, R.S., Oetting, E.R., and Swaim, R.C. The Driver's Angry Thoughts Questionnaire: A Measure of Angry Cognitions When Driving. Cognitive Therapy and Research, 27(4), pp. 383-402, 2003.

Developing and Testing an Objective Measure of Message Sensation Value

Effective targeting of high sensation-seeking adolescents, who are most at risk for drug abuse, requires creation of high sensation value messages. Previous research has focused on subjective reactions of receivers as the primary way to define message sensation value (MSV). In contrast, this study treats message sensation value as the formal and content features (audio, visual and format) of a message that contribute to subjective message sensation evaluations. Study goals were to: (1) identify message design features that would aid in the development of effective prevention messages targeting high sensation seekers; (2) develop an objective measure of message sensation value based on formal and content features of messages; and (3) determine whether high message sensation value messages were associated with higher subjective evaluations of message sensation value. A total of 418 undergraduates each viewed 10 public service announcements (PSAs) selected at random from a pool of 109 PSAs that had been previously coded for message sensation value. As hypothesized, the data analysis found that perceived MSV is at least in part a product of the formal and content features of a PSA. Morgan, S.E., Palmgreen, P., Stephenson, M.T., Hoyle, R.H., and Lorch, E.P. Associations Between Message Features and Subjective Evaluations of the Sensation Value of Antidrug Public Service Announcements. Journal of Communication, 53(3), pp. 512-526, 2003.

Pilot Study Findings of a Preventive Intervention with African American Families

The authors report the results of a pilot of the Strengthening Families Program: For Parents and Youth 10-14 with a sample of African American families with young adolescents (n=110). This study was undertaken to address the gap in knowledge regarding the efficacy of substance use prevention programs with African American populations. Participants were randomized to an intervention and a waitlist control group. Outcome data were collected from all participants by telephone survey before and after the six weekly 2-hour intervention sessions, then once more after the program was offered to the waitlist control group. Implementation feasibility clearly was demonstrated and observer ratings showed high adherence to the intervention protocol. Trial findings showed positive results for intervention-targeted child behaviors, such as setting goals and managing stress. The intervention did not have effects on targeted parenting skills expected to mediate child skill-building. Spoth, R., Guyll, M., Chao, W., and Molgaard, V. Exploratory Study of a Preventive Intervention with General Population African American Families. Journal of Early Adolescence, 23(4), pp. 435-468, 2003.

The Role of Assertiveness and Decision Making in Early Adolescent Substance Initiation

This study examined the mediating processes linking individual rights assertiveness and decision-making to early adolescent substance initiation, along with the moderating effect of gender on those processes. Individual rights assertiveness was defined as learned, goal-oriented behavior that increases the likelihood that personal needs will be met. Decision-making skills were defined as active strategies to gather information, with pros and cons and choose appropriate actions. Self-report measures were collected from a non-treatment cohort of rural, young adolescents participating in a prevention trial (N=357). Analyses were conducted to test mediational models across three waves of data collected over a period of 18 months. Results indicated that individual rights assertiveness and decision-making had indirect effects on substance initiation through effects on negative outcome expectancies and refusal intentions. Gender differences were found in both the average level and the pattern of relationships among the variables. For girls, refusal intentions were negatively associated with later substance initiation. For boys, early levels of substance initiation were negatively associated with later levels of negative expectancies and refusal intentions. Trudeau, L., Lillehoj, C., Spoth, R., and Redmond, C. The Role of Assertiveness and Decision Making in Early Adolescent Substance Initiation: Mediating Processes. Journal of Research on Adolescence, 13(3), pp. 301-328, 2003.

Development of A Culturally Grounded Prevention Approach

Research has shown that students respond more favorably to drug prevention programs when they see their culture and themselves represented in the prevention message. Additionally, studies highlight important ethnic differences in drug behaviors and attitudes, indicating that students' ethnic culture should be considered in the creation of prevention programs. Still there are few effective, culturally grounded programs like the 'keepin' it R.E.A.L.' curriculum, designed for ethnically diverse seventh grade students residing in a large southwestern city. This curriculum was developed by incorporating several theoretical perspectives such as Communication Competence Theory, Narrative Theory, and the Focus Theory of Norms and culturally grounding through the use of youths narratives that reflect their local, youth, and ethnic cultures. This descriptive paper illustrates the process of curriculum design, focusing on the methods used to ensure cultural grounding. Gosin, M., Marsiglia, F.F., and Hecht, M.L. Keepin' it R.E.A.L.: A Drug Resistance Curriculum Tailored to the Strengths and Needs of Pre-Adolescents of the Southwest. Journal of Drug Education, 33(2), pp. 119-142, 2003.

School-based Programs for Social, Emotional and Academic Development

A comprehensive mission for schools is to educate students to be informed, responsible, socially skilled, healthy, caring, and contributing citizens. To support this mission a growing number of school-based prevention and youth development programs have been developed. However, the impact of these programs is limited because of insufficient coordination with other components of school operations and inattention to implementation and evaluation factors necessary for strong program impact and sustainability. Widespread implementation of beneficial prevention programming requires development of research-based, comprehensive school reform models that improve social, health, and academic outcomes; educational policies that demand accountability for fostering children's full development; professional development that prepares and supports educators to implement programs effectively; and systematic monitoring and evaluation to guide school improvement. Greenberg, M. T., Weissberg, R.P., O'Brien, M.U., Zins, J.E., Fredericks, L., Resnik, H., and Elias M.J. Enhancing School-Based Prevention and Youth Development Through Coordinated Social, Emotional, and Academic Learning. American Psychologist, 58(6-7), pp. 466-474, 2003.

Substance Abuse Among Very Young Juvenile Offenders

Although the relationship between delinquency and substance use in adolescence is well documented, less is known about substance-use initiation in childhood for juvenile delinquent populations. This study examined early substance initiation in childhood as reported by adolescents who were incarcerated for juvenile offenses (93 males, 96 females; 58% African American, 42% European American). Youth were individually interviewed using an adapted version of substance-related questions from the National Household Survey on Drug Abuse. Juvenile justice system records were reviewed to characterize offense histories. A majority of males and females reported using at least one substance (other than cigarettes) such as alcohol, marijuana, or inhalants by age 13. Alcohol use reportedly occurred by age 10 for 17% of the youth. For a substantial portion, early initiation turned into frequent early use. For example, 32% of the males and 39% of the females reported drinking alcoholic beverages at a frequency of at least several times per month by age 13. Limited evidence related

early substance initiation with subsequent substance abuse. Offense status is related to early substance initiation for females but not males. Early substance use is a significant problem among youth who end up in the juvenile justice system. Prinz, R.J., and Kerns, S.E.U. Early Substance Use by Juvenile Offenders. Child Psychiatry and Human Development, 33(4), pp. 263-277, 2003.

Problem Behavior Screening in First Grade

First grade teacher ratings of aggressive, hyperactive-inattentive, and low levels of pro-social behaviors made unique contributions to the prediction of school outcomes (measured 2 years later) for 755 children. Person-oriented analyses compared the predictive utility of 5 screening strategies based on child problem profiles to identify children at-risk for school problems. Children with elevations in any 1 of the 3 behavior problem dimensions were identified as "at-risk". A broad screening strategy used with these children showed lower specificity than other measures, but superior sensitivity, odds ratios, and overall accuracy in the prediction of school outcomes than the other screening strategies that were more narrowly focused or were based on a total problem score. Flanagan, K.S., Bierman, K.L., and Kam, C.M. Identifying At-Risk Children at School Entry: The Usefulness of Multi-Behavioral Problem Profiles. Journal of Clinical Child and Adolescent Psychology, 32(3), pp. 396-407, 2003.

Parent Knowledge about Monitoring Behavior and Adolescent Delinquency

Links between parental monitoring-relevant knowledge and adolescent delinquent behavior were tested for correlated rates of developmental change and reciprocal associations. For 4 years beginning at age 14, adolescents (N = 396) reported on their delinquent behavior and on their parents' knowledge of their whereabouts and activities. Parents completed measures of their adolescents' delinquent behavior. Parent monitoring-relevant knowledge was negatively correlated with delinquent behaviors at baseline. Increases over time in parent monitoring knowledge were associated with decreases in parent-reported delinquent behavior. Reciprocal associations indicate that low levels of parental knowledge predict increases in delinquent behavior and that high levels of delinquent behavior predict decreases in parent knowledge. Both youth-driven and parent-driven processes may account for the correlated developmental changes and reciprocal associations. Laird, R.D., Pettit, G.S., Bates, J.E., and Dodge, K.A. Parents' Monitoring-Relevant Knowledge and Adolescents' Delinquent Behavior: Evidence of Correlated Developmental Changes and Reciprocal Influences. Child Development, 74(3), pp. 752-768, 2003.

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Research Findings - Services Research

Post-Discharge Recovery Management Checkups Can Improve Outcomes for 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 (59% female, 85% African American, and 75% aged 30-49) randomly assigned to either RMC or an attention (assessment only) control group. 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 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.

Case Managers Minimally Facilitate Delivery of Services in Addiction Treatment Programs

This study examined whether designated case management staff facilitated delivery of comprehensive medical and psychosocial services in substance abuse treatment programs. Researchers employed a multilevel, prospective cohort study of 2829 clients admitted to selected substance abuse treatment programs, including long-term residential, outpatient, and methadone treatment modalities. Program directors reported program use of staff specifically designated as case managers. After treatment discharge, clients reported their receipt of 9 supplemental services during the treatment episode. In multivariate models controlling for multiple program-level and client-level factors, program-level availability of designated case managers increased client-level receipt of only 2 of 9 services, and exerted no effect on service comprehensiveness, compared to programs that did not have designated case managers. These findings do not support the common practice of designating case management staff as a means to facilitate comprehensive services delivery in addiction treatment programs. Friedmann, P.D., Hendrickson, J.C., Gerstein, D.R., and Zhang, Z. Designated Case Managers as Facilitators of Medical and Psychosocial Service Delivery in Addiction Treatment Programs. The Journal of Behavioral Health Services & Research, 22(27), pp. 86-98, 2003.

Provision of Timely Addiction Treatment Up in 1990s, But Accessibility Problems Persist for Some

This study examined organization-level characteristics associated with the accessibility of outpatient addiction treatment. Program directors and clinical supervisors from a nationally representative panel of outpatient substance abuse treatment units in the United States were surveyed in 1990 (N=481), 1995 (N=387), and 2000 (N=480). Accessibility was measured from clinical supervisors' reports of whether the treatment organization provided "treatment on demand" (an average wait time of 48 hours or less for treatment entry), and of whether the program turned away any patients. In multivariable logistic models, provision of "treatment on demand" increased two-fold from 1990 to 2000 (OR, 1.95; 95 percent CI, 1.5 to 2.6),

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while reports of turning patients away decreased nonsignificantly. Private for-profit units were twice as likely to provide "treatment on demand" (OR, 2.2; 95 percent CI, 1.3 to 3.6), but seven times more likely to turn patients away (OR, 7.4; 95 percent CI, 3.2 to 17.5) than public programs. Conversely, units that served more indigent populations were less likely to provide "treatment on demand" or to turn patients away. Methadone maintenance programs were also less likely to offer "treatment on demand" (OR, .65; 95 percent CI, .42 to .99), but more likely to turn patients away (OR, 2.4; 95 percent CI, 1.4 to 4.3). Although the provision of timely addiction treatment appears to have increased throughout the 1990s, accessibility problems persist in programs that care for indigent patients and in methadone maintenance programs. Friedmann, P.D., Lemon, S.C., Stein, M.D., and D'Aunno, T.A. Accessibility of Addiction Treatment: Results From A National Survey of Outpatient Substance Abuse Treatment Organizations. Health Services Research, 38(3), pp. 887-903, 2003.

Smoking Cessation Does Not Negatively Affect Drug Abuse Treatment Outcome

Although cigarette smoking is endemic among illicit drug users, drug abuse treatment programs rarely encourage smoking cessation and often discourage it. The purpose of this study was to determine whether smoking cessation after entering drug abuse treatment influenced drug use 12 months after drug abuse treatment. Researchers analyzed 2,316 cigarette smokers in the Drug Abuse Treatment Outcome Study (DATOS), a national, longitudinal study of drug abuse treatment. Heckman probit selection models assessed the association of self-reported smoking cessation while in drug abuse treatment on self-reported drug abstinence in the year after treatment completion, while simultaneously accounting for possible nonparticipation bias. Controlling for multiple factors, smoking cessation was significantly associated with greater abstinence from drug use after completion of drug abuse treatment. Despite drug abuse treatment programs' hesitance to encourage smokers to quit, smoking cessation does not negatively impact drug use outcomes. Lemon, S.C., Friedmann, P.D., and Stein, M.D. The Impact of Smoking Cessation on Drug Abuse Treatment Outcome. Addictive Behaviors, 28(7), pp. 1323-1331, 2003.

Medical and Psychiatric Conditions Prevalent among Alcohol and Drug Treatment Patients in an HMO

Prior research on health conditions related to substance abuse largely focused on alcohol and patients treated in publicly-funded programs, inpatients, and the general population. This study compares the prevalence of medical and psychiatric conditions among 747 substance abuse patients and 3,690 demographically matched controls from the same health maintenance organization, and examines whether any heightened prevalence for substance abuse patients (relative to controls) varies according to demographic subgroups and type of substance. Approximately one third of the conditions examined were more common among substance abuse patients than among matched controls, and many of these conditions were among the most costly. Researchers also found that pain-related diagnoses, including arthritis, headache, and lower back pain, were more prevalent among such patients, particularly those dependent on narcotic analgesics. These findings point to the importance of examining comorbid medical conditions and substance abuse in both primary and specialty care. Findings regarding pain-related diagnoses among patients dependent on narcotic analgesics highlight the need for linkages between primary care and substance abuse treatment. Moreover, optimal treatment of many common medical disorders may require identification, intervention, and treatment of an underlying substance abuse disorder. Mertens, J.R, Lu, Yun W., Parthasarathy, S., Moore, C. and Weisner, C.M. Medical and Psychiatric Conditions of Alcohol and Drug Treatment Patients in an HMO. Archives of Internal Medicine, 163(20), pp. 2511-2517, 2003.

Comorbid Psychiatric Disorders in Youth in Juvenile Detention

This epidemiological study seeks to estimate 6-month prevalence of comorbid psychiatric disorders among juvenile detainees by demographic subgroups including gender, race/ethnicity, and age. Participants in this longitudinal study include 1,829 youth (age 10-18 years) initially arrested and detained between 1995 and 1998 at the Cook County Juvenile Temporary Detention Center in Chicago, IL. Subjects were randomly selected to participate in the study. Results indicate significantly more females (57%) than males (46%) met the criteria for 2 or more mental health disorders represented in the *DSM-III-R*. Nearly 14% of the girls and 11% of the boys had both a major mental disorder (psychosis, manic episode, or major depressive episode) and a substance use disorder. Nearly 30% of the girls and 20% of the boys with substance use disorders had major mental health disorders. Rates of comorbidity were higher among non-Hispanic whites and older adolescents. Abram, K.M., Teplin,

L.A., McClelland, G.M., and Dulcan, M.K. Comorbid Psychiatric Disorders in Youth in Juvenile Detention. Archives of General Psychiatry, 60, pp. 1097-1108, 2003.

Head Injury Is An Indicator of Co-Occurring Problems Among Drug Abusers

This study examined 661 drug-abusing inmates detained in a state prison, who self-reported a history of head injury, health problems, and mental health disorders. Participants included individuals who had previously participated in drug abuse treatment, were currently enrolled in prison-based drug abuse treatment, and individuals who had never participated in drug treatment. Research subjects were divided into three groups: those with no head injury; those with one head injury; and those with two or more head injuries. Results indicate inmates with head injuries had a significantly greater number of health problems, higher levels of alcohol and marijuana use, and significantly more mental health problems including depression, anxiety, suicidal thinking, difficulties concentrating, and violent behavior. The investigators suggest assessment for head injury is an important part of treatment and service planning for drug abusing offenders. Walker, R., Hiller, M., Staton, M., and Leukefeld, C. Head Injury Among Drug Abusers: An Indicator of Co-Occurring Problems. Journal of Psychoactive Drugs, 35(3), pp. 343-353, 2003.

Analytic Method Facilitates Understanding of Multiple Source Reports on Linkage to Primary Care

In studies designed to measure health outcomes, researchers often obtain data on patients' utilization of health services from multiple sources. This common practice raises key methodological challenges in data analysis, including how data should best be represented and interpreted in statistical models. In the HELP (Health Evaluation and Linkage to Primary care) study, 642 subjects without primary medical care, and who were undergoing alcohol or drug detoxification, were enrolled in a randomized controlled trial of a health evaluation intervention to link them with primary care. The outcome of interest was attendance at a primary care appointment (linkage to primary care) after discharge from the detoxification unit. Both self-report and administrative sources of linkage were collected. Researchers applied methodology developed by Fitzmaurice et al., (American Journal of Epidemiology, 1995) to fit a single regression that allowed inclusion of all multiple-source outcomes in a single multivariate regression analysis. This model allowed testing for source differences in outcome and estimation of different source effects where necessary and included data from subjects with partially observed source observations. These methods were applied to the analysis of the HELP study using correlated survival regression models to assess the magnitude and significance of the relationship between predictor variables and linkage. Researchers concluded that when multiple sources of outcome data are combined into a single model, as done in this study, comparisons between the different source reports can be made quantitatively, which can yield more precise and accurate understandings of the underlying questions of interest. Horton, N.J., Saitz, R., Laird, N.M., and Samet, J.H. A Method of Modeling Utilization Data from Multiple Sources: Application in a Study of Linkage to Primary Care. Health Services and Outcomes Research Methodology, 3, pp. 211-223, 2003.

Hepatitis C: Critical Treatment Target Among Offenders in Correctional Facilities

Chronic infection with hepatitis C virus (HCV) is the most common blood-borne illness in the United States, affecting nearly 2 percent of all Americans, or an estimated 4-5 million individuals. Although most individuals with chronic infection are not expected to progress to end-stage liver disease or death, hepatitis C is the most common indication for liver transplantation in the U.S., and it is responsible for 10,000 deaths annually. HCV can be transmitted through blood and blood product transfusions, hemodialysis and high-risk sexual practices, but the leading risk factor for HCV infection is injection drug use (IDU). While the hepatitis C epidemic is substantial in the country as a whole, it has become a major concern in correctional settings. Prevalence of HCV infection in prisons is 8- to 20-fold higher than in the community, with infection rates between 16 and 41 percent and evidence of chronic infection in 12-35 percent. An estimated one out of three Americans with chronic hepatitis C infection rotates through correctional facilities annually. Despite the slow progression of most infections, illness and death within correctional systems is already substantial, likely explained by a large number of infections acquired decades ago. Hepatitis C infection is a leading cause of illness and death among in-custody inmates in some correctional facilities and an emerging cause in others. Allen, S.A., Rich, J.D., Schwartzapfel, B., and Friedmann, P.D. Hepatitis C Among Offenders--Correctional Challenge and Public Health Opportunity. Federal Probation, 67(2), pp. 22-26, 2003.

Short-term Alcohol and Drug Treatment Outcomes Predict Long-term Outcome

Although addiction is recognized as a chronic, relapsing condition, few treatment studies, and none in a commercially insured managed care population, have measured long-term outcomes. The authors examined the relationship of 6-month treatment outcomes to abstinence 5 years post-treatment, and whether the predictors of abstinence at 5 years were different for those who were, and were not, abstinent at 6 months. The sample (N = 784) is from an outpatient (day hospital and traditional outpatient) managed care chemical dependency program. Subjects were interviewed at baseline, 6 months, and 5 years. Logistic regression analysis was used to assess which individual, treatment and extra-treatment characteristics predicted alcohol and drug abstinence at 5 years. Abstinence at 6 months was an important predictor of abstinence at 5 years. Among those abstinent at 6 months, predictors of abstinence at 5 years were older age, being female, 12-step meeting attendance, and recovery-oriented social networks. Among those not abstinent at 6 months, being alcohol dependent rather than drug dependent, 12-step meeting attendance, treatment readmission, and recovery-oriented social networks predicted abstinence at 5 years. Findings of this study demonstrate a clear association between short-term and long-term treatment success. In addition, these results strongly support the importance of recovery-oriented social networks for those with good short-term outcomes, and the beneficial impact of readmission for those not initially successful in treatment. Weisner, C., Ray, G.T., Mertens, J.R., Satre, D.D., and Moore, C. Short-term Alcohol and Drug Treatment Outcomes Predict Long-term Outcome. Drug and Alcohol Dependence, 71(3), pp. 281-294, 2003.

Best Characteristics of Adolescent Gateway Drug Prevention Programs Identified

This paper identifies the best characteristics of gateway prevention programs that prevent or reduce adolescents' use of alcohol, tobacco, and marijuana. A comprehensive literature review of the performance of school-, family-, and community-based drug prevention programs covering the last 20 years was conducted to identify the best characteristics of successful drug prevention programs: involving parents; teaching life and resistance skills and normative education; enacting laws and policies against adolescent drug use; encouraging peer participation; conducting a media campaign; and retaining program participants. School administrators, parents, and community leaders can use the knowledge in this paper to design drug prevention programs that accommodate specific risk factors and types of gateway drug use by adolescents. Montoya, I.D., Atkinson, J., and McFaden, W.C. Best Characteristics of Adolescent Gateway Drug Prevention Programs. Journal of Addictions Nursing, 14, pp. 75-83, 2003.

Gaps in the Drug-free and Methadone Treatment Program Response to Hepatitis C

Drug treatment programs are potential sites for the delivery of Hepatitis C prevention and care services to drug users. Using data collected from a random sample (N=595) of drug treatment programs in the United States, this study compares the provision of HCV services by drug-free and methadone maintenance treatment programs (MMTPs). It then examines and compares perceived inadequacies in this service provision from the perspective of the managers in the two types of programs. Findings indicate that MMTPs are providing more HCV services than drug-free programs, and that a greater proportion of MMTPs compared to drug-free programs are dissatisfied with their current level of HCV service provision. Managers of drug-free programs would like to offer patients more HCV education, while MMTP mangers would like to provide more HCV testing to their patients, and more support and care for patients who are HCV+. Strauss, S., Astone, J., Vassilev, Z., Des Jarlais, D., and Hagan, H. Gaps in the Drug-free and Methadone Ttreatment Program Response to Hepatitis C. Journal of Substance Abuse Treatment, 24, pp. 291-297, 2003.

Estimating the Client Costs of Addiction Treatment

The costs of addiction treatment services are an important determinant of a program's cost-effectiveness, and therefore, of its relevance to addiction treatment providers, insurance companies, and patients. This article introduces the Client DATCAP (Drug Abuse Treatment Cost Analysis Program) and presents process, survey-specific, and quantitative findings from a pilot study to estimate the client costs of attending outpatient and inpatient treatment. The preliminary findings suggest that the self-administered Client DATCAP is a feasible and practical instrument for estimating costs incurred by clients in treatment, with completion time

amounting to less than 10 minutes. Furthermore, client costs had a considerable range across respondents, with time costs consistently accounting for the largest cost component. Findings from the pilot study led to the development and release of edition 2 of the outpatient and inpatient modules of the Client DATCAP. Salome, H.J., French, M.T., Miller, M., McLellan, A.T. Estimating the Client Costs of Addiction Treatment: First Findings From the Client Drug Abuse Treatment Cost Analysis Program (Client DATCAP). Drug Alcohol Depend, 71(2), pp. 195-206, 2003.

Cost of Residential Addiction Treatment in Public Housing

The cost of providing addiction treatment services in a variety of settings is useful information for program administrators, policy makers, and researchers. This study estimates the economic costs of providing substance abuse treatment services at Safeport, a three-phase residential treatment program serving addicted women living in public housing. Economic (opportunity) costs are estimated for each phase separately and for the complete program. Results indicate that the total cost of providing treatment services at Safeport in 2001 was $1,325,235. This total cost comprises $549,737 for stabilization or early abstinence (Phase I), $400,098 for relapse prevention and self-sufficiency (Phase II), and $375,400 for independent living preparation and long-term recovery (Phase III). Average daily census (number of clients/families on a typical day) was just over 11 clients/families in each phase or 34 clients/families for the entire program. The average length of stay was 12 weeks for Phase I, 20 weeks for Phase II, 18 weeks for Phase III, and 50 weeks overall. The average weekly cost per client amounted to $930 for Phase I, $677 for Phase II, $635 for Phase III, and $748 over the full program. The average cost per treatment episode amounted to $11,163 for Phase I, $13,541 for Phase II, $11,435 for Phase III, and $36,136 for the complete program. Future research should compare these cost estimates with corresponding outcome data from Safeport to perform a comprehensive economic evaluation. Alexandre, P.K., Roebuck, M.C., French, M.T., Barry, M. The Cost of Residential Addiction Treatment in Public Housing. Journal of Substance Abuse Treatment, 24(4), pp. 285-290, 2003.

Cost-Effectiveness of Prison-Based Treatment and Aftercare Services

This study performed a cost-effectiveness analysis of the Amity in-prison therapeutic community and Vista aftercare programs for criminal offenders in California. For the average treatment participant, the cost of treatment was $4,112, which led to approximately fifty-one fewer days incarcerated (36% less) than the average individual in the control group. For the average offender, treatment reduced recidivism at a cost of $80 per incarceration day. For participants who received both in-prison treatment and aftercare services, an additional day of incarceration was avoided at a cost of $51 per day relative to those that received in-prison treatment only. Results show that offering a continuum of treatment has the potential to reduce re-incarceration among substance-abusing offenders. McCollister, K.E., French, M.T., Prendergast, M., Wexler, H., Sacks, S. and Hall, E. Is In-Prison Treatment Enough? A Cost-Effectiveness Analysis of Prison-Based Treatment and Aftercare Services for Substance-Abusing Offenders. Law & Policy, 25(1), pp. 63-82, 2003.

Providers' Views on Treating the Dually Diagnosed

Service delivery to dually diagnosed individuals is often impeded by the divergent treatment approaches used by mental health and substance misuse treatment providers. This paper describes findings from a survey of mental health and substance misuse treatment program administrators and staff in Los Angeles County (n = 275) on their views about treating the dually diagnosed. All groups agreed about the challenges of treating dually diagnosed patients; however, there were differences both between and within providers in the two treatment systems on other aspects of treatment. The study is limited as a nonrepresentative sample of programs within a large urban county, but programs were selected because of their participation in county-sponsored activities to improve service delivery to the dually diagnosed. Substance misuse administrators and staff-as opposed to mental health counterparts-strongly endorsed strict adherence to abstinence and use of confrontational approaches. Grella, C.E. Contrasting the Views of Substance Misuse and Mental Health Treatment Providers on Treating the Dually Diagnosed. Substance Use and Misuse, 38(10), pp. 1433-1446, 2003.

Tennessee Serves More Youth with Fewer Services through Medicaid Managed Care

This study assessed trends in access to and use of behavioral health services for school-aged children in Tennessee's Medicaid managed care program (TennCare),

between 1995 and 2000. Researchers used data from the Bureau of TennCare on claims, encounters, and enrollment in analyses of enrollment periods for children and adolescents who were 4-17 years old at the time of service or enrollment. Measures were calculated in four areas: overall access to behavioral health services; use of inpatient services; use of outpatient specialty treatment services; and use of supportive services like case management and medication management. Study results showed that the number of youths receiving a behavioral service increased by nearly half between 1995 and 2000. At the same time, the number of youths enrolled in TennCare increased by 19 percent. The annual access rate increased from about 72 youths per 1,000 enrollees to about 92. However, the volume of services for children fell, and access rates were low relative to estimated need. The system made less use of inpatient services and relied more on outpatient services, particularly case management and medication management services. Researchers concluded that children's access rates for behavioral health services improved even as the TennCare program expanded to cover more children. However, the system served more youths in part by reducing the volume of services for children receiving treatment and substituting more supportive services. Saunders, R.C. and Heflinger, C.A. Tennessee Serves More Youth with Fewer Services through State's Medicaid Managed Care Program. Psychiatric Services, 54, pp. 1364-1371, 2003.

Treating Drug-Abusing Offenders Under California Proposition 36

This study summarizes initial differences in the way five California counties are implementing California Proposition 36, which allows drug abuse offenders to receive treatment rather than jail time. Using first year data, investigators examined variations and similarities in implementation, such as treatment approaches, urine testing, and patient mix. Except for San Francisco, treatment admissions increased during the first year of Proposition 36 over the previous year (up 27% in Kern, 21% in Riverside, 17% in Sacramento, and 16% in San Diego). Most increases were in outpatient drug-free programs. Results are consistent with Proposition 36 aims that emphasize referral of nonviolent drug offenders to community-based treatment. Results suggest that Proposition 36 is bringing previously untreated drug abusers to treatment. Compared to non-Proposition 36 patients, Proposition 36 patients were more likely to be employed males being treated for the first time in outpatient abstinence-oriented programs for methamphetamine or marijuana use. Non-Prop 36 patients were more likely to be treated in residential programs or methadone maintenance programs, and were more likely to report heroin use or injection drug use. Hser, Y., Teruya, C., Evans, E., Longshore, D., Grella, C., and Farabee, D. Treating Drug-abusing Offenders: Initial Findings from a Five-County Study on the Impact of California's Proposition 36 on the Treatment System and Patient Outcomes. Evaluation Review, 27(5), pp. 479-504, 2003.

Changes in Smoking Status Among Substance Abusers

Impact of change in smoking status on 12-month substance abuse treatment outcomes was examined among 749 HMO participants. At follow-up, 13% of the 395 smokers quit and 12% of the 254 nonsmokers started/relapsed back to smoking. At treatment entry, quitters were less likely to be diagnosed alcohol dependent compared to smokers; starters/resumers were more likely to be diagnosed as alcohol and drug dependent compared to all groups. Total days abstinent was greatest for quitters and nonsmokers. Self-initiated smoking cessation appears nondetrimental and may be beneficial to substance abuse treatment. Individuals who start/resume smoking after entry into substance abuse treatment may be at greater risk of relapse and are understudied. Kohn, C.S., Tosh, J.Y. and Weisner, C.M. Changes in Smoking Status among Substance Abusers: Baseline Characteristics and Abstinence from Alcohol and Drugs at 12-month Follow-up. Drug and Alcohol Dependence, 69(1), pp. 61-71, 2003.

Clinical Characteristics Differ by Age, Suggesting Age Variation in Treatment Needs

At baseline, older adults showed higher levels of DSM-IV alcohol dependence, lower rates of drug dependence, and fewer psychiatric symptoms, relative to younger individuals. Source of suggestions to enter treatment differed by age. Older and middle-aged patients were more likely to have an abstinence goal and to stay in treatment longer than younger adults. Improvement in ASI severity scores differed by age. Lower rates of dependence and hostility, and greater motivation and length of stay in treatment, which were all associated with greater age, positively affect prognosis of older adults in treatment. Baseline differences by age group in clinical characteristics suggest variation in treatment needs. Satre, D.D., Mertens, J., Arean, P., and Weisner, C. Contrasting Outcomes of Older, Middle-aged, and Younger Adult

Chemical Dependency Patients in a Managed Care Program. Journal of Studies on Alcohol, 64(4), pp. 520-530, 2003.

Some Substance Abuse Interventions for Adolescents Reduce Social Costs

An economic evaluation of five outpatient adolescent treatment approaches (12 total site-by-conditions) was conducted. The economic cost of each of the 12 site-specific treatment conditions was determined by the Drug Abuse Treatment Cost Analysis Program (DATCAP). Economic benefits of treatment were estimated by first monetizing a series of treatment outcomes and then analyzing the magnitude of these monetized outcomes from baseline through the 12-month follow-up. The average economic costs of treatment ranged from $90 to $313 per week and from $839 to $3,279 per episode. Relative to the quarter before intake, the average quarterly cost to society for the next 12 months (including treatment costs) significantly declined in 4 of the 12 site-by-treatment conditions, remained unchanged in 6 conditions, and increased in 2 treatment conditions (both in the same site). These results suggest that some types of substance-abuse intervention for adolescents can reduce social costs immediately after treatment. French, M.T., Roebuck, M.C., Dennis, M.L., Godley, S.H., Liddle, H.A., and Tims, F.M. Outpatient Marijuana Treatment for Adolescents: Economic Evaluation of a Multisite Field Experiment. Evaluation Review, 27(4), pp. 421-459, 2003.

Treatment of Sleep Disturbance in Alcohol Recovery

Sleep disturbance is common during recovery from alcoholism and can precipitate relapse. Although sleep complaints are commonly managed with medication, little is known about their management among recovering alcoholic patients. Researchers surveyed a self-weighted, random systematic sample of 503 members of the American Society of Addiction Medicine (ASAM) to examine addiction medicine physicians' medical management of sleep disturbance among patients in early recovery from alcoholism. After 3 mailings, 311 (62%) responded. Of respondents, 64% had offered pharmacological treatment to an insomniac, alcoholic patient in the first 3 months after detoxification, but only 22% offered medication to more than half of such patients. Trazodone was the preferred therapy, chosen first by 38% of respondents, followed by other sedating antidepressants (12%), and antihistamines (12%). The mean duration of therapy for trazodone and other sedating antidepressants exceeded one month. Experts in addiction medicine appear reluctant to prescribe medication to sleep-disturbed patients in early recovery from alcoholism. When they do prescribe, trazodone, other sedating antidepressants, and antihistamines are favored, despite limited evidence for or against this indication. Although the treatment of disordered sleep among alcoholic patients in early recovery may have merit to prevent relapse, controlled studies of these sleep agents are needed. Friedmann, P.D., Herman, D.S., Freedman, S., Lemon, S.C., Ramsey S., and Stein, M.D. Treatment of Sleep Disturbance in Alcohol Recovery: A National Survey of Addiction Medicine Physicians. Journal of Addictive Diseases, 22(2), pp. 91-103, 2003.

Voluntary, Community-Based Alcohol Screening is Feasible and Can Benefit Drinkers

Researchers assessed the feasibility of the 1999 voluntary, community-based National Alcohol Screening Day (NASD) by determining 1) the extent to which community and college sites were registered to hold screenings and the extent to which the subjects came to participate, 2) the demographic and clinical characteristics of participants at screening sites, and 3) the extent to which individuals who were referred for evaluation and treatment adhered to follow-up recommendations. Registered community and college sites were documented. Screening forms returned by the participants were analyzed. A subgroup of randomly selected participants from community and college sites was contacted by telephone. A total of 1,218 community sites and 499 college sites participated in NASD. At the 1,089 sites that reported results, 32,876 people participated, 18,043 were screened, and 5,959 were referred for treatment. Forty-three percent of those screened had a score of 8 or more on the Alcohol Use Disorders Identification Test (AUDIT), indicating harmful or hazardous drinking. Only 13% of those screened had previous alcohol treatment. In the subgroup that participated in the follow-up survey (N=704), community participants (N=337) had higher mean scores on the AUDIT than the college participants (N=337). Approximately 50% of the community participants and 20% of the college participants adhered to the recommendation to pursue follow-up. The researchers conclude that voluntary, community-based screening for alcohol problems is feasible and provides education, screening, and referral for many individuals with harmful or hazardous drinking behavior. Greenfield, S.F., Keliher, A., Sugarman, D., Kozloff, R.,

Reizes, J.M., Kopans, B., and Jacobs, D. Who Comes to Voluntary, Community-Based Alcohol Screening? Results of the First Annual National Alcohol Screening Day, 1999. American Journal of Psychiatry, 160(9), pp. 1677-1683, 2003.

DATStats: Drug Abuse Treatment Cost Analysis

The Drug Abuse Treatment Cost Analysis Program (DATCAP) was developed and launched in the early 1990s to help addiction researchers and administrators estimate the economic costs of substance abuse interventions. This paper presents summary results from 85 DATCAPs completed over the past 10 years. After first grouping the DATCAPs into 9 treatment modalities, cost measures (normalized to 2001 dollars) are reported along with client caseload information. Additionally, the distribution of costs across 6 resource categories is presented for each of the treatment modalities. The average weekly economic cost per client ranged from 82 US dollars per week for outpatient drug court interventions to 1,138 US dollars per week for adolescent residential treatment. As expected, labor was overwhelmingly the most utilized resource across all modalities, ranging from 48% to 88% of total economic cost. Addiction researchers, program administrators, and policymakers now have cost estimates and resource distribution information for various treatment modalities serving diverse populations. Roebuck, M.C., French, M.T., and McLellan, A.T. DATStats: Results From 85 Studies Using the Drug Abuse Treatment Cost Analysis Program. Journal of Substance Abuse Treatment, 25(1), pp. 51-57, 2003.

Lower Levels of Educational Attainment Predict Shorter Time to Relapse Among Alcohol-Dependent Men and Women

This study investigated the relationship between educational attainment and drinking outcomes after discharge from inpatient treatment for alcohol dependence. Researchers consecutively recruited 41 women and 60 men hospitalized for alcohol dependence between 1993 and 1996 and followed them up monthly for 1 year. Structured interviews were conducted during hospitalization and at monthly intervals after discharge for 1 year to provide data to examine the relationship between educational attainment before treatment and postdischarge drinking outcomes, including time to relapse. After covariate adjustment, educational level was a significant predictor of drinking outcomes. Lower levels of educational attainment before entry into treatment predicted shorter times to first drink and relapse in both women and men. The association of educational attainment and treatment outcome for alcohol dependence warrants further investigation. Greenfield, S.F., Sugarman, D.E., Muenz, L.R., Patterson, M.D., He, D.Y., and Weiss, R.D. The Relationship Between Educational Attainment and Relapse Among Alcohol-Dependent Men and Women: A Prospective Study. Alcoholism: Clinical and Experimental Research, 27(8), pp. 1278-1285, 2003.

Sense of Belonging in School as a Protective Factor Against Drug Abuse Among Native American Urban Adolescents

This article presents the results of a study conducted with 243 Native American students who were part of a multi-ethnic sample of adolescents attending middle school in a large urban center in the Southwest region of the United States. Native adolescents who felt a stronger sense of belonging in their school were found to report a lower lifetime use of alcohol and cigarettes, lower cigarette and marijuana use in the previous month, lower frequency of current use of these substances, fewer substances ever used, and a later age of initiation into drug use than other Native students. Research implications are discussed in relationship to school environment, culturally-grounded prevention curricula, and school social work practice. Napoli, M., Marsiglia, F.F., and Kulis, S. Sense of Belonging in School as a Protective Factor Against Drug Abuse Among Native American Urban Adolescents. Journal of Social Work Practice in the Addictions, 3(2), pp. 25-41, 2003.

Informed Consent for Laboratory Testing for Drugs of Abuse in Medical Settings

Laboratory testing for drugs of abuse is often conducted in medical settings, with little consideration of the technical limitations and the potential for legal and social harm to patients. The authors consider several technical problems associated with such testing, including the lack of chain-of-custody procedures, the possibility of false-positive results with screening immunoassays, and the infrequency of confirmatory testing. Important ethical issues arise because of the sensitive nature of drug test results, the ramifications of false-positive results, the limitations of confidentiality protection, and the practice of testing without the patient's knowledge. Taken together, these technical and ethical concerns suggest that drug testing policies in

medical settings should specify which conditions require explicit informed consent and create procedures for protecting this sensitive information. Warner, E.A., Walker, R.M. and Friedmann, P.D. Should Informed Consent be Required for Laboratory Testing for Drugs of Abuse in Medical Settings? American Journal of Medicine, 115, pp. 54-58, 2003.

Client-Level Predictors of Adherence to Multi-Systemic Family Therapy

This study seeks to examine factors that facilitate or impede the adoption of an evidence-based treatment for adolescent drug abusers and their families. Specifically, investigators examined client-level correlates of therapist adherence to Multi-systemic Therapy (MST) implemented in community practice settings. MST has received empirical support as an efficacious intervention for adolescents with serious antisocial and drug abuse problems and has been transported to treatment programs in over 30 states. Data for this study were derived using a non-experimental, short-term, prospective-longitudinal design. Families were nested within therapists and family, child, and caregiver data were collected at intake. Therapist adherence to MST was measured monthly. Study participants included 233 families referred to MST by juvenile justice and social services agencies. Youth were referred because of criminal behavior and/or drug abuse. Sixty-six MST therapists from nine treatment organizations participated in the study. Regression analyses were conducted to predict therapist adherence focusing on a different domain of family characteristics: demographic characteristics, referral characteristics, and pretreatment youth functioning. Variations in therapist adherence to MST were observed in relation to demographic and functioning variables at the client level. Caregivers experiencing educational and economic disadvantage report higher therapist adherence to MST than highly educated and economically advantaged caregivers. Therapist adherence to MST was higher when there was a match between the ethnicity of the therapist and caregiver. Finally, therapist adherence to MST was higher when youth were referred for status offenses and substance abuse and lower when youth were referred for a combination of criminal and substance abuse problems and when they had more arrests pre-treatment. Overall, the investigators suggest the current study demonstrates the complexity of implementing evidence-based practice in community settings. Schoenwald, S.K., Halliday-Boykins, C. and Henggeler, S.W. Family Process, 42(3), pp. 345-359, 2003.

Posttreatment Victimization and Violence Among Adolescents Following Residential Drug Treatment

This article examines the relationships among experiences of childhood abuse, psychiatric disorders, self-reported victimization, and violent behavior, with a focus on gender differences. Data were obtained from interviews at treatment entry and 5-year post-treatment for 446 adolescent clients in therapeutic community (TC) drug treatment programs throughout the United States and Canada. Fifty-eight percent of the sample indicated that they engaged in serious violent behaviors (e.g., beatings, threatening or using weapons against other people, or violent crimes such as assaults, rapes, murders) in the 5 years following their separation from TC treatment. Multivariate logistic regression analyses revealed that victimization in the posttreatment period was the most significant factor associated with violent behavior, and pretreatment childhood abuse experiences and psychiatric disorders were not significantly related to the odds of violent behavior. There were significant gender differences in self-reported victimization and violent behavior. The findings suggest that violence in young adulthood for males is related to increasing involvement in violent lifestyles that include drug trafficking, while violence among females is associated with the social and psychological consequences of drug involvement and victimization. High rates of violent involvement and victimization among former adolescent clients suggests the utility of incorporating interventions such as safety-oriented strategies for females or interventions that address involvement in the drug use lifestyles (i.e., use and dealing) for both males and females into residential treatment to reduce the likelihood of future violence. Hawke, J.M., Jainchill, N. and De Leon, G. Posttreatment Victimization and Violence Among Adolescents Following Residential Drug Treatment. Child Maltreatment, 8(1), pp. 58-71, 2003.

Growth Curve Modeling Shows Longer Treatment Retention Related to Initial Reduction in Cocaine Use But Not to Later Changes in Use

This study examined longitudinal treatment effects among cocaine users. The study examined a sample of 371 cocaine users screened from arrestees in jails and from patients in sexually transmitted disease clinics and emergency rooms, all in Los Angeles County during 1992-1994. Of the 371 subjects, 121 had never been in treatment, and 250 reported a history of participation in drug user treatment (145

subjects' first treatment was for cocaine use; 105 were treated for a drug other than cocaine). Data were collected during face-to-face interviews using a natural history interview instrument. Researchers used a series of growth curve models to investigate treatment effects on cocaine use. For those who had been in treatment for cocaine use, use of cocaine decreased from approximately 70% before treatment to 12% after treatment entry, while no such changes were observed among those who had never been in treatment or those in treatment for other drugs. Relative to non-treated users, cocaine-treated participants showed a greater likelihood of pretreatment use for both initial status (OR = 3.58) and growth rate (OR = 1.05). After treatment entry, cocaine-treated participants as compared to nontreated participants had a lower likelihood of use (OR = 0.27), although their cocaine use after the initial status increased at a greater rate (OR = 1.03). Treated users were five times less likely to use when they were in treatment than when they were out of treatment. Longer treatment retention was related to initially reduced use but not to later rates of change in cocaine use. The study findings support that treatment for cocaine use is effective in reducing cocaine use. Longitudinal models provide opportunities to demonstrate the dynamic relationships between treatment and outcome. Chou, C.P., Hser, Y.I. and Anglin, M.D. Longitudinal Treatment Effects Among Cocaine Users: A Growth Curve Modeling Approach. Substance Use & Misuse, 38(9), pp. 1323-1343, 2003.

Deriving Service Costs for a Clubhouse Psychosocial Rehabilitation Program

This article (a) discusses "function cost," a concept to estimate costs where consumers are involved both in delivery and receipt of services; (b) develops a methodology for costing service units for psychosocial rehabilitation clubhouses; and (c) presents a case study of a clubhouse program. Using function cost to estimate the value of member time results in costs being on average about 10% higher than when using opportunity cost. Because the case-study clubhouse is typical in key dimensions, the methods used here appear generalizable to other programs and should have utility for other rehabilitation-based services for individuals with mental illness. Cowell, A.J., Pollio, D.E., North, C.S., Stewart, A.M., McCabe, M.M. and Anderson, D.W. Deriving Service Costs for a Clubhouse Psychosocial Rehabilitation Program. Administration and Policy in Mental Health, 30(4), pp. 323-340, 2003.

Gender Differences and Treatment Outcomes Among Methadone Patients in the Drug Abuse Treatment Outcome Study

This study examined gender differences among 727 individuals in 21 methadone treatment programs. At treatment entry, a greater proportion of men abused alcohol, lived with their parents, were under legal supervision, and were employed; a greater proportion of women received public assistance, were depressed, had a substance abusing spouse, and engaged in high-risk sexual behavior. Cocaine use was associated with continued heroin use for both men and women, regardless of treatment participation. Using alcohol, living with one's parents, and having a negative reference group were associated with poorer treatment outcomes among women who received methadone treatment during the follow-up period; criminal justice pressure was associated with abstinence for men who were not in treatment. Grella, C.E., Joshi, V. and Anglin, M.D. Gender Differences and Treatment Outcomes Among Methadone Patients in the Drug Abuse Treatment Outcome Study. Journal of Maintenance in the Addictions, 2(1/2), pp. 103-128, 2003.

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

Research Findings - CTN

CTN-0001&0002 - More opiate addicts undergoing short term (13 days) inpatient or outpatient detoxification completed the treatment and were drug free when treated with buprenorphine/naloxone than clonidine: Inpatient 29% vs. 5%, out patient 77% vs. 22%). (Ling)

CTN-0005 - Substance abusing patients assigned to one 2-hour clinical evaluation session of Motivational Interviewing completed more counseling sessions and were more likely to be enrolled at the treatment program during the next 28 days than the standard care patients. (Ball and Carroll)

CTN-0006 &0007 - Stimulant abusers entering methadone compared to those entering drug free programs are older, more likely to have medical problems, less likely to have work history, more likely to be using opiates, stimulants & sedatives, and less likely to be alcohol or cannabis dependent. Both groups have substantial unemployment, substantial psychiatric co-morbidity, high rates of nicotine use, and modest rates of cannabis use. (Stitzer)

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

Research Findings - Intramural Research

Development and Plasticity Section, Cellular Neurobiology Research Branch

Stable Expression of hrGFP by Mouse Embryonic Stem Cells: Promoter Activity in the Undifferentiated State and During Dopaminergic Neural Differentiation Three promoters, cellular polypeptide chain elongation factor 1 alpha (EF1), cytomegalovirus (CMV), and Rous sarcoma virus (RSV) were examined for stable transgene expression in mouse embryonic stem (ES) cells and their progeny during dopaminergic neural differentiation. In undifferentiated ES cells the EF1 promoter was highly effective, while CMV had moderate activity. After 3 months in culture, expression of humanized renilla green fluorescent protein (hrGFP) was unchanged for the EF1 promoter and decreased for CMV. At the nestin-positive stage of differentiation, hrGFP and nestin were colocalized in about 20% of cells for EF1, in contrast to 80% of cells for the CMV promoter. In tyrosine hydroxylase (TH)-positive neurons neither the EF1 nor CMV promoter were effective. The RSV promoter was inactive in undifferentiated, nestin-positive, and TH-positive cells. Thus, EF1 and CMV are effective promoters for transgene expression in undifferentiated ES cells and nestin-positive neural precursors. Zeng, X. Chen, J., Sanchez, J.F., Coggiano, M., Dillon-Carter, O., Petersen, J., and Freed, W.J. Stem Cells, 21(6), pp. 647-653, 2003.

The Use of Microarrays to Characterize Neuropsychiatric Disorders: Postmortem Studies of Substance Abuse and Schizophrenia Neuropsychiatric disorders are generally diagnosed based on a classification of behavioral and, in some cases, specific neurological deficits. The lack of distinct quantitative and qualitative biological descriptors at the anatomical and cellular level complicates the search for and understanding of the neurobiology of these disorders. The advent of microarray technology has enabled large-scale profiling of transcriptional activity, allowing a comprehensive characterization of transcriptional patterns relating to the pathophysiology of neuropsychiatric disorders. Authors review some of the unique methodological constraints related to the use of human postmortem brain tissue in addition to the generally applicable requirements for microarray experiments. Microarray studies undertaken in neuropsychiatric disorders such as schizophrenia and substance abuse by the use of postmortem brain tissue indicate that transcriptional changes relating to synaptic function and plasticity, cytoskeletal function, energy metabolism, oligodendrocytes, and distinct intracellular signaling pathways are generally present. These have been supported by microarray studies in experimental models, and have produced multiple avenues to be explored at the functional level. The quality and specificity of information obtained from human postmortem tissue is rapidly increasing with the maturation and refinement of array-related methodologies and analysis tools, and with the use of focused cell populations. The development of experimental models of gene regulation in these disorders will serve as the initial step towards a comprehensive genome-linked analysis of the brain and associated disorders, and help characterize the integration and coordinate regulation of complex functions within the CNS. Lehrmann, E., Hyde, T.M., Vawter, M.P., Becker, K.G., Kleinman, J.E., and Freed, W.J. Current Molecular Medicine, 3(5), pp. 437-446, 2003.

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

Understanding the Molecular Mechanism of Sigma-1 Receptors: Towards a Hypothesis that Sigma-1 Receptors are Intracellular Amplifiers for Signal Transduction Although sigma receptors were discovered in 1982, the biochemical and physiological roles of sigma receptors have just begun to unveil. Sigma receptors

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are non-opioid, non-phencyclidine receptors that contain two subtypes: sigma-1 and sigma-2 receptors. The sigma-1 receptor has been cloned and its sequence does not resemble that of any mammalian protein. This review will be on sigma-1 receptors. Sigma-1 receptors contain 223 amino acids and reside primarily at the endoplasmic reticulum. Sigma-1 receptors exist mainly in the central nervous system, but also in the periphery. Sigma-1 receptor ligands include cocaine, (+)-benzomorphans like (+)-pentazocine and (+)N-allyl-normetazocine (or (+)-SKF-10047), and endogenous neurosteroids like progesterone and pregnenolone sulfate. Many pharmacological and physiological actions have been attributed to sigma-1 receptors. These include the regulation of IP3 receptors and calcium signaling at the endoplasmic reticulum, mobilization of cytoskeletal adaptor proteins, modulation of nerve growth factor-induced neurite sprouting, modulation of neurotransmitter release and neuronal firing, modulation of potassium channels as a regulatory subunit, alteration of psychostimulant-induced gene expression, and blockade of spreading depression. Behaviorally, sigma-1 receptors are involved in learning and memory, psychostimulant-induced sensitization, cocaine-induced conditioned place preference, and pain perception. Notably, in almost all the aforementioned biochemical and behavioral tests, sigma-1 agonists, while having no effects by themselves, caused the amplification of signal transductions incurred upon the stimulation of the glutamatergic, dopaminergic, IP3-related metabotropic, or nerve growth factor-related systems. Thus, it is hypothesized that sigma-1 receptors, at least in part, are intracellular amplifiers creating a supersensitized state for signal transduction in the biological system. Su, T.P. and Hayashi, T. Current Medical Chemistry, 10, pp. 2073-2080, 2003.

Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Direct Activation by Dopamine of Recombinant Human 5-HT1A Receptors: Comparison with Human 5-HT2C and 5-HT3 Receptors The effects of dopamine (DA) on the function of human 5-HT(1A) receptors expressed in Xenopus oocytes and CHO-K1 cells were investigated. In addition, the effect of DA on the activation of three different types of human 5-HT receptors (5-HT(1A), 5-HT(2C), and 5-HT(3)) were studied comparatively. In oocytes coexpressing 5-HT(1A) receptors and G-protein-activated potassium channels (GIRK1), 5-HT or DA induced currents with respective EC(50) of 4.2 nM and 11.2 microM. Maximal responses induced by DA were 85 +/- 4% of 5-HT currents and blocked by 5-HT(1A) antagonist, WAY-100635. In CHO-K1 cells expressing 5-HT(1A) receptors, 5-HT and DA inhibited the specific binding of [(3)H]-8-OH-DPAT with IC(50) of 10.2 nM and 1.4 microM, and both 5-HT and DA inhibited the forskolin-induced cAMP accumulation. In oocytes expressing 5-HT(2C) receptors, 5-HT and DA induced currents with respective EC(50) of 6.2 nM and 67.7 microM. Maximal DA responses were 42 +/- 3% of 5-HT currents and blocked by the 5-HT(2) antagonist, piperazine. In oocytes expressing 5-HT(3) receptors, 5-HT and DA induced currents with respective EC(50) of 2.1 microM and 266.3 microM. Maximal DA responses were 37 +/- 3% of 5-HT responses and blocked by 5-HT(3) antagonist LY-278584. Results indicated that the relative potency of DA increased in the order of 5-HT(3) > 5-HT(1A) > 5-HT(2C), and relative efficacy increased in the order of 5-HT(1A) > 5-HT(2C) > 5-HT(3). Results suggest that although DA activates different subtypes of human 5-HT receptors directly, the potency and efficacy of the binding site varies significantly among different receptors. Oz, M., Zhang, L., Rotondo, A., Sun, H., and Morales, M. Synapse, 50, pp. 303-313, 2003.

Diadenosine Tetraphosphate Protects Against Injuries Induced by Ischemia and 6-Hydroxydopamine in Rat Brain Diadenosine tetraphosphate (AP4A), an endogenous diadenosine polyphosphate, reduces ischemic injury in the heart. In this study, IRP investigators report the potent and protective effects of AP4A in rodent models of stroke and Parkinson's disease. AP4A, given intracerebroventricularly before middle cerebral artery (MCA) ligation, reduced cerebral infarction size and enhanced locomotor activity in adult rats. The intravenous administration of AP4A also induced protection when given early after MCA ligation. AP4A suppressed terminal deoxynucleotidyl transferase-mediated biotinylated UTP nick end labeling (TUNEL) induced by hypoxia/reperfusion in primary cortical cultures, and reduced both ischemia-induced translocation of mitochondrial cytochrome c and the increase in cytoplasmic caspase-3 activity *In vivo*. The purinergic P2/P4 antagonist di-inosine pentaphosphate or P1-receptor antagonist sulfonylphenyl theophylline, but not the P2-receptor antagonist suramin, antagonized the effect of AP4A, suggesting that the observed protection is mediated through an anti-apoptotic mechanism and the activation of P1- and P4-purinergic receptors. AP4A also afforded protection from toxicity induced by unilateral medial forebrain bundle injection of 6-hydroxydopamine (6-OHDA). One month after lesioning, vehicle-treated rats exhibited amphetamine-

induced rotation. Minimal tyrosine hydroxylase immunoreactivity was detected in the lesioned nigra or striatum. No KCl-induced dopamine release was found in the lesioned striatum. All of these indices of dopaminergic degeneration were attenuated by pretreatment with AP4A. In addition, AP4A reduced TUNEL in the lesioned nigra 2 d after 6-OHDA administration. Collectively, these data suggest that AP4A is protective against neuronal injuries induced by ischemia or 6-OHDA through the inhibition of apoptosis. The authors propose that AP4A may be a potentially useful target molecule in the therapy of stroke and Parkinson's disease. Wang, Y., Chang, C.F., Morales, M., Chiang, Y.H., Harvey, B.K., Su, T.P., Tsao, L.I., Chen, S., and Thiemermann, C. Journal of Neuroscience, 23(21), pp. 7958-7965, 2003.

HSV Amplicon Delivery of Glial Cell Line-Derived Neurotrophic Factor is Neuroprotective Against Ischemic Injury Direct intracerebral administration of glial cell line-derived neurotrophic factor (GDNF) is neuroprotective against ischemia-induced cerebral injury. Utilizing viral vectors to deliver and express therapeutic genes presents an opportunity to produce GDNF within localized regions of an evolving infarct. We investigated whether a herpes simplex virus (HSV) amplicon-based vector encoding GDNF (HSVgdnf) would protect neurons against ischemic injury. In primary cortical cultures HSVgdnf reduced oxidant-induced injury compared to the control vector HSVlac. To test protective effects *In vivo*, HSVgdnf or HSVlac was injected into the cerebral cortex 4 days prior to, or 3 days, after a 60-min unilateral occlusion of the middle cerebral artery. Control stroke animals developed bradykinesia and motor asymmetry; pretreatment with HSVgdnf significantly reduced such motor deficits. Animals receiving HSVlac or HSVgdnf after the ischemic insult did not exhibit any behavioral improvement. Histological analyses performed 1 month after stroke revealed a reduction in ischemic tissue loss in rats pretreated with HSVgdnf. Similarly, these animals exhibited less immunostaining for glial fibrillary acidic protein and the apoptotic marker caspase-3. Taken together, these data indicate that HSVgdnf pretreatment provides protection against cerebral ischemia and supports the utilization of the HSV amplicon for therapeutic delivery of trophic factors to the CNS. Harvey, B.K., Chang, C.F., Chiang, Y.H., Bowers, W.J., Morales, M., Hoffer, B.J., Wang, Y., and Federoff, H.J. Experimental Neurology, 183(1), pp. 47-55, 2003.

Long-term Exposure to the Active ingredient in Marijuana, D9-tetrahydrocannabinol, Causes Tolerance at the CB1 Receptor and Blocks Long-term Synaptic Plasticity in the Nucleus Accumbens Prior studies have demonstrated direct actions of cannabinoid receptor agonists in brain slices containing the nucleus accumbens. These studies demonstrated that activation of cannabinoid CB1 receptors inhibited GABA release in the nucleus accumbens entirely by a presynaptic mechanism (Hoffman and Lupica, J. Neurophysiology, 85: 72-83). The present study extends these findings by demonstrating that chronic Δ^9-THC exposure caused marked tolerance to these presynaptic effects of cannabinoids. In these experiments, electrophysiological recordings were performed in nucleus accumbens brain slices prepared from rats following 7 days treatment with Δ^9-THC or the synthetic cannabinoid agonist, WIN 55,212-2. Investigators found that tolerance developed to the acute inhibitory effects of WIN 55,212-2 at both glutamatergic and GABAergic synapses in the nucleus accumbens following chronic Δ^9-THC. This finding is significant because it represents the first time that physiological tolerance to cannabinoids at defined synapses in the CNS has been described. Another consequence of long-term exposure to Δ^9-THC was that a specific form of synaptic plasticity, known as long-term depression (LTD) of glutamatergic synaptic transmission, was completely blocked in the nucleus accumbens of rats chronically treated with Δ^9-THC, but not in vehicle controls. Since LTD is critically dependent on endogenous cannabinoids in the nucleus accumbens (i.e. it is absent in CB1 receptor knockouts), these data suggest that chronic treatment with Δ^9-THC can alter the sensitivity of synapses to endogenous cannabinoids, and that tolerance to Δ^9-THC is associated with a deficit in synaptic plasticity. Hoffman, A.F., Oz, M., Caulder, T. and Lupica, C.R. The Journal of Neuroscience, 23, pp. 4815-4820, 2003.

Functional Localization of Cannabinoid Receptors and Endogenous Cannabinoid Production in Distinct Neuron Populations of the Hippocampus The mammalian hippocampus is thought to be one of the primary brain regions involved in the cognitive disrupting effects of marijuana in humans and animals. This is likely because it contains some of the highest levels of cannabinoid CB1 receptors in the brain. GABAergic interneurons represent a small fraction (<10%) of the neuronal population in the hippocampus. However, single interneurons can provide widespread input to hundreds of principal (pyramidal) cells, whose axons comprise

the primary output pathway of the hippocampus. Previous work by IRP investigators demonstrated that activation of presynaptic CB1 receptors resulted in the inhibition of GABA-mediated synaptic transmission onto pyramidal neurons in the hippocampus. In order to determine whether synaptic inputs to hippocampal interneurons are also regulated by cannabinoids, whole-cell electrophysiological recordings in distinct interneuron populations were performed. In this study, authors found that, whereas glutamatergic inputs to pyramidal cells were presynaptically inhibited by the cannabinoid agonist WIN55,212-2, glutamatergic inputs to interneurons were unaffected by this agonist. In contrast, GABAergic inputs to the interneurons were inhibited by WIN55,212-2, and this effect was reversed by the CB1 receptor antagonist SR141716A. Also, using a sensitive electrophysiological bioassay for endogenous cannabinoid release, known as depolarization-induced suppression of inhibition (DSI), they found that pyramidal cells, but not interneurons, released endogenous cannabinoids. The localization of endogenous cannabinoid release to pyramidal neurons suggests that the role of these molecules may be limited to the regulation of specific synapses. This work identifies a novel neuronal pathway for consideration when examining the substrates responsible for the disruption of memory by marijuana. Hoffman, A.F., Riegel, A.C., and Lupica, C.R. European Journal of Neuroscience, 18, pp. 524-534, 2003.

MRI Physics Unit, Neuroimaging Research Branch

Circular Spectrum Mapping of Diffusion Imaging for Identifying Brain Fiber Structures Dr. Y. Yang and his colleagues in the Neuroimaging Branch developed a new imaging method to map intravoxel structures of white matter, especially fiber crossings, using circular spectrum decomposition based on high-angular resolution measurements of apparent diffusion coefficients (ADC). The basic premise of this method is to determine the ADC values voxelwise on the unit circle spanned by the major and median eigenvectors of the diffusion tensor, and then apply a 1D Fourier-transform onto this circle. The 0th, 2nd, and 4th order harmonic components of the circular spectrum provide effective indices for mean diffusivity, linear fiber, and orthogonal fiber crossing diffusion respectively. A theoretical frame work has been established for the novel diffusion imaging technique. Simulations on a digital phantom demonstrated the effectiveness of the technique to identify fiber intersections. *In vivo* experiments on normal subjects showed that high 4th-order components (fiber crossings) can be observed in a number of brain regions, including pons, medulla, and areas around corpus callosum. This new technique provides an innovative tool for mapping fiber crossings inside the brain. Information obtained from this technique would be used for improving fiber-tracking techniques and for better delineating neuronal pathways under normal and pathological conditions. W. Zhan, H. Gu, S. Xu, D. A. Silbersweig, E. Stern, Y. Yang, Magnetic Resonance Medicine, 49, pp. 1077-1088, 2003.

Psychobiology Section, Medications Discovery Research Branch

Behavioral Effects of Cocaine in Dopamine D5 Receptor Knockout Mice Dopamine D1-like antagonists block several effects of cocaine, including its locomotor-stimulant and discriminative-stimulus effects. Because these compounds generally lack selectivity among the dopamine D1 and D5 receptors, the specific roles of the subtypes have not been determined. Dopamine D5 receptor knockout (DA D5R KO), heterozygous (HET) and wild-type (WT) mice were used to study the role of D5 dopamine receptors in the effects of cocaine. In addition, effects of the D1-like antagonist, SCH 39166 were also studied to further clarify the roles of D1 and D5 dopamine receptors in the discriminative-stimulus effects of cocaine. Cocaine dose-dependently stimulated activity in each genotype, with the highest level of activity induced in the DA D5R WT mice. Both DA D5R KO and HET mice showed reduced levels of horizontal activity compared to WT mice. All three genotypes acquired the discrimination of 10 mg/kg cocaine; doses of 1.0 - 10.0 mg/kg produced dose-related increases in the number of cocaine-appropriate responses. SCH 39166 produced a dose-dependent rightward shift in the cocaine dose-effect curve in all genotypes, with similar apparent affinities. The present data suggest an involvement of DA D5R in the locomotor stimulant effects of cocaine. In addition, the data indicate that there is little involvement of the DA D5R in the discriminative-stimulus effects of cocaine. In addition, the antagonism data suggest a role of the D1 receptor in the behavioral effects of cocaine. Elliot, E.E, Sibley, D.R. and Katz, J.L. Psychopharmacology, 169, pp. 161-168, 2003.

Clinical Psychopharmacology, Medications Discovery Research Branch

High-dose Fenfluramine Administration Decreases Serotonin Transporter Binding, but not Serotonin Transporter Protein Levels, in Rat Forebrain

Administration of D-fenfluramine (D-FEN) or parachloroamphetamine (PCA) can produce long-lasting decreases in serotonin transporter (SERT) binding and tissue levels of serotonin (5-HT) in rat forebrain. These changes have been viewed as evidence for 5-HT neurotoxicity, but no studies have measured SERT protein levels. In the present study, we determined the effect of high-dose D-FEN or PCA, administered according to a "neurotoxic" dosing regimen, on the density of SERT sites using ligand binding methods and on SERT protein levels using Western blots. Rats were sacrificed 2 days and 2 weeks after administration of drug or saline. The density of SERT was determined in homogenates of caudate and whole brain minus caudate. D-FEN and PCA decreased SERT binding by 30% to 60% in both tissues and at both time points. Similarly, D-FEN and PCA administration profoundly decreased tissue 5-HT and 5-HIAA in frontal cortex. Despite the large decreases in SERT binding and depletion of tissue 5-HT that occurred with D-FEN administration, SERT protein expression, as determined by Western blot analysis, did not change in either tissue or time point. PCA administration decreased SERT protein by about 20% only at the 2 day point in the caudate. Drug treatments did not change expression of glial fibrillary acidic protein (GFAP), a hallmark indicator of neuronal damage, in whole brain minus caudate in the 2 week group. These results support the hypothesis that decreases in tissue 5-HT and SERT induced by that D-FEN- and PCA binding sites reflect neuroadapative changes, rather than neurotoxic effects. Rothman, R.B., Jayanthi, S., Wang, X., Dersch, C.M., Cadet, J.L., Prisinzano, T., Rice, K.C. and Baumann, M.H. Synapse, 50, pp. 233-239, 2003.

***in vitro* Characterization of Ephedrine-related Stereoisomers at Biogenic Amine Transporters and the Receptorome Reveals Selective Actions as Norepinephrine Transporter Substrates** Ephedrine is a long-studied stimulant available both as a prescription and over-the-counter medication, as well as an ingredient in widely marketed herbal preparations, and is also used as a precursor for the illicit synthesis of methamphetamine. Ephedrine is related to phenylpropanolamine, a decongestant removed from the market place due to concerns that its use increased the risk of hemorrhagic stroke. Standard pharmacology texts emphasize that ephedrine is both a direct and indirect adrenergic agonist, activating adrenergic receptors both by direct agonist activity as well as by releasing norepinephrine via a carrier-mediated exchange mechanism. Chemically, ephedrine possesses two chiral centers. In the present study, IRP scientists characterized the stereoisomers of ephedrine, and the closely related compounds, pseudoephedrine, norephedrine, pseudonorephedrine (cathine), methcathinone, and cathinone, at biogenic amine transporters and a large battery of cloned human receptors (e.g. 'receptorome'). The most potent actions of ephedrine-type compounds were as substrates of the norepinephrine transporter (EC50 values of about 50 nM) followed by substrate activity at the dopamine transporter. Screening the receptorome demonstrated weak affinity at a2-adrenergic and 5-HT7 receptors (Ki values 1-10 uM) and no significant activity at b-adrenergic or a1 receptors. Viewed collectively, these data indicate that the pharmacological effects of ephedrine-like phenylpropanolamines are likely mediated by norepinephrine release and, although sharing mechanistic similarities with, differ in important respects, those of the phenylpropanonamines methcathinone and cathinone, and the phenyisopropylamines methamphetamine and amphetamine. Rothman, R. B., Vu, N., Roth, B.L., Hufeisen, V.S.J., Compton-Toth, J. and Glennon, R.A., Journal of Pharmacology and Experimental Therapeutics, 307, pp. 138-145, 2003.

(+)-Fenfluramine and its Major Metabolite, (+)-Norfenfluramine, are Potent Substrates for Norepinephrine Transporters (±)- Fenfluramine is an amphetamine analog that was once widely prescribed as an appetite suppressant. While (±)-fenfluramine is no longer clinically available, the mechanisms underlying its anorectic properties are still of interest. Upon peripheral administration, stereoisomers of (±)-fenfluramine are N-de-ethylated to form the metabolites, (+)- and (-)-norfenfluramine. It is well accepted that isomers of (±)-fenfluramine and (±)-norfenfluramine interact with serotonin (5-HT) transporters to release 5-HT from neurons. However, the effects of these drugs on other monoamine transporters are not well characterized. In this study, IRP scientists examined the interaction of stereoisomers of (±)-fenfluramine and (±)-norfenfluramine with transporters for 5-HT, norepinephrine (NE), and dopamine (DA). Results from *in vitro* assays confirmed these drugs are potent substrates for 5-HT transporters: (+)-fenfluramine, (-)-fenfluramine, (+)-norfenfluramine, and (-)-norfenfluramine released [3H]5-HT from synaptosomes with EC50 values of 52 nM, 147 nM, 59 nM, and 287 nM, respectively. Importantly, (+)-fenfluramine and (+)-norfenfluramine released [3H]NE with EC50 values of 302 nM and 73 nM. Results from *In vivo* microdialysis experiments showed that intravenous injection of (+)-norfenfluramine elevates extracellular levels of 5-HT, NE and DA in rat frontal cortex. The effects of (+)-norfenfluramine on NE and DA

were antagonized by pretreatment with the NE uptake blocker, nisoxetine. In summary, administration of fenfluramines can increase synaptic levels of 5-HT, NE and DA in the cortex, and (+)-norfenfluramine likely contributes to these effects. Release of NE and DA evoked by (+)-norfenfluramine is at least partly mediated via NE transporters. Results of this study emphasize the potential involvement of noradrenergic mechanisms in the actions of fenfluramines. Rothman, R. B., Clark, R.D., Partilla, J.S. and Baumann, M.H., Journal of Pharmacology and Experimental Therapeutics, 305, pp. 1191-1199, 2003.

Neurobiology of Relapse Section, Behavioral Neuroscience Research Branch

Molecular Neuroadaptations in the Accumbens and Ventral Tegmental Area During the First 90 days of Forced Abstinence from Cocaine Self-administration in Rats Cocaine self-administration is associated with a propensity to relapse in humans and reinstatement of drug seeking in rats after prolonged withdrawal periods. These behaviors are hypothesized to be mediated by molecular neuroadaptations within the mesolimbic dopamine system. However, in most studies of drug-induced neuroadaptations, cocaine was experimenter-delivered and molecular measurements were performed after short withdrawal periods. In the present study, rats were trained to self-administer intravenous cocaine or oral sucrose (a control non-drug reward) for 10 days (6-h/day) and were sacrificed following 1, 30, or 90 days of reward withdrawal. Tissues from the accumbens and ventral tegmental area (VTA) were assayed for candidate molecular neuroadaptations, including enzyme activities of cAMP-dependent protein kinase (PKA) and adenylate cyclase (AC), and protein expression of cyclin-dependent kinase 5 (cdk5), tyrosine hydroxylase (TH) and glutamate receptor subunits (GluR1, GluR2, and NMDAR1). In the accumbens of cocaine-trained rats, GluR1 and NMDAR1 levels were increased on days 1 and 90, while GluR2 levels were increased on days 1 and 30, but not day 90; PKA activity levels were increased on days 1 and 30, but not day 90, while AC activity, TH, and cdk5 levels were unaltered. In the VTA of cocaine-trained rats, NMDAR1 levels were increased for up to 90 days, while GluR2 levels were increased only on day 1; TH and Cdk5 levels were increased only on day 1, while PKA and AC activity levels were unaltered. Cocaine self-administration produces long-lasting molecular neuroadaptations in the VTA and accumbens that may underlie cocaine relapse during periods of abstinence. Lu, L., Grimm, J.W., Shaham, Y., Hope, B.T. Journal of Neurochemistry, 23, pp. 742-747, 2003.

Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch

Histamine H3 Receptor Antagonists Potentiate Methamphetamine Self-administration and Methamphetamine-induced Accumbal Dopamine Release Methamphetamine administration increases brain levels of histamine and neuronal histamine attenuates several of methamphetamine's behavioral effects. The role of different subtypes of histamine receptors in this negative feedback, however, remains unclear. The aim of the present study was to evaluate the effects of two histamine H3 receptor antagonists, clobenpropit and thioperamide, on rewarding and neurochemical effects of methamphetamine utilizing three in-vivo methodologies. In rats self-administering methamphetamine intravenously under a fixed-ratio schedule, pre-session treatment with thioperamide (1.0 - 3.0 mg/kg, SC) or clobenpropit (1.0 - 3.0 mg/kg, SC) potentiated the reinforcing effects of methamphetamine, as indicated by a dose-dependent increase in responding for a low 0.03 mg/kg dose of methamphetamine, that by itself failed to maintain responding above saline substitution levels, and a decrease in responding for a higher 0.06 mg/kg training dose of methamphetamine. In contrast, neither thioperamide nor clobenpropit treatment increased responding during saline substitution. In other rats trained to discriminate IP injection of 1.0 mg/kg methamphetamine from IP injection of saline, both thioperamide and clobenpropit (0.3 - 3.0 mg/kg, SC) dose dependently increased methamphetamine-appropriate responding when administered with a low 0.3 mg/kg IP dose of methamphetamine, which by itself produced predominantly saline-appropriate responding. However, thioperamide and clobenpropit produced only saline-appropriate responding when administered with saline vehicle. Finally, thioperamide and clobenpropit potentiated methamphetamine-induced elevations in extracellular dopamine levels in the shell of the nucleus accumbens, but did not increase brain dopamine levels when given alone. These findings point to histamine H3 receptors as a new and important receptor system modulating the reinforcing, subjective and neurochemical actions of methamphetamine. Munzar, P., Tanda, G., Justinova, Z., and Goldberg, S.R. Neuropsychopharmacology http://www.acnp.org/citations/NPP12160303323/default.pdf

Involvement of Adenosine A1 and A2A Receptors in the Adenosinergic Modulation of the Discriminative-Stimulus Effects of Cocaine and

Methamphetamine in Rats Adenosine, by acting on adenosine A1 and A2A receptors, is known to antagonistically modulate dopaminergic neurotransmission. IRP investigators have recently reported that nonselective adenosine receptor antagonists (caffeine and 3,7-dimethyl-1-propargylxanthine) can partially substitute for the discriminative-stimulus effects of methamphetamine. In the present study, by using more selective compounds, the authors investigated the involvement of A1 and A2A receptors in the adenosinergic modulation of the discriminative-stimulus effects of both cocaine and methamphetamine. The effects of the A1 receptor agonist N6-cyclopentyladenosine (CPA; 0.01-0.1 mg/kg) and antagonist 8-cyclopentyl-1,3-dimethylxanthine (CPT; 1.3-23.7 mg/kg) and the A2A receptor agonist 2-p-(2-carboxyethyl)phenethylamino-5'-N-ethylcarboxamidoadenosine hydrochloride (CGS 21680; 0.03-0.18 mg/kg) and antagonist 3-(3-hydroxypropyl)-8-(3-methoxystyryl)-7-methyl-1-propargylxanthin phosphate disodium salt (MSX-3; 1-56 mg/kg) were evaluated in rats trained to discriminate either 1 mg/kg methamphetamine or 10 mg/kg cocaine from saline under a fixed-ratio 10 schedule of food presentation. The A1 and A2A receptor antagonists (CPT and MSX-3) both produced high levels of drug-lever selection when substituted for either methamphetamine or cocaine and significantly shifted dose-response curves of both psychostimulants to the left. Unexpectedly, the A2A receptor agonist CGS 21680 also produced drug-appropriate responding (although at lower levels) when substituted for the cocaine-training stimulus, and both CGS 21680 and the A1 receptor agonist CPA significantly shifted the cocaine dose-response curve to the left. In contrast, both agonists did not produce significant levels of drug-lever selection when substituted for the methamphetamine-training stimulus and failed to shift the methamphetamine dose-response curve. Therefore, adenosine A1 and A2A receptors appear to play important but differential roles in the modulation of the discriminative-stimulus effects of methamphetamine and cocaine. Justinova, Z., Ferré, S., Segal, P.N., Antoniou, K., Solinas, M., Pappas, L.A., Highkin, J.L., Hockemeyer, J., Munzar, P., and Goldberg, S.R. Journal of Pharmacology and Experimental Therapeutics, 307, pp. 977-986, 2003.

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

Reliability and Validity of the Tobacco Craving Questionnaire and Validation of a Craving-induction Procedure The purpose of this study was to determine the reliability and validity of the Tobacco Craving Questionnaire (TCQ) and the validity of imagery scripts to elicit self-reported tobacco craving. Current cigarette smokers (24 men, 24 women) not attempting to quit or reduce smoking engaged in active imagery of three auditory scripts that described no-, low-, and high-intensity of smoking urge. After each imagery condition, participants completed the 47-item TCQ, a Mood Form, and Visual Analog Scale (VAS) questions. Reliability of measures was demonstrated by internal consistency and unidimensionality of the four TCQ factors across imagery conditions. Criterion-related validity was demonstrated by an orderly increase in scores on the TCQ and VAS craving measures as a function of craving intensity of the imagery scripts. Increases in effect size parameters and parallel decreases in the stability of test-retest reliability for all craving measures indicated the validity of the imagery procedure. Convergent and discriminant validity were established by the craving scripts increasing self-reported craving, the no-craving (positive-affect) script increasing positive mood, the no-craving script not affecting craving, and the craving scripts not affecting positive mood. Findings further demonstrated the reliability and validity of the TCQ as a multi-factorial instrument to assess the construct of tobacco craving and suggested that the lability of craving, rather than inconsistency and instability in its measurement, was responsible for observed effects. Singleton, E.G., Anderson, L.M.and Heishman, S.J., Addiction, 98, pp. 1537-1546, 2003.

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

Program Activities

New NIDA PAs and RFAs

The R25 grant mechanism, newly titled **Research Education Grants in Drug Abuse and Addiction,** has been re-issued. The objective of the R25 is to be a flexible and specialized mechanism designed to foster the development of drug addiction researchers through creative and innovative educational programs. These educational experiences will attract, train, and further the career development of physician scientists and other health professionals, underrepresented minority scientists, and adolescent, pediatric and geriatric researchers interested in pursuing research relevant to the mission of NIDA.

On October 10, 2003, NIDA re-issued the Program Announcement, **Drug Abuse Aspects of HIV/AIDS and Other Infections (PA-04-007)**. This PA supports a range of investigator-initiated studies on drug abuse aspects of HIV/AIDS and other serious infections that cut across multiple disciplines, including, among others: virology, bacteriology, molecular epidemiology, etiology, therapeutics and vaccines, ethnography and behavioral epidemiology, mathematical modeling and simulations, and the behavioral and social sciences. Program officials in NIDA's Center on AIDS and Other Medical Consequences of Drug Abuse may be contacted for inquiries.

On September 15, 2003, NIDA issued an RFA entitled **Novel Approaches to Phenotyping Drug Abuse (RFA-DA-04-005)**. Through this RFA, NIDA requests applications that propose and evaluate novel approaches to understanding the drug abuse phenotype(s). Specifically, the purpose of this initiative is to support innovative studies that better describe, discriminate and predict the complex nature and course of drug abuse so as to offer more precise phenotypic indicators for testing the hypothesized underlying genetic and environmental risk for drug abuse. Letter of Intent Receipt Date for this RFA was December 22, 2003; Application Receipt Date was January 22, 2004.

On October 31, 2003, NIDA issued an RFA entitled **Behavioral and Cognitive Processes Related to Adolescent Drug Abuse (RFA-DA-04-009)**. This RFA invites applications in the area of behavioral, cognitive and social cognitive research that have the potential to address issues related to drug abuse and addiction during adolescence. The objective of this RFA is to stimulate research that has the potential to advance our understanding of the causes, consequences, prevention and treatment of adolescent drug abuse and addiction. Letter of Intent Receipt Date for this RFA was January 20, 2004; Application Receipt Date is February 20, 2004.

On October 31, 2003, NIDA issued an RFA entitled **Animal Models of Adolescent Drug Abuse: Integrative Studies of Brain and Behavioral Development (RFA-DA-04-011)**. Through this RFA, NIDA seeks to stimulate research that uses an integration of neurobiological and behavioral approaches to study adolescent brain development. Applicants are expected to use animal models and an integrated approach to focus on the development of regions of the brain that are involved in drug-taking behavior and/or altered by acute or chronic exposure to drugs of abuse. Letter of Intent Receipt Date for this RFA is February 17, 2004; Application Receipt Date is March 17, 2004.

On December 1, 2003, NIDA issued an RFA entitled **Medications Development for Cannabis-Related Disorders (RFA-DA-04-014)** to focus on the identification, evaluation and development of safe and effective pharmacological treatments for cannabis-related disorders (CRDs), such as cannabis abuse or dependence, and cannabis-induced disorders (e.g., intoxication, delirium, psychotic disorder, and

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anxiety disorder), and their comorbidity with other medical and psychiatric disorders (e.g., depression), with special interest in the treatment of children and adolescents. Cannabis use includes marijuana, hashish, and other tetrahydrocannabinol (THC) containing substances.

On December 4, 2003, NIDA issued an RFA entitled **Prevention Research for the Transition to Adulthood (RFA-DA-04-013)**. Through this RFA, NIDA seeks research grant applications focused on the transitional period spanning late adolescence and young adulthood that test the efficacy of interventions to prevent and/or reduce drug use, abuse and related problems including HIV-risk behaviors. Letter of Intent Receipt Date for this RFA is February 20, 2004; Application Receipt Date is March 23, 2004.

On December 10, 2003, NIDA issued an RFA entitled **HIV/AIDS and Other Infections Among Drug Users in the Criminal Justice System (RFA-DA-04-015)**. The purpose of this RFA is to support innovative research projects (R21s and R03s) to advance knowledge and understanding of the epidemiology, prevention, and treatment service needs of drug users in the criminal justice system who have or are at high-risk for HIV and other infectious diseases, and who receive legal supervision in the community setting. The RFA is a collaborative effort between NIDA's Center on AIDS and Other Medical Consequences of Drug Abuse (CAMCODA) and the Services Research Branch of the Division of Epidemiology, Services, and prevention Research (DESPR). Letter of Intent Receipt Date for this RFA is February 23, 2004; application Receipt Date is March 23, 2004. Program contacts are Elizabeth Lambert, CAMCODA and Redonna Chandler, DESPR.

On December 23, 2003, NIDA issued an RFA entitled **Targeted Integrative Research in Drug Abuse and HIV/AIDS in Pregnancy (RFA-DA-04-010)**. Through this RFA, NIDA invites targeted integrative research on epidemiological, prevention and treatment service approaches that focus on drug abuse, HIV/AIDS and other medical consequences of drug abuse specifically relevant to pregnant women and females of childbearing age. Letter of Intent Receipt Date for this RFA is February 17, 2004; Application Receipt Date is March 17, 2004.

On January 9, 2004, NIDA issued an RFA entitled **Consequences of Marijuana Use on the Developing Brain (RFA-DA-04-016)**. The purpose of this RFA is to support investigations of the effects of exposure to marijuana--the most commonly used illicit drug among teenagers in the U.S.-on the developing brain. Letter of Intent Receipt Date for this RFA is March 16, 2004; Application Receipt Date is April 16, 2004.

PAs/RFAs Issued With Other NIH Components/Agencies

On October 16, NIDA, in collaboration with NIMH, NIAAA, and NCI, issued a new Program Announcement (PA) entitled **National Cooperative Drug Discovery Groups for the Treatment of Mood Disorders or Nicotine Addiction (NCDDG-MD/NA) (PAR-04-009)**. The intent of this solicitation is to invite applications from academic and pharmaceutical industry investigators interested in participating with the sponsoring NIH Institutes in a National Cooperative Drug Discovery Group (NCDDG-MD/NA) Program to accelerate innovative drug discovery, the development of pharmacologic tools for basic and clinical research in mood disorders or nicotine addiction, and, in the case of mood disorders, the development and validation of models for evaluating novel therapeutics.

On October 8, 2003, NIDA, in collaboration with NIAAA and NIDDK, issued a PA entitled **Mechanisms of Alcoholic Pancreatitis (PA-04-005)**. Through this PA, the sponsoring Institutes are seeking research grant applications that will investigate the underlying molecular, biochemical and cellular mechanisms by which long-term alcohol ingestion leads to the development of pancreatitis.

On October 8, 2003, NIDA, in collaboration with numerous other NIH Institutes, issued a PA entitled **Neurotechnology Research, Development and Enhancement (PA-04-006)**. The purpose of this PA is to encourage submission of new research project grant (R01) and exploratory/developmental grant (R21) applications to research and develop innovative technologies, methodologies, or instrumentation for basic or clinical studies of the brain or behavior in humans or animal models.

On November 18, 2003, NIDA, in collaboration with numerous other NIH Institutes, issued a PA entitled **Bioengineering Research Partnerships (PAR-04-023)**. The purpose of this PA is to encourage submission of new research project grant (R01) applications to support Bioengineering Research Partnerships (BRPs) for basic, applied, and translational multidisciplinary research that addresses important

biological or medical research problems.

On November 18, 2004, NIDA, in collaboration with NIAAA and NIMH, issued a PA entitled **HIV/AIDS, Severe Mental Illness and Homelessness (PA-04-024)**. The goal of this PA is to refocus research on persons with severe mental illness (SMI), either before or after HIV infection, and to expand HIV-related research to homeless persons. This PA solicits studies on the SMI population and/or homeless persons with special attention to the development, implementation, and evaluation of effective HIV-prevention interventions and their dissemination and translation to the community and public health service organizations.

On December 8, 2003, NIDA, in collaboration with a number of other NIH Institutes, issued a PA entitled **Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral Fellows (F31) (PA-04-032)**. This program will provide predoctoral training support for doctoral candidates who have successfully completed their comprehensive examinations or the equivalent by the time of award and will be performing dissertation research and training.

On January 15, 2004, NIDA and a number of other NIH components jointly issued a PA entitled **ELSI Regular Research Program (R01) (PA-04-050)**. This PA is designed to solicit research projects that anticipate, analyze and address the ethical, legal and social implications (ELSI) of the discovery and use of new information and technologies resulting from human genetic and genomic research.

On January 15, 2004, NIDA and a number of other NIH components jointly issed a PA entitled **ELSI Small Grant Research Program (R03) (PA-04-051)**. This PA is designed to solicit research projects that anticipate, analyze and address the ethical, legal and social implications (ELSI) of the discovery and use of new information and technologies resulting from human genetic and genomic research.

On October 3, 2003, NIDA, together with NIAAA and NCI issued an RFA entitled **Transdisciplinary Tobacco Use Research Centers (RFA-CA-04-012)**. The reissue of this RFA reflects recognition of the public health impact of tobacco use and the scientific need for integrative transdisciplinary research across the full spectrum of basic and applied research on tobacco use and control. Letter of Intent Date for this RFA was December 26, 2003; Application Receipt Date was January 23, 2004.

On October 28, 2003, NIDA issued a Notice entitled **Testing Mechanisms of Action for Behavioral Therapies for Substance Use Disorders (NOT-DA-04-002)**. The purpose of this initiative is to provide supplemental funding to existing behavioral treatment studies to encourage studies of how behavioral treatments operate. NIDA views the identification of therapy mechanisms of action as a key step in developing efficacious behavioral treatments that can be delivered in community settings. This supplement program is intended to stimulate research on the causal mechanisms of behavioral treatments, including studies of particular treatments, studies of possible common mechanisms across multiple treatments, and studies developing psychometrically-sound instruments for assessing therapeutic mechanisms of action.

On December 10, 2003, NIDA, in collaboration with NIAAA, issued an RFA entitled **Group Therapy for Individuals in Drug Abuse or Alcoholism Treatment**. The purpose of this Request for Applications (RFA) is to invite research applications addressing group-format behavioral treatments for drug abuse and/or alcohol use disorders (AUD). Applications that focus on interventions to reduce the spread of infectious disease in substance abuse treatment populations are also of interest. This RFA builds on a meeting convened by the National Institute on Drug Abuse (NIDA) in 2003 on the challenges in conducting research on group therapy, and is part of an ongoing commitment of NIDA and National Institute on Alcohol Abuse and Alcoholism (NIAAA) to support the development and testing of behavioral treatments for drug abuse and AUD that can be delivered in community substance abuse treatment settings. Letter of Intent Date for this RFA was January 20, 2004; Application Receipt Date is February 20, 2004.

On December 16, 2003, NIDA, in collaboration with SAMHSA, the Agency for Healthcare Research and Quality (AHRQ) and the Health Resources and Services Administration (HRSA), issued an RFA entitled **Screening and Intervention for Youth in Primary Care Settings (RFA-DA-04-006)**. This RFA seeks to build on recent efforts to address problematic alcohol and nicotine use in primary care settings in order to similarly expand the availability and delivery of efficacious drug abuse interventions. Letter of Intent Date for this RFA was January 19, 2004; Application Receipt Date is February19, 2004.

On January 15, 2004, NIDA and NIMH issued a joint 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 (both injection and non-injection drug use) and who are (a) at high risk for HIV and other infectious diseases, (b) living with HIV/AIDS, and/or (c) affected by HIV/AIDS.

Other Program Activities

CTN Protocol Update

Wave 1 Protocols:

- Five CTN studies have closed enrollment. A total of 5,234 patients have been screened with 2,547 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 sites across 3 states. A total of 455 participants have enrolled in this study so far. Three of the five participating sites have reached their targeted enrollment of 100 clients.

Wave 2 Protocols:

- Protocol CTN 0003 (Bup/Nx: Comparison of Two Taper Schedules) began enrollment on June 30, 2003. This study will be carried out at 11 sites across 8 nodes. The targeted enrollment is 480 participants. Participation is currently at 10% 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 on April 9, 2003. This study will be carried out at 12 Community Treatment Programs across 7 Nodes. One-hundred twenty-seven participants have been enrolled in the last six months at nine sites. The other 3 sites will be enrolling once IRB approvals are finalized. Participation is currently less than 10% of the targeted enrollment.
- CTN 0010 (Buprenorphine/Naloxone Facilitated Rehabilitation for Opioid Dependent Adolescents/Young Adults) began enrollment on July 17, 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.
- CTN 0011 (A Feasibility Study of a Telephone Enhancement Procedure - TELE - to Improve Participation in Continuing Care Activities) began enrollment in January 2003. A total of 339 patients in four sites have enrolled since the beginning of the study. This is a feasibility study and is carried out at four sites across three nodes. Three of the four sites have reached the targeted enrollment. Participation is at 94% of the targeted enrollment of 360.
- 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, has started enrolling participants.
- Protocol CTN 0021(Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome for Spanish-Speaking Individuals Seeking Treatment for Substance Abuse) has begun enrollment. This is the first Spanish only protocol in the CTN. It will be conducted at 6 bi-lingual sites across 5 nodes.

Wave 3 Protocols: The third wave of protocols is progressing and some are near implementation.

- 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 being recruited for therapist training. BSFT will be implemented at 13 sites across 10 nodes plus Puerto Rico. This intervention is the first CTN study to target adolescents and their families.

- Protocol CTN 0015, Women's Treatment for Trauma and Substance Use Disorder: A Randomized Clinical Trial, is working towards protocol implementation in February or March of 2004 for its first "wave" of sites. At this point, all counselors and supervisors have completed the required centralized training on the intervention. Many have also been certified, which requires submitting four videotapes to be rated by the staff at the Lead Node. Staff are also in the process of being certified to administer the ASI and CIDI, which are two of the CTN's required battery of assessment instruments. All sites are in the process of obtaining certification of their data systems, as well as scheduling their local QA initiation monitoring visits.
- Protocol CTN 0016, Patient Feedback: A Performance Improvement in Outpatient Settings, is progressing towards implementation in the spring of 2004. The Quality Assurance Plan for this feasibility study was recently approved. Currently, sites are scheduling their local node QA monitoring visits, as well as those to be conducted by NIDA's contract monitoring organization.
- 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) were reviewed at the April 2003 Data and Safety Monitoring Board (DSMB) Meeting. Sites are being finalized for those protocols. They will be carried out at numerous sites across the Network. It is expected that these will start enrolling in January/February 2004.
- Protocol CTN 0020, Job Seekers Training for Patients with Drug Dependence, was also reviewed at the April 2003 Data Safety and Monitoring Board Meeting. The protocol team very recently created an operations manual. Training in the intervention will occur in the spring of 2004, separately in three different regions of the country. The Case Report Forms have been drafted and are currently being reviewed by the Data Management and Analysis Subcommittee.

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.

NIDA/SAMHSA-ATTC Blending Initiative

The interagency agreement called the NIDA/SAMHSA-ATTC Blending Initiative encourages the use of current evidence-based treatment interventions by professionals in the drug abuse treatment field. "Blending Teams," comprised of staff from CSAT's Addiction Technology Transfer Center (ATTC) Network and NIDA researchers, will develop a strategic dissemination plan for introducing particular research findings using a number of different mechanisms for effective adoption within communities, such as trainings, self-study programs, workshops, and distance learning opportunities. Two NIDA-CSAT Blending Teams have been created to date. The first team, which convened in October 2003, is developing Buprenorphine awareness training and materials for non-physicians in the drug abuse and addiction field. The second team met in December 2003, and they are charged with the development of training materials and products to assist program managers, supervisors, administrators, and policy makers to use the results of the Addiction Severity Index (ASI) for management and program planning decisions. Dr. Suman Rao, OSPC, serves as the NIDA point-of-contact and liaison with SAMHSA.

NRC and IOM report

The NRC and IOM report on "New Treatments for Addiction: Behavioral, Ethical, Legal, and Social Questions" has been completed. NIDA Senior Staff were briefed in January

2004 by members of the NRC/IOM Committee that compiled this report. The full report will be distributed to the NACDA Taskforce on Bioethics for their review, endorsement, and for discussion with NIDA on how best to develop research in this emerging field.

VMAT2 Blockade and Methamphetamine-Induced Neurotoxicity: Implications for Medications Development

On December 5, 2003, in Bethesda, MD, Dr. Nathan Appel, DTR&D, chaired a consultants meeting entitled "VMAT2 Blockade and Methamphetamine-Induced Neurotoxicity: Implications for Medications Development." Dr. Frank Vocci presented the Medications Discovery Program to the consultants, describing its history, organization, accomplishments, and current undertakings. Dr. Bryan Yamamoto (Boston University) then spoke on effects of methamphetamine on brain neurochemistry and neuroanatomy, Dr. Annette Fleckenstein (University of Utah) spoke on effects of methamphetamine on brain membrane monoamine transporters and VMAT2, Dr. Raul Gainetdinov (Duke University) spoke on effects of methamphetamine in VMAT2 knockout animals compared to wild types, and Dr. Linda Dwoskin (University of Kentucky) spoke on biochemistry and behavioral pharmacology of lobeline. A group of listening consultants - consisting of experts in toxicology, pharmacokinetics, and pathology related to medications discovery - provided feedback to NIDA. The consultants recommended *in vivo* animal studies and a number of endpoints that NIDA could use to evaluate the safety of a potential methamphetamine abuse medication whose effects include VMAT2 blockade.

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

Al'absi, Mustafa N. -- University of Minnesota Twin Cities
Psychobiological Mechanisms of Stress & Smoking Relapse

Andersen, Susan L. -- Mc Lean Hospital, Belmont, MA
Early Drug Exposure And Drug Reward Mechanisms

Anthony, James C. -- Johns Hopkins University
Cross-National Studies of Drug Involvement: WMH2000

Arkes, Jeremy -- Rand Corporation
Do Changes In The Economy Affect Teenage Drug Use?

Baizer, Joan S. -- State University of New York at Buffalo
Methylphenidate & Gene Expression In the Rat Brain

Balsam, Peter D. -- Barnard College
Timing: Pharmacology and Conditioning

Bardo, Michael T. -- Yaupon Therapeutics, Inc.
Novelty, Dopamine and Response To Amphetamine

Barth, Alison L. -- Carnegie-Mellon University
Experience Dependent Plasticity In A FosGFP Mouse

Becker, Jill B. -- University of Michigan At Ann Arbor
Gender Differences In Drug Abuse

Bernstein, Ilene L. -- University of Washington
Neural Plasticity and Sensitization of Salt Appetite

Bickel, Warren K. -- University of Vermont & State Agricultural College
Delay Discounting In Drug Dependence

Blanco, Carlos -- New York State Psychiatric Institute
Screening For Comorbidity In Substance Abuse Clinics

Bolland, John M. -- University of Alabama In Tuscaloosa
Strengthening Neighborhood Investment: An Evaluation

Brown, Richard A. -- Butler Hospital, Providence, RI
Distress Tolerance Treatment For Early Smoking Lapsers

Cahill, Lawrence F. -- University of California Irvine
Investigation of Dopamine Function In Human Amygdala

Clair, Scott D. -- Iowa State University of Science & Technology
Assessing Oral HIV Testing Among Brazilian Drug Users

Comer, Sandra D. -- New York State Psychiatric Institute
Prescription Opioid Effects In Drug and Non-Drug Abusers

Conklin, Cynthia A. -- University of Pittsburgh at Pittsburgh
Personalized Cues As Factors In Smoking Relapse

Costello, Elizabeth -- Duke University
Multi-Site Longitudinal Analysis-Psychiatric Risk of SUD

Cunningham-Williams, Renee M. -- Washington University
Validity and Measurement Issues In Pathological Gambling

Dakof, Gayle A. -- University of Miami-Medical
Family-Based Juvenile Drug Court Services

De Biasi, Mariella G. -- Baylor College of Medicine
Mouse Models For Nicotine's Interaction With Stress

Dennis, Michael L. -- Chestnut Health Systems
Early Re-Intervention Experiment2 (Er12)

Dey, Sudhansu K. -- Vanderbilt University
Endocannabinoid Signaling During Early Pregnancy

Dodge, Kenneth A. -- Duke University
Development and Prevention of Substance Use Problems

Dorsey, Cynthia M. -- Mc Lean Hospital, Belmont, MA
Neurochemical Substrates of Sleep Homeostasis

Dunlap, Eloise -- National Development & Research Institutes
Transient Domesticity & Violence In Distressed Household

Dwoskin, Linda P. -- University of Kentucky
Development of Novel Treatments For Nicotine Addiction

Ellickson, Phyllis L. -- Rand Corporation
Long Term Results of Alert Plus

Evans, Suzette M. -- New York State Psychiatric Institute
Effects of Smoked Heroin Across the Menstrual Cycle

Farah, Martha J. -- University of Pennsylvania
Normal Impulsivity: A Cognitive Neuroscience Analysis

France, Charles P. -- University of Texas Health Sciences Center, San Antonio
Discriminative Stimulus Effects of Opioid Withdrawal

Fuchs, Perry N. -- University of Texas Arlington
Supraspinal Processing of Pain Affect

Fuller, Bret E. -- Oregon Health & Science University
Methadone Benefit Elimination--Oregon Health Plan

Galizio, Mark -- University of North Carolina Wilmington
Drugs of Abuse and Complex Behavior

Gariti, Peter -- University of Pennsylvania
Light Smoking Program

Gauda, Estelle B. -- Johns Hopkins University
Clonidine Treatment for Neonatal Abstinence Syndrome

Gifford, Andrew N. -- Brookhaven Science Associates-Brookhaven Lab
Animal Model For Inhalant Abuse

Gilbert, David G. -- Southern Illinois University Carbondale
Nicotine: Cognition-Affect Interactions

Goodkin, Karl -- University of Miami-Medical
HIV-1 Cognitive-Motor Disorders: Definition In Argentina

Goodman, Murray -- University of California San Diego

Peptidomimetic Opioids, Synthesis, Structure & Biology

Hanson, Glen R -- University of Utah
Neurotensin and Methamphetamine Effects

Heimer, Robert -- Yale University
Integrating Sex & Drug Related HIV Risk & Transmission

Henggeler, Scott W. -- Medical University of South Carolina
Adoption and Implementation of Adolescent EBT State-Wide

Hirsh, Jay -- University of Virginia Charlottesville
Non-Invasive Self Administration Methodology For Mice

Hollis, Jack F. -- Kaiser Foundation Research Institute
Implementing Tobacco Control In Dental Practice

Honda, Christopher N. -- University of Minnesota Twin Cities
Purinergic Mechansism of Nociception

Houtsmuller, Elisabeth J. -- Johns Hopkins University
Novel Lapse-Responsive Approach To Smoking Cessation

Javitch, Jonathan A. -- Columbia University Health Sciences
Archaeal & Bacterial Homologs of Dopamine Transporter

Johnson, Bankole A. -- University of Texas Health Sciences Center San Antonio
Lab Trials To Develop Medications For Cocaine Dependence

Johnston, Lloyd D. -- University of Michigan At Ann Arbor
A Cohort-Sequential Panel Study of Drug Use, Ages 19-45

Jones, Hendree E. -- Johns Hopkins University
Treating the Partners of Drug Using Pregnant Women: Stage II

Killen, Joel D. -- Stanford University
Behavioral Maintenance Treatment For Smoking Cessation

Killen, Joel D. -- Stanford University
Selegiline Patch for Treatment of Nicotine Dependence

Kirby, Kimberly C. -- Treatment Research Institute, Inc. (TRI)
A Behavioral Model for Maintenance of Drug Abstinence

Koblin, Beryl -- New York Blood Center
HIV Vaccine Trials In Women

Kozikowski, Alan P. -- University of Illinois at Chicago
Chemistry and Pharmacology of New Nicotine Ligands

Kuhn, Cynthia M. -- Duke University
GHB Tolerance and Dependence

Lam, Wendy K. -- Research Triangle Institute
Family Intervention For Children and Crack-Using Mothers

Latimer, William W. -- Johns Hopkins University
Neurological Influences on Drug Prevention Intervention

Lerman, Caryn E. -- University of Pennsylvania
Pharmacogenetic Investigation of Naltrexone

Lewis, Sarah J. -- Barry University
Antiretroviral-Tip for Substance Users

Li, Kui -- University of Texas Medical Galveston
Impact of HCV Ns3/4a Protease On Host Innate Immunity

Linehan, Marsha M. -- University of Washington
Emotion Regulation In Suicidal Patients With BPD

Lum, Paula -- University of California San Francisco
A Randomized Trial of Vaccine Adherence In Young IDU

Lynch, Thomas R. -- Duke University
Evaluation of Dialectical Behavior Therapy (DBT)

Madden, Gregory J. -- University of Wisconsin Eau Claire
Behavioral Economics In Closed Economies

Malcolm, Robert J. -- Medical University of South Carolina
CBT and Modafinil for Cocaine Addiction

Mannelli, Paolo -- Thomas Jefferson University
Place of Low-Dose Naltrexone In Opiate Detoxification

Marlowe, Douglas B. -- Treatment Research Institute, Inc. (TRI)
Matching Services To Client Needs In Drug Court

Martino, Steve -- Yale University
Training Strategies For Motivational Interviewing

Mayes, Linda C. -- Yale University
Arousal and Attention In Cocaine-Exposed Children

McCann, Una D. -- Johns Hopkins University
Sleep and Nocturnal Endocrine Function In MDMA Usera

Mccurdy, Christopher R. -- University of Mississippi
Salvinorin A: A Structurally Novel Opioid Agonist Lead

McMahon, James M. -- National Development & Research Institutes
Couples HIV Intervention Randomized Controlled Trial

McMahon, Lance R. -- University of Texas Health Sciences Center San Antonio
Drug Discrimination and THC Withdrawal In Monkeys

Miesenbock, Gero -- Sloan-Kettering Institute for Cancer Research
Genetically Encoded Phototriggers of Neuronal Activity

Miller, Laurie -- New England Medical Center Hospitals
Neurodevelopmental Outcome In Russian Orphanage

Miranda, Robert -- Brown University
Mechanisms Relating Conduct Disorder and Drug Abuse

Mitchell, Suzanne H. -- Oregon Health & Science University
Interactions Between Impulsivity and Cigarette Smoking

Moore, Richard D. -- Johns Hopkins University
HIV Disease Outcomes In Drug Users In Clinical Practice

Morral, Andrew -- Rand Corporation
Case-Mix Adjustment For Adolescent Treatment Evaluations

Murrin, Leonard C. -- University of Nebraska Medical Center
Regulation of Mu Opioid Receptor Signal Transduction

Napier, T. Celeste -- Loyola University Medical Center
5-HT & Medication Development For Methamphetamine Abuse

Nelson, Elliot C. -- Washington University
Opioid Dependence: Candidate Genes and G X E Effects

Neumaier, John F. -- University of Washington
The Role of Serotonin Receptors In Brain Reward Circuits

Newton, Thomas .F -- University of California Los Angeles
Perindopril-Methamphetamine Interaction Study

Nunes, Edward V. -- New York State Psychiatric Institute
MI Training: Live Supervision By Tele-Conference

O'Leary, Daniel S. -- University of Iowa
Acute Marijuana Effects on Regional Cerebral Blood Flow

Oser, Carrie B. -- University of Georgia
Adoption & Implementation of Naltrexone In Private Treatment Centers

Ouellet, Lawrence J. -- University of Illinois at Chicago
HIV and the Sexual Networks of IDUs and Drug-Using MSM

Overman, William H. -- University of North Carolina Wilmington

Decision Making In Adolescent Substance Abusers

Pentel, Paul R. -- Minneapolis Medical Research Foundation, Inc.
Immunization To Block the Effects of Nicotine

Pollio, David E. -- Washington University
Family Services For Runaway Homeless Youth

Rao, Uma -- University of Texas Southwest Medical Center Dallas
Stress Response and Smoking Cessation In Depressed Youth

Richardson, Gale A. -- University of Pittsburgh at Pittsburgh
Effects of Prenatal Cocaine Use: 15-Year Follow-Up

Riley, Elise D. -- University of California San Francisco
Drugs, Gender and Healthcare Use Among HIV+ Homeless

Ringwalt, Christopher L. -- Pacific Institute for Research and Evaluation
Diffusion of Drug Prevention Curricula Nationwide

Robertson, Angela A. -- Mississippi State University
HIV Risk Reduction Among Young Incarcerated Females

Roll, John M. -- Friends Research Institute, Inc.
Behavior Change: Reinforcement Schedule Effects

Roth, Bryan L. -- Case Western Reserve University
Diterpines As Selective Kappa Opioid Receptor Agonists

Saewyc, Elizabeth M. -- University of Minnesota Twin Cities
Enacted Stigma, Gender & Risk Behaviors of School Youth

Schnitzer, Mark J. -- Stanford University
Chronic Brain Imaging Using Fluorescence Endoscopy

Severson, Herbert H. -- Oregon Research Institute
Tobacco Quitlines: An Adjunct To Dental Interventions

Shannon, Richard Patrick -- Allegheny-Singer Research Institute
Chronic Cocaine Effects On Normal and Diseased Hearts

Sheidow, Ashli J. -- Medical University of South Carolina
Development of Outpatient MST For Dually Diagnosed Youth

Siegel, Steven J. -- University of Pennsylvania
Evoked Potentials and Vulnerability To Ketamine In Mice

Singer, Lynn T. -- Case Western Reserve University
Cocaine Exposed Children At School Age

Singhal, Pravin C. -- North Shore-Long Island Jewish Research Institute
HIV Associated Nephropathy In Drug Addicts

Sinha, Debasish -- Johns Hopkins University
Modulation of Ciita By Cannabinoids In Human Microglia

Slomkowski, Cheryl -- Miriam Hospital
Sibling Influence On Smoking In Everyday Settings

Solarsh, Geoffrey C. -- University of Natal
Developmental Disabilities In A Time of AIDS

Sulkowski, Mark S. -- Johns Hopkins University
Management/Hepatitis C/HIV-Infected and Uninfected IDUs

Swan, Gary E. -- SRI International
Biometric and Measured Genetic Research On Smoking

Szeto, Hazel H. -- Weill Medical College of Cornell University
Systemically-Active Opioid Peptide Analogs

Taylor, Jane R. -- Yale University
Cognitive Dysfunction After Chronic PCP, THC and Cocaine

Taylor, Jane R. -- Yale University
Incentive Motivation In Addiction: PKA Mechanisms

Teicher, Martin H. -- Mc Lean Hospital, Belmont, MA
Early Stress and Neural Substrates Relevant To Addiction

Trudell, Mark L. -- Louisiana State University-University of New Orleans
Synthesis of Potential Cocaine Therapeutics

Upadhyaya, Himanshu P. -- Medical University of South Carolina
Combined Pharmaco/Behavior Therapy In Adolescent Smokers

Vassileva, Jasmin L. -- University of Illinois at Chicago
Neuro-Cognitive Aspects af Opiate Abuse & Antisocial Behavior

Wagner, Fernando A. -- Morgan State University
Opportunities and Actual Drug Use Among Hispanics

Wallack, Stanley S. -- Brandeis University
Adoption of Buphenorphine In Office Practice

Walsh, Margaret M. -- University of California San Francisco
Reimbursement and Intensity of Dentists' Training

Winters, Ken C. -- University of Minnesota Twin Cities
Brief Intervention for Drug Abusing Students

Woody, George E. -- University of Pennsylvania
Addiction Treatment In Russia: Oral and Depot Naltrexone

Wu, Gang-Yi -- Baylor College Of Medicine
Map Kinase Signaling and Dendritic Spine Plasticity

Yaksh, Tony L. -- University of California San Diego
Characterization of Toxicity With Spinal Opiates

Yeomans, David C. -- Stanford University
Recombinant Herpes Injection Into Trigeminal Ganglia

Yu, Xiao-Fang -- Johns Hopkins University
Implications of HIV In Low HCV Clearance In Chinese IDUs

Zigmond, Michael J. -- University of Pittsburgh at Pittsburgh
Developmental Stress and Vulnerability To Brain Injury

Zule, William A. -- Research Triangle Institute
Modeling HIV Diffusion Through Drug Using Networks

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Extramural Policy and Review Activities

Receipt, Referral, and Review

NIDA received 955 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 674 applications.

OEA arranged and managed 16 review meetings in which 295 applications were evaluated. OEA's reviews included applications in chartered, standing review committees; applications in conflict-of-interest with standing committees; and submissions to special initiatives. In addition, OEA's Contracts Review Branch (CRB) arranged and managed 5 contract proposal reviews and one concept review.

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 four Special Emphasis Panels to review applications in conflict with the chartered committees. Special Emphasis Panels were also constituted for the Minority Institutions Drug Abuse Research Development Program (MIDARP), Centers applications, two Program Projects, Behavioral Science Track Award for Rapid Transition (B/START), Conference Grants, and Cutting Edge Basic Research Awards (CEBRA). Two Special Emphasis Panels reviewed RFA submissions.

OEA managed the following RFA reviews:

- DA 04-001: Stress and Drug Abuse: Epidemiology, Etiology, Prevention, and Treatment
- DA 04-002: Neuroimaging the Effects of Drugs of Abuse on the Development of the Human Nervous System

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

- N01DA-4-8842: Non-clinical ADME Studies
- N01DA-4-8841: Toxicological Evaluations of Potential Medications To Treat Drug Addiction
- N01DA-4-2203: Clinical Trials Network Pharmacy Support
- N01DA-4-1203: National Hispanic Science Network On Drug Abuse
- N01DA-4-7745: NIDA Center for Genetic Studies

Concept Reviews:

- N01DA-4-8844: Analytical Chemistry and Stability Testing of Treatment Drugs

The CTN Protocol Review Board met in Gaithersburg, Maryland, on August 13-14, 2003, to review the fourth wave of new protocols. A second meeting was held on December 18, 2003, to review the recommended revisions to the new protocols.

Extramural Outreach

Dr. Teri Levitin, Director, OEA, spoke to graduate students and faculty at the University of Virginia, Department of Psychology about NIDA and NIH review procedures and policies.

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Dr. Levitin participated in the NIDA Minority Health Scholars Network meeting, speaking about extramural issues, including review at NIDA and CSR.

Mr. Richard Harrison, OEA, participated in the Annual Conference of American Indian Science and Engineering Society in Albuquerque, New Mexico and managed the NIDA exhibit for that conference's Career Fair.

Staff Training and Development

The OEA Symposium Series, a forum for staff training and sharing of ideas and information, continued through the summer. Topics addressed have included stimulating creativity among grantees, special grant mechanisms for innovative research and junior investigators, and policy updates. The symposium series is organized and hosted by Dr. Mark Swieter.

Other Activities

The OEA has continued to assist in meeting requirements related to the President's Management Agenda objective regarding competitive sourcing, with staff involved in various aspects of the NIH competition of grants support functions.

Dr. Teri Levitin served on an NIH-wide committee on review criteria for clinical research/clinical trials applications.

Dr. Levitin continues to serve on the NIH Roadmap committee that is developing the NIH Director's Pioneer Award.

Dr. William Grace, OEA, provided staff support for the National Advisory Council on Drug Abuse Workgroup on HIV/AIDS, coordinating its meetings and working with its members and NIDA staff to facilitate its activities.

Dr. Rita Liu, OEA, co-organized the NIDA mini convention at the 2003 Society for Neuroscience Meetings and co-chaired a session on "Structure, Function and Regulation of the Dopamine Transporter" that was part of the mini convention.

Drs. Khursheed Asghar, Chief, Basic Sciences Review Branch, OEA; Teri Levitin, Director, OEA; and Rita Liu, Associate Director for Receipt and Referral, attended the Society for Neuroscience and represented NIDA at the booth and other several events at this meeting.

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Congressional Affairs

(Prepared February 3, 2004)

The House and Senate adjourned Sine Die on December 8 and December 9, 2003, respectively. Congress reconvened on January 20, 2004, to open the second session of the 108th Congress.

FY 2004 Appropriations

H.R. 2673 - On December 8, 2003, the House passed the conference report for H.R. 2673, the Agriculture Appropriations, FY 2004 (the Omnibus Appropriations bill for FY 2004) by a vote of 242 to 176. This bill contains Government-wide funding provisions for seven separate appropriations bills including Labor, Health and Human Services (H.R. 2660), which funds NIH; Transportation and Treasury (H.R. 2989); Foreign Operations (H.R. 2800); Commerce-Justice-State (H.R. 2799); District of Columbia (H.R. 2765); Veterans, Housing and Urban Development (H.R. 2861); and Agriculture (H.R. 2673).

The Senate took up the measure when it returned for the second session of the 108th Congress in January 2004. On January 22, 2004, the Senate by a vote of 65-28 passed the conference report for H.R. 2673, (the Omnibus Appropriations bill for FY 2004); on January 23, 2004, the President signed H.R. 2673 into law as P.L. 108-199. Upon enactment, NIH receives $27,729 million, an increase of 2.8 percent. NIDA will receive $997,414,000. Also included in the bill is a 0.59 percent across the board cut that applies to non-defense programs. The bill includes a 2.2 percent program evaluation tap as proposed by the Senate for DHHS, including NIH.

Highlights of the Consolidated Appropriations Act, FY 2004 (HR 2673)

- *NIH Director's Transfer Authority:* Continues NIH Director's 1-percent transfer authority; 3- percent AIDS transfer by Director of NIH and Director of OAR. These funds are determined jointly by these Directors and allocated directly to OAR for distribution to ICs.
- *Evaluation Tap:* Includes Senate bill language authorizing transfer of up to 2.2 percent of Public Health Service funds for evaluation activities.
- *Secretary's Transfer Authority:* Continues the transfer of not more than 1 percent between appropriations and the limitation that no appropriation can be increased by more than 3 percent by the transfer. With House and Senate approval, an appropriation can increase by an additional 2 percent.
- *Human Embryo Research (HER):* Retains HER prohibition language identical to the FY 2003 Labor, HHS, Education Appropriations bill.
- *Congressional Requests:* Continues Senate language (and FY 2003 language) that directs that specific information requests from the Chairmen and Ranking Members of the Subcommittees on Labor, Health and Human Services, and Education, and Related Agencies, on scientific research or any other matter, shall be transmitted to the Committees on Appropriations in a prompt professional manner and within the time frame specified in the request. The conferees further direct that scientific information requested by the Committees on Appropriations and prepared by Government researchers and scientists be transmitted to the Committees on Appropriations uncensored and without delay."
- *Extramural Salary Cap:* Retains Executive Level I Salary Cap as in FY

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2003.

- *Across the Board Reduction:* "The conference agreement includes a rescission of $1,800,000,000 funds made available to the Department of Defense and made available in P.L. 107-38 and P.L. 107-117, as well as a 0.59 percent across-the-board rescission to discretionary budgetary resources provided in Fiscal Year 2004 regular appropriations Acts (except Defense and Military Construction), as well as to any previously enacted Fiscal Year 2004 advance appropriation."
- *Stem Cells:* The conferees have included a provision prohibiting funds to process patents of human organisms.
- *SAMHSA:* The conference agreement includes $3,370,813,000 for substance abuse and mental health services, of which $3,253,763,000 is provided through budget authority and $117,050,000 is provided through the evaluation set-aside. The conference agreement includes bill language establishing a limitation of five percent of the block grant appropriation for funding of data collection activities as proposed by the Senate.
- *Office of National Drug Control Policy (ONDCP) National Youth Anti-Drug Media Campaign - The Conferees state that:* "While the conferees are encouraged by data released by the Partnership for a Drug-Free America showing welcome trends in the incidence of youth drug use, the conferees wish to reemphasize the need to demonstrate that such trends can be linked to the Media Campaign itself. The conferees therefore direct ONDCP to submit to the Committees on Appropriations an evaluation plan for the Media Campaign covering fiscal years 2004-2008 no later than 120 days after enactment of this Act. In addition, the conferees direct ONDCP to provide to the Committees on Appropriations a detailed report regarding the type and content of all advertising, its timing and placement in media markets, and the matches provided for all advertising. In order to ensure that a sufficient amount will be spent on advertising, the conferees agree to provide that no less than 78 percent of the funds provided shall be spent on the purchase of advertising time and space." Conferrees agree to: $145,000,000 to support a ONDCP National Youth Anti-drug Media Campaign and $70,000,000 to continue a program of matching grants to drug-free communities, of which $1,000,000 shall be a directed grant to CADCA for the National Community Anti-Drug Coalition Institute.
- *COLA/Pay Raises for Federal Employees:* Provides for a 4.1 percent increase in the adjustment in rates of basic pay for the statutory pay systems that takes effect in FY 2004 and shall be effective as of the first day of the first applicable pay period beginning on or after January 1, 2004. Funds to carry out this requirement will be paid from each applicable department for salaries and expenses for FY 2004.

Bills of Interest

HR 2086 - On May 14, 2003, Representative Souder (R-IN) introduced HR 2086, the Office of National Drug Control Policy Reauthorization Act of 2003. The bill was referred to House Energy and Commerce, House Government Reform, House Judiciary, House Select Intelligence, Senate Judiciary Committees. On Sept. 30, 2003, the measure, as amended, passed in the House by voice vote, under suspension of the rules (two-thirds vote required). (Text of bill, as amended and passed in the House, appears in the Sept. 30, 2003, Congressional Record.) On Oct. 1, 2003, it was received in the Senate and referred to the Senate Judiciary Committee. (Related Bills: S1860).

HR 3634 - On November 21, 2003, Representative Souder (R-IN) introduced HR 3634, a measure similar to S 1887. Both bills would amend the Controlled Substance Act to lift the patient limitation on prescribing drug addiction treatments by medical practitioners in group practices. The House bill has been referred to the House Energy and Commerce and the House Judiciary Committees.

S 1860 - On Nov. 14, 2003, S 1860, the Office of National Drug Control Policy Reauthorization Act of 2003, was introduced in the Senate by Sen. Hatch, R-Utah. The measure was referred to the Senate Judiciary Committee. (Related bills: HR 2086).

S 1887 - On November 18, 2003, Senator Hatch (R-UT), with Senators Biden (D-DE) and Levin (D-MI) introduced S 1887, a bill to amend the Controlled Substances Act to

lift the patient limitation on prescribing drug addiction treatments by medical practitioners in group practices. This measure would specifically affect the use of buprenorphine products for opiate addiction treatment. The Senate bill was referred to the Senate Judiciary Committee. (Related bills: HR 3634).

Hearings and Briefings

January 27, 2004 - At the request of majority staff to the Government Reform Subcommittee on Criminal Justice, Drug Policy and Human Resources, Dr. Wilson Compton, Director, DESPR, NIDA, briefed Subcommittee staff on measuring effectiveness of drug addiction treatment. Dr. Susan Weiss, Chief, Science Policy Branch, OSPC, and Mary Mayhew, SPB, accompanied Dr. Compton. Ms. Stephanie Colston, SAMHSA, also participated.

February 12, 2004 - The House Government Reform Subcommittee on Criminal Justice, Drug Policy and Human Resources (Representative Mark Souder [R-IN], Chairman) will hold a hearing on measuring the effectiveness of addiction treatment and to consider how to make the U.S. treatment system more effective. Dr. Nora Volkow, Director, NIDA and Jim Stone, Deputy Administrator, SAMHSA will testify.

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

International Activities

At the **4th Annual Binational Meeting of the U.S. - Mexico Border Health Commission**, held December 12, 2003, in Saltillo, Coahuila, Mexico, the U.S. Department of Health and Human Services (DHHS) and the Mexican Ministry of Health signed a letter of intent to increase cooperation in drug abuse research programs and exchange materials and scientific professionals. DHHS Secretary Tommy G. Thompson and Mexico's Health Minister, Julio Jose Frenk Mora, officiated. The letter of intent recognizes the importance of cooperation in accomplishing common goals and interests and provides for the intent to work together to develop collaborations in the fields of biomedical and behavioral research related to drug abuse and addiction. The agreement will build upon previous binational activities between the United States and Mexico and will be carried out through Mexico's National Council Against Addictions and NIDA. Dr. Steven W. Gust, Director of NIDA's International Program participated in the meeting.

NIDA and the Spanish National Plan on Drugs (PNSD), the government agency responsible for drug policy and programs in Spain, executed a formal **Exchange of Letters** during a ceremony at the Spanish Embassy in Washington, D.C., on October 22, 2003. NIDA Director Dr. Nora D. Volkow, and The Honorable Gonzalo Robles Orozco, the then PNSD Government Delegate, represented the two institutions. Mr. Robles is now Government Delegate for Foreign Affairs and Immigration. NIDA and PNSD first cosponsored binational scientific meetings on drug abuse in 1997. The relationship between the two organizations progressed informally through additional meetings, research training, scientific exchanges, and limited support for collaborative research efforts. Following the October 2002 creation of the PNSD foundation, National Institute of Drug Research and Training (INIFD), NIDA and PNSD began exploring ways to expand their cooperative activities.

The Exchange of Letters ceremony preceded a two-day binational research symposium, **U.S. - Spain Binational Workshop on Drug Abuse and Addiction Research**, October 23-24, 2003, where NIDA grantees and staff joined their Spanish counterparts to summarize the status of drug abuse research programs in both countries and to identify areas for future collaboration on biomedical and behavioral research related to drug abuse. NIDA Associate Director Dr. Timothy P. Condon outlined the organization of NIDA; reviewed the epidemiology of drug abuse in the United States; summarized the findings of NIDA-supported research; and discussed the Institute's efforts to discover how factors such as history, environment, and physiology interact with drugs of abuse and behavior to affect the development, progression, and treatment of drug abuse and addiction. Dr. Condon also listed NIDA's research priorities, including prevention of drug abuse among children and adolescents through studies of genetics, environment, co-morbidity, and treatment intervention targets; training researchers; and collaborating with other NIH institutes, other U.S. agencies, and the international community. National Plan on Drugs (PNSD) Government Delegate Gonzalo Robles described the structure of the PNSD and the National Institute of Drug Research and Training (INIFD); reviewed the epidemiology of drug abuse in Spain; outlined PNSD research areas; and discussed PNSD's active participation in international, regional, and bilateral cooperative agreements. He listed PNSD research priorities, including school- and family-based prevention programs, improving prevention and treatment programs, providing research training, and conducting studies on the neurobiology, clinical and therapeutical pharmacology, psychiatry, and clinical psychology of drug abuse. Drs. Steven W. Gust and M. Patricia Needle of NIDA's International Program (IP) and INIFD Vice President Juan Carlos Pérez Aguilar explained the research funding, training, and exchange opportunities

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supported by NIDA and INIFD respectively.

Workshop participants formed three working groups to identify potential collaborative research topics and teams. The Epidemiology and Prevention Working Group was co-chaired by Drs. Eve Reider, DESPR, and Teresa Salvador-Llivina, Centro de Estudios sobre Promoción de la Salud, Madrid; Treatment, by Drs. Ivan Montoya, DTR&D, and José Pérez de los Cobos, Hospital del la Santa Creu i Sant Pau, Barcelona; and Basic Science, by Drs. Jerry Frankenheim, DNBR, and Maria Isabel Colado Meg'a, Universidad Complutense, Madrid. The groups recommended the following topics for potential binational collaborations:

- Epidemiology and Prevention Working Group
    - Principles of prevention science
    - Compare components of successful programs and how they work across countries
    - Compare difficulties in using evidence-based prevention
    - Translate research into programs, especially those for different cultures
- Treatment Working Group
    - Comorbidity, particularly in adolescents, and with nicotine and psychiatric disorders
    - Services research to measure patient satisfaction, comorbidity, staff burnout, and therapeutic alliances
    - Physiological measures, such as electroretinogram studies, to identify physiological components of craving and develop anti-methadone antibodies, rapid tests to detect methadone, and mechanisms to collect outcome variables on PDAs
    - Randomized clinical trials in Spain to test Vigabatrin as a treatment for cocaine dependence
- Basic Science Working Group
    - Expand existing collaborations that are investigating the effects of nicotine on synaptic plasticity, effects of cannabinoids on nicotine action and behavior, involvement of kineases in cannabis reward, the role of cytokine and microglia on the hyperthermia and neurotoxicity induced by amphetamine derivatives, the involvement of sigma receptors in the plasticity induced by cocaine, the role of the endocannabinoid system in relapse, regulation of delta receptors by cocaine, and changes in the striatum neural function during acquisition of cocaine self-administration and the dopamine receptor role in acquiring the behavior
    - Administrative supplements better accommodate the rapid pace of basic science than do R01 grants
    - Europe offers a unique setting for studies of the combined effects of marijuana and tobacco because marijuana is almost always smoked with tobacco there.

In a concluding session, meeting participants cited the quality and breadth of the research presentations, the similarity in goals adopted by NIDA and PNSD, and the personal connections facilitated by the meeting in predicting that research collaborations could be developed. The participants requested that time for follow-up meetings be arranged during the June 2004 NIDA International Forum meeting.

NIDA and the Dutch Addiction Program (DAP), a joint program of the Netherlands Organisation for Scientific Research (NWO) and the Health Research and Development Council (ZonMW), hosted the **Third Binational Workshop on Drug Abuse and Addiction** in Amsterdam on September 27, 2003. Participants discussed possibilities for future binational clinical trials, reviewed progress reports on three previously funded binational research projects, and examined four new collaborative research proposals. The four newly funded research teams address drug abuse through the areas of treatment, epidemiology, genetic influences on addiction, and prevention:

- Dr. William Fals-Stewart, State University of New York at Buffalo, and

Dr. Paul M. G. Emmelkamp, University of Amsterdam, will evaluate the clinical efficacy of abbreviated Behavioral Couples Therapy versus the standard-length treatment in the study.

- Dr. Geoffrey P. Hunt, Scientific Analysis Corporation, and Drs. Dike van de Mheen and Nicole Maalsté, Addiction Research Institute Rotterdam, will use qualitative methods to examine the complex interrelationship between club drugs, the users, and the social settings for club drugs in order to develop prevention and intervention strategies.
- Dr. Mary Jeanne Kreek, Rockefeller University, and Dr. Jan van Ree, Rudolf Magnus Institute for Neurosciences of Utrecht, will identify hereditary polymorphisms in human mu-opioid receptors that might influence individual susceptibility to or protection from addiction and treatment outcomes in the study. Using animal models, the team also will assess the significance of the probable consequences of polymorphisms for the addiction process.
- Drs. Alan W. Stacy and Steve Sussman, University of Southern California, and Dr. Reinout W. Wiers, Maastricht University, will assess the predictive value of measuring implicit cognition as an indicator of future substance abuse by high-risk adolescents. The team then will evaluate the impact of a brief prevention intervention (individualized motivational interviewing) on both drug abuse and the operation of implicit cognitions.

The three binational teams that began work in 2001 provided updates on their research:

- Dr. Alfons A.M. Crijnen, Erasmus Medical Center, Rotterdam, and Dr. Hanno Petras, Johns Hopkins University, reported on their comparison of U.S. and Dutch randomized controlled prevention intervention trials that target aggressive and oppositional behavior to prevent initial drug use. The researchers have documented that the intervention mediates Attention Deficit Hyperactivity behaviors, and agreed on a technique to equilibrate different measures into one latent variable to conduct the bicultural analyses.
- Dr. Dirk J. Korf, University of Amsterdam, and Dr. Lana Harrison, University of Delaware, discussed their investigation of the interaction of drugs, alcohol, and violence among juvenile detainees and school dropouts in Philadelphia, Amsterdam, and the Canadian cities of Toronto and Montreal. Data collection is finished in all sites except Montreal, and preliminary analysis shows both similarities and differences among sites and between detainees and dropouts.
- Dr. Dorret I. Boomsma, Free University of Amsterdam, and Dr. Xiangning (Sam) Chen, Virginia Commonwealth University (VCU), described the collaborative research that uses data from sibling pairs in a Dutch study that implicated genetic factors in smoking initiation, liability to heavy tobacco use, and nicotine dependence. The team is attempting to replicate-on a different sample using complementary methods-the location and identity of specific genes identified by a VCU genome scan as potentially controlling susceptibility to nicotine dependence. The epac gene, which is involved in the cAMP transduction pathway, is among the candidate genes that suggest promising linkage results for nicotine dependence.

Participants also discussed the requirements for future binational collaboration on clinical trials. ZonMW Addiction Research Program Vice Chairman Dr. Nick F. Ramsey identified two major prerequisites for conducting clinical trials within the treatment community: building adequate infrastructure, and building research-oriented expertise in community-based treatment centers. Dr. Gerard M. Schippers, Amsterdam Institute for Addiction Research, outlined the organization of Dutch Substance Abuse Treatment Services and described clinical trials conducted recently in the Netherlands. He concluded that NIDA and Dutch researchers could easily design, deliver treatment during, and fund binational clinical trials, but that recruitment might pose logistical or organizational problems.

More than 100 drug abuse researchers, treatment providers, and policymakers participated in the third **U.S. - Russia Binational Workshop, Pharmacotherapies for Addiction: Basic and Clinical Science**, September 28 - October 1, 2003, in St. Petersburg, Russia. NIDA and Pavlov Medical University cosponsored the meeting to

examine the impact of preclinical and clinical research on addiction treatment and review U.S. and European pharmacological treatments for opiate dependence. Participants also reviewed research on pharmacological and behavioral addiction treatment strategies for patients with comorbid psychiatric or infectious diseases. Participants reported that the meeting helped them understand the importance of using preclinical and clinical research findings to develop effective pharmacological and behavioral drug abuse treatments, drug policies, prevention programs, and service delivery mechanisms. Presenters reviewed scientific advances that have contributed to the development of effective therapies for opioid addiction. NIDA Director, Dr. Nora D. Volkow, described how neuroimaging techniques have enhanced development and evaluation of both pharmacological and behavioral treatments. Dr. Frank Vocci, DTR&D, described how research findings that chronic opiate abuse produces long-term alterations in brain systems have led to new investigations of pharmacotherapies to modulate the dysregulated pathways of an addicted brain. Dr. Irina P. Anokhina, Russian National Research Center on Addictions, Moscow, described how researchers build on advances in genetics and neurochemistry to develop pharmacotherapies directly targeting the biological mechanisms that govern addiction. Dr. Juana Tomás-Rosselló, United Nations Office on Drugs and Crime, used data from the United Nations, WHO, European Union, and U.S. National Institutes of Health to demonstrate that pharmacotherapy is an element of effective drug treatment programs and is indicated in regions that experience a high prevalence of opioid abuse and related problems. Scientists from Norway, the Netherlands, Russia, Ukraine, and the United States described opioid pharmacotherapies used in their countries, and a panel of researchers discussed the experience with buprenorphine in Finland, France, and the United States. The meeting, which was organized by Dr. M. Patricia Needle, IP, and Dr. Edwin Zvartau, Pavlov Medical University, also celebrated the maturation of the NIDA-Pavlov cooperative agreement, which was formalized in 1996.

NIDA expanded its scientific exchange programs for senior scientists, creating **The Distinguished International Scientist Collaboration Award for U.S. Citizens and Permanent Residents (USDISCA)** to support direct collaboration between American researchers and their colleagues outside the United States. Like the original NIDA Distinguished International Scientist Award (DISCA) program, which was created in 2000, this competitive award allows veteran NIDA grantees to work with their colleagues from other countries. Recipients of both awards are expected to produce significant results (perhaps a new investigative finding, a scientific publication, or a research grant proposal), advance scientific knowledge about drug abuse and addiction, and, where applicable, offer mechanisms to apply enhanced research skills in either country. New initiatives will receive priority, as will applicants who document matching support. USDISCA awards support 1-3 month scientific visits to a drug abuse researcher in another country by NIDA grantees with a minimum of 7 years experience in drug abuse research beyond the doctoral level, and a scientific record that includes peer-reviewed publications. The award provides a $6,250 monthly allowance and airfare for one round trip between the United States and the other country. Only U.S. citizens and permanent residents are eligible for the new USDISCA award. Foreign applicants should continue to apply for the original DISCA award.

NIDA has selected Dr. Bertil B. Fredholm, Sweden, to receive a Distinguished International Scientist Collaboration Award (DISCA). Dr. Fredholm, Chairman of the Department of Physiology and Pharmacology at the Karolinska Institute in Stockholm, has been collaborating with Dr. Michael Schwarzschild, Massachusetts General Hospital, on research designed to clarify the role of adenosine signaling in models of cocaine- and amphetamine-induced drug seeking. The scientists' laboratories have already jointly developed a double (A1-A2A) adenosine receptor knockout mouse line to be used in the research. During the research visit supported by the DISCA award, Drs. Fredholm and Schwarzschild will conduct one set of experiments and discuss the precise organization of the remaining experiments, which will employ locomotor sensitization and self-administration models of drug addiction to assess the mechanisms by which endogenous neuromodulators influence the altered dopaminergic reward circuitry underlying addictive disorders. Dr. Fredholm was a 1972-1973 Fogarty International Center Fellow at the University of California-San Diego, and has made numerous extended laboratory visits to colleagues in the United States, Argentina, and Japan. He is president of the Nordic Pharmacological Society, an adjunct member of the Nobel Committee, and an Editorial Board member for Pharmacological Reviews, Trends in Pharmacological Sciences, Journal of Molecular Neuroscience, Neuropharmacology, Pharmacology and Toxicology, and Molecular Neuroscience.

Scientists from China and Italy have been selected as 2004 NIDA INVEST Research Fellows. Dr. Lan Zhang, Sichuan University, Chengdu, China, will work with Dr. Kenneth S. Kendler, Virginia Commonwealth University (VCU), Richmond, on genetic studies of nicotine dependence. Dr. Marco Bortolato, University of Cagliari, Monserrato, Italy, will work with Dr. Daniele Piomelli, University of California, Irvine, to evaluate the role of endocannabinoids in the psychotomimetic effects of psychostimulants. In addition to conducting post-doctoral research with a NIDA grantee at a U.S. institution, INVEST Research Fellows also participate in an orientation program at NIDA and receive travel support to attend scientific meetings. Fellows and their mentors jointly develop a collaborative research proposal for implementation in the Fellows' home country.

During her Fellowship, Dr. Zhang will learn and use high throughput single nucleotide polymorphism typing technologies and apply these techniques to study candidate genes for nicotine dependence in subjects selected from the Mid-Atlantic Twin Registry. She will also learn and apply statistical methods to the analysis of candidate gene studies. A lecturer and attending psychiatrist at Sichuan University, Dr. Zhang has been the principal investigator on genetic-epidemiological studies funded by the Chinese National Science Foundation, Chinese Ministry of Health, and the Chinese Medical Board Foundation. In 2000, she conducted research in molecular genetics at the Institute of Psychiatry, King's College, London, UK. Her research has been published in the American Journal of Medical Genetics and in Chinese scientific journals and textbooks. In preparation for their collaborative research, Drs. Zhang, Kendler, and Sam Chen, Director of the Molecular Genetics Laboratory at the Virginia Institute for Psychiatric and Behavioral Genetics, exchanged research visits in 2001 and 2002.

Dr. Bortolato will use high-performance liquid chromatography/mass spectrometry techniques to determine whether psychostimulant drugs can affect endocannabinoid synthesis in the limbic and motor regions of the rat brain and behavioral techniques to test whether the responses to these drugs can be modulated by pharmacological treatments that influence endocannabinoid signaling. A behavioral pharmacologist, Dr. Bortolato is a research assistant and postdoctoral student in the University of Cagliari Department of Neuroscience, where he lectures on pharmacology, and has co-authored articles published in the *European Journal of Pharmacology and Psychopharmacology*, as well as in Italian scientific journals. His fellowship will expand his training in molecular and cellular neuroscience.

Dr. M. Patricia Needle and Dale Weiss, IP, joined Mr. Bill Dant, Institute for International Education, for a September 24, 2003, meeting with the 2003-2004 **Hubert H. Humphrey Drug Abuse Research Fellows** and Humphrey Fellowship program staff at Johns Hopkins University, Baltimore, Maryland. The NIDA representatives discussed the Humphrey Fellows' six-week professional affiliations with NIDA grantees. The Fellows include Ana Djordevic, M.D., Serbia and Montenegro; Mariano Hembra, Philippines; Reminder Kaur, M.B.B.S., M.P.M., Malaysia; Boris Lobodov, M.D., Russia; David Otiashvili, M.D., Georgia; Riza Sarasvita, Indonesia; Vladimir Stempliuk, Brazil; Chenghua Tian, M.D., Ph.D., China; and Tomas Zabransky, M.D., Ph.D., Czech Republic. NIDA sponsors the competitive, 10-month Fellowships in cooperation with the U.S. Department of State, the Institute of International Education, and The Johns Hopkins University. Through a combination of academic courses and professional experience, Fellows learn about NIDA-supported drug abuse research and the application of research to the development of prevention programs, treatment protocols, and government policy.

NIDA provided travel support to two Russian researchers who presented at the symposium, **U.S.-Georgia Biomedical Collaboration: Past Accomplishments, Current Status, and Future Opportunities in the Caucasus**, held October 16-18, 2003, in Tbilisi, Georgia, to discuss collaborative research on drug abuse, HIV/AIDS, tuberculosis, sexually transmitted diseases, hepatitis, palliative care, cancer, tobacco dependence, and tobacco-related disease. Dr. Dmitri Lioznov, Pavlov Medical University, St. Petersburg, Russia, discussed NIDA and NIH-supported research collaborations on HIV prevention and treatment conducted by Pavlov and the University of Pennsylvania. Former NIDA INVEST Research Fellow Dr. Tatiana Tsarouk, Scientific Research Institute of Addictions, Moscow, described the NIDA-supported collaborative study of school-based drug abuse prevention programs being conducted in Seattle and Moscow. The workshop was co-sponsored by the Fogarty International Center and the Georgian Ministry of Labour, Health and Social Affairs, with support from the U.S. Civilian Research & Development Foundation (CRDF), the U.S. Department of State, the Office of Global Health Affairs U.S. Department of Health and Human Services, Emory University, and the Georgian Academy of

Sciences.

NIDA provided travel support to Dr. Linda B. Cottler, Washington University, St. Louis, to meet with Dr. Jih-Heng Li, Director-General of the **National Bureau of Controlled Drugs**, Taiwan Department of Health in October 2003. During the visit, the two scientists discussed revisions to the drug abuse case report sheet used by various reporting agencies in Taiwan to obtain additional data on the use patterns of drugs and alcohol as well as on predictor variables, including risk and protective factors. They also finalized plans for a collaborative study on the use, abuse, and dependence of MDMA (Ecstasy), other club drugs, and inhalants. Dr. Cottler also explored additional opportunities for collaboration with investigators at the National Taiwan University College of Public Health.

Two researchers, Drs. Dan Lubman and Murat Yucel, from the University of Melbourne, Australia visited NIDA on September 23, 2003. The purpose of the visit was to discuss methodological issues and potential collaborations. NIDA representatives meeting with the visitors included: Drs. Jerry Flanzer and Naimah Weinberg, DESPR, Drs. Minda Lynch and Steve Grant, DNBR, Dr. Vince Smeriglio, CAMCODA, and Dr. Rita Liu, OEA.

NIDA was one of five institutes participating in a program sponsored by the U.S. Department of State International Visitor Program on October 1, 2003. The title of the program was, "Tobacco and Alcohol Abuse: A Freedom Support Grant Program for Kazakhstan". The goal of the program was to provide public health professionals from Kazakhstan opportunities to observe how alcohol and tobacco abuse are addressed in the U.S. as a public health issue. During the program the participants examined how the U.S. runs public health education campaigns, youth outreach programs and media campaigns. The program also provided the participants with information on alcohol and drug abuse treatment in the U.S. Dr. Jag Khalsa, CAMCODA, represented NIDA. The other NIH institutes participating included, NIAID, FIC, NIAAA, and NCI.

Three law enforcement officials from Brazil visited NIDA on October 29, 2003. The purpose of the visit was to provide information about drug abuse prevention programs as both military and civilian police officers in Brazil have begun to receive professional training to address community relations and to identify best practices. NIDA representative, Dr. Shakeh Kaftarian, DESPR, met with the visitors.

Dr. Steve Gust and Dale Weiss, International Program, met with Dr. David Powell, President, The International Center for Health Concerns, Dr. R. Munidasa Winslow of the Institute for Mental Health, Singapore, and with Dr. Jeff Hoffman, Danya International, on October 27, 2003. Discussions centered on treatment efforts in China and other Asian countries.

Mr. Björn Fries, the Swedish National Drug Policy Coordinator, Ms. Christina Gynnå, Administrative Director, Mr. Walter Kegö, Head of Police and Custom Issues, and Dr. Fred Nyberg, Head of Research Issues, all from the Swedish National Drug Policy Coordinator office visited NIDA on November 5, 2003. The purpose of the visit was to get an overview of NIDA, information about research funding and NIDA priorities. Drs. Timothy P. Condon, Associate Director, NIDA, and Steven Gust, International Program, welcomed the visitors. Other representatives from NIDA that met with the group were Dr. Meyer Glantz, DESPR, Drs. Jamie Biswas and Roberta Khan, DTR&D, and Dr. Rita Liu, OEA.

Dr. Cathrine Sasek, OSPC and Dr. Shakeh Kaftarian, DESPR, met with Naama Zweig, Head of Prevention at the Israel Anti-Drug Authority, and Dr. Sharon Rabinovitz-Shenkar of BarIlan University, Israel on November 5, 2003. School based curriculums, especially for young children and prevention programs, were discussed.

Mr. Oscar Edmundo Ortiz Sanchez, Head Evaluation Department, Provisional Detention Center, Quito, Ecuador, visited NIDA under the auspices of the U.S. Department of State International Visitor program. Mr. Ortiz Sanchez met with Dr. Bennett Fletcher, DESPR, and discussed issues of incarcerated drug abusers and the significant problem of drug abuse in Ecuador.

Dr. Frank Vocci, DTR&D, and Dale Weiss, IP, represented NIDA at a briefing for Kaoru Misawa, the newly appointed Scientist (Narcotic Drugs and Psychotropic Substance Project), Quality Assurance and Safety of the World Health Organization. Other DHHS organizations attending the briefing included Office of the Secretary, DHHS, FDA and SAMSHA.

Ms. Silvia Tortajada of the Fundacion de Ayuda Contra la Drogadiccion (Spanish Foundation Against Drug Addiction) and Mr. Antonio Vidal of the Sociedad Espanola de

Toxicomanias (Spanish Society on Drug Abuse), Valencia, Spain, visited NIDA and other HHS agencies on December 16-18, 2003, to learn about U.S. government research, programs and publications in the areas of prevention and treatment of drug abuse. During their visit to NIDA, they met with Dr. Larry Seitz, DESPR, Dr. Jacques Normand, CAMCODA and Dr. Ivan Montoya, DTR&D.

Wilson Compton, M.D., M.P.E. and Meyer Glantz, Ph.D., both of DESPR, presented papers at the July 2003 World Psychiatric Association Conference in Paris, France. Dr. Compton's paper was on conducting drug abuse research from a public health perspective and Dr. Glantz's paper, developed by the Analytic Unit of the Division of Epidemiology, Services and Prevention Research was entitled "Twenty years of adolescent drug use: Comparing multiple sources" and was written by Meyer Glantz, Ph.D., James Colliver, Ph.D., Marc Brodsky, M.S., Bennett Fletcher, Ph.D., Howard Chilcoat, Ph.D., and Wilson Compton, M.D. Dr. Glantz's paper examined critical questions about widely used epidemiological data. Studies meeting criteria of representativeness and methodological rigor were identified. Published and publicly available data from the MTF, NHSDA, YRBSS, NCS, ADHealth, NLSY, NSPY, NELS and NSAUS studies were used to create variables that are comparable across the studies for age and drug use by adolescents in the years 1975 through 2001. Data for two age-school grade ranges, 17 - 18 years old -12th grade and 15 -16 years old - 10th grade were compared for past month alcohol and cigarette use, and past year marijuana, cocaine, and heroin use. Concurrence of findings varied by age and substance with the NHSDA reporting lower use levels than the other surveys. Concurrent and divergent findings were presented for each age group and drug and the implications of these findings were discussed.

Meyer Glantz, Ph.D., as NIDA's collaborating investigator in the National Comorbidity Study, represented the Institute at the July 2003 World Mental Health Consortium Meeting in Paris, France. As a member of the Consortium and the Substance Use Data Analysis Workgroup, Dr. Glantz will be collaborating in the analysis and publication of national and international data on drug abuse and associated factors.

On October 29, 2003 Dr. Juan Carlos Melero of Spain met with Drs. Elizabeth Robertson, Pat Needle, Shakeh Kaftarian, Aria Crump and Elizabeth Ginexi at NIDA to continue discussions about possible research projects and collaborations.

Dr. Shakeh Kaftarian met with a group of scientists from Israel's Anti-Drug Authority on October 29, 2003 and presented an overview of NIDA's prevention research portfolio. This meeting took place at NIDA.

Moira O'Brien, DESPR chaired the 7th Border Epidemiology Work Group Meeting (BEWG), September 11-12, 2003, in San Diego, California. Participants included representatives from the Mexican Ministry of Health and 14 Border areas in 5 Mexican States and 9 areas in 4 U.S. States. The most recent available data on patterns and trends in drug abuse in border areas were presented. Methamphetamine abuse continues to spread from western and southwestern BEWG areas eastward. Cocaine/crack abuse remains at high levels along the eastern U.S./Mexico border and in the Midwestern State of Sonora. Primary heroin treatment admissions remained relatively stable from 2001 to 2002 in most Mexican areas but increased in San Diego and Texas areas. Marijuana continues to be a major drug of abuse in all BEWG areas. In the Texas Lower Rio Grande Valley in 2002, around 70 percent of primary treatment admissions among youths were for marijuana abuse, as were 66 percent of adolescent admissions in El Paso and 33 percent in Douglas.

Dr. Frank Vocci presented a talk on Laboratory-Based Approaches for Developing Medications for Stimulant Dependence Treatment at the International Society of Addiction Medicine in Amsterdam on September 26, 2003.

Dr. Frank Vocci presented two talks: Overview of Buprenorphine treatment in the USA, and Medications Development for the Management of Opiate Dependence at the NIDA-Pavlov Medical University International Workshop " Pharmacotherapies for Addiction: Basic and Clinical Science" in St. Petersburg on September 29-30, 2003.

Dr. Frank Vocci met with Dr. Brion Sweeney, a consultant psychiatrist to the Government of Ireland, to discuss pharmacotherapies for opiate dependence on November 4, 2003 in Bethesda, MD.

Dr. Frank Vocci chaired a session and presented a talk on GABA B Receptors as a Medications Target for Cocaine Dependence at the Australian Professional Society on Alcohol and other Drugs on November 17, 2003. Dr. Vocci also met with the Australian Expert Committee on The Feasibility of Studying Naltrexone to discuss depot and implantable naltrexone dosage forms on November 16, 2003. Dr. Vocci

also met with Dr. Robert Ali, who has an academic appointment in the Department of Pharmacology at the University of Adelaide as well as being the Director of the WHO Collaborating Centre for the study of Drug and Alcohol Problems. Dr. Ali discussed a possible US- Australia collaboration to perform treatment research in Asian studies, most notably Vietnam.

Drs. Frank Vocci and Dorynne Czechowicz, along with representatives from FDA, CSAT and HHS International health, met with Dr. Mauro Mizawa of the World Health Organization to discuss WHO's intended reviews of drugs and medicines under international control treaties on November 25, 2003 in Rockville, MD.

Drs. Frank Vocci and Ahmed Elkashef visited four psychiatric hospitals in Cairo from November 30-December 2, 2003 both privately owned and those associated with medical schools to determine the nature and extent of substance abuse disorders and the use of medications for management of drug dependencies. Both Drs. Vocci and Elkashef presented on NIDA research at the Behman Hospital on December 1, 2003.

Dr. Ivan Montoya, DTR&D, was a guest speaker at the Social Development Symposium organized by the Interamerican Development Bank and held in Washington DC, November 3-5, 2003.

In a collaborative effort with the Fogarty International Center's International Cooperative Biodiversity Groups, the DTR&D is participating in the support of two grants for the discovery of new medications from natural sources: "Studies of the Flora and Predator Bacteria of Jordan (R21TW006628, PI Nicholas Oberlies) and "Building New Pharmaceutical Capabilities in Central Asia" (U01TW006674, PI Ilya Raskin). These grants were in response to RFA TW-03-004 "Fogarty International Center ICBG". The purpose of this program is to integrate drug discovery from natural products with conservation of biodiversity and economic development in source countries.

Ana Anders, Senior Advisor on Special Populations, SPO, presented a paper at the "Centros de Integracion Juvenil" annual conference in Mexico City, November 2003.

Dr. William Corrigall, DNBR, represented NIDA at Society for Research on Nicotine and Tobacco Europe meeting in Padua, Italy November 19-22, 2003.

Dr. Jonathan Pollock, DNBR, presented "Genetics of Substance Dependence Disorders," at the World Congress on Psychiatric Genetics, Quebec City, Canada on October 6, 2003.

Betty Tai, Ph.D., Director, CCTN, provided an update of NIDA's CTN at the Tenth International Conference on Treatment of Addictive Behaviors meeting in Heidelberg, Germany, September 4-8, 2003. The meeting theme was "From Research to Practice and Back Again". She joined panel members, Bill Miller, Everett Rogers, and Tom McLellan for a round table discussion: "What does it take for evidence-based treatments to be adopted in practice?"

Peter Hartsock Dr.PH., served on the organizing committee of the 11th International Conference on AIDS, Cancer, and Related Problems, which was held October 5-10, 2003 in St. Petersburg Russia. At the conference, Dr. Hartsock co-chaired sessions on drug abuse and HIV/AIDS and on HIV/AIDS in the military. He also visited the sites of research projects currently funded by NIDA and the Fogarty International Center.

Jag H. Khalsa, Ph.D. of CAMCODA presented a satellite symposium on the Medical Management of HIV/HCV Co-infection in Addicted Patients at the 5th Annual Meeting of the International Society of Addiction Medicine (ISAM), Amsterdam, the Netherlands, September 26, 2003. The symposium was directed towards psychiatrists, clinical psychologists and other health care providers engaged in the health care of addicted patients co-infected with HIV and HCV. An international panel of clinicians and scientists discussed current issues and medical management practices for patients with co-infection and a history of substance abuse. Topics included: the epidemiology of co-infections among drug abusers in the US and international settings (Drs. Xiao-Fong Yu and Rebecca Garten, Johns Hopkins); natural history of liver disease in HCV/HIV (Dr. Jack Stapleton, University of Iowa); neurobehavioral aspects (Dr. Eileen Martin, University of Illinois); diagnosis, medical management of care and treatment (Dr. Diane Sylvestre, UCSD); HAART in HIV/HCV co-infection (Dr. Curtis Cooper, U. Ottawa); and research funding opportunities at NIDA/NIH (Dr. Khalsa). Proceedings of this symposium and of an upcoming symposium at the Annual Meeting of ASAM, to be held in Washington, DC in April 2004, will be published in the scientific literature.

Jag H. Khalsa, Ph.D. of CAMCODA, at the invitation of NIH Office of AIDS Research (OAR), one of the co-sponsors of a Workshop on Grant Writing at the 3rd Central American Conference on STDs and HIV/AIDS, Panama City, Panama, October 16, 2003, discussed NIDA's efforts in supporting research on HIV/AIDS and other co-occurring infections among drug abusers and offered a number of useful suggestions as to how to write successful research grant applications. The workshop was simultaneously translated into Spanish/English. It was suggested that (NIH) should provide research and economic support to clinicians, scientists, and other health care providers, and offer more such workshops in the region (Central and Latin America) where there is a significant problem with STDs nd HIV/AIDS, especially in vulnerable populations. The workshop was chaired by Dr. Robert Eisinger of OAR. Program staff from NIAAA, NIAID, and NICHD also presented their institutes' efforts in supporting research on STDs and HIV/AIDS.

Peter Hartsock, Dr.PH., CAMCODA, participated in the World Bank's meeting on HIV/AIDS in the Former Soviet Union (FSU), held in Washington, D.C. on October 21, 2003. Drug abuse was discussed as a major factor in the spread of HIV/AIDS in the FSU. The World Bank expressed interest in working with NIDA and USAID in support of collaborative research activities.

Dr. Jerry Flanzer, DESPR, presented a talk entitled Services Linkages: An Integral Component of Substance Abuse Prevention and Treatment in Theory But Not in Reality, and he moderated a session on research issues related to substance abuse and corrections at the 46th Annual International Conference of the International Council on Alcohol and Other Addictions (ICAA), October 5, 2003, Toronto, Ontario, Canada.

Dr. Yihong Yang, Neuroimaging Branch, IRP, was invited as a keynote speaker in the Annual Congress of Chinese Radiological Society held November 8-10, 2003 in Guangzhou, China. The title of his talk was "CBF-Based Functional MRI."

Dr. Yihong Yang, IRP, was invited as a keynote speaker in the International Conference on Functional MRI held on December 9-10, 2003 in Taipei, Taiwan. He gave two talks at the conferences, entitled "Perfusion-Based Functional MRI - Technical Issues and Applications" and "Brain Structure and Connectivity - Diffusion Tensor Imaging and Beyond."

Dr. David Gorelick gave an invited workshop on psychopharmacology and pharmacological treatment of substance abuse at the XIV annual congress of the Federación Latinoamericana de Psiquiatria de la Infancia y la Adolescencia held in Asuncion, Paraguay, September 18-21, 2003. Dr. Gorelick also gave several scientific presentations and discussed possible scientific collaborations with attendees.

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Meetings/Conferences

On October 29-30, 2003 and January 6-7, 2004, NIDA convened the final two meetings of the **Health Services Research Blue Ribbon Task Force** in Washington D.C. The primary objective of the Task Force was to conduct a comprehensive review of NIDA's existing health services research portfolio and to provide recommendations for future research at NIDA. The Task Force was composed of treatment and prevention researchers, representatives from the Office of National Drug Control Policy, the Substance Abuse and Mental Health Services Administration. The co-chairs were Drs. A. Thomas McLellan and Constance Weisner, both members of the National Advisory Council on Drug Abuse.

As part of a NIDA-funded contract with the NRC and IOM to examine the ethical issues raised by studies of the genetics of drug abuse, a conference was held at the National Academy of Sciences on November 13-14, 2003. Participants discussed issues related to Institutional Review Boards (IRBs), legal consequences if genes for drug abuse are discovered, and matters of privacy and discrimination. An over-riding message of this meeting was the need to educate all stakeholders (public, press, advocacy groups, justices, providers, etc.) about the interpretation of genetics' results. The greatest ethical challenges are likely to come from misinterpretation of genetic findings, especially for complex diseases like drug addiction.

On October 7-8, 2003, NIDA convened the final meeting of the **Clinical Trials Network Work Group** in Washington D.C. The purpose of this Work Group was to evaluate the current status of the Clinical Trials Network program and to advise NIDA on future strategies to accelerate the transfer of research to practice through the Clinical Trials Network. The Work Group Chair, Dr. David Rosenbloom and Work Group members prepared a report based on their findings and recommendations.

NIDA held its first **SATH-CAP (Sexual Acquisition and Transmission of HIV Cooperative Agreement Program) Steering Committee meeting** on December 9th and 10th, 2003 in Washington DC. PIs and Co-PIs from each of four research sites (UCLA, Yale, University of Illinois at Chicago, and RTI), and one coordinating center (RAND) participated in the meeting, chaired by David Vlahov, Ph.D., of the New York Academy of Medicine and NIDA's Scientific Officer (Jacques Normand, Ph.D., of CAMCODA) and Program Official (Elizabeth Lambert, M.Sc., of CAMCODA).

NIDA co-sponsored two workshops with NIMH on HIV/HCV coinfection entitled **HIV/Hepatitis C Coinfection: Impact on Nervous System Disease Burden and HIV/Hepatitis C Coinfection: Behavioral and Clinical Research in Mental Health and Drug Abuse** in October 2003. Combined proceedings will be published in AIDS. Thomas Kresina, Ph.D. served as the NIDA coordinator and a speaker in both workshops.

NIDA's Division of Epidemiology, Services, and Prevention Research (DESPR) sponsored a symposium on **Translating Evidence-Based Smoking Cessation Strategies into Community Practice** at the 2003 National Conference on Tobacco or Health, Boston, MA, November 11, 2003. The seminar, organized by Dr. Beverly Pringle, featured the following NIDA grantees who presented findings from their research: Dr. Belinda Borrelli, Brown Medical School; Dr. Judith Ockene, University of Massachusetts Medical Center; and Dr. Steven Y. Sussman, University of Southern California.

The **National Academies Workshop on the Genetics of Drug Addiction** was held in Washington, D.C., November 13-14, 2003.

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A **NIDA Genetics Consortium Meeting** was held on December 4, 2003 in Rockville, M.D.

The **CTN National Steering Committee Meetings** were held in Westminster, Colorado, September 9-12, 2003.

- Dr. Nora Volkow provided the keynote address; she spoke on NIDA's research priorities under her leadership and stressed the importance the CTN plays in the translation of research to practice.
- The CTP Caucus met on September 10, 2003. Dr. Volkow was invited to participate at this meeting. The Caucus gave a resounding welcome to Dr. Volkow and discussed their interests and concerns.
- The CTN Executive Committee met on September 10, 2003 (before the Steering Committee Meeting) and September 11, 2003 (immediately following the Steering Committee) in Colorado. The EC focused its discussion on the development of a CTN roadmap.

Mr. Richard A. Millstein, J.D., then-Deputy Director, NIDA, provided welcome remarks at the 3rd Annual Scientific Meeting of the NIDA National Hispanic Science Network, Miami Beach, Florida, October 2, 2003.

Mr. Millstein presented the keynote address at the First International Roundtable on Addictions Research and Policy of the 46th International Council on Alcohol and Addictions, Toronto, Canada, October 20, 2003.

Mr. Millstein presented to student scholars on career opportunities at NIDA, provided conference welcome remarks, chaired a panel on neuroimaging, and presented on funding opportunities at NIDA at the 10th Conference on Behavior, Clinical Neuroscience, Substance Abuse and Culture, Los Angeles, California, October 22-23, 2003.

Mr. Millstein chaired the Minority Health Scholars Network meeting, a combined meeting of NIDA's four ethnic minority workgroups, Bethesda, Maryland, November 5-6, 2003.

Dr. Timothy P. Condon, newly appointed NIDA Director, and Director, OSPC, presented "Changing the Conversation: National Institute on Drug Abuse" at the National TASC Conference on Drugs and Crime in Raleigh, North Carolina on October 19, 2003.

Dr. Timothy P. Condon presented "NIDA's Research Dissemination Efforts" at the NIDA Clinical Trials Network Workgroup in Washington, D.C. on October 7, 2003.

Dr. Timothy P. Condon presented "Science Advances in the Emerging Drug Problem: Blending Research to Practice" at the NAADAC 2003 Annual Conference - Advancing the Addiction Professional: Facing Today's Challenges in Washington, D.C. on September 15, 2003.

Dr. Timothy P. Condon presented "Other NIDA Blending Practice and Research Initiatives" at the National Institute on Drug Abuse Clinical Trials Network: What the Research Means to Single State Agencies in Westminster, Colorado on September 7, 2003.

Dr. Cindy Miner, Deputy Director, OSPC, presented an "Overview of NIDA Communication Strategies" at the NIDA Primary Care Physician Outreach Workgroup Meeting on December 1, 2003, in Bethesda, Maryland.

Dr. Cindy Miner, Deputy Director, OSPC, presented an overview of OSPC outreach activities at the NIDA Combined Ethnic Minority Workgroup meeting in Bethesda, Maryland on November 5, 2003.

Dr. Cindy Miner, Deputy Director, OSPC, participated in the NIMH sponsored Research Breakfast for Early Career Investigators at the American Academy of Child and Adolescent Psychiatry meeting in Miami, Florida on October 16, 2003.

Dr. Cindy Miner, Deputy Director, OSPC, lead the NIDA/NIMH Grant Writing Workshop at the American Academy of Child and Adolescent Psychiatry meeting in Miami, Florida on October 15, 2003.

Drs. Yu Lin and Nancy Pilotte, DNBR, co-chaired a symposium, "Endocannabinoids in the Brain: From Micro to Macro" at the Society for Neuroscience Annual Meeting in New Orleans, LA on November 7, 2003.

Dr. Christine Colvis, DNBR, chaired a symposium, "Mechanisms of Receptor and Transporter Trafficking" at the Society for Neuroscience Annual Meeting in New Orleans, LA on November 7, 2003.

Dr. Robert Riddle, DNBR, chaired a symposium, "Embryogenesis of Reward-Based Behavior" at the Society for Neuroscience Annual Meeting in New Orleans, LA on November 7, 2003.

Drs. Susan Volman and Pushpa Thadani, DNBR, co-chaired a symposium, "Young Investigators: Research and Funding Opportunities at NIDA" at the Society for Neuroscience Annual Meeting in New Orleans, LA on November 7, 2003.

Dr. David Shurtleff, Acting Director, DNBR, chaired a symposium, "Signal Transduction Mechanism in Drug Abuse and Addiction" at the Society for Neuroscience Annual Meeting in New Orleans, LA on November 7, 2003.

Dr. Paul Schnur, Acting Deputy Director, DNBR, chaired a symposium, "Neurobiological Mechanisms of Drug & Natural Reward" at the Society for Neuroscience Annual Meeting in New Orleans, LA on November 7, 2003.

Dr. Susan Volman, DNBR, chaired a symposium, "Cognition and Behavior: Functional Changes in Synaptic Transmission and Drug Abuse" at the Society for Neuroscience AnnualMeeting in New Orleans, LA on November 10, 2003.

Dr. Jonathan Pollock, DNBR, chaired a symposium, "Synaptic Transmission and Excitability: Genetically Encoded Biosensors for Defining Neuronal Circuits and Synaptic Change" atthe Society for Neuroscience Annual Meeting in New Orleans, LA on November 11, 2003.

Robert Riddle, Ph.D., DNBR and Eric Nestler, M.D. Ph.D. organized an Invited Symposium entitled RNAi: A New Tool in Neuropsychopharmacology at the annual meeting of the American College of Neuropharmacology held in San Juan, Puerto Rico on December 8, 2003.

Rao Rapaka, Ph.D., DNBR, Joni Rutter, Ph.D., DNBR and George Uhl, M.D., Ph.D., IRP organized a meeting entitled Drug Metabolism: Roles of Pharmacogenomics, Transporters, and Drug-Drug Interactions that was held in Rockville, MD, December 8-10, 2003.

Minda R. Lynch, Ph.D., DNBR, co-chaired a workshop entitled "Accumbal Glutamate in the Relapse to Cocaine" at the Winter Brain Research Conference in Copper Mountain, Colorado during the month of January 2004. Invited speakers included; Chris Pierce from Boston University School of Medicine; Marina Wolf from Chicago Medical School; David Self from the University of Texas Southwest Medical Center; and Krista McFarland from the Medical University of South Carolina.

Dionne Jones, Ph.D., CAMCODA, coordinated and served as a discussant in a panel presentation on "Collaborations Across Continents between the United States and Southern Africa: Drug Abuse, HIV, and Other Adverse Consequences" at the American Public Health Association Annual Meeting in San Francisco, CA, November 15-19, 2003.

Thomas Kresina, Ph.D., CAMCODA, co-organized a workshop with Brown University entitled "The Use of Directly Observed Therapy and Other Community Based Efforts to Get HAART to Those Who Are Not Getting It" at the 10th Conference on Retroviruses and Opportunistic Infections, February 9, 2003. The proceedings of the workshop, comprising 10 articles on HAART, methadone, DOT, and co-morbidities will be published in an upcoming supplement to *Clinical Infectious Diseases*.

Thomas Kresina, Ph.D., served as a panelist on the US Medicine Institute for Health Studies roundtable entitled "Comprehensive Screening for HCV: The Federal Role As Catalyst" on November 6, 2003.

Thomas Kresina, Ph.D., served on the planning committee and as a moderator of the Forum for Collaborative HIV Research meeting entitled "Racial and Ethnic Minority Issues in HIV Treatment and Prevention", October 29-30, 2003.

Peter Hartsock. Dr.PH., participated in the 10th Anniversary Conference of the Chemical and Biological Arms Control Institute (CBACI) in Washington, DC, on November 16, 2003. CBACI is currently conducting studies on the international trade of narcotics and the spread of HIV/AIDS and other medical problems.

Wilson Compton, M.D., M.P.E. presented a paper on policy-related research at the

National Insitute on Drug Abuse at the annual meeting of the Robert Wood Johnson Foundation Substance Abuse Policy Research Program in Utah, December 2003.

Dr. Compton chaired a session of the annual meeting of the Campbell Collaboration Briefing Conference on Place Based Randomized Trials at The Rockefeller Foundation, New York, N.Y., December, 2003.

On November 19, 2003, Dr. Elizabeth Robertson, DESPR, made a presentation to The Exchange: A Public/Private Sector Focus on Substance Abuse at the Metropolitan Washington Council of Governments. The title of the presentation was, Preventing Drug Abuse Among Children and Adolescents: The Five Year Update and Review.

On October 14, 2003 Dr. Elizabeth Robertson represented NIDA at a planning follow-up meeting to the New York Academy of Science Adolescent Mind meeting held in New York City on September 18-20, 2003. Plans were made for follow-up activities to augment continued dialog on the significance of research on adolescent brain, cognitive and social development.

Dr. Susan Martin, DESPR, organized a panel on Potential Iatrogenic Effects of Interventions and made a presentation titled "Potential Iatrogenic Effects of Drug Education and Preventive Intervention Programs" at the annual meeting of the American Society of Criminology in Denver, Colorado on November 20, 2003.

On October 1-2, 2003, Dr. Lynda Erinoff, ERB, DESPR, represented NIDA's Women and Gender Research Group at the University of Kentucky, Center on Research on Violence Against Women conference, "Toward a National Research Agenda on Violence Against Women."

On November 7, 2003, Dr. Lynda Erinoff co-chaired a session on the "Neurobiological Basis of Impulsivity" at the NIDA mini convention at the Society for Neuroscience annual meeting.

Dr. Jack Stein, Chief, SRB, DESPR, facilitated a focus group on research dissemination efforts for the criminal justice system at the National TASC Meeting, Raleigh, NC, October 19-20, 2003.

Dr. Jack Stein participated in a meeting of the Health Services Research Information Advisory Committee for the Library of Medicine, November 3, 2003.

Dr. Jerry Flanzer, DESPR, was a panelist at the Research Funding and Career Development Workshop: New Funding and Initiatives at the National Hispanic Science Network on Drug Abuse, Miami Beach, FL, October 2-4, 2003.

Dr. Beverly Pringle, DESPR, presented discussant remarks at a symposium on Substance Abuse Prevention, Treatment, and Service Delivery for Adolescent Girls, at the Annual Convention of the American Psychological Association, Toronto, Ontario, Canada, August 7, 2003.

Dr. Beverly Pringle, DESPR, chaired a symposium on Translating Evidence-Based Smoking Cessation Strategies into Community Practice, at the 2003 National Conference on Tobacco or Health, Boston, MA, November 11, 2003.

Dr. Frank Vocci, Director, DTR&D, attended the National Hispanic Sciences Network in Miami on October 3, 2003.

Drs. Frank Vocci and David Pating of ASAM co-organized an evening symposium on the Treatment of Cocaine Dependence at the American Society for Addiction Medicine's State of the Art in Addiction Medicine Conference on October 30 in Washington, D.C. Drs. George Uhl, Regina Carelli, David Roberts, and Yavin Shaham presented on their research in cocaine addiction. Dr. Vocci discussed the research and chaired a question-answer session at the end of the presentations.

Drs. Henry Francis, Thomas Kresina, Ann Anderson, Ahmed Elkashef, and Frank Vocci organized a consultants meeting on the combined treatment of opiate dependence and HIV disease on October 31, 2003, in Rockville. Drs. Gerald Friedland of Yale and Walter Ling of UCLA co-chaired the meeting. Dr. Francis spoke about the integration of medical systems to treat both disorders and Dr. Vocci presented on the development of buprenorphine for management of opiate dependence.

Dr. Frank Vocci presented an overview of medications development activities at a consultants meeting on VMAT2 Blockade and Methamphetamine: Implications for Medications Development on December 5, 2003, in Bethesda, MD.

Dr. Frank Vocci presented a talk on Multiple Neuronal Systems Thought to be

Involved in Nicotine Dependence at the National Conference on Tobacco or Health in Boston on December 12, 2003.

Drs. Steven Grant and Laurence Stanford, DTR&D, presented "Drug Addiction - a Brain Disease at the U.S. Department of Education Office of Safe and Drug-Free Schools 2033 National Conference in Bethesda on October 27, 2003.

Dr. Laurence Stanford participated in the NIH MRI Study of Normal Human Brain Development Annual Workshop on October 29 and 30, 2003. NIDA has recently joined the NICHD, NIMH, and NINDS in supporting the MRI Study of Normal Human Brain Development, a multi-site project designed to develop a database of the structural development of the human brain from birth through late adolescence.

Dr. Steven Grant, DTR&D, presented a talk entitled "Imaging Negative Reinforcement" in the symposium on Negative Reinforcement in Addiction at the American Society for Addiction Medicine State of the Art Conference in Washington, D.C. on October 30, 2003.

Dr. Joseph Frascella, DTR&D, participated in and chaired a session at a CTAC/ONDCP meeting of the Scientific Review Steering Committee in New Orleans, LA, November 8, 2003.

Dr. Joseph Frascella and NIDA Director Dr. Nora Volkow participated in a forum on Neuroethics at the Society for Neuroscience meeting in New Orleans, LA, November 11, 2003.

Dr. Joseph Frascella participated in a meeting at the Arizona Science Center to help develop a series of science exhibits on brain development and drug abuse, Phoenix, AZ, October 30-31, 2003.

Dr. Joseph Frascella participated in National Hispanic Research Network Annual Conference in Miami Beach, FL, October 2-4, 2003.

Dr. Joseph Frascella conducted a half-day seminar in grant writing at the Florida International University, Miami, FL, October 3, 2003.

Dr. Joseph Frascella participated in Latino Behavioral Health Institute's Ninth Annual Conference entitled *Promoting Effective Behavioral Health Care for Latinos* in Los Angeles, CA, September 21-24, 2003.

Dr. Melissa W. Racioppo, DTR&D, presented several workshops at the October meeting of the American Association of Marriage and Family Therapy (AAMFT) in Long Beach, CA. The workshops included a full-day orientation to Federal grant writing, and two targeted talks about NIDA's behavioral treatment priorities.

Dr. Ivan Montoya, DTR&D, participated in the organizing committee and chaired a grant-writing workshop at the Third Meeting of the National Hispanic Science Network on Drug Abuse held in Miami on October 2 to 4, 2003.

Dr. Ivan Montoya chaired a session at the Latino Mental Health Meeting held in Princeton, NJ on November 7 and 8th, 2003.

Dr. William Corrigall, DNBR, presented the Victor Cohn Lecture at George Washington University Department of Pharmacology on October 8, 2003. His presentation was entitled "Neurochemical Mechanisms in Nicotine Reinforcement".

Dr. Corrigall presented a seminar on "Neuroscience and Addiction: Advancing to New Treatments for Tobacco" at the Mayo Clinic Nicotine Dependence Conference, October 19-22, 2003.

Dr. Corrigall presented a seminar at University of Minnesota on October 22, 2003 entitled "Neuroscience of Nicotine Addiction: What Do We Know and Where Do We Go?"

Dr. Corrigall presented in a symposium at the Annual Investigator Meeting of the California Tobacco Related Disease Research Program December 3-5, 2003; his topic was The Nicotine and Tobacco Addiction Program at NIDA.

Drs. George Uhl, Kathryn Cunningham, Minda Lynch, and Jonathan Pollock organized "Serotonin and Dopamine: Interactive Contributions to Psychostimulant Reinforcement and Aversion" in Rockville, MD on September 28, 2003.

Drs. Jonathan Pollock, DNBR, NIDA, Chris Austin (NHGRI), and Richard Woychik (Jackson Laboratory) organized the Banbury Meeting on Genome Wide Targeted

Mutagenesis at the Cold Spring Harbor Laboratory, Cold Spring Harbor, NY on September 30-October 1, 2003.

Dr. Jonathan Pollock, DNBR, organized the symposium "Molecular Genetics of Drug Addiction and Alcohol Dependence," for the American Society for Human Genetics, Los Angeles, CA., on November 7, 2003.

Dr. Cora Lee Wetherington, NIDA's Women & Gender Research Coordinator, chaired the symposium, "Smoking Cessation: The Right Treatment for the Right Gender," at the National Conference on Tobacco or Health, Boston, MA, December 10-12, 2003.

Dr. Lula Beatty, Chief, Special Populations Office (SPO), gave a keynote presentation titled "Importance of Community Participatory Partnerships Curriculum, Research and Practice" at the 10th Annual HBCU Faculty Symposium on October 23, 2003 in Charlotte, North Carolina.

Dr. Lula Beatty gave a keynote presentation titled "Working Together to Improve Drug Abuse Treatment for Girls and Women" at the Weaving and Vision conference sponsored by the Marin Services for Women on September 25, 2003 in Marin County, California.

Dr. Lula Beatty participated in a meeting to discuss the development of a Native American protocol within the CTN on November 24, 2003 in Albuquerque, New Mexico.

Ana Anders, SPO, presented at the Border Epidemiolgy Work Group in San Diego, CA in September 2003.

Ana Anders co-chaired a grant writing training workshop at the Latino Behavioral Health Institute in Los Angeles, CA, September 2003.

Ana Anders participated in the planning and implementation of the National Hispanic Science Network annual conference iin Miami, FL, October 2003.

Ana Anders participated in the planning of a workshop of Spanish scientists visiting the U.S. October 2003.

Ana Anders co-chaired a meeting of the National Hispanic Science Network on Drug Abuse and the Asian American and Pacific Islander Workgroup at the Minority workgroup Meeting in Bethesda, MD, November 2003.

Pamela Goodlow, SPO, assisted in the coordination of "NIDA's mini-convention Poster Session for Young Investigators: Funding and Research Opportunities at NIDA" during the Annual Society for Neuroscience meeting, November 2003, in New Orleans, Louisiana.

Flair Lindsey, SPO, presented information on the Summer Research with NIDA program to undergraduate students at Spelman College during their annual Summer Internship Fair on November 16, 2003 in Atlanta, Georgia.

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Media and Education Activities

Press Releases

October 22, 2003 - **NIDA Goes Back to School**. At a press briefing held in Washington, D.C., Dr. Nora D. Volkow, director of the National Institute on Drug Abuse (NIDA), National Institutes of Health, announced the Institute's Back to School initiative, which provides students and teachers with informative, accurate information about addiction and drug abuse. One component of NIDA Goes Back to School is "**NIDA for Teens: The Science Behind Drug Abuse**," an interactive Web site officially launched at the event. Available at www.teens.drugabuse.gov, the site was developed with help from the Kids Design Team and the University of Baltimore's School of Information Arts and Technologies.

October 31, 2003 - **NIDA NewsScan #26 - Special Funding Issue**

- Novel Approaches to Phenotyping Drug Abuse
- International Bioethics Education and Career Development
- Molecular Genetics of Drug Addiction Vulnerability
- Interactions Between Stem Cells and the Microenvironment *In vivo*
- SBIR/STTR Phase II Competing Continuation Awards
- Basic and Translational Research in Emotion

November 10, 2003 - **Treatment Providers Need to be Aware that a Myriad of Health Problems Often Accompany Substance Abuse**. Results of two new studies, funded in part by the National Institute on Drug Abuse (NIDA), National Institutes of Health, show that people with substance abuse disorders often have accompanying medical or psychiatric conditions that can include bone fractures, muscle injuries, pain disorders, depression, anxiety, and even psychoses. The studies are published in the November issues of *Archives of Internal Medicine* and *Archives of General Psychiatry*.

December 8, 2003 - **New Research in Animals Reveals Possible Long-Term Effects of Stimulants on Brain and Behavior**. Three new studies conducted in animals, published in the December issue of the journal Biological Psychiatry, provide evidence that misuse of the stimulant methylphenidate (Ritalin) may have long-term effects on the brain and behavior. While methylphenidate and other stimulant medications are the recommended treatments for Attention Deficit Hyperactivity Disorder (ADHD), based on the more than 150 controlled studies demonstrating their safety and efficacy when used as prescribed, these three studies showed changes in the brains of young (adolescent or pre-adolescent) animals that persisted into adulthood. In both animals and humans, the brain continues to develop throughout adolescence. If the current studies are applicable to humans, they could have important implications for young people who use stimulants for recreational purposes.

Articles of Interest

September 9, 2003, *The New York Times*-"Smoking Tied to Kidney and Spleen Damage"-NIDA study mentioned.

September 22, 2003, *Newsday*-"Epilepsy Drug Eyed for Cocaine Addiction"-Interview with Frank Vocci, Ph.D.

October 21, 2003, *Washington Post*-"The Pain to Come"-Interview with Wilson Compton, Ph.D.

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November 26, 2003, *JAMA*-"NIDA's New Leader: From Rejection to Direction"- Interview with Nora D. Volkow, M.D.

December 4, 2003, *Nature Magazine*-"Scientists Go to Jail to Crack Substance Abuse" - Interview with Nora D. Volkow, M.D.

Dr. Frank Vocci, Director, DTR&D, was interviewed by Laura Scoles of the Journal for Minority Medical Students in September 2003 regarding buprenorphine as a new treatment and pharmacotherapies for cocaine dependence.

Dr. Frank Vocci was interviewed in September 2003 by Mike Schwartz of the Press Enterprise in Riverside CA regarding the buprenorphine/naloxone paper in the New England Journal of Medicine.

Dr. Frank Vocci was interviewed in November 2003 by Brandon Tubbs of the Anniston Star regarding methamphetamine addiction treatment.

Dr. Frank Vocci was interviewed in November 2003 by Mary Beuzard of Science and Life regarding the nicotine vaccine.

Dr. Frank Vocci was interviewed in November 2003 by ABC Radio in Brisbane, Australia regarding NIDA's research portfolio and treatment research.

Dr. David Gorelick, IRP, was quoted about adverse effects from cocaine use in a recent article "Close-up: Cocaine." The article appeared in October, 2003 issues of Junior Scholastic, Scholastic Choices, and Scholastic Science World magazines.

Educational Activities

On October 26, 2003, Sara Rosario PILB/OSPC, participated in the 3rd Annual Radio Unica Hispanic Heath Fair held in Dallas, TX. Ms. Rosario represented NIH at the agency's information booth at this fair. NIDA collaborated with other IC's to provide funding, staffing, and publications in both English and Spanish for this event. The Radio Unica Hispanic Health Fair traveled to 12 major Hispanic market cities in 2003, in an effort to provide information on major health problems, and help reduce health disparities among the Hispanic/Latino population in the United States.

NIDA has launched a new outreach program to involve primary health care physicians in the early recognition and assessment of, and intervention with, substance abusing patients and their families. As part of this initiative NIDA, along with Sheppard Pratt Health System, and other partners, sponsored an educational seminar for primary health care providers to give them vital drug abuse information that they can use in their practice. The seminar was held at the Sheppard Pratt Conference Center in Baltimore on December 17, 2003. NIDA Director, Dr. Nora D. Volkow was one of the featured speakers.

In collaboration with the Maryland chapter of the American Academy of Pediatrics, coalition partners, and corporate sponsors, NIDA hosted a tent at the New Year's Eve Spectacular, a free and widely attended alcohol-, drug-, and smoke-free community event featuring fireworks. The event, held in Baltimore on December 31, 2003, is a component of NIDA's physician outreach initiative. It served as an assessment tool to determine the impact of community outreach for possible implementation at a national level. The purpose of NIDA's involvement in this event was to communicate with and encourage physicians, specifically the pediatricians, to put into practice the Institute's research findings on effective drug abuse prevention.

Exhibits/Conferences

January 20-23, 2004: *Community Anti-Drug Coalitions of American National Leadership Forum XIV*

February 12-17, 2004: *American Association for the Advancement of Science Annual Conference*

February 18-21, 2004: *Society for Research on Nicotine and Tobacco Annual Meeting*

March 8-10, 2004: *Drug Discovery Technology Europe 2004*

March 11-14, 2004: *Society for Research on Adolescence 10th Biennial Meeting*

March 31 - April 3, 2004: *PRIDE 27th Annual World Drug Conference*

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

Planned Meetings

On February 26-27, 2004, Drs. Melissa Racioppo and Lisa Onken of the Behavioral Treatment Development Branch, will co-chair a meeting on **Mechanism of Action of Behavioral Treatments**.

On March 4-5, 2004, Drs. Cece McNamara and Lisa Onken of the Behavioral Treatment Development Branch will co-chair a meeting: **Using Information Technology to Improve Assessment, Treatment and Training of Substance Abuse Treatment Providers**.

On March 16, 2004, Dr. M.D. Majewska, DTRD, will chair a NIDA-sponsored workshop in Bethesda, MD, on **Utilization of Transcranial Magnetic Stimulation (TMS) in the Treatment of Drug Abuse and other Brain Disorders**. It is expected that the meeting will stimulate research on utilization of TMS as a diagnostic and therapeutic tool in the treatment of drug dependence.

On April 19, 2004 at the Cognitive Neuroscience Society Annual Meeting, Dr. Steven Grant will chair a symposium on **Substance Abuse: A Disorder of Cognition and Brain**. The leading edge of the emerging view that dysfunction of brain circuits involved in fundamental cognitive processes make critical contributions to the clinical features of substance abuse disorders will be presented by four young investigators funded through a NIDA RFA on Cognitive Aspects of Substance Abuse: Dr. Hugh Garavan, Medical College of Wisconsin, Dr. Julie Fiez, University of Pittsburgh, Dr. Kevin LaBar, Duke University and Dr. Julie Stout, Indiana University.

On May 4, 2004, at the American Psychiatry Association Annual Meeting, Dr. Steven Grant will chair a symposium: **Drugs and Other Addictions; Does One Size Fit All?** Similarities and differences will be presented 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: Dr. Marc Potenza, Yale School of Medicine, Dr. Nathan Shipira, Univeristy of Florida, Dr. Nancy Petry, University of Connecticut, and Dr. Linda Cottler, Washington University.

National CTN Steering Committee Meetings are planned for the following dates and locations: May 11-13, 2004, in Gaithersburg, Maryland; and September 27-29, 2004, in Detroit, Michigan.

The **CTN Data and Safety Monitoring Board** will meet March 18-19, 2004, July 15-16, 2004, and November 16-17, 2004 in Gaithersburg, Maryland. The group will review the continuing progress of the CTN's protocols.

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Publications

NIDA Publications

Science & Perspectives Volume 2 Issue 1
NIH Pub. No. 03-5033
The second issue of NIDA's peer-reviewed journal for the drug abuse researchers and treatment providers highlights ways in which dialogue between scientific investigators and clinical practitioners is improving drug abuse treatment and research. An important goal of the journal is to inspire its readers to join the shared dialogue emerging from this partnership.

The first "Research Review" article proposes integrating substance abuse treatment with criminal justice supervision to achieve more economical use of resources as well as levels of monitoring appropriate to individual clients' drug use and criminal justice history. A second "Research Review" article presents the state of current knowledge about treating adolescents with comorbid substance abuse and psychiatric disorders, and the author identifies gaps in knowledge, particularly with respect to psychiatric medications, for further investigation.

One of two "Clinical Perspectives" articles describes a New York State agency's efforts to treat nicotine addiction along with other drug abuse in an inpatient program. The other article illustrates how 12-step treatment works as part of a total addiction recovery program at one longstanding, community-based treatment facility in Ohio. Both articles offer recommendations on how other programs can adapt these approaches to their own treatment program and how additional research could lead to understanding and better treatment outcomes. Other sections of this issue include:

- The article "Fishbowls and Candy Bars: Using Low-Cost Incentives to Increase Treatment Retention," which demonstrates that community programs need not invest large amounts of money in order to adopt contingency management and use it effectively with their clients;
- "Graphic Evidence," which presents a striking visual representation of brain activity during cue-induced craving; and
- A continuing education (CE) quiz for counselors, which offers the opportunity to earn two NAADAC-certified CE hours.

Research Report Series: Therapeutic Communities (Spanish)
NIH Pub. No. 04-4877(S)
Based on over 30 years of scientific inquiry and observation, this research report provides information on therapeutic communities and their role in treating drug addiction.

Epidemiologic Trends in Drug Abuse - Community Epidemiology Work Group, Volume I - June 2003
NIH Pub. No. 04-5364A
This report provides an ongoing assessment of drug abuse in major metropolitan areas of the United States with the purpose of keeping both public and private sector policymakers and researchers informed with current and accurate data.

Epidemiologic Trends in Drug Abuse - Community Epidemiology Work Group, Volume II - June 2003
NIH Pub. No. 04-5365A
This report provides an in-depth analysis of the epidemiologic trends and special reports for a limited audience made up primarily of drug abuse researchers who

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utilize this volume to identify potential areas for further research.

NIDA NOTES

NIDA NOTES, Volume 18, Issue 2
NIH Pub. No. 03-4378
In the Director's Column, Dr. Nora Volkow discusses brain imaging techniques that provide new views of brain structure and activity, allowing researchers to watch small brain structures in minute detail and observe changes over fractions of seconds after drugs enter the brain's tissues. Noted is a new NIDA-National Institute of Mental Health initiative that will lead to a better understanding of the impact of drugs on the development and functioning of the human brain.

The lead story focuses on the use of perfusion MRI (pMRI), a new imaging technology that is simpler and less expensive to administer than PET, and has been used to confirm earlier PET scan evidence linking methamphetamine abuse to human brain damage. The pMRI images show blood-flow abnormalities that correlate with abusers' impaired response times in cognitive tests.

This issue also discusses research that found a multicultural version of a substance use prevention program to be at least as effective as culturally targeted versions. A research news article describes the three foci of NIDA's National Prevention Research Initiative: basic prevention research, transdisciplinary prevention research centers, and large-scale community prevention field trails. Other research news discusses last May's NIDA-sponsored symposium, "Foundations and Innovations in the Neuroscience of Addiction," which honored the late Dr. Roger M. Brown, as well as a symposium on the discovery, development, and delivery of smoking cessation medications at the 2003 Annual Meeting of the Society for Research on Nicotine and Tobacco. NIDA teamed with the National Cancer Institute and the Institute on Alcohol Abuse and Alcoholism to sponsor this symposium. The Bulletin Board features news on the seventh annual PRISM Awards, which Dr. Volkow attended. The Tearoff presents key elements of this fall's NIDA Goes Back to School Initiative, designed to convey the dynamism of science education-especially in the drug abuse and addiction field-to students and their parents, teachers, and school counselors.

NIDA NOTES, Volume 18, Issue 4
NIH Pub. No. 03-4378
In the Director's Column, Dr. Nora Volkow discusses decision-making and the addicted brain. Noted is addiction as an integrated process that may explain how drug exposure triggers changes throughout the brain, from initial intoxication and reinforcement through craving, to compulsive continued drug use despite destructive consequences. The emerging picture of addiction as a disease of compulsion and disrupted control suggests new possibilities for treatment.

The lead article examines NIDA-supported research exploring the disrupted and destructive decision-making that characterizes drug abuse and addiction. Research has begun to shed light on the neurobiological mechanisms by which drugs disrupt the "thinking" regions of the frontal brain and lead to harmful decisions. Researchers evaluated substance abusers' decision making through use of a computerized card game involving short- and long-term gain or loss. By revealing different degrees of decision-making impairment, the research may hold clues for treatment and help select appropriate therapeutic approaches.

This issue also discusses emerging research findings with ketamine, a fast-acting, potentially lethal, general anesthetic that, when injected, poses new disease risks for homeless and other street-involved youths. Another article presents research findings on a D3 receptor antagonist that blocked cocaine reward in rats and offers promise for future medications to help control addictive behavior. Also addressed is twins research that found early marijuana use to be linked to increased risk of progression to other illicit drug use and possibly to drug abuse or dependence. The Bulletin Board notes the award of the HHS Honor for Distinguished Service to the Buprenorphine Work Group, comprising representatives from NIDA, the Food and Drug Administration, and the Substance Abuse and Mental Health Services Administration. The Tearoff announces the release of the second edition of the highly regarded Preventing Drug Use Among Children and Adolescents: A Research-Based Guide for Parents, Educators, and Community Leaders. Accompanying this edition is an In Brief companion piece for quick reference.

CTN PUBLICATIONS

- During the months September - December, 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 patient brochures and one clinician brochure for the Basic Strategic Family Therapy protocol (CTN-0014) were approved and distributed throughout the Network.
- Two patient brochures for the Smoking Cessation protocol (CTN-0009) and one patient brochure for the MET Pregnant protocol (CTN-0013) were translated into Spanish and distributed throughout the Network.

NIDA INVEST Letters

NIDA INVEST Letter, Fall 2003

The main article in this issue focused on the NIDA International Forum, held June 13-19, 2003, in Miami, Florida. The NIDA International Forum has grown from 65 participants representing 26 countries in 2001 to 180 participants from 49 countries and territories in 2003. Presenters from international drug abuse organizations summarized findings on global changes in drug abuse patterns, and a panel discussion highlighted NIDA-supported international research collaborations in Thailand and Russia. A special workshop on publishing scientific papers in international journals focused on organizing a scientific paper, meeting a journal's criteria before the peer-review stage, and responding to referees' comments. In the column, "From the Field," Dr. George Woody summarized his experiences conducting international collaborative research with colleagues in Brazil and Russia. An insert announced the new Distinguished International Scientist Collaboration Awards for U.S. Citizens and Permanent Residents that support 1- to 3-month research visits by veteran NIDA researchers to their collaborators in other countries. Other stories reported on the NIDA Southern Africa Initiative Meeting held June 1-3, 2003 in Cape Town, South Africa, graduation ceremonies for the 2002-2003 Hubert H. Humphrey Drug Abuse Research Fellows, and plans for the 2004 NIDA International Forum.

NIDA INVEST Letter, Winter, 2004

The main article in this issue reported on the third U.S. - Russia Binational Workshop, Pharmacotherapies for Addiction: Basic and Clinical Science, cosponsored September 28 - October 1, 2003, in St. Petersburg, Russia by NIDA and Pavlov Medical University. Participants focused on the role of preclinical and clinical research findings in developing effective pharmacological and behavioral drug abuse treatments, drug policies, prevention programs, and service delivery mechanisms. In a ceremony opening the workshop, Pavlov Medical University awarded an honorary doctorate to NIDA grantee Dr. George Woody, University of Pennsylvania, in recognition of his decade of work on collaborations with investigators at Pavlov to improve substance abuse treatment and reduce HIV transmission. The feature article examined the expansion of the unique binational collaboration between NIDA and the Dutch Addiction Program, which announced funding for four new collaborative research projects September 27, 2003, during the Third Binational Workshop on Drug Abuse and Addiction in Amsterdam. Other stories included an interview with former NIDA Hubert H. Humphrey Drug Abuse Research Fellow Olga Toussova, and the "From the Field" column written by Dr. James Inciardi, University of Delaware, and Hilary Surratt, University of Delaware.

OTHER PUBLICATIONS

Addiction

Volume 99, Issue 1, Page 141, January 2004

Dr. M. Patricia Needle, IP, has a Note in this issue of *Addiction*, which is published by the Society for the Study of Addiction to Alcohol and Other Drugs. Dr. Needle outlines the contributions made by some of the 100 scientists from more than 40 nations that have participated in one of NIDA's three international research training and professional development exchange programs: the NIDA INVEST Research Fellowship, the NIDA Hubert H. Humphrey Drug Abuse Research Fellowship, and the NIDA Distinguished International Scientist Collaboration Award.

A Special Issue of the Journal of Urban Health (80(4), suppl. 3, December 2003) was released on "HIV Acquisition and Transmission Among Drug -Using Populations: Future Research Strategies." Editors of the Special Issue, which was made possible by NIDA, include Jacques Normand and Elizabeth Lambert of CAMCODA, and David Vlahov of the New York Academy of Medicine. It includes a variety of papers by NIDA grantees on different aspects of the changing epidemiology of HIV among drug users and their sex partners, strategies for HIV prevention, and discussions of new and emerging research gaps and questions to shape the next generation of HIV

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Melissa Racioppo, Ph.D., of the Behavioral Treatment Development Branch, DTR&D, wrote an article entitled "Is Treatment on This Plane?" published in the November/December 2003 issue of Family Therapy Magazine, a publication of the American Association for Marriage and Family Therapy.

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Jag H. Khalsa, Ph.D., of CAMCODA, participated as the agency representative in the preparation of a report released in September 2003 entitled "Federal TB Task Force Plan in Response to the Institute of Medicine Report, Ending Neglect: The Elimination of TB in the United States".

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Staff Highlights

Honors and Awards

Mr. Richard A. Millstein, J.D., the then-Deputy Director, NIDA, received the Lifetime Achievement Award from the Tenth Annual Conference on Behavior, Clinical Neuroscience, Substance Abuse and Culture "for your many years of devoted advocacy toward development of substance abuse research for underserved populations", October 23, 2003.

Dr. Jonathan Katz, IRP, was appointed as Editor for Behavioral Pharmacology for the *Journal of the Experimental Analysis of Behavior*, and as Associate Editor, *Pharmacology and Therapeutics*.

On December 12, 2003, **Dr. Lisa Onken**, DTR&D, received a Meritorious Research Service Commendation from the American Psychological Association. The award was for building a model program of basic to clinical translation research, and for building the behavioral therapies development program.

Dr. Cora Lee Wetherington, NIDA's Women & Gender Research Coordinator, gave the keynote address at the Alcohol & Drug Problems Association of North America (ADPA) national women's conference, September 14 -16, 2003, Buffalo, NY and was presented with an award for her "Outstanding Federal Service" in promoting research on women and gender differences.

CAPT Steve Oversby, DTR&D, volunteered to serve as a Mental Health Specialist with the American Red Cross from September 19th to October 3rd 2003 during the aftermath of Hurricane Isabel, in Virginia Beach, VA. CAPT Oversby and CAPT Armen Thoumaian discovered a trailer park that had not been adequately served and were able to alert the ARC and Civil authorities. The Trailer Park consisted of 240 families, 40 of who suffered total destruction of their trailers. Many were living in tents, near open sewer drains, and were being harassed by vandals at night. The American Red Cross, Civil Authorities, and Social Services intervened with a successful outcome.

On October 30, 2003 **Dr. Laurence Stanford**, DTR&D, received an NIH Merit Award for his participation in the reorganization of the integrated review group structure of the NICHD Division of Scientific Review.

Staff Changes

Richard A. Millstein, J.D., NIDA Deputy Director since 1988, in January 2004 began an assignment on detail as the Acting Deputy Director of the NIH John E. Fogarty International Center for Advanced Study in the Health Sciences. In this position he will take a leadership role in guiding Fogarty's efforts to reduce the global burden of disease through research and research training that prepares current and future scientists to meet health challenges, and look for new ways to strengthen ties between Fogarty and NIDA. Fogarty, through partnerships with NIH institutes, international organizations (including WHO and PAHO), foundations (such as Rockefeller and Gates), and non-governmental organizations supports over 20 programs of research training, research capacity-building, and research, focused on developing countries. These programs extend to over 100 countries and involve over 5,000 scientists in the U. S. and abroad. The Fogarty mission is to identify global changes, anticipate their effects on health and well-being, and mobilize scientific resources to reduce disparities in global health.

Timothy P. Condon, Ph.D. has been named Deputy Director of NIDA. Dr. Condon

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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 (OSPC). Dr. Condon has held prominent science policy positions at NIDA since he arrived in 1992. He served as the Chief of the Science Policy Branch and the Acting Deputy Director of OSPC until 1996 when former NIDA Director Dr. Alan Leshner appointed him NIDA's first Associate Director for Science Policy, as well as the Director of OSPC. Prior to joining NIDA, Dr. Condon coordinated research and service programs at the former Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) for four years serving as the Deputy Associate Administrator for Policy Coordination and Deputy Associate Administrator for Science. From 1986 to 1989 he served as Science Policy Analyst and Project Director at the U.S. Congress, Office of Technology Assessment (OTA), where he directed an assessment of emerging technologies in the neurosciences. Dr. Condon received his Ph.D. in neuroscience from the Ohio State University College of Medicine. He pursued postdoctoral research in neuroendocrinology and neuropharmacology at the University of California at Los Angeles' Brain Research Institute and at the Oregon Health Sciences University where he also served on the faculty.

Susan Weiss, Ph.D. was appointed Chief, Science Policy Branch, OSPC, in October 2003. Dr. Weiss has been with OSPC since June 2003. Previously, Dr. Weiss was the Senior Director of Research at the National Mental Health Association, the Nation's largest and oldest grassroots advocacy organization devoted to improving the mental health of all Americans through the support of public education, healthcare reform, implementation and deployment of evidence-based practices, and research. Prior to that, she served as the Chief, Unit on Behavioral Biology in the Biological Psychiatry Branch of the National Institute of Mental Health (NIMH). Her research program at the NIMH sought to characterize the evolving nature of psychiatric and neurologic illnesses through the use of animal models, in order to help in the development of novel treatment options for patients with disorders of affect, anxiety, and substance abuse. She has authored or co-authored more that 140 journal articles and book chapters.

Robin Mackar, M.P.H. has been selected to serve as Deputy Branch Chief, SPB. Ms. Mackar joined OSPC's Science Policy Branch in March of 1996. While in SPB, Ms. Mackar has taken a lead role in writing materials that disseminate science findings to a wide variety of audiences, including Congress, researchers, constituents and the public. Prior to becoming a NIDA employee, Ms. Mackar worked as a communications manager at the US Agency for International Development and for three years as a policy analyst in the NIH, Office of Science Education Policy in the Office of the Director at the NIH. She served for two years as a Peace Corps volunteer in West Africa after receiving her undergraduate degree in Journalism from Pennsylvania State University. Upon her return from Africa, she worked with several newspapers while completing her Master's Degree in Public Health.

Mark Green, Ph.D. has been selected to serve as Deputy Director, OEA. Dr. Green has been at NIDA for three years and has over 22 years experience in extramural programs. He received a Ph.D. in pharmacology from New York Medical College and started working for the government in 1979, at NIOSH (National Institute for Occupational Safety and Health). Initially he was a Criteria Manager, charged with evaluation of health hazards in the workplace and then served as the Executive Secretary of the Safety and Occupational Health (SOH) study section, which evaluated epidemiological and prevention studies in the workplace, as well as biomedical aspects of exposures to agents and environments. In 1983, he joined the National Institute on Alcohol Abuse and Alcoholism, where he was a program officer, for two years, in the Division of Extramural Research, followed by two years as an SRA in the Office of Scientific Affairs. After that Dr. Green served as a Science and Policy Analyst for a little over a year before becoming Chief of the Extramural Project Review Branch. He held this position for the 12 years prior to joining NIDA as Chief of the Clinical, Epidemiological and Applied Sciences Review Branch. Dr. Green has worked with both grant and contract review committees and worked with the research areas of prevention, epidemiology, clinical trials, health services, neuroscience, and physiology. He has been active at many technical assistance forums, working with researchers to enhance skills in application preparation. Since coming to NIDA, he has continued to work primarily on issues involving peer review and extramural policy.

Jag H. Khalsa, Ph.D. has been appointed as Acting Head of the Medical Consequences Unit of CAMCODA.

Gayathri Jeyarasasingam, Ph.D. joined OSPC's Science Policy Branch in November

2003 as a Health Scientist Administrator. Prior to coming to NIDA, Dr. Jeyarasasingam was a Program Director in the Office of Minority Health and Research at the NINDS where she managed a portfolio of research and education programs aimed at promoting diversity in the neuroscience research workforce. She completed a Ph.D. in Neurobiology at the University of California, Davis, conducted research at the Parkinson's Institute studying the role of nicotinic acetylcholine receptors in muscle cell degeneration and neuroprotection, and then served as a Scientific Review Administrator at the NIMH.

Dr. Theresa Montini has joined the CCTN as Health Scientist Administrator. Previously, she served as a Scientific Review Administrator of the Behavioral and Social Science Approaches to Preventing HIV/AIDS Study Section at NIH's Center for Scientific Review. Dr. Montini received her doctorate in medical sociology from the University of California-San Francisco, did post-doctoral work in alcohol studies at the NIAAA National Alcohol Research Center at the University of California-Berkeley, and post-doctoral work in Health Policy and Health Services Research at the Institute for Health Policy Studies, UCSF School of Medicine. As an assistant professor at the Institute for Health Policy Studies, she was the principal investigator on a NIAAA-funded study of nicotine cessation and smoking bans in alcoholism treatment, a co-investigator on a NIDA-funded study of the conditions under which community-based treatment providers adopt innovative drug abuse treatment interventions (Joe Guydish, PI), and an advisor to the California-Arizona Clinical Trials Network Research Node (Jim Sorensen, PI). Dr. Montini has served as an appointed member of the editorial board of the journal *Gender & Society*, and serves as a peer reviewer for a number of journals, including *Journal of General Internal Medicine* and *Tobacco Control*.

Arnaldo R. Quinones, M.D. has joined the CCTN as a Medical Officer. Dr. Quinones received his medical degree from the University of Puerto Rico, School of Medicine in 1987. He completed training in internal medicine at the Tulane University Medical School in New Orleans, Louisiana. He is board certified in internal medicine. After completion of his internal medicine residency program, he completed a fellowship in hematology at the Washington Hospital Center in Washington, DC. From 1992-1994, he served in the U.S. Air Force as an active duty officer. During this time he was appointed as Assistant Chief of Hematology for Kessler Medical Center, in Biloxi, Mississippi. He also worked in the pathology department as the officer in charge of quality assurance and blood utilization practices. During this time he was awarded the Meritorious service medal from the United States Air Force. After his discharge from active duty, Dr. Quinones worked in the private sector and most recently as Medical Director for a non-profit organization in the area of HIV/AIDS. He has been the Principal Investigator for multiple Phase I, II, and III clinical trials in coordination with the pharmaceutical industry.

Denise Burns joined CAMCODA as a Program Assistant in September 2003. Ms. Burns has 20 years of diverse experience in office organization administration, database management, and customer fulfillment service relations. Before joining CAMCODA, she completed a 6-month assignment with Microsoft Corporation and served 6 years as a Senior Fulfillment Administrator at Fannie Mae Foundation. Ms. Burns is currently pursuing a Bachelor's Degree in Mass Media Communications.

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Grantee Honors

Dr. Peter D. Friedmann, Associate Professor of Medicine & Community Health at Brown Medical School in Providence, Rhode Island, was named Treasurer of the Association for Medical Education in Substance Abuse (AMERSA).

Dr. Constance Weisner, Professor in the Department of Psychiatry at the University of California at San Francisco and Senior Researcher at Kaiser Permanente, has been reappointment to the International Expert Advisory Council on Drug Dependence and Alcohol Problems, World Health Organization, Geneva, 2003 ss 2007.

Dr. Lori K. Holleran, Assistant Professor at The University of Texas at Austin School of Social Work, was awarded the Outstanding Investigator Award by the University of Texas' Center for Health Promotion and Disease Prevention Research in Underserved Populations (CHPR) for her pilot work exploring issues of culture and acculturation related to substance abuse prevention for high risk youth. In addition, she received the 2003-2004 Texas Exes Teaching Excellence Award for her effectiveness teaching clinical social work and substance abuse courses.

Dr. Michael Hecht, received the National Communication Association's African American Communication and Culture Division's 2003 Distinguished Scholarship Award for the book African American Communication: Exploring Identity and Culture. The book was co-authored by Ronald Jackson and Sidney Ribeau.

Dr. John E. Lochman, of the University of Alabama became Board Certified in Clinical Child and Adolescent Psychology, American Board of Clinical Child and Adolescent Psychology. He was also elected as Secretary-Treasurer of the American Board of Clinical Child and Adolescent Psychology and was selected to be a Fellow of the Academy of Cognitive Therapy.

Joan Zweben, Ph.D. of the CTN California-Arizona Node, was awarded the Vernelle Fox Award from the California Society of Addiction Medicine (CSAM). She is only the second non-physician to receive this award.

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