Director's Report to the National Advisory Council on Drug Abuse - February, 2005

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Director's Report to the National Advisory Council on Drug Abuse - February, 2005

Research Findings - Basic Neurosciences Research

Acetaldehyde Enhances Acquisition of Nicotine Self-Administration in Adolescent Rats

Tobacco use has one of the highest rates of addiction and relapse of any abused drug. Paradoxically, however, in animal models of reinforcement nicotine appears weak compared to other abused drugs. The reinforcing effects of tobacco smoke may be greater than nicotine alone due to complex interactions between the many constituents of tobacco smoke. One such constituent, acetaldehyde, has been thought to be reinforcing when inhaled. This compound may, therefore, augment nicotine's reinforcing properties. Juvenile and adult male rats were implanted with intravenous catheters and tested for nicotine self-administration 4 days later, at postnatal day 27 or 90, respectively. Animals were offered one of the following solutions: nicotine (30 mg/kg/injection), acetaldehyde (16 mg/kg/inj), nicotine (30 mg/kg/inj) plus acetaldehyde (16 mg/kg/inj), or saline. The youngest animals responded significantly more for nicotine plus acetaldehyde than for saline or for either drug alone. Tests with receptor antagonists indicated that these drug effects are mediated by central, but not peripheral, nicotinic receptors. There was an age-related decline in self-administration of nicotine plus acetaldehyde. Taken together, these results indicate that acetaldehyde, at the low concentrations found in tobacco smoke, interacts with nicotine to increase responding in a stringent self-administration acquisition test where nicotine alone is only weakly reinforcing, and that adolescent animals are more sensitive to these actions than adults. The authors suggest that animal models of tobacco addiction could be improved by combining acetaldehyde, and possibly other smoke components, with nicotine to more accurately reflect the pharmacological profile of tobacco smoke. Belluzzi, J.D., Wang, R. and Leslie, F.M. Acetaldehyde Enhances Acquisition of Nicotine Self-Administration in Adolescent Rats. Psychopharmacology (epub), 2004.

The CB2 Receptor Shows Promise as Target for Novel Pain Therapies

NIDA funded research has been examining the potential use of CB2-selective cannabinoid agonists in the treatment of pain. CB2-selective cannabinoid agonists are of special interest because CB2 receptors are located peripherally in the nervous system; thus agents that activate these receptors are unlikely to have the abuse potential of centrally acting cannabiniods. In a recently published study, Dr. Andrea Hohmann (University of Georgia) found that a CB2-selective cannabinoid agonist (AM1241) suppressed the development of capsaicin-evoked thermal and mechanical hyperalgesia and allodynia. AM1241 also produced a dose-dependent suppression of capsaicin-evoked nocifensive behavior. This AM1241-induced suppression capsaicin-evoked pain behavior was completely blocked by a CB2 antagonist. These data provide evidence that the activation of CB2 receptors is sufficient to produce analgesia in a persistent pain state, thus bolstering the case that the CB2 receptor may be an important therapeutic target for novel pain therapies. Hohmann, A.G., Farthing, J.N., Zvonok, A.M. and Makriyannis, A. Selective Activation of Cannabinoid CB2 Receptors Suppresses Hyperalgesia Evoked by Intradermal Capsaicin, Journal of Pharmacology and Experimental Therapeutics, 308(2), pp. 446-453, 2004.

Intrathecal CART (55-102) Enhances the Spinal Analgesic Actions of Morphine in Mice

Cocaine- and amphetamine-regulated transcript (CART) peptides are peptide neurotransmitters that have been implicated in feeding, reward and reinforcement. In this study, the researchers had made the observation that CART also appears to be

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present in regions of the nervous system associated with pain. They hypothesized that CART peptides might be involved in regulating pain transmission. There are at least two naturally occurring, active peptides that are generated by enzymatic processing of CART. Damaj and colleagues tested the peptide referred to as CART (55-102). They found that injecting CART (55-102) alone into the cerebrospinal fluid of mice did not affect pain levels in their model. However, injecting CART (55-102) in addition to morphine enhanced the pain-reducing effects of morphine. Understanding how this enhancement occurs may provide for the development of therapies that will result in improved effectiveness of morphine, which means patients would need less morphine to get equivalent pain relief. Damaj, M.I., Hunter, R.G., Martin, B.R. and Kuhar, M.J. Intrathecal CART (55-102) Enhances the Spinal Analgesic Actions of Morphine in Mice. Brain Research, 1024(1-2), pp. 146-149, 2004.

Excitation-Neurogenesis Coupling in Adult Neural Stem/Progenitor Cells

Although many in vivo manipulations can influence neurogenesis in the adult hippocampus, it is not known whether adult neural stem/progenitor cells (NPCs) can intrinsically sense excitatory neural activity and thereby implement a direct coupling between excitation and neurogenesis. Additionally, it is not known how the coupling between activity and neurogenesis plays a role in modulating hippocampal-type memory processing networks. Dr. Karl Deisseroth and his colleagues at Stanford University School of Medicine showed that excitatory stimuli can act directly on adult hippocampal NPCs to favor neuron production. The excitation is sensed via Ca(v)1.2/1.3 (L-type) Ca(2+) channels and NMDA receptors on the proliferating precursors. Excitation through this pathway inhibits the expression of the genes responsible for the expression of glia (genes Hes1 and Id2) and increases the expression of NeuroD, a positive regulator of neuronal differentiation. These activity-sensing properties of the adult NPCs, when applied as an "excitation-neurogenesis coupling rule" within a Hebbian neural network, predict significant advantages for both the temporary storage and the clearance of memories. Deisseroth, K., Singla, S., Toda, H., Monje, M., Palmer, T.D. and Malenka, R.C. Excitation-neurogenesis Coupling in Adult Neural Stem/Progenitor Cells. Neuron, 42(4), pp. 535-552, 2004.

Dopamine D1 and D2 Receptor Co-Activation Generates a Novel Phospholipase C-Mediated Calcium Signal

Although dopamine D1 and D2 receptors each belong to distinct subfamilies of dopamine receptors, it is clear that they are functionally linked. However, it is not well understood how this linkage occurs. In this study, Dr. Susan George and her research team at the University of Toronto showed that agonist stimulation of co-expressed D1 and D2 receptors increased intracellular calcium levels in a signaling pathway that was not activated by either receptor alone or when only one of the co-expressed receptors was activated by a selective agonist. Calcium signaling by D1-D2 receptor co-activation was abolished after treatment with a phospholipase C inhibitor (but not with pertussis toxin or inhibitors of protein kinase A or protein kinase C). This indicates that they couple to the G(q) pathway. George et al. also show, by co-immunoprecipitation from rat brain and from cells co-expressing the receptors, that D1 and D2 receptors are part of the same heteromeric protein complex. Finally, they used immunohistochemistry to show that these receptors are co-expressed and co-localized in individual neurons of human and rat brains. Lee, S.P., So, C.H., Rashid, A.J., Varghese, G., Cheng, R., Lanca, A.J., O'Dowd, B.F. and George, S.R. Dopamine D1 and D2 Receptor Co-activation Generates a Novel Phospholipase C-mediated Calcium Signal. Journal of Biological Chemistry, 279(34), pp. 35671-35678, 2004.

Rats Reared in Enriched Environments Have More Robust Glutamatergic Neurotransmission in the Prefrontal Cortex and Improved Performance in a Spatial Memory Task Than Animals Reared in Impoverished or Normal Environments

Rearing rats in impoverished (IC) and enriched (EC) environmental conditions alters synaptic plasticity and cognitive processes. Metabotropic glutamate receptors (mGluRs) are known to play a key role in synaptic and behavioral plasticity. In the present study, the effect of rearing conditions on the expression of mGluR proteins in the prefrontal cortex (PFC) was assessed by immunoblotting. A significant difference in the content of prefrontal mGluR1 and mGluR5 (ie group I) and mGluR2/3 (ie group II) was observed between IC and EC rats. To functionally characterize this difference, in vivo microdialysis was used to verify differences in mGluR regulation of extracellular glutamate in the PFC. The results indicate that the capacity of group I and II mGluRs to elevate extracellular glutamate levels was significantly blunted in the PFC of IC rats compared to either EC subjects, or rats reared in normal environmental conditions (ie NIH standards). Group II mGluR receptors regulate

Staff Highlights

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performance in a forced T-maze spatial memory task that involves the PFC, and IC rats demonstrated deficits in this task relative to EC rats. These data suggest that reduced mGluR transmission in the PFC produced by impoverished, relative to enriched, rearing environments may contribute to cognitive deficits. Melendez, R.I., Gregory, M.L., Bardo, M.T. and Kalivas, P.W. Impoverished Rearing Environment Alters Metabotropic Glutamate Receptor Expression and Function in the Prefrontal Cortex. Neuropsychopharmacology, 29(11), pp. 1980-1987, 2004.

Differences in Maternal Styles of Rearing May Predispose to or Protect Individuals From the Development of Addiction

While many people experiment with drugs, relatively few individuals develop a true addiction. Dr. Michael Meaney and his colleagues hypothesized that, in rats, such individual differences in the actions of addictive drugs might be determined by postnatal rearing conditions. To test this idea, they investigated whether stimulant- and stress-induced activation of nucleus accumbens dopamine transmission and dopamine-dependent behaviors might differ among adults rats that had been either repeatedly subjected to prolonged maternal separation or a brief handling procedure or left undisturbed (non-handled) during the first 14 days of life. They found that, in comparison with their handled counterparts, maternally separated and non-handled animals are hyperactive when placed in a novel setting, display a dose-dependent higher sensitivity to cocaine-induced locomotor activity and respond to a mild stressor (tail-pinch) with significantly greater increases in nucleus accumbens dopamine levels. In addition, maternally separated animals were found to sensitize to the locomotor stimulant action of amphetamine when repeatedly stressed under conditions that failed to sensitize handled and non-handled animals. Finally, quantitative receptor autoradiography revealed a lower density of nucleus accumbens-core and striatal dopamine transporter sites in maternally separated animals. They also found greatly reduced D3 dopamine receptor binding and mRNA levels in the nucleus accumbens-shell of handled animals. Together, these findings provide compelling evidence that disruptions in early postnatal rearing conditions can lead to profound and lasting changes in the responsiveness of mesocorticolimbic dopamine neurons to stress and psychostimulants, and suggest a neurobiological basis for individual differences in vulnerability to compulsive drug taking. Brake, W.G., Zhang, T.Y., Diorio, J., Meaney, M.J. and Gratton, A. Influence of Early Postnatal Rearing Conditions on Mesocorticolimbic Dopamine and Behavioural Responses to Psychostimulants and Stressors in Adult Rats. European Journal of Neuroscience, 19, pp. 1863-1874, 2004.

Classifying New Drugs of Abuse - "*Flatliners*" and "*Blue Mystic*"

Within the past few years, two sulfur-containing agents have appeared on the clandestine market, and their increasing popularity has resulted in actions to schedule them under the Controlled Substances Act. One is 1-(4-methylthio-phenyl)-2-aminopropane or 4-MTA (known as "*Flatliners*" and "*Golden Eagles*"), and the other is 2-(2,5-dimethoxy-4-n-propylthiophenyl)-1-aminoethane or 2C-T-7 (known as "T7," "*Blue Mystic*," and "*Tripstasy*"). Both of these substances are substituted phenylalkylamines, as are the amphetamines and mescaline. However, sulfur-containing drugs of abuse are rare, and there is little information on the behavioral actions of 4-MTA and 2C-T-7. A reasonable approach to the scientific understanding of new drugs of abuse is to test them in rats trained to distinguish (i.e., to discriminate) known, well-characterized drugs of abuse from vehicle. Behaviorally active drugs of various pharmacologic categories provide relatively distinct internal stimuli to the rats, which are trained to press a "drug-appropriate" lever for a food reward when they detect that they have been administered a drug like the training drug. They are trained to press a different lever when they are administered the vehicle. Tests of stimulus generalization (substitution) were performed with 4-MTA and 2C-T-7 using a two-lever drug discrimination task with groups of rats trained to discriminate either the hallucinogen DOM [1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane], or the stimulant cocaine, or the "empathogen" MDMA ("*Ecstasy*") from vehicle. 4-MTA (ED50 = 0.8 mg/kg) substituted only for the MDMA stimulus, whereas 2C-T-7 (ED50 = 0.8 mg/kg) substituted only for the DOM stimulus. Thus, 4-MTA appears to be MDMA-like, and 2C-T-7 seems best classified as an hallucinogen. These results are consistent with what little is known about the action of 4-MTA and 2C-T-7 in humans. Khorana, N., Pullagurla, M.R., Dukat, M., Young, R. and Glennon, R.A. Stimulus Effects of Three Sulfur-containing Psychoactive Agents. Pharmacology Biochemistry and Behavior, 78, pp. 821-826, 2004.

VTA Dopamine Neurons are Less Sensitive to NE Inhibition During the Early Phases of Cocaine-seeking Behavior - A Cellular Phenotype Correlated with

Cocaine-seeking Behavior, but not Cocaine

The reinforcing properties of psychostimulants depend critically on their effects on dopamine (DA) neurons in the ventral tegmental area (VTA). Dr. John Williams's group characterized cellular responses associated with the rewarding component of drug seeking behavior by evaluating the DA neuronal activities measured in triple-yoked animals that self-administered cocaine or that received cocaine or saline passively. His group evaluated the adaptive changes of DA neurons in slice preparations of the VTA. They found that the natural dis-inhibitory regulation of norepinephrine (NE) on the metabotrophic glutamate receptor (mGluR)-mediated hyperpolarization of VTA DA neurons, always found in normal animals, was also unchanged in animals passively given cocaine for 3 days. In contrast, animals that self-administered the cocaine for 3 days showed a transient, reduced dis-inhibitory effect of NE. The adaptation of VTA neuron sensitivity to NE drive at early state of the development of drug-seeking behavior represented a cellular phenotype of self-motivation behavior that was not evident in animals receiving cocaine via passive administration. That is, the adaptation correlated with efforts of the animal to attain cocaine. The diminished dis-inhibitory effect of NE on VTA neurons was still detectable 14 days later in self-administering rats. A similar response developed by 14 days in animals receiving cocaine. It is not yet known whether the same molecules are responsible for the adaptation at both early and later stages of cocaine administration. Paladini, C.A., Mitchell, J.M., Williams, J.T. and Mark, G.P. Cocaine Self-administration Selectively Decreases Noradrenergic Regulation of Metabotropic Glutamate Receptor-mediated Inhibition in Dopamine Neurons. Journal of Neuroscience, 24(22), pp. 5209-5215, 2004.

Different Calcium Signaling Mechanisms Underlie the Interaction of Neuroactive Molecules at VTA Dopamine Neurons

VTA dopamine neurons receive glutamatergic, adrenergic and muscarinic inputs. Receptors that couple to phosphoinositide hydrolysis, which include metabotropic glutamate receptors (mGluRs), adrenoceptors and muscarinic receptors, can either activate or inhibit VTA dopamine cells, depending on the pattern of receptor stimulation. Transient activation of alpha1 adrenoceptors with norepinephrine produces an outward current recorded in brain slices that contain midbrain dopamine neurons. The norepinephrine-mediated outward (hyperpolarizing) current was induced by activation of a potassium conductance through release of calcium from intracellular stores. In contrast to the mGluR-mediated outward current, the outward current induced by alpha1 adrenoceptors often consisted of multiple peaks. Activation of alpha1 adrenoceptors also induces a wave of calcium release that spread through the soma and proximal dendrites without a decline in amplitude or rate of propagation and, therefore, differs qualitatively from that induced by mGluRs. Finally, the alpha1 adrenoceptor-activated outward current was more sensitive to the calcium store-depleting agents ryanodine and caffeine. Thus, although both alpha1 adrenoceptors and mGluRs mobilize calcium from intracellular stores, they do it differently and mobilize different pools of calcium. The results suggest that noradrenergic innervation of dopamine cells can directly inhibit the activity of dopamine cells. Psychostimulants, such as amphetamine, will therefore have a direct effect on the firing pattern of dopamine neurons through a combination of actions on dopamine and alpha1 adrenoceptor activation. Paladini, C.A. and Williams, J.T. Noradrenergic Inhibition of Midbrain Dopamine Neurons. Journal of Neuroscience, 24(19), pp. 4568-4575, 2004.

Cell-permeable Peptide Antioxidants Targeted to Inner Mitochondrial Membrane Inhibit Mitochondrial Swelling, Oxidative Cell Death, and Reperfusion Injury

Reactive oxygen species (ROS) play a key role in promoting mitochondrial cytochrome c release and induction of apoptosis. ROS induce dissociation of cytochrome c from cardiolipin on the inner mitochondrial membrane (IMM), and cytochrome c may then be released via mitochondrial permeability transition (MPT)-dependent or MPT-independent mechanisms. Dr. Szeto and colleagues have developed peptide antioxidants that target the IMM, and used them to investigate the role of ROS and MPT in cell death caused by t-butylhydroperoxide (tBHP) and 3-nitropropionic acid (3NP). The structural motif of these peptides centers on alternating aromatic and basic amino acid residues, with dimethyltyrosine providing scavenging properties. These peptide antioxidants are cell-permeable and concentrate 1000-fold in the IMM. They potently reduced intracellular ROS and cell death caused by tBHP in neuronal N2A cells (EC50 in nM range). They also decreased mitochondrial ROS production, inhibited MPT and swelling, and prevented cytochrome c release induced by Ca2+ in isolated mitochondria. In addition, they inhibited 3NP-induced MPT in isolated

mitochondria and prevented mitochondrial depolarization in cells treated with 3NP. ROS and MPT have been implicated in myocardial stunning associated with reperfusion in ischemic hearts, and these peptide antioxidants potently improved contractile force in an ex vivo heart model. It is noteworthy that peptide analogs without dimethyltyrosine did not inhibit mitochondrial ROS generation or swelling and failed to prevent myocardial stunning. These results clearly demonstrate that overproduction of ROS underlies the cellular toxicity of tBHP and 3NP, and ROS mediate cytochrome c release via MPT. These IMM-targeted antioxidants may be very beneficial in the treatment of aging and diseases associated with oxidative stress. Zhao, K., Zhao, G-M., Wu, D., Soong, Y., Birk, A.V., Schiller, P.W. and Szeto, H.H. Journal of Biological Chemistry, 279(33), pp. 34682-34690, 2004.

Cannabinoids and Pregnancy

Ectopic pregnancy is a major reproductive health issue. Although other underlying causes remain largely unknown, one cause of ectopic pregnancy is embryo retention in the fallopian tube. In a recent study, Dr. Haibin Wang and his associates, Vanderbilt University of Medical Center, Nashville, TN, show that genetic or pharmacologic silencing of cannabinoid receptor CB1 causes retention of a large number of embryos in the mouse oviduct, eventually leading to pregnancy failure. This was reversed by isoproterenol, a beta-adrenergic receptor agonist. Impaired oviductal embryo transport is also observed in wild-type mice treated with methanandamide. Collectively, their results suggest that aberrant cannabinoid signaling impedes coordinated oviductal smooth muscle contraction and relaxation crucial to normal oviductal embryo transport. Colocalization of CB1 and beta2-adrenergic receptors in the oviduct muscularis implies that a basal endocannabinoid tone in collaboration with adrenergic receptor coordinates oviductal motility for normal journey of embryos into the uterus. Besides uncovering a new regulatory mechanism, this study could be clinically relevant to ectopic pregnancy. Wang, H., Guo, Y., Wang, D., Kingsley, P.J., Marnett, L.J., Das, S.K., DuBois, R.N. and Dey, S.K. Nature Medicine, 10, pp. 1074-1080, 2004.

Plasmon Resonance Spectroscopy

Binding of an agonist to a GPCR such as the delta receptor (DOR) is believed to involve an overall change in the receptor "inactive" or ground state conformation, including movement of helices III, VI, and VII, to generate one or more "active" receptor states which can then couple to various G-proteins which interact with the intracellular loops at the cytoplasmic side or face of the receptor. Receptor ground state disruption of various hydrophobic, ionic, and hydrogen bond amino acid residue contacts between the N-terminus and extracellular loops 1-3 is brought about by ligand binding, which takes place largely at the opposite face of the receptor, in relation to the G-protein binding sites. Agonist delta ligands having differing structures (such as peptide or non-peptide) may activate the receptor by stabilizing different delta receptor conformations, and these can interact with different G-proteins (such as Go or Gi), leading to activation of different second messenger pathways. The binding of the agonist to the receptor promotes nucleotide exchange of GTP for GDP, and dissociation of the G-protein GABG heteromer into GA and BG subunits. Dr. Victor Hruby and his associates have recently reported on the use of an optical technique known as surface plasmon resonance, based on the theory of thin films, in order to measure the affinity of a delta receptor-ligand complex, and that of a receptor-ligand-GTPGS complex. A thin metal film (silver or gold) is coated upon a silicon dioxide dielectric layer, the latter being in contact with an aqueous buffer in which ligand or GTPGS can be introduced. A solubilized receptor can be pre-incorporated into a lipid bilayer which is then spread on the silica surface. Incident laser light, at a particular incidence angle, on the metal film will excite electronic oscillations known as plasmons, and the resonance is detected as a decrease in the reflected light intensity. Molecules such as receptors and their complexes immobilized at the silica surface can change the resonance angle as a function of their orientation, and their contribution to layer thickness and refractive index. The method does not require radiolabeling, fluorescent labels, separate GTPGS or cAMP assays, or the use of antibodies against particular G-protein subtypes. Since it depends upon relative changes in angle (millidegree), it does not require knowing the actual concentration of G-protein and receptor in the bulk aqueous solution in order to determine binding constants. Generally, the ligand may be pre-bound to the receptor before immobilization in the lipid, and the G-protein or GTPGS then introduced into the aqueous solution. Some of the results of this work include: (a) dissociation constants could be determined for full and partial agonists, and for antagonists binding to the human DOR in the absence of added G protein, which were comparable to in-vitro radiolabeled binding assay values. (b) considerable selectivity was shown in the

binding of various ligands to different G protein subtypes; the presence of different G-protein subtypes also produced different GTPGS binding results. (c) agonist affinity (but not antagonist affinity) was increased by the presence of the G-protein, and in general, the presence of BG subunits improved the ligand binding compared to the presence of GA subunits alone. (d) significant differences in resonance angles were found depending on whether the incident light was parallel or perpendicularly polarized, i.e., the technique depends on the orientation of the immobilized receptor in the lipid bilayer. Since both ligand binding and G-protein binding can be separately measured, it is assumed that some receptors can be immobilized with the extracellular face pointing toward the aqueous phase, and some with the intracellular face pointing toward the aqueous phase. (e) adding GTPGS to a ligand-receptor complex produced a decrease in resonance angle associated with the disassembly of the G-protein heteromer, and exchange of GTP for GDP. (f) the technique can be used to follow the kinetics of binding an agonist such as DPDPE to the DOR, which was found to be biphasic (suggesting the formation and dissociation of an intermediate in the absence of G-proteins, and monophasic (and comparatively faster) in the presence of G-proteins. One prospect for the further use of this technique is to develop ligands selective for various G-protein subtypes, and thereby selective for a particular signaling pathway (such as analgesia) without activating side effect pathways. Alves, I.D., Ciano, K.A., Boguslavski, V., Varga, E., Salamon, Z., Yamamura, H.I., Hruby, V.J., and Tollin, G., Journal of Biological Chemistry, 279(43), pp. 44673-44682, 2004.

Further Structurally Constrained Analogues of cis-(6-Benzhydrylpiperidin-3-yl) benzyamine with Elucidation of Bioactive Conformation: Discovery of 1,4-Diazabicyclo[3,3,1] nonane Derivatives and Evaluation of Their Biological Properties for the Monoamine Transporters

The purpose of this study was to develop a series of 3,6-disubstituted piperidine derivatives, structurally constrained versions of flexible piperidine analogues, with preferential affinity for dopamine tranporter (DAT). In an attempt to further rigidify this structure to study influence of rigidity on binding and in vivo activity, the PI and his coworkers have developed a series of 4,8-disubstituted 1,4-diazabicyclononane derivatives and tested them for their affinity at the DAT, serotonin transporter (SERT), and norepinephrine transporter (NET) in the brain by measuring their potency in competing for the binding of [^{3}H]WIN 35,428, [^{3}H]citalopram, and [^{3}H]nisoxetine, respectively. Selected compounds were also tested for their ability to inhibit uptake of [^{3}H]DA. The SAR study led to the discovery of potent lead compound which exhibited high affinity and selectivity for DAT (IC50 = 22.5 nM; SERT/DAT = 384 and NET/DAT > 444). The PI and coworkers further stated that overall current SAR results corresponded well with the results from less constrained 3,6-disubstituted versions of these compounds albeit the former class exhibited more stringent requirements in molecular structure for activity. However the potent compounds in the current series exhibited greater selectivity for the DAT compared to their corresponding lesser constrained 3,6-disubstituted versions indicating an effect of rigidity in selective interaction with transporter protein. In an attempt to elucidate the bioactive conformational structure of the lead molecules in the current and the 3,6-disubsituted series, a preliminary molecular modeling study was carried out where the most rigid derivative was used as a template structure. Two compounds (-)-2 and (-)-10c (see in the publication) exhibited stimulant activity in locomotor tests in mice in which (-)-2 exhibited a slower onset and longer duration of action compared to (-)-10c. Both compounds occasioned complete cocaine-like responding in mice trained to discriminate 10 mg/kg ip cocaine from vehicle. Kolhatkar, R., Cook, C.E., Ghoral, S.K., Deschamps, J., Beardsley, P.M., Reith, M.E.A. and Dutta, A.K. Journal of Medicinal Chemistry, 47, pp. 5101-5113, 2004.

Cannbinoid Systems Related to Disease Progression

There have been clinical studies indicating marijuana (THC) alleviates progression and some symptoms of multiple sclerosis (M.S.). As found in other studies focusing on AIDS-related diseases, THC inhibits some immune functions. This report provides some understanding of the basic neural-immune factors that may be key to this process. Lymphocyte/endothelial interactions are not only an area related to M.S., they are also important in HIV invasive processes. Multiple sclerosis (MS) is the most common of the immune demyelinating disorders of the central nervous system (CNS). Leukocyte/ endothelial interactions are important steps in the progression of the disease and substances that interfere with these activities have been evaluated as potential therapeutic agents. Cannabinoid receptor agonists have been shown to down-regulate immune responses and there is preliminary evidence that they may slow the progress of MS. The purpose of this investigation was to determine how

cannabinoid receptor agonists interfere with leukocyte rolling and adhesion. This was investigated in an experimental auto-immune encephalomyelitis (EAE) model using six to eight week old C57BL/6 mice. Mouse myelin oligodendrocyte protein and pertussis toxin were used to induce EAE. WIN 55212-2, CB1 and CB2 antagonists were given. By use of in vivo intravital microscopy, leukocyte/endothelial interactions were evaluated via a cranial window implanted two days before. The results demonstrated that EAE increases leukocyte rolling and firm adhesion in the brain, and that this increased leukocyte/endothelial interaction can be attenuated by administration of WIN 55212-2. Furthermore, use of the selective antagonists for the CB1 receptor (SR141716A) and the CB2 receptor (SR144528) in this study demonstrated that the cannabinoid's inhibitory effects on leukocyte/endothelial interactions can be mediated by activating CB2 receptor. Ni, X., Geller, E.B., Eppihimer, M.J., Eisenstein, T.K., Adler, M.W. and Tuma, R.F. Win 55212-2, A Cannabinoid Receptor Agonist, Attenuates Leukocyte/endothelial Interactions in an Experimental Autoimmune Encephalomyelitis Model. Multiple Sclerosis 10, pp. 158-164, 2004.

Cannabinoids and Cell Death

An important issue in cellular science focuses on attrition of certain cells and systems: apoptosis. This mitochondrial directed process is very important in the turnover of immune cells that are constantly being replaced. This study focuses on dendritic cell systems and observed stimulation of apoptosis by the cannabinoid system. The precise role of cannabinoid receptors CB1 and CB2, as well as endogenous ligands for these receptors, on immune cells remains unclear. In the current study, the NIDA supported investigators examined the effect of endogenous and exogenous cannabinoids on murine bone marrow-derived dendritic cells (DCs). Addition of Delta(9)-tetrahydrocannabinol (THC), a major psychoactive component found in marijuana or anandamide, an endogenous cannabinoid, to DC cultures induced apoptosis in DC. DCs expressed CB1 and CB2 receptors and the engagement of both receptors was necessary to trigger apoptosis. Treatment with THC induced caspase-2, -8, and -9 activation, cleavage of Bid, decreased mitochondrial membrane potential, and cytochrome c release, suggesting involvement of death-receptor and mitochondrial pathways. DCs from Bid-knockout mice were sensitive to THC-induced apoptosis thereby suggesting that Bid was dispensable. THC treatment induced phosphorylation and enhanced the transcription of several apoptotic genes regulated by NF-kappaB. Moreover, inhibition of NF-kappaB was able to block THC-induced apoptosis in DCs. Lastly, in vivo treatment of mice with THC caused depletion of splenic DCs. Together, this study demonstrates for the first time that endogenous and exogenous cannabinoids may suppress the immune response through their ability to induce apoptosis in DCs. Do, Y., McKallip, R.J., Nagarkatti, M. and Nagarkatti, P.S. Activation Through Cannabinoid Receptors CB1 and CB2 on Dendritic Cells Triggers NF-kappa B-dependent Apoptosis: Novel Role for Endogenous and Exogenous Cannabinoids in Immunoregulation. Journal of Immunology, 173, pp. 2373-2382, 2004.

Opioid and Chemokine Systems Interaction in Neuron Activity

Chemokine receptors were early identified with movement of immune cells to target infectious agents. Subsequently, studies demonstrated the importance of these systems (plus the CD4 receptor) for the entry of HIV into immune cells. More recently, this group has found chemokines on neurons. This study provides some insight into what happens with these receptors. Both the chemokine SDF-1-alpha and the human immunodeficiency virus-1 (HIV-1) coat protein gp120 can bind to CXCR4 chemokine receptors but with different signaling consequences. To understand the molecular basis for these differences, the NIDA supported investigators tagged the rat CXCR4 receptor with enhanced cyan (ECFP) and yellow (EYFP) derivatives of the green fluorescent protein and investigated CXCR4 receptor dimerization in human embryonic kidney cells using fluorescence resonance energy transfer (FRET). Elevated FRET was detected under basal conditions from chemokines receptor-cotransfected cells indicating a high level of CXCR4 receptor dimerization. In comparison, chemokine and mu-opioid receptor-cotransfected cells displayed a much lower FRET signal. The FRET signal resulting from EYFP-CXCR4- and ECFP-CXCR4-expressing cells could be attenuated by coexpressing nontagged CXCR4 receptors suggesting competition with fluorophore-tagged receptors in the membrane. Nontagged mu-opioid, kappa-opioid, and muscarinic receptors also decreased the FRET between the tagged CXCR4 receptor pairs but to a lesser extent. Application of the CXCR4 receptor agonist SDF-1alpha further increased the FRET signal from tagged CXCR4 receptors, an effect that was inhibited by the CXCR4 antagonist. FRET analysis of tagged hCD4 constructs demonstrated that there was significant association of human CD4 and

CXCR4, as well as dimerization. These data suggest that CXCR4 dimerization is involved in SDF-1alpha- and gp120-induced signaling events. Toth, P.T., Ren, D.J., Miller, R.J. Regulation of CXCR4 Receptor Dimerization by the Chemokine SDF-1 Alpha and the HIV-1 Coat Protein gp120: A Fluorescence Resonance Energy Transfer (FRET) Study. Journal of Pharmacology and Experimental Therapeutics, 310, pp. 8-17, 2004.

Delta Opioids on Immune Cell Maturation

The different types of opiate receptors differentially affect immune processes. The delta opioid receptor appears important in the maturation process of lymphocytes, especially T-cells. The following study focuses on the early stage of T-cell delineation process. The delta-opioid receptor-1 (DOR-1) as well as delta-opioid enkephalin peptides are expressed during maturation of T cells, although the functional significance of their expression remains unclear. Based on results which show that the administration of the highly selective delta-opioid agonist D-Pen(2), D-Pen(5)]enkephalin (DPDPE) induces an altered pattern of T-cell differentiation in fetal thymic organ culture (FTOC), these NIDA supported researchers hypothesized that DOR-1 is involved in the negative selection process. Our results show that superantigen-induced clonal deletion is promoted by DPDPE and significantly impaired in DOR-1-deficient mice. These results suggest that delta-opioids may play a homeostatic role in the negative selection process during T-cell development. McCarthy, L.E., Nitsche, J.F., Pintar, J.E. and Rogers, T.J. The Delta-opioid Receptor Participates in T-cell Development by Promoting Negative Selection. Journal of Neuroimmunology, 153, pp. 91-98, 2004.

Nicotine Activation of 4* Receptors: Sufficient for Reward, Tolerance, and Sensitization

Addiction to nicotine has been shown by twin studies to have a significant genetic component. Previous studies have also shown that beta2 subunit and the alpha4 subunits of the nicotinic acetylcholine receptor is required for the rewarding properties of nicotine. These previous studies do not show that either subunit of the receptor is sufficient (acting by itself) to mediate the actions of nicotine on reward, tolerance, and sensitization. To demonstrate that gene variants of the alpha 4 subunit of the nicotinic acetylcholine receptor is sufficient, Tapper and his colleagues created mutant mice in which the ninth amino acid, a leucine, is changed to an alanine in the pore-forming M2 domain. The alpha4beta2 nicotinic acetylcholine receptors were made hypersensitive by the amino acid substitution. Mutant mice when challenged with low doses of nicotinic agonists were more sensitive to the rewarding properties of nicotine and showed enhanced rates of tolerance and sensitization. These results suggest that gene variants in the alpha4 subunit of the nicotinic acetylcholine receptor can alter the sensitivity of the receptor to nicotinic receptors and may alter vulnerability to addiction to nicotine. Consistent with the idea that variants or polymorphisms in the alpha4 nicotine receptor alter vulnerability to nicotine addiction is the finding by Feng et al. Feng and his colleagues report that two single nucleotide polymorphisms in the coding region of exon 5 are associated with a protective effect against addiction. Tapper A.R., McKinney, S.L., Nashmi, R., Schwarz, J., Deshpande, P., Labarca, C., Whiteaker, P., Marks, M.J., Collins, A.C. and Lester, H.A. Science, 306 (5698), pp. 1029-1032, 2004; Feng,.Y., Niu, T., Xing, H., Xu, X., Chen, C., Peng, S., Wang, L., Laird, N. and Xu, X. American Journal of Human Genetics, 75(1), pp. 112-121, 2004.

Reduced Cellular Expression and Activity of the P129T Mutant of Human Fatty Acid Amide Hydrolase: Evidence for a Link Between Defects in the Endocannabinoid System and Problem Drug Use

Fatty acid amide hydrolase (FAAH) inactivates the activity of a large class of signaling lipids, including anandamide, N-palmitoyl ethanolamine, and oleomide. Animal studies indicate that FAAH serves as the primary catabolic regulator of fatty acid amide signaling in the nervous system and thus plays an important role in many neurobehavioral processes. Drs. Sipe and Cravatt and colleagues have identified a single nucleotide polymorphism in the FAAH gene that converts a conserved proline residue to a threonine at amino acid position 129 (P129T). This polymorphism was previously shown by these researchers to be associated with problem drug and alcohol use. To determine the functional effect of this polymorphism, Dr. Cravatt's group compared the expression and activity of the protein containing the proline allele to the protein containing the variant (threonine) allele in both peripheral T lymphocytes and transfected cells. The purified proteins of both forms were found to exhibit similar catalytic properties and structural stability; however the P129T variant protein was expressed at significantly lower levels than the more common proline containing protein. They examined whether post-translational mechanisms,

differences in rates of cellular turnover, or proteosome mediated degradation could be responsible for the decreased levels of the P129T variant protein, but no significant differences were found. Altogether, these studies suggest that the reduced cellular expression levels of the P129T-FAAH protein may be caused by a post-translational mechanism that precedes the productive folding of this enzyme. In summary, this is the first evidence that the natural polymorphism in the human FAAH gene associated with problem drug use produces a mutant enzyme (P129T) with defective biochemical and cellular properties. This study highlights the idea that significant functional variability exists in the endocannabinoid system in the human population, and can be explained in part by genetic variation. Chiang, K.P., Gerber, A.L., Sipe, J.C., and Cravatt, B.F. Reduced Cellular Expression and Activity of the P129T Mutant of Human Fatty Acid Amide Hydrolase: Evidence for a Link Between Defects in the Endocannabinoid System and Problem Drug Use. Human Molecular Genetics, 13, pp. 2113-2119, 2004.

System-based Proteomic Analysis of the Interferon Response in Human Liver Cells

NIDA supports a P30 Center Grant to Dr. Michael Katz at the University of Washington in which proteomics and gene expression profiling are used to study the host response to hepatitis C (HCV), a sequealae and major public health problem in intravenous drug users. One of the major host factors used to fight hepatitis C and other viral infection are interferons. In response to viral infection, infected cells synthesize interferon. Gamma interferon is used to treat HCVy infection. However, many HCV infected individuals do not respond to interferon therapy. To determine the mechanism by which interferon acts to clear HCV infection of liver Dr. Katze and his colleagues conducted a global quantitative proteomic analysis in a human hepatoma cell line (Huh7) in the presence and absence of IFN treatment. Of the 1364 proteins observed, 54 were upregulated more than 2 fold while another 24 were down regulated. Using this approach Dr. Katze discovered two new proteins, LAMB1 and ADRM, induced by interferon that are cell adhesion molecules. These cell adhesion molecules may be important interferon mediated cell migration, attachment, and cell cell interaction. Other classes of molecules upregulated by interferon were G coupled and Jak-State signaling pathways, proteins involved in ubiquination (required for protein degredation), and four liver specific interferon response proteins. These finding validate the proteomics approach because some of these proteins like the Jak-Stat pathway were known to be involved in the mediating the actions of interferon on HCV infection. Proteins suppressed by interferon included proteins in the wnts and keratins involved regulating cytoskeleton function. Using a bioinformatics software package, Cytoscape, Dr. Katze was able to identify proteins that interact with one another. Such bioinformatics tools permit detailed visualization of biological network that has not been possible previously. The identification of new molecules induced by interferon and the protein network that mediates interferon response will enable scientists to identify new drug targets and treatments for HCV infection. Yan, W., Lee, H., Yi, E.C., Reiss, D., Shannon, P., Kwieciszewski, B.K., Coito, C., Li, X.J., Keller, A., Eng, J., Galitski, T., Goodlett, D.R., Aebersold, R. and Katze, M.G. Genome Biology, 5(8), p. R54, 2004.

Director's Report to the National Advisory Council on Drug Abuse - February, 2005

Research Findings - Basic Behavioral Research

Environmental Enrichment Decreases DAT in the PFC, Concomitant with Sensitization of DAT-activated Locomotion

Rats reared in an enriched environment (EC), provided with social stimulation and novel objects, appear less fearful as adults and show different responses to psychomotor stimulants than animals reared in isolation (IC). EC animals have greater behavioral activation to amphetamine, but an attenuated sensitization with repeated drug treatment. They also have decreased drug intake when trained to self-administer i.v. amphetamine. The behavioral effects of EC rearing may be linked to neuroanatomical changes, as EC rats have increased cortical spine counts, dendritic length and branching, as well as greater numbers of synapses and synaptic buttons contacting dendritic spines and shafts. Drs. Michael Bardo, Linda Dwoskin, and colleagues at the University of Kentucky examined dopamine transporter (DAT) function in the prefrontal cortex (PFC) and subcortical mesolimbic regions of EC rats to determine if changes in central dopaminergic mechanisms might be responsible for different effects of d-amphetamine. EC versus IC conditions were in effect from post-natal days 21 through 53. After this time, all animals were tested for behavioral response to an acute dose of the DAT inhibitior GBR 12935, for sensitization to repeated DAT inhibition (seven GBR injections/14 days), and assays were performed for [3H] dopamine (DA) uptake, [3H]GBR 12935 binding, and DA, DOPAC concentrations. EC rats had lower basal levels of locomotion, but showed exaggerated behavioral stimulation to acute GBR, in comparison to the IC group. EC animals also showed significant sensitization of this effect after seven GBR injections, whereas the IC group did not. On neurochemical measures of central DA function, EC and IC groups did not differ on Ki values for GBR inhibition of DA uptake into synaptosomes of medial PFC (mPFC), striatum (STR) or nucleus accumbens (NAS). When kinetic parameters of DA uptake were determined, EC significantly decreased Vmax only in the mPFC, with no concomitant change in Km. To determine if EC induced decreases of Vmax were due to a decrease in number of DAT sites, saturation analysis of GBR binding was performed. However, no differences between Bmax or Kd were found for any brain area. Lastly, HPLC analysis of DA and DOPAC content revealed significant differences between EC and IC rats for DOPAC only in the mPFC, where this metabolite was lower in EC animals. The behavioral observations from this study parallel those reported for EC animals treated with acute amphetamine, but differ from those when EC animals have received repeated amphetamine, which is associated with attenuated sensitization. Different mechanisms of drug-induced DAT inhibition and DAT reversal may be responsible for these opposite effects. The findings reported here also suggest that EC may alter the dopaminergic substrate for behavioral effects of psychostimulants by decreasing DAT function and DA metabolism in the mPFC. A specific role for the mPFC in psychostimulant-induced behavioral effects is congruent with prior experimental evidence implicating PFC glutamatergic regulation of subcortical DA regions in the acute and chronic effects of these drugs. Zhu, J., Green, T., Bardo, M.T. and Dwoskin, L. P. Environmental Enrichment Enhances Sensitization to GBR 12935-induced Activity and Decreases Dopamine Transporter Function in the Medial Prefrontal Cortex. Behavioral Brain Research, 148, pp. 107-117, 2004.

Adolescent Rats Do Not Form Learned Associations Between Nicotine and Associated Environmental Cues

Eighteen percent of U.S. teens are smokers and recent preclinical, as well as epidemiological evidence, suggests that adolescents have a differential response to the drug nicotine than is seen in adulthood. Adolescent rats have been shown to be

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more sensitive to the locomotor activating effects of nicotine, but some studies reveal that they do not develop behavioral sensitization with repeated nicotine treatment. Neuroadaptations involved in the development of sensitization are believed to play a role in the escalation of drug intake that characterizes addiction. Drs. Charles Landry, Ann Kelley, and colleagues have also examined age-related differences in acute locomotor response to nicotine and the development of behavioral sensitization. Furthermore, they determined if there are differences between adolescent and adult rats in drug-paired cue conditioning. In these studies, conducted with male rats, adults were 70 days of age, and adolescents were 28-42 days old. To assess effects of acute nicotine, all rats were injected with 0.1 mg/kg s.c. and observed in photocell activity chambers after habituation. Adolescents were more active than adults in the test chamber upon their initial, non-drug exposure (habituation), and also when they were injected with saline or nicotine. Also, adolescent animals had a greater mean locomotor count after nicotine, compared to their saline-injected controls, for the first 20 min of the test session. Adult animals, however, showed a typical pattern of initial, behavioral suppression, followed by a rise in activity counts over the session. When given 10 days of 0.4mg/kg s.c. nicotine (Adoles/nic, Adult/nic) or saline (Adoles/sal, Adult/sal) paired with 90-min in a discrete environment, Adult/nic rats showed a significant linear trend for increased locomotor activity, but Adoles/nic rats did not. In tests for cue conditioning, rats from all four groups were given a mock injection and locomotor activity was again monitored in the test chamber for 90 min. Adult animals showed the usual conditioned locomotor activation, as ambulation was greater in the Adult/nic group than in Adult/sal animals. However, there was no difference in ambulatory counts between Adolescents from the nic versus the sal groups. The main finding from this study is that adolescents, (i.e., males), do not seem to develop the usual learned associations that are formed between effects of the drug nicotine, and surrounding environmental cues. In adults, incentive motivational properties of these cues are believed to serve as strong Ôtriggers' for activating and sustaining smoking behavior. The authors speculate that this difference might be linked to prolonged development of the prefrontal cortex, which continues through the adolescent period, and serves as an important substrate for central mechanisms of attention. Furthermore, in agreement with some earlier studies, the observation that adolescent rats fail to develop nicotine sensitization suggests that plasticity-related changes produced by repeated nicotine may be different from those previously measured in adults. Schochet, T.L., Kelley, A.E. and Landry, C.F. Differential Behavioral Effects of Nicotine Exposure in Adolescent and Adult Rats. Psychopharmacology, 175, pp. 265-273, 2004.

Sex Differences in the Escalation of Intravenous Cocaine Following Long- or Short-access to Self-administration

Drs. Megan Roth and Marilyn Carroll from University of Minnesota examined sex differences in the escalation of cocaine self-administration using a procedure similar to that previously reported with male rats (Ahmed and Koob, 1998;1999). This procedure is regarded as an animal model of the transition from drug use to addiction. Initially, rats were given access to cocaine either 6 hours/day (Long Access or LgA) or 1 hour/day (Short Access or Sh) for 21 days. This differential access phase was followed by a post-differential access phase in which all rats had 3 hours/day access to cocaine. As shown previously with male rats, Drs. Roth and Carroll found that for both sexes, in the differential access phase the LgA group self-administered more cocaine infusions than the ShA group. Moreover, they found that LgA females self-administered significantly more cocaine infusions than LgA males. In the post-differential-access phase in which all rats had 3 hours/day access to cocaine, and escalation from use to abuse was measured, LgA females self-administered more cocaine infusions than either LgA males, ShA males or ShA females. This study suggests that given opportunity, females will self-administer more than males and females are more sensitive than males to factors that contribute to the escalation of cocaine intake. Roth, M.E. and Carroll, M.E. Sex Differences in the Escalation of Intravenous Cocaine Intake Following Long- or Short-access to Cocaine Self-administration. Pharmacology, Biochemistry and Behavior, 78, pp. 199-207, 2004.

Morphine's Effects on Brain-Stimulation Reward Thresholds in Young and Aged Rats

There is a dearth of both human and animal research investigating whether there are changes in the rewarding properties of drugs as a function of age. There is evidence, however, that mu-receptor density decreases with age and that dopamine D1 and D2 receptors, which mediate the rewarding effects of mu opioids, also decrease with age. These changes raise the question of whether there are corresponding changes in the rewarding properties of the mu-receptor agonist morphine. This question was

examined by Dr. Conan Kornetsky and his colleagues at Boston University using the brain-stimulation reward (BSR) procedure. It is well established that morphine and other abused drugs lower the threshold for BSR; however, the ability of an abused drug to alter the threshold for BSR has not been previously reported as a function of age. In the present experiment, the researchers compared the threshold for BSR (delivered into the lateral hypothalamic region of the medial forebrain bundle) and the ability of morphine to lower the BSR threshold in aged (24 months) and young (5-month) rats. The results indicated that while the older rats had a significantly lower baseline threshold for BSR, morphine produced a similar lowering of the BSR threshold in the two groups. These results suggest that the rewarding effect of morphine does not diminish with age, but rather is preserved. This lack of change in morphine's rewarding effects with age, despite evidence of decreases in opioid receptor density and compromises of the mesolimbic dopaminergic systems with age, warrants further investigation. Jha, S.H., Knapp, E.M. and Kornetsky, C. Effects of Morphine on Brain-Stimulation Reward Thresholds in Young and Aged Rats. Pharmacology, Biochemistry and Behavior, 79, pp. 483-490, 2004.

A New Invertebrate Model System for Investigating the Reinforcing Properties of Psychostimulants

Recent studies in the invertebrate genetic model organism, the fruit fly, suggest that such model systems can be useful for studying molecular, biochemical, and behavioral aspects of drug addiction. However, studies of motivational and learning processes, which are typical of mammalian responses to drugs of abuse, are difficult to carry out in fruit flies. Dr. Robert Huber has therefore begun exploring the use of crayfish as an invertebrate model for measuring the rewarding properties of psychostimulants. The crayfish provides a well-studied neurobiological model system, with a nervous system containing fewer than 1000 individually identifiable, monoamine-containing neurons. Thus, this invertebrate system may serve as a unique model for studying the primary site of action of psychostimulant drugs. In his report, the first set of experiments demonstrated that intramuscular injections of cocaine and amphetamine have robust and distinguishable effects on crayfish behavior. Cocaine produced a rigid flexed body posture, even at low doses, whereas amphetamine caused an exploratory response, sometimes interrupted by grooming bouts. Thus, the effects of amphetamine on crayfish behavior appeared more analogous to those reported for mammals. In the second part of the study, the reinforcing properties of psychostimulants were tested in a series of conditioned place preference (CPP) experiments. The animals were allowed to move freely in an aquarium with two distinct types of floor designs. They were fitted with cannulae so that drugs could be delivered when they were in one or the other of the environments, in a balanced design across animals. Amphetamine, and to a lesser extent cocaine, both produced a CPP. That is, when tested after conditioning, animals spent significantly more time in the drug-paired environment. These results extend studies in other invertebrates to demonstrate that psychostimulants have reinforcing effects on crayfish behavior and suggest that crayfish can provide a complementary approach to using other invertebrate species in addiction research. These findings also support the hypothesis that the fundamental neurobiological alterations involved in drug reinforcement and perhaps addiction may be evolutionarily ancient. Panksepp, J.B. and Huber, R. Ethological Analyses of Crayfish Behavior: A New Invertebrate System for Measuring the Rewarding Properties of Psychostimulants. Behavioural Brain Research, 153, pp. 171-180, 2004.

A Non-human Primate Model of the Behavioral and Physiological Effects of Childhood "Stress Inoculation"

Retrospective studies of resilience in humans have indicated that childhood exposure to moderate stress serves to "inoculate" against subsequent stressful experiences and to enhance coping skills that safeguard against the development of stress-related disorders in adolescence and adulthood. Dr. David Lyons and his colleagues have tested this hypothesis in a prospective study on squirrel monkeys. Twenty monkeys were randomly assigned to either intermittent stress inoculation (IS) or a nonstress control condition (NS) for 10 weeks, starting at postnatal week 17 when they had just been weaned but were still emotionally attached to their mothers. For the IS, individual monkeys were removed from their natal group for one hour once a week and placed in a cage adjacent to an unfamiliar adult. This separation induced isolation calls, locomotor agitation, and an increase in cortisol that returned to baseline soon after reunion with the family. At postnatal week 35, each mother-offspring dyad underwent testing in a moderately stressful novel environment to assess offspring anxiety and stress hormone concentrations. At postnatal week 50, after acclimation to an initially stressful wire-mesh box attached to the home cage, the young monkeys were tested for voluntary exploration and play in the box as an inferential measure of

anxiety. In the novel environment test, IS compared with NS offspring demonstrated diminished anxiety as measured by decreased maternal clinging, enhanced exploratory behavior, and increased food consumption. IS offspring also had lower basal plasma ACTH and cortisol and lower post-stress corticoptropin and cortisol levels. In the home-cage wire-box test, IS offspring showed enhanced exploratory and play behaviors compared with NS offspring. This study is the first prospective evidence in non-human primates that moderately stressful early experiences strengthen socioemotional and neuroendocrine resistance to subsequent stressors. Dr. Lyons is pursuing studies with this model to investigate resistance to the effects of drugs of abuse, in contrast to models of chronic stress. Additionally, this preclinical model of stress inoculation will be used to elucidate the etiology and neurobiology of stress resistance. Parker, K.J., Buckmaster, C.L., Schatzberg, A.F. and Lyons, D.M. Prospective Investigation of Stress Inoculation in Young Monkeys. Archives of General Psychiatry, 61, pp. 933-941, 2004.

Studies in Animal Models of Psychiatric Illness Used to Test Hypotheses about Co-morbidity with Drug Abuse

Co-morbidity of substance abuse disorders (SUDs) and other psychiatric illnesses is extremely common. The self-medication hypothesis - that people abuse drugs to control symptoms of their mental illness - is often invoked to explain this co-morbidity, but an alternative explanation is that the neuropathology responsible for psychiatric illnesses also increases the vulnerability for SUDs. Dr. Andrew Chambers has been testing this hypothesis in rat models. Rats with neonatal lesions of the ventral hippocampus (NVHL) exhibit a behavioral syndrome that models multiple features of schizophrenic symptomatology including positive symptoms that can be ameliorated with neuroleptics, negative symptoms, and concomitant cognitive deficits. In earlier studies in collaboration with Dr. David Self, Dr. Chambers showed that NVHL rats, compared to controls, have accelerated acquisition of cocaine self-administration, a greater propensity to binge during maintenance, a resistance to extinguish drug seeking, and greater relapse behaviors. In a recent study in collaboration with Dr. Jane Taylor, Dr. Chambers further tested drug responsivity in NVHL rats by assessing locomotor sensitization to cocaine in adulthood. NVHL animals showed greater activity in response to an initial cocaine injection compared with sham-lesioned and saline-treated groups, and they had elevated locomotor sensitization curves in response to daily cocaine injections over 7 days. In a single session 4 weeks later, NVHL continued to show cocaine-induced locomotor responses to cocaine which were higher than those of sham-lesioned animals. This altered pattern of sensitization in NVHL animals suggests that SUD vulnerability may arise from the same pathophysiological mechanisms that are responsible for schizophrenic symptomatology. In a second study, they performed similar experiments in rats with olfactory bulbectomies (OBX). This lesion model has been suggested to mimic many features of clinical affective disorders, as it produces behavioral abnormalities that include abnormal social interactions, increased aggression, and abnormal responses to fear-inducing or novel stimuli. In addition, OBX animals have alterations in limbic structures thought to be critical in the pathophysiology of affective disorders, and the behavioral symptoms are responsive to chronic, but not acute, antidepressant treatment. OBX animals also have an increased propensity to self-administer amphetamine. To further investigate whether OBX might serve as a useful model for studying the neuropathology of dual diagnosis disorders, Dr. Chambers and his colleagues studied locomotor activity in OBX rats in response to novelty and after acute and repeated injections of cocaine. Lesioned animals showed greater locomotor activity in response to a novel environment and significantly heightened locomotor activation upon initial cocaine exposure. However, over 7 days of repeated cocaine injections, OBX animals did not increase their response to cocaine, suggesting that they are "presensitized" - that is, their response is already at such a high level that it does not increase with repeated psychostimulant treatment (as is typically seen in non-lesioned animals). These studies and previous work by these investigators and others demonstrate that NVHL and OBX models involve perturbations of the neurobiological substrate responsible for the behavioral effects of drugs of abuse. The studies also support the potential utility of these models for studying neurobiological mechanisms involved in co-morbidity. Chambers, R.A. and Taylor, J.R. Animal Modeling Dual Diagnosis Schizophrenia: Sensitization to Cocaine in Rats with Neonatal Ventral Hippocampal Lesions. Biological Psychiatry, 56, pp. 308-316, 2004; Chambers, R.A., Sheehan, T., and Taylor, J.R. Locomotor Sensitization to Cocaine in Rats with Olfactory Bulbectomy. Synapse, 52, pp. 167-175, 2004.

Behavioral Correlates of Synaptic Potentiation in the Ventral Tegmental Area

In previous studies, the laboratories of Dr. Antonello Bonci and Dr. Robert Malenka

showed that single injections of drugs of abuse potentiate excitatory input to the VTA by increasing synaptic currents through AMPA glutamate receptors. In two recent studies, they examined the behavioral correlates and other features of this synaptic enhancement. In one study from Dr. Bonci's laboratory, the researchers examined correlations between amount of synaptic enhancement and drug-induced locomotor activity or stereotypy after single and repeated injections of cocaine. Glutamatergic synaptic enhancement was positively correlated with locomotor activity and stereotypy after single injections, but there was no further increase in synaptic potentiation after seven days of injections, nor was the amount of potentiation correlated with the degree of behavioral sensitization produced by multiple injections. These results suggest that cocaine-induced synaptic plasticity at VTA excitatory synapses is transient and depends upon the last cocaine injection (i.e., it is not influenced by previous history of cocaine exposure). The authors propose that cocaine-induced locomotor activity in na•ve animals reflects motivational effects of the drug, and that the correlated synaptic plasticity is involved in the formation of associations between drug-paired cues and these motivational effects. Another study, from Dr. Malenka's laboratory, combined behavioral and molecular approaches. In this study, the investigators demonstrated that cocaine-induced synaptic enhancement involves an up-regulation of AMPA receptors, and that the receptor subunit GluRA is necessary for this upregulation. Thus, synaptic enhancement was not seen in GluRA(-/-) mice. GluRA(-/-) mice did, however, show behavioral sensitization with repeated injections of cocaine, indicating that synaptic potentiation in the VTA is not necessary for the induction of sensitization. Next, the investigators tested GluRA(-/-) mice in two cocaine-conditioned behaviors. The mice did not show a conditioned locomotor response when exposed to a context previously paired with cocaine, nor did they exhibit a preference for environments where cocaine was administered (i.e., a conditioned place preference). The authors suggest that drug-induced enhancement of excitatory synaptic transmission in midbrain DA neurons, although not required for behavioral sensitization, may contribute to the development of incentive motivation with drug-associated cues. The results of these two studies elucidate cellular mechanisms underlying drug-induced excitatory enhancement in the VTA and the role of synaptic potentiation in specific drug-induced behaviors. Borgland, S.L., Malenka, R.C. and Bonci. A. Acute and Chronic Cocaine-induced Potentiation of Synaptic Strength in the Ventral Tegmental Area: Electrophysiological and Behavioral Correlates in Individual Rats. Journal of Neuroscience, 24, pp. 7482-7490, 2004; Dong, Y., Saal, D., Thomas, M., Faust, R., Bonci, A., Robinson, T. and Malenka, R.C. Cocaine-induced Potentiation of Synaptic Strength in Dopamine Neurons: Behavioral Correlates in GluRA(-/-) Mice. Proceedings of the National Academy of Sciences U.S.A, 101, pp. 14282-14287, 2004.

Glutamate-associated Plasticity in the VTA is Necessary for the Acquisition and Expression of Morphine Conditioned Place Preference

The mesocorticolimbic dopamine (DA) system has long been implicated in reinforcement involved in drug abuse, but more recent research has focused on the role of DA in learning and motivation for drug-related conditioned behaviors, including drug-induced place conditioning. In this study, Drs. Glenda Harris and Gary Aston-Jones and colleagues asked whether neural plasticity in the glutamatergic inputs to VTA is involved in associating environmental stimuli with morphine reinforcement. Opiates increase DA release from the VTA by suppressing inhibitory inputs to the DA neurons, while conditioned environmental stimuli are thought to excite DA neurons via glutamatergic afferents. Previous studies have shown that these glutamatergic inputs are enhanced when an animal is exposed to opiates, and in other brain systems, glutamatergic synaptic enhancement is known to depend on activation of cAMP-dependent protein kinase A (PKA). Thus, the investigators tested whether activation of the glutamate receptors and protein kinase A is needed for acquisition and expression of a morphine-conditioned place preference (CPP). Rats were given focal, bilateral microinjections of either the NMDA antagonist AP5, the AMPA antagonist CNQX, or vehicle into the VTA prior to each of three morphine-conditioning sessions. Both the AMPA and NMDA receptor antagonists blocked the development of morphine CPP. A PKA inhibitor also blocked the acquisition of morphine CPP when given into the VTA immediately after morphine conditioning. In separate experiments, microinjections of glutamate antagonists or the PKA blocker given immediately prior to the preference test blocked expression of morphine CPP. Although these studies did not directly measure synaptic plasticity in the VTA, the necessity of NMDA and AMPA receptor activation, and involvement of the second messenger PKA, strongly implicate synaptic enhancement in morphine CPP. These data suggest that the VTA is an important site for synaptic modifications involved in the learning and memory of environmental cues predicting drug reward. Harris, G.C., Wimmer, M., Byrne, R., Aston-Jones, G. Glutamate-associated Plasticity in the Ventral Tegmental Area is

Necessary for Conditioning Environmental Stimuli with Morphine. Neuroscience, 129, pp. 841-847, 2004.

Impulsivity and Relapse to Smoking

Individual differences in some personality traits increase susceptibility for relapse to smoking. NIDA supported researcher, Dr. Dennis McChargue, studied the effect of trait impulsivity on abstinence maintenance, or its failure, relapse. Trait impulsivity is defined as a long-standing preference for readily available rewards, coupled with difficulty delaying or resisting response to such rewards. Previous research has shown that trait-impulsive people are initially drawn to use cigarettes for their rewarding properties, but little is known about how impulsivity affects smoking cessation. The roles of craving, positive and negative affect were also studied for their effect on relapse. The present research was part of a larger study designed to test the efficacy of a 1-day workshop intervention to promote tobacco abstinence. Workshops focused on training participants in the use of smoking cessation and mood management skills. Following the workshop, participants were paid to quit smoking for 48 hr. Relapse status was assessed at 24 and 48 hr post-quit and at four weekly follow-up sessions. Breath samples were analyzed for carbon monoxide (CO) and saliva samples were analyzed for cotinine. Participants were judged to have relapsed if they reported any amount of smoking on 7 consecutive days or any smoking in each of 2 successive weeks. Participants also were considered to have relapsed if they reported abstinence but had Ecolyzer values great than 10 parts per million CO or cotinine values greater than 20ng/ml. Results indicated that more impulsive participants relapsed more quickly than less impulsive participants. That is, smokers with higher levels of trait impulsivity had greater difficulty maintaining abstinence than those with lower levels. However, there was no relation between relapse and either craving, or positive or negative affect. That is, the adverse effect of impulsivity on abstinence was not attributable to heightened craving or to negative affect or to decreased positive affect. These findings suggest that processes other than craving and affective changes may account for an impulsive smoker's difficulty maintaining abstinence. One possible explanation is that rewarding environmental stimuli, including cigarettes, may be especially salient for impulsive smokers, making such stimuli difficult to ignore and prompting responses to smoking- related cues. Doran, N., Spring, B., McChargue, D., Pergadia, M. and Richmond, M. Impulsivity and Smoking Relapse. Nicotine and Tobacco Research, 6, pp. 641-647, 2004.

Cannabinoids and Opioids Interact To Reduce Heroin Self Administration In Rats

Interactions between cannabinoid and opioid systems have important implications for addictive behaviors. In recently completed research, George Koob and his colleagues tested the effect of a cannabinoid CB1 receptor antagonist (SR141716A, 0.03 - 3.0 mg/kg) on heroin (0.03 mg/kg/infusion) self-administration in dependent and non-dependent rats. The investigators compared both dependent and non-dependent animals because it has been hypothesized that drug abuse in the non-dependent individual is motivated by primary reinforcing properties of the drug, whereas the opiate intake by the dependent abuser appears motivated by negatively reinforcing effects of relief from aversive withdrawal symptoms. In this study, rats were trained to self-administer heroin and were then tested for the effects of SR141716A. Following tests at 5 doses of the SR compound, animals were implanted with two morphine pellets, allowed to self-administer heroin and then the dose-response function for SR141716A was re-established. The results indicated that in morphine dependent animals, but not in their non-dependent counterparts, SR141716A at the 3.0 mg/kg dose suppressed heroin self-administration. This differential response to cannabinoid CB1 receptor antagonist in non-dependent and dependent conditions may have a neuropharmacological basis in recently described changes of cannabinoid receptor expression after chronic opioid exposure. Moreover, these results encourage further study of the potential role of cannabinoid CB1 receptor antagonists for the treatment of opiate addiction. Navarro, M., Carrera, M.R.A., del Arco, I., Trigo, J.M., Koob, G.F., de Fonseca, F.R. Cannabinoid Receptor Antagonist Reduces Heroin Self-Administration Only in Dependent Rats. European Journal of Pharmacology, 501, pp. 235-237, 2004.

Greater Vulnerability for Relapse in Rats Provided with Long Access Cocaine Self-administration: Relation to Dopamine D2 mRNA

Rats given an opportunity to self-administer cocaine (coc) for 6 hr/day show an escalation of drug intake over days, whereas those self-administering for 1 hr/day have steady rates of daily intake. Drs. Mary Jeanne Kreek, John Mantsch and colleagues recently examined whether drug escalation predicts vulnerability to relapse

in a reinstatement model. They also assessed mRNA for dopamine D2 receptors in the caudate-putamen nuclei and nucleus accumbens (NAS). Central D2 receptor substrates have been related to the reinforcing effects of psychostimulants and are altered with long-term coc administration. Animals were divided into three groups: One short-access group (SAc), and two long-access groups (LAc). All groups were trained to bar press for 0.5 to 2mg/kg/infusion i.v. coc in multi-dose sessions until the groups were performing similarly. Over the next 14 days, all animals continued to be tested in this multi-dose procedure for 1 hr/day, but then the SAc rats remained in the chambers for 7 more hours with no drug available. LAc groups were also tested for 1 hr with the multi-dose procedure, but a LAc-Low dose group (LAc-L) continued to self-administer 0.5 coc for the next 7 hr, while a LAc-High dose group (LAc-H) continued to self-administer 2.0 coc; thus, all animals remained for 10 hr/day in the self-administration chamber. Extinction sessions and two tests of reinstatement, with 0.5, and 2.0mg/kg priming doses of coc, followed. Immediately after the second reinstatement test, animals were sacrificed for mRNA. Over these 14 days, SAc rats showed a slight increase in daily mg/kg coc intake by day 12. LAc-L rats also took more coc during the end of this two week session; in fact, significantly more by day 11. But LAc-H rats showed a steady increase in drug intake over days that was significantly greater, by the 5th session, than the daily dose of cocaine self-administered on day one. While SAc rats reinstated after priming with a single i.v. dose of 2.0 mg/kg, LAc-L animals reinstated with priming doses of either 0.5 or 2.0 mg/kg coc. Statistically significant reinstatement (versus vehicle response means) could not be demonstrated for the SAc-H group due to high inter-subject variability; however, this group had mean bar press rates on the active lever, (previously associated with coc delivery), that were two to three times greater than those of the SAc or LAc-L groups. Furthermore, overall reinstatement responses (two priming doses collapsed) were significantly greater in the LAc-H group when compared to SAc rats. Although not statistically different in an overall analysis, D2 receptor mRNA in the NAS was two times greater for LAc-H rats than for SAc animals (0.92 vs. 0.47 pg/ug total RNA), with values for LAc-L falling in between. Multiple regression analyses revealed that cocaine reinstatement (at the 0.5 dose) was related to D2 mRNA, when this measure was collapsed over the two brain regions. In this study, access and coc dose affected daily intake in a self-administration paradigm, and greater mg/day intake predicted greater reinstatement with cocaine priming. Although differences in D2 receptor mRNA do not necessarily result in increased functional protein, previous studies have shown that D2 agonists can precipitate reinstatement. Thus, the present relationship between the mRNA for D2 receptors and reinstatement supports an important role for the D2 site in compulsive drug taking behavior. Mantsch, J.R., Yuferov, V., Mathieu-Kia, A.-M., Ho, A. and Kreek, M.J. Effects of Extended Access to High Versus Low Cocaine Doses on Self-administration, Cocaine-induced Reinstatement and Brain mRNA Levels in Rats. Psychopharmacology, 175, pp. 26-36, 2004.

Substitutes for Tobacco Smoking: A Behavioral Economic Analysis

Researchers from the University of Vermont recently examined smokers' preference for cigarettes, nicotine gum, and nicotine-free cigarettes using a behavioral economic design. In a series of experiments cigarette-deprived smokers responded on a lever to receive puffs from a cigarette. As the number of lever presses per puff increased, or "price" per puff increased, smoking decreased indicating what economists refer to as elastic demand for cigarette puffs. In separate studies when either nicotine gum or a nicotine-free cigarette was also available, cigarette puff decreased more, suggesting that these two commodities serve as "substitutes" for cigarettes. It is not surprising that nicotine gum can substitute for cigarette smoking as this experiment and other previous clinical research have shown. What is surprising is nicotine-free cigarettes can also reduce smoking of nicotine cigarettes. While it is widely believed that people smoke to obtain the reinforcing effects of nicotine, it is now becoming evident that the "non-pharmacological" aspects of smoking are also reinforcing. This finding is in line with recent pre-clinical animal nicotine self-administration data showing that rats previously trained to press a lever to obtain nicotine in the presence of a light stimulus-cue will also respond to turn on the light without a nicotine infusion. These data further indicate that by virtue of the light being "paired" with nicotine, the light is now desirable. Similarly for the tobacco smoker, other aspects of smoking when paired with nicotine intake may become desirable as well. Taken as a whole, these results show that both pharmacological and non-pharmacological factors can maintain cigarette smoking, and that both factors need to be considered when treating tobacco addiction. Johnson, M.W., Bickel, W.K. and Kirshenbaum, A.P. Substitutes for Tobacco Smoking: A Behavioral Economic Analysis of Nicotine Gum, Denicotinized Cigarettes, and Nicotine-containing Cigarettes. Drug and Alcohol Dependence, 74, pp. 253-264, 2004.

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Director's Report to the National Advisory Council on Drug Abuse - February, 2005

Research Findings - Behavioral and Brain Development Research

Interpersonal Maladjustment as Predictor of Mother's Response to Relational Parenting Intervention

This research team previously demonstrated that a Relational Psychotherapy Mothers' Group (RPMG) was more effective in improving parenting than standard drug counseling (DC) for mothers enrolled in methadone maintenance. The research team recently examined whether mother's interpersonal maladjustment predicted a differential response to RPMG in a sample of 52 mothers and 24 children ages 7 and 16 who had completed baseline, post-treatment, and 6-month follow-up assessments. Results indicated an interaction effect; as maternal interpersonal maladjustment increased, parenting problems improved for mothers in the RPMG group, but remained the same or worsened for DC mothers. Mothers' and children's reports of child maltreatment risk were in or near the normal range for RPMG mothers but in or near clinical range for DC mothers at post-treatment and follow-up. RPMG mothers reported improved affective interactions and the DC group reported no such improvements, regardless of mothers' level of interpersonal maladjustment. These findings highlight the importance of including parenting interventions in substance abuse treatment and the value of interpersonally oriented interventions for substance-abusing mothers and their children. Suchman, N.E., McMahon, T.J., and Luthar, S.S. Journal of Substance Abuse Treatment, 27, pp. 135-143, 2004.

Sensation Seeking and Symptoms of Disruptive Disorder: Association with Nicotine, Alcohol, and Marijuana Use in Early and Mid-Adolescence

This cross-sectional study examined the association of Sensation Seeking (SS) and symptoms of Disruptive Disorders and investigated the associations of each with the risk of nicotine, alcohol, and marijuana use in a sample of 127 boys and 81 girls aged 11-14 years recruited from child psychiatry, pediatric adolescent, and pediatric family clinics. Results indicated that sensation seeking was correlated with Conduct Disorder (CD) and Oppositional Defiant Disorder (ODD), however, when analyzed by gender, there was a significant correlation between SS and CD for boys, but no significant correlations between Sensation Seeking and any of the Disruptive Disorders for girls. Sensation seeking was associated with nicotine, alcohol, and marijuana use; ODD was associated with nicotine use; and Conduct Disorder was associated with alcohol and marijuana use for boys and girls, and smokeless tobacco use for boys. Results from a series of gender specific regression analyses found that SS and ODD predicted nicotine use by girls and SS and CD predicted alcohol and marijuana use by boys. For all other analyses of cigarette, alcohol, and marijuana use, SS was the only significant predictor. Measurement of Sensation Seeking and symptoms of Disruptive Disorder in clinic setting can help identify and characterize youth who are at increased risk for drug use during early and mid-adolescence. Martin, C.A., Kelly, T.H., Rayens, M.K., Brogli, B., Himelreich, K., Brenzel, A., Bingcang, C.M., and Omar, H. Psychological Reports, 84, pp. 1075-1082, 2004.

Risk-taking Propensity and Risky Sexual Behavior of Individuals in Residential Substance Use Treatment

This study examined the relationship between risk-taking propensity and risky sexual behavior (RSB) in a sample of 76 mostly male (76%), African American (91%) adult residents of inner-city residential substance-use treatment facilities. The study utilized self-report measures and a computer administered behavioral task of risk-taking propensity, the Balloon Analogue Risk Task or BART. Results indicated that impulsivity, self-esteem, and risk-taking propensity were independently related to

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RSB. The study reports that risk-taking propensity was significantly related to risky sexual behavior even after taking into account age, gender, impulsivity, self-esteem, and depressive symptoms. In this model, risk-taking propensity and self-esteem were the only significant predictors of RSB. This study suggests the importance of risk-taking propensity as a factor underlying RSB and risk for HIV/AIDS. Lejuez, C.W., Simmons, B.L., Aklin, W.M., Daughters, S.B. and Dvir, S. Addictive Behaviors, 29, pp. 1643-1647, 2004.

Depression, Negative Self-Image, and Suicidal Attempts as Effects of Substance Use and Substance Dependence

This study examined the degree to which cocaine/crack, marijuana, and alcohol use and dependence from 26.5 to 37 years of age predicted depression, negative self-image, negative personal outlook, and suicidal attempts by age 37 in an inner-city sample of 277 African American men and women. Results from this sample, derived from the National Collaborative Perinatal Project (NCPP), found that substance use and dependence predicted mental health outcomes, controlling for prior depression, psychiatric treatment, and suicide attempts and that these predictions differed by gender. Overall, measures of substance use and dependence demonstrated relatively more predictions of suicide attempts for the men and negative self-image and negative personal outlook for the women. For the female sample, making a suicide attempt was predicted by cocaine/crack use and substance dependence, number of suicide attempts was predicted by cocaine/crack use, and depression was predicted by marijuana use. Negative self-image was predicted by substance use, illicit drug use, and substance dependence, and negative personal outlook was predicted by cocaine/crack use, substance use, and illicit drug use. For the male sample, making a suicide attempt was predicted by illicit drug use and substance use, number of suicide attempts was predicted by cocaine/crack use, illicit drug use, substance use, and substance dependence, and depression was predicted by illicit drug use. Negative personal outlook was predicted by cocaine/crack use, substance use, and substance dependence. There were no significant predictors of negative self-image for males. This study highlights gender differences in the important role of substance use in mental health outcomes. Friedman, A.S., Terras, A., Zhu, W. and McCallum, J. Journal of Addictive Diseases, 23(4), pp. 55-71, 2004.

Drug Injection Practices Among High-Risk Youths: The First Shot of Ketamine

Little is known about ketamine injection practices, associated risk behaviors, or the demographic characteristics of ketamine injectors. This study employed an ethno-epidemiological methodology and interviewed 40 young (<25 years old) ketamine injectors in New York during 2000-2002 about ketamine injection initiation as well as histories of other injection drug use and involvement in the street economy. Ninety percent of the sample had a history of sniffing ketamine and 63% had a history of selling ketamine prior to ketamine injection initiation. This study compared two groups of ketamine users: 23 ketamine initiates (youths who initiated injection drug use with ketamine) and 17 other initiates (youths who initiated injection drug use with another drug, such as heroin, and later transitioned into ketamine injection). Results indicated that intramuscular injections were more common among ketamine initiates, whereas intravenous injections were more common among other initiates. Drug form and local knowledge within injection groups were important factors underpinning this relationship: liquid ketamine was injected primarily intramuscularly; powder ketamine was injected primarily intravenously virtually irrespective of injection drug use history. In addition, the comparison between ketamine initiates and other initiates revealed differences regarding knowledge about injecting drugs; risk behaviors at initiation; involvement in the street economy, including homelessness and experience dealing drugs; and city or location of ketamine injection initiation. These findings suggest that ketamine injection is an emerging practice among a new hidden population of injection drug users in cities throughout North America. Ketamine injector's variable risk knowledge and injection practices suggest risk for HIV, HCV, and HBV. Lankenau, S.E. and Clatts, M.C. Journal of Urban Health, 81(2), pp. 232-248, 2004.

Prenatal Cocaine: Quantity of Exposure and Gender Influences on School-Age Behavior

Investigators at Wayne State University have reported that both level of prenatal cocaine exposure and gender were significantly associated with school-age behavioral outcomes. Prenatal cocaine exposure was defined in two ways: dichotomous and ordinal. The dichotomous measure consisted of no exposure or any pregnancy exposure. The ordinal measure had three levels (none, some, persistent), with

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persistent prenatal exposure defined as continued cocaine use up until delivery as evidenced by positive maternal and/or infant urine testing at delivery. Data analyses were based on a total of 473 children, 204 of whom were prenatally exposed to cocaine; 24 of the cocaine-exposed children were classified as having persistent exposure. Behavior at 6 years of age was assessed using a teacher-report scale involving fourteen problem behavior areas. Boys with any prenatal cocaine exposure scored significantly higher (more problem behaviors) than non-exposed boys on the hyperactivity item. No similar cocaine effect was observed for girls. Boys, but not girls, with persistent exposure had more problems in central processing, motor skills, handling abstract concepts, and passivity to the environment. Covariates controlled for include prenatal exposure to alcohol and other illicit drugs, and postnatal drug use in the home. Delaney-Black, V., Covington, C., Nordstrom, B., et al. Prenatal Cocaine: Quantity of Exposure and Gender Moderation. Developmental and Behavioral Pediatrics, 25(4), pp. 254-263, 2004.

Prenatal Cocaine Exposure and Language Development

Recently-published results from two separate projects provide new information regarding associations between prenatal cocaine exposure and aspects of language development. From the University of Miami, Vogel and colleagues report that when the children in their study were 3 years old (424 children, 226 cocaine-exposed, 198 non-cocaine-exposed), there was a decrease in expressive language score with increasing level of prenatal cocaine exposure. Receptive language was more modestly, and not significantly, related to prenatal cocaine exposure. Using the same language assessment scale, the Clinical Evaluation of Language Fundamentals - Preschool (CELF-P), Lewis and co-investigators at Case Western Reserve University report that for their sample of 4-year-olds (189 cocaine-exposed and 185 non-cocaine-exposed), children exposed to cocaine in utero had poorer expressive and total language scores, and had more mild receptive language delays than nonexposed children. In both studies, the analyses took into account several key variables (e.g., prenatal exposures to alcohol, tobacco, and marijuana). Morrow, C.E., Vogel, A.L., Anthony, J.C., et al. Expressive and Receptive Language Functioning in Preschool Children with Prenatal Cocaine Exposure. Journal of Pediatric Psychology, 29(7), pp. 543-554, 2004; Lewis, B.A., Singer, L.T., Short, E.J., et al. Four-Year Language Outcomes of Children Exposed to Cocaine in Utero. Neurotoxicology and Teratology, 26(5), pp. 617-627, 2004.

Longitudinal Mapping of Cortical Thickness and Brain Growth in Normal Children

Using computer-matching algorithms and new methods of measuring cortical thickness, Dr. Elizabeth Sowell and her colleagues recently published an article in which they mapped changes in brain morphology in a sample of 45 children scanned two years apart from the ages of 5 to 11 years. Measurements of brain size over this age range showed that the greatest growth occurs in the prefrontal cortex, as well as the temporal and occipital cortices. Measures of the thickness of gray matter and white matter showed that over the age range scanned there is considerable variability in changes that occur in different areas of cerebral cortex. The thickness of the gray matter increases in the areas in the frontal and temporo-parietal cortices associated with language and gray matter thickness decreases in many other cortical areas. Since the gray matter thinning actually takes place in cortical areas in which cortical volume is increasing, it is likely that there is a corresponding increase in white matter development in these areas, possibly reflecting the maturation of connectional pathways. Significantly, the decrease in gray matter thickness in the left dorsal frontal and parietal lobes was strongly correlated with improved performance on a test of verbal skills. This paper represents the first report of changes in gray matter thickness, brain size, and structure/function relationships in children followed longitudinally during a time of rapid cognitive development. Data such as these can serve as the basis for defining relationships between brain morphology and cognitive changes in disrupted development. Sowell, E.R., Thompson, P.M., Leonard, C.M., Welcome, S.E., Kan, E. and Toga, A.W., The Journal of Neuroscience 24(38), pp. 8223-8231, 2004.

The Fate of Perfluoro-Tagged Metabolites of L-DOPA in Mice Brains

Dopamine occurs in quantities in the mammalian CNS too small to be detected by current magnetic resonance neuroimaging methods. Fluorine atoms, however, can be detected by magnetic resonance spectroscopy (MRS). In an effort to render dopamine detectable with MRS, Dr. Sherry Dingman and colleagues have developed isomers of L-DOPA tagged with multiple fluorine atoms. In this study, Dr. Dingman has demonstrated that these tagged isomers, when injected into mice intraperitoneally,

are taken up into brain tissue and converted into molecules of fluorine-tagged dopamine. Thus it may be possible to use fluorine-tagged neurotransmitter precursors, such as those used here, to allow for the study of transmitters and transmitter systems in vivo using magnetic resonance imaging. Dingman, S., Mack, D., Branch, S., Thomas, R., Guo, C., and Branch, C., Journal of Immunoassay and Immunochemistry 25(4), pp. 359-370, 2004.

Differential Cingulate and Caudate Activation Following Unexpected Nonrewarding Stimuli

Considerable research has been devoted to the investigation of reward processing and much of this research, conducted in nonhuman primates, has demonstrated that cells in some dopamine-rich areas of the brain respond to differences between expected and actual rewards. In this study, Dr. B.J. Casey has used functional magnetic resonance imaging to examine the activation patterns of cortical and subcortical brain areas to the occurrence of an unexpected event or the absence of an expected event. It was found that the anterior cingulate region and the caudate nucleus were responsive to these stimulus conditions, with activity in the anterior cingulate increasing when an unexpected event occurred and activity in the caudate decreasing when an expected event did not occur. These findings demonstrate that neural activity in dopamine-rich regions of the brain can be activated by a variety of stimuli, including those not specifically associated with reward. Davidson, M.C., Horvitz, J.C., Tottenham, N., Fossella, J.A., Watts, R., Ulug, A.M. and Casey, B.J., NeuroImage. 23, pp. 1039-1045, 2004.

Mapping Cortical Change in Alzheimer's Disease, Brain Development, and Schizophrenia

Dr. Elizabeth Sowell and her colleagues have described a sophisticated image analysis algorithm, based on data collected from many individuals that can identify patterns of brain structure and function during the course of development and in populations in which the brain has been altered by aging, disease, or abnormal development. The methods that they describe use pattern-matching and can be used to compare and pool data across different populations and over time. These methods may also prove useful in demonstrating the effects of therapies aimed at ameliorating the progression of disease or the sequelae of abnormal development. Thompson, P.M., Hayashi, K.M., Sowell, E.R., Gogtay, N., Giedd, J.N., Rapoport, J.L., de Zubicaray, G.I., Janke, A.L., Rose, S.E., Semple, J., Doddrell, D.M., Wang, Y., van Erp, T.G., Cannon, T.D. and Toga, A.W. NeuroImage 23, S2-S18, 2004.

In Utero Marijuana Exposure Associated with Abnormal Amygdala Dopamine D2 Gene Expression in the Human Fetus

Dr. Yasmin Hurd and her colleagues, using in situ hybridization histochemistry, have published the first description of neurobiological effects of in utero exposure to cannabis in the human fetus. Their results demonstrate that cannabis exposure during prenatal development causes a decrease in dopamine D2 mRNA expression in the amygdala and that the magnitude of this decrease was positively correlated with the level of exposure. Importantly, this decrease in D2 mRNA was gender-specific, occurring in males but not in females. This alteration in the mesocorticolimbic dopaminergic brain circuitry during development may contribute to the emotional and cognitive deficits that have been reported in children prenatally exposed to cannabis. Wang, X., Dow-Edwards, D., Anderson, V., Minkoff, H., Hurd, Y.L. Biological Psychiatry 56, pp. 909-915, 2004.

Director's Report to the National Advisory Council on Drug Abuse - February, 2005

Research Findings - Clinical Neuroscience Research

Executive Dysfunction in Cocaine Addiction: Evidence for Discordant Frontal, Cingulate, and Cerebellar Activity

Dr. Hugh Garavan and colleagues at Trinity University used event-related fMRI to investigate neuronal activity associated with compromised abilities of cocaine users to exert control over strong prepotent behaviors as demands on working memory increase. Increasing working memory load was found to further degrade performance of cocaine abusers on a GO-NOGO response inhibition task and increase the hypoactivity in the anterior cingulate and right prefrontal cortices previously found in cocaine abusers. Furthermore, unlike drug-naive controls, and opposite to the anterior cingulate pattern, cocaine users showed an over-reliance on the left cerebellum, a compensatory pattern previously seen in alcohol addiction. The results indicate that cocaine users find it difficult to inhibit their own actions, particularly when working memory demands, which have been shown previously to increase during cue-induced craving for the drug, are increased. The results reveal a neuroanatomical basis for this dysexecutive component to addiction, supporting the suggested importance cognitive functions may play in prolonging abuse or predisposing users toward relapse. Hester, R., Garavan, H. J. Neuroscience, 24(49), pp. 11017-11022, 2004.

PFC Dysfunction in Abstinent Cocaine Abusers

The anterior cingulate cortex (ACC) and lateral prefrontal cortex (LPFC) are brain regions important to executive cognitive functions (ECF). The aim of this study was to determine if cocaine abusers have impaired function of these ROI's. Dr. Bolla from Johns Hopkins and colleagues used (PET 15O-H2O) imaging during performance of a modified version of the Stroop Task to determine ACC and LPFC function in 23-day abstinent chronic cocaine users. Overall, the cocaine abusers showed less activation than non-drug using controls in the left ACC and the right LPFC and greater activation in the right ACC. The average use of weekly cocaine was negatively correlated with activity in the rostral ACC and right LPFC. It is possible that the disruption of ECF in substance abusers could interfere with attempts to stop drug use and undermine treatment efforts. Since impairment in ECF may be a common feature of various neuropsychiatric disorders, these findings have applicability beyond the neurobiology of addiction. Bolla, K., Ernst, M., Kiehl, K., Mouratidis, M., Eldreth, D., Contoreggi, C., Matochik, J., Kurian, V., Cadet, J. and London, E. J Neuropsychiatry Clinical Neurosciences, 16(4), pp. 456-464, 2004.

Residual Neuropsychological Effects of MDMA in Individuals with Minimal Exposure to Other Drugs

Dr. John Halpern and colleagues at McLean Hospital investigated whether residual cognitive deficits reported in users of illicit 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") are due to MDMA, as opposed to other drug use or additional confounding factors. They administered a battery of neuropsychological tests to 23 young MDMA users who reported minimal exposure to any other drugs, including alcohol, and to 16 comparison individuals equally involved with the rave subculture, but reporting no MDMA use. MDMA users as a whole performed worse than non-users on most test measures, but these differences only reached statistical significance on two measures. Heavy users (> 60 lifetime doses) displayed significant deficits on many measures, particularly those associated with mental processing speed and impulsivity, but moderate users displayed virtually no differences from non-users on any measures. These differences did not appear explainable by differences in family-

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of-origin variables, verbal IQ, levels of depression, or time since last MDMA use. These data from unusually "pure" frequent users of illicit MDMA provides direct evidence that residual cognitive deficits in heavy MDMA users are not simply due to the use of other drugs. Halpern, J.H., Pope, H.G., Sherwood, A.R., Barry, S., Hudson, J.I., Yurgelun-Todd, D. Drug and Alcohol Dependence, 75, pp. 135-147, 2004.

Decreased Absolute Amygdala Volume in Cocaine Addicts

Dr. Hans Brieter and colleagues at Massachusetts General Hospital used structural MRI to examine the volumes of the amygdala and hippocampus in cocaine-addicted subjects. Compared to matched healthy controls, the amygdala but not the hippocampus was significantly reduced in volume in cocaine abusers, and the right-left amygdala asymmetry in control subjects was absent in the cocaine addicts. Topological analysis of amygdala suggested the volume difference were due alterations in the corticomedial and basolateral nuclei. Since amygdala volume did not correlate with any measure of cocaine use, these findings suggest that reduced amygdala volume predisposes the individual to cocaine dependence. Makris, N., Gasic, G.P., Seidman, L.J., Goldstein, J.M., Gastfriend, D.R., Elman, I., Albaugh, M.D., Hodge, S.M., Ziegler, D.A., Sheahan, F.S., Caviness, V.S., Tsuang, M.T., Kennedy, D.N., Hyman, S.E., Rosen, B.R. and Breiter, H.C. Neuron 44(4), pp. 729-740, 2004.

Adaptation of the Attention Network in HIV Brain Injury

Human immunodeficiency virus (HIV)-positive patients commonly have attention and concentration problems. However, it remains unclear how HIV infection affects the attention network. Therefore, blood oxygenation level dependent functional magnetic resonance imaging (BOLD-fMRI) was performed in 36 subjects (18 HIV and 18 seronegative [SN] controls) during a set of visual attention tasks with increasing levels of attentional load. Compared with SN controls, HIV subjects showed similar task performance (accuracies and reaction times) but decreased activation in the normal visual attention network (dorsal parietal, bilateral prefrontal, and cerebellar regions) and increased activation in adjacent or contralateral brain regions. Cognitive performance (assessed with NPZ-8), CD4, and viral load all correlated with activated BOLD signals in brain regions that activated more in HIV subjects. Furthermore, HIV subjects activated more than SN controls in brain regions that showed load-dependent increases in activation (right prefrontal and right parietal regions) but less in regions that showed a saturation effect with increasing load. These findings suggest that HIV-associated brain injury leads to reduced efficiency in the normal attention network, thus requiring reorganization and increased usage of neural reserves to maintain performance. Chang, L., Tomasi, D., Yakupov, R., Lozar, C., Arnold, S., Caparelli, E. and Ernst, T. Annals Neurology, 56(2), pp. 259-272, 2004.

White Matter Hyperintensities in Subjects with Cocaine and Opiate Dependence and Healthy Comparison Subjects

Dr. Marc Kaufman and colleagues at McLean Hospital used structural MRI to investigate white matter signal hyperintensities (WMH), a marker of white matter damage, in patients with cocaine or opiate dependence. The severity of WMH was assessed separately for deep (and insular) and periventricular WMH, using a modified composite version of the rating scales of Fazekas and Coffey. The cocaine-dependent group (n=32) had greater severity of WMH than the opiate-dependent group (n=32), which in turn had greater severity of WMH than the age- and sex-matched healthy comparison group (n= 32). The cocaine-dependent group had greater lesion severity of deep and insular WMH than the opiate-dependent group and the healthy comparison group (odds ratio > 3.25 for deep WMH; odds ratio > 4.38 for insular WMH). For periventricular WMH, there were no significant differences between the three groups. The frontal lobes were the predominant locations of WMH in both substance-dependent groups. The greater prevalence and severity of WMH in cocaine-dependent subjects than in opiate-dependent subjects may reflect the fact that cocaine induces more ischemia via vasoconstriction than opiates. Lyoo, I.K., Streeter, C.C., Ahn, KH., Lee, H.K., Pollack, M.H., Silveri, M.M., Nassar, L., Levin, M., Sarid-Segal, O., Ciraulo, D.A., Renshaw, P.F., Kaufman, M.J. Psychiatry Research-Neuroimaging 131(2), pp. 135-145, 2004.

Motivation-Dependent Responses in the Human Caudate Nucleus

Dr. Julie Fiez and colleagues at the University of Pittsburg used event-related fMRI to determine how the dorsal striatum, particularly the caudate nucleus, responds to changes in the motivational context of a task. Normal subjects were given positive and negative feedback upon guessing the value of an unknown card. The motivational context of the task was manipulated by dividing trials into periods of high incentive

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(where visual feedback indicated monetary rewards and punishments) and low incentive (where visual feedback indicated only accuracy). Activity in the caudate nucleus was strongly influenced by the different incentive periods. Larger differences between positive and negative feedback were observed during periods of high incentive. These results suggest that changes in motivation are capable of modulating basal ganglia activity, and further support an important role for the caudate nucleus in affective processing. Delgado, M.R., Stenger, V.A. and Fiez, J.A. Cerebral Cortex 14(9), pp. 1022-1030. 2004.

Dissociable Effects of Arousal and Valence on Prefrontal Activity

Dr. Kevin LaBar and colleagues at Duke University investigated the role of the prefrontal cortex (PFC) activity in emotional evaluation and subsequent memory using with event-related functional MRI (fMRI) in normal subjects. Consistent with the valence hypothesis, specific regions in left dorsolateral PFC were more activated for positive than for negative picture evaluation, whereas regions in right ventrolateral PFC showed the converse pattern. Dorsomedial PFC activity was sensitive to emotional arousal, whereas ventromedial PFC activity was sensitive to positive valence, consistent with evidence linking these regions, respectively, to emotional processing and self-awareness or appetitive behavior. Finally, successful encoding (Dm) activity in left ventrolateral and dorsolateral PFC was greater for arousing than for neutral pictures. This finding suggests that the enhancing effect of emotion on memory formation is partly due to an augmentation of PFC-mediated strategic, semantic, and working memory operations. These results underscore the critical role of PFC in emotional evaluation and memory, and disentangle the effects of arousal and valence across PFC regions associated with different cognitive functions. These results provide insight into how the PFC may process stimuli that can evoke cue-elicited drug craving. Dolcos, F., LaBar, K.S., Cabeza, R. Neuroimage 23(1), pp. 64-74, 2004.

An ERP Index of Task Relevance Evaluation of Visual Stimuli

Dr. Geoffery Potts of Rice University investigated whether the anterior P2 (P2a) evoked potential component (also known as the frontal selection positivity FSP, or the frontal P3) reflects the neural processes involved in feature selection, stimulus evaluation, or response production. The present study employed a visual target detection (oddball) design with different response conditions: passive (no response), overt (keypress), and covert (silent count), to examine the impact of task relevance and response production on the frontal P2a in normal subjects. The results suggest that the P2a is an index of stimulus evaluation, rather than response production in that he P2a was present to task-relevant stimuli but had the same scalp topography and estimated source-dipole locations in both overt and covert responding. These results suggest that the P2a may be useful in clinical studies involving the saliency of drug-related stimuli. Potts, G. Brain and Cognition. 56(1), pp. 5-13, 2004.

Cerebral Phosphorus Metabolite Abnormalities in Heroin-Dependent Subjects

Dr. Perry Renshaw and colleagues at McLean hospital used Phosphorous Magnetic Resonance Spectroscopy (P-31MRS) to investigate cerebral bioenergetic and phospholipid abnormalities in heroin-dependent subjects. Compared with healthy comparison subjects (n=15), heroin abusers during the first month of methadone maintenance (MM) exhibited reduced phosphocreatine (PCr) levels (-15.3%) and elevated phosphodiesters (+ 12.9%, PDE) in an axial slice prescribed through the orbitofrontal and occipital cortices, which included the basal ganglia and frontal cortex. A treatment duration effect on metabolite values was found when MM subjects were stratified into subgroups based on treatment duration. Reduced PCr was observed only after 8+ days of MM, and phosphomonoesters (PME) were elevated in the 15-28 day MM group. Taken together, these cross-sectional data suggest that the first month of MM treatment may be associated with altered cerebral bioenergetics and phospholipid metabolite levels. Silveri, M.M., Pollack, M.H., Diaz, C.I., Nassar, L.E., Mendelson, J.H., Yurgelun-Todd, D.A., Renshaw, P.F.and Kaufman, M.J. Psychiatry Research-Neuroimaging 131(3), pp. 217-226, 2004.

The Effects of Vagus Nerve Stimulation on Decision-Making

Dr. Antoine Bechara and colleagues at the University of Iowa investigated whether the vagus nerve may be a possible conduit for somatic afferent signals pertinent to decision-making. The somatic marker hypothesis (SMH) views the participation in decision-making by the body proper as integral to emotional biasing and hence key to choosing in an advantageous manner. Eight epileptic patients with implanted left vagus nerve stimulators were tested on the Iowa Gambling Task. Using a

counterbalanced design, each participant performed the gambling task under a condition in which low-level vagus nerve stimulation (VNS) was covertly delivered, and another condition in which no VNS was delivered. Participants showed improved performance, that is, made more advantageous choices, in the stimulated relative to the unstimulated condition. Although these results should be viewed as preliminary, they suggest that the vagus nerve is a conduit for afferent somatic signals that can influence decision-making. Martin, C.O., Denburg, N.L., Tranel, D., Granner, M.A. and Bechara, A. Cortex 40(4-5), pp. 605-612, 2004.

Regional Cerebral Blood Flow and Plasma Nicotine after Smoking Tobacco Cigarettes

Dr. Edward Domino and colleagues at the University of Michigan used PET imaging with [15O] water to determine whether regional cerebral blood flow (rCBF) in specific brain areas is correlated with arterial plasma nicotine concentrations after tobacco smoking. Twenty-one healthy adult tobacco smokers of both genders were studied after overnight tobacco abstinence. Subjects smoked tobacco cigarettes that were either of average (1.0 mg) or low (0.08 mg) nicotine. Six separate scans were taken about 12 min apart with the subjects' eyes closed and relaxed. Increases in normalized rCBF were obtained in the occipital cortex, cerebellum, and thalamus, and decreases in the anterior cingulate, nucleus accumbens, amygdala, and hippocampus immediately after smoking the first average nicotine yield cigarette of the morning. After smoking the second average nicotine yield cigarette, the effects were less than smoking the first. Low-nicotine cigarettes produced fewer changes in rCBF than those after the first average cigarette. Correlations with arterial nicotine on rCBF were statistically significant in brain areas with the greatest changes in relative blood flow such as the cerebellum and occipital cortex. These studies suggest that nicotine delivery by tobacco smoking is only one of the factors which contribute to changes in rCBF. Domino, E.F., Ni, L.S., Xu Y.J., Koeppe R.A., Guthrie, S. and Zubieta J.K., Progress In Neuropsychopharmacology & Biological Psychiatry 28(2), pp. 319-327, 2004.

Director's Report to the National Advisory Council on Drug Abuse - February, 2005

Research Findings - Epidemiology and Etiology Research

Cigarette Access for Minors Has Been Declining, But Remains High

Investigators from the Monitoring the Future Study examined trends in middle and high school students' perceived ease, methods, and locations of access to cigarettes, and assessed differences related to their sociodemographic characteristics and smoking status. Annual data from nationally representative samples of 8th-, 10th-, and 12th-grade students were analyzed for the 1997-2002 period. Analyses revealed that perceived ease of access decreased significantly among never and past smokers. Decreased individual purchasing in retail outlets, as well as decreased purchasing from vending machines, were reported by 8th- and 10th-grade students. All grades reported decreased purchasing from self-service placements of cigarettes. Decreases in access were not reported across all retailer types, and no significant increases were seen in the percent of underage purchasers who reported being asked to show identification. Both gender and ethnicity were significantly related to where and how underage youth reported obtaining cigarettes. Findings show that: (1) cigarette access for minors has been declining, but remains high; (2) perceived access to cigarettes clearly increases with level of smoking; and (3) policies to reduce such access may be having an impact as evidenced by decreased retail and vending machine purchases and self-service purchases. The authors conclude that states should continue to strengthen efforts to reduce youth cigarette access, especially in the areas of confirming buyer age via identification checks, and should make efforts to decrease access across all retailer types. Johnston, L.D., O'Malley, P.M., and Terry-McElrath, Y.M. Methods, Locations, and Ease of Cigarette Access for American Youth, 1997-2002. American Journal of Preventive Medicine, 27, pp. 267-276, 2004.

Stress Burden and the Lifetime Incidence of Psychiatric Disorder in Young Adults: Racial and Ethnic Contrasts

With the exception of studies of individual traumatic events, the significance of stress exposure in psychiatric disorder previously has not been effectively examined. The purpose of this study was to address the hypothesis that accumulated adversity represents an important risk factor for the subsequent onset of depressive and anxiety disorders. Analyses were conducted on a community-based study of psychiatric and substance use disorders among a large, ethnically diverse cohort representative of young adults in South Florida. Adversity was estimated with a count of major and potentially traumatic events experienced during one's lifetime and prior to the onset of disorder. Most interviews took place in the homes of participants, with 30% conducted by telephone. The authors obtained a random sample of individuals aged 18 to 23 years from a previously studied representative sample of young adolescents. Because participants in the prior study were predominantly boys, a supplementary sample of girls was randomly obtained from the early-adolescence school class rosters. A total of 1803 interviews were completed, representing a success rate of 70.1%. Results indicated that the level of lifetime exposure to adversity was found to be associated with an increased risk of subsequent onset of depressive and/or anxiety disorder. This association remained clearly observable when childhood conduct disorder, attention-deficit/hyperactivity disorder, prior substance dependence, and posttraumatic stress disorder were held constant and when the possibility of state dependence effects was considered. This evidence suggests that high levels of lifetime exposure to adversity are causally implicated in the onset of depressive and anxiety disorders. Turner, R.J., and Lloyd, D.A. Stress Burden and the Lifetime Incidence of Psychiatric Disorder in Young Adults: Racial and Ethnic Contrasts. Arch Gen Psychiatry, 61, pp. 481-488, 2004.

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Staff Highlights

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In Memoriam

Abuse Experiences in a Community Sample of Young Adults

This study documents significant associations among lifetime abuse experiences, psychiatric diagnoses, and sexual risk behaviors in a multiethnic community sample of young men and women (N = 1803) in South Florida. Self-report data were collected via structured interviews as part of a longitudinal follow-up of a larger school-based study. Participants were grouped according to extent of lifetime abuse experiences. Cumulative lifetime abuse experiences were associated with increased risk for a broad range of individual lifetime psychiatric disorders, as well as cumulative lifetime psychiatric disorders. Both cumulative abuse experiences and cumulative psychiatric disorders were independently associated with (a) higher levels of sexual risk behaviors and (b) higher risk for lifetime sexually transmitted diseases (STDs). Implications for selective prevention of sexual risk behaviors and STDs among young adults with histories of abuse and psychiatric disorders are discussed. Tubman, J.G., Montgomery, M.J., Gil, A.G., Wagner, E.F. Abuse Experiences in a Community Sample of Young Adults: Relations with Psychiatric Disorders, Sexual Risk Behaviors, and Sexually Transmitted Diseases. Am J Community Psychol, 34, pp. 147-162, 2004.

Risk and Protective Factors related to Physical Violence Against Impoverished Women

Violence represents a significant threat to the health of impoverished women. Few studies have examined what characteristics might be associated with increased risk of violence or protection from physical violence directed at such women, although this information is important in informing violence prevention and intervention efforts. According to the authors, this is the first study that has prospectively examined, in representative probability samples of impoverished women, multiple risk and protective factors to understand their relative importance to physical victimization. Study participants were 810 women in Los Angeles County, 402 in shelters and 408 in Section 8 low-income housing, who completed structured interviews at baseline and 6-month follow-up. Significant ($p < .05$) multivariate predictors of physical violence experienced during the 6 months prior to follow-up interview were physical or sexual violence experienced as a child, physical violence experienced during the 6 months prior to baseline interview, having multiple sexual partners, psychological distress, and poor social support. Results of this study highlight the persistence of physical violence in the lives of impoverished women and plausible, prospective risk factors for this violence. Findings also highlight opportunities to reduce women's risk of experiencing violence through enhancing women's social support and mental health. Wenzel, S.L., Tucker, J.S., Elliott, M.N., Marshall, G.N., and Williamson, S.L. Physical Violence Against Impoverished Women: A Longitudinal Analysis of Risk and Protective Factors. Women's Health Issues, 14, pp. 44-54, 2004.

Early-adolescent Substance Use and Subsequent Young-adult Substance Use Disorders and Psychiatric Disorders

This study examined the associations among early-adolescent substance use, subsequent young-adult substance use disorders, and psychiatric disorders among a community sample of males. Early-adolescent data were collected in classroom surveys (1990-1993), and young-adult data were collected in face-to-face interviews (1998-2000). Results showed strong associations between early-adolescent substance use and young-adult substance use disorders and psychiatric disorders. The magnitudes of these associations varied by racial/ethnic group and were strongest among African Americans and foreign-born Hispanics, who reported the lowest early-adolescent substance use. These findings suggest that early-adolescent substance use is most strongly associated with a later pattern of dysfunction among the racial/ethnic groups that reported the lowest levels of early use. The implications of these findings in the context of primary and secondary prevention are discussed. Gil, A.G., Wagner, E.F., and Tubman, J.G. Associations Between Early-adolescent Substance Use and Subsequent Young-adult Substance Use Disorders and Psychiatric Disorders among a Multiethnic Male Sample in South Florida. Am J Public Health, 94, pp. 1603-1609, 2004.

The Co-occurrence of Violence, Substance Use and Disorder, and HIV-Risk Behavior among Sheltered and Low-income Housed Women in Los Angeles County

Violence against women, substance use and disorder, and HIV represent three significant threats to the health of women, yet little is known about the extent of these epidemics among indigent women. This study investigates and documents differences in the prevalence and co-occurrence of physical and sexual violence, substance use and disorder, and HIV risk behavior in sizable probability samples of

sheltered homeless and low-income housed women. Retrospective self-reports were obtained through structured interviews with stratified random samples of women residing in shelters (N = 460) and low-income housing (N = 438) in Los Angeles County, California. Results indicated that sheltered women were more likely than housed women to report experiencing physical and sexual violence, substance use and disorder, HIV risk behavior, and co-occurrence of these problems in the past year. Differences remained when propensity weights were used to equate the groups on demographic and background characteristics. Findings suggest remarkable need for services among communities of indigent women. Higher rates of problems among women in shelters highlight the importance of differentiating among subgroups of indigent women in community-based prevention and intervention activities and tentatively suggest a protective influence of housing. Wenzel, S.L., Tucker, J.S., Elliott, M.N., Hambarsoomians, K., Perlman, J., Becker, K., Kollross, C., Golinelli, D. Prevalence and Co-occurrence of Violence, Substance Use and Disorder, and HIV Risk Behavior: A Comparison of Sheltered and Low-income Housed Women in Los Angeles County. Prev Med., 39, pp. 617-624, 2004.

The Influence of Social and Work Exchange Relationships on Organizational Citizenship Behavior

Previous studies explain situational antecedents of organizational citizenship behavior (OCB) using social exchange theory. However, the effects of factors such as perceptions of job characteristics on OCB seem to require a different explanatory mechanism. This article proposes that these effects can be explained through a new exchange relationship called work exchange. A theory for the situational antecedents of OCB that includes economic, work, and social exchange relationships is developed. The theory is tested using structural equations. Cardona, P., Lawrence, B.S., and Bentler, P.M. The influence of social and work exchange relationships on organizational citizenship behavior. Group and Organization Management, 29, pp. 219-247, 2004.

Child Sexual Abuse and HIV: An Integrative Risk Reduction Approach

In recent years, researchers have noted a significant association between child sexual abuse (CSA) and HIV. This association has important implications for HIV prevention and intervention. First, the fact that women who contract HIV are more likely to have been sexually abused as children suggests a continuum of victimization, such that early victimization may confer greater sexual risk-taking and likelihood of revictimization, resulting in HIV infection. Thus, the possible pathways between CSA and HIV need to be elucidated in order to prevent further negative outcomes. Second, the implications for HIV research and intervention are significant. Sexual abuse during childhood is associated with disturbances in the self that pervade an individual's development, and these disturbances are likely to maintain HIV risk behaviors unless ameliorated. Therefore, individuals who are HIV-positive and have a history of child sexual abuse may face "double jeopardy" for negative outcomes, including additional risks for reinfection, sexual revictimization, physical impairment, and non-adherence to HIV treatment that are beyond those associated with HIV infection. Intervention approaches for HIV-positive women with sexual abuse histories need to consider pathways of risk, ameliorate the disruptions in development that result from CSA, and address the additional additive and interactive influences of HIV and CSA on health outcomes. This chapter presents a brief overview of the consequences of CSA that may lead to higher risk for HIV, offers a critique of early intervention paradigms, and presents an integrative risk-reduction approach for HIV-positive women with CSA histories, currently in clinical trial, that addresses the link between CSA and HIV in a developmental and cultural context. Finally, preliminary findings from the intervention and implications for future directions are discussed. Chin, D., Wyatt, G., Carmona, J. V., Loeb, T.B., and Myers, H. Child Sexual Abuse and HIV: An Integrative Risk Reduction Approach. In L. Koenig, A. O'Leary, L. Doll, and Pecquegnat, (Eds.), From Child Sexual Abuse to Adult Sexual Risk: Trauma, Revictimazation, and Intervention, pp. 233-250. Washington D.C.: American Psychological Association, 2004.

An EM Algorithm for Fitting Two-level Structural Equation Models

Maximum likelihood is an important approach to analysis of two-level structural equation models. Different algorithms for this purpose have been available in the literature. In this paper, the authors present a new formulation of two-level structural equation models and develop an EM algorithm for fitting this formulation. This new formulation covers a variety of two-level structural equation models. As a result, the proposed EM algorithm is widely applicable in practice. A practical example illustrates the performance of the EM algorithm and the maximum likelihood statistic. Liang, J., and Bentler, P. M. An EM Algorithm for Fitting Two-level Structural Equation Models.

Psychometrika, 69, pp. 101-122, 2004.

Adolescent Predictors of Young Adult and Adult Alcohol Involvement and Dysphoria in a Prospective Community Sample of Women

The adolescent predictors of later alcohol involvement (AI), dysphoria (D), and their shared association (AD) among women have not been adequately established. Three waves of data from an ethnically diverse community sample of women, assessed over 16 years are used to study how various psychosocial factors in adolescence influenced later drinking, depression, and their shared association. Structural equation models revealed that several adolescent ecodevelopmental and social development model variables influenced their later outcome in young adulthood and adulthood. The strongest relation was between adolescent Social Conformity and adult AD (b = -.46) over a 16-year period, emphasizing the impact of this construct. Numerous other relations were revealed. For instance, less satisfaction with school during adolescence predicted adult AI. Having a good bond to the family in adolescence predicted a lower quantity of alcohol consumed during adulthood. Lower satisfaction with "what you want to be" during adolescence predicted young adult D. Higher levels of adolescent relationship satisfaction and school satisfaction predicted less suicidal ideation as an adult. Prevention interventions focusing on increasing socially conforming attitudes and on strengthening relationships both in and out of the home during adolescence are likely to be effective in reducing aspects of AI, D, and AD for women in the general community. Locke, T. F., and Newcomb, M.D. Adolescent Predictors of Young Adult and Adult Alcohol Involvement and Dysphoria in a Prospective Community Sample of Women. Prevention Science, 5, pp. 151-168, 2004.

Tobacco Smoking and Depressive Symptomatology

Whereas an association between cigarette smoking and depression has been established in Anglo populations, replication of tobacco-depression associations in countries where smoking is growing may provide important new insights. The objectives of this study were to estimate the association of depressive symptomatology with tobacco smoking, number of cigarettes smoked daily, and smoking cessation in a representative sample of the Mexican population. The data come from the Third National Addictions Survey (1998) conducted by the Mexican Ministry of Health, representative of Mexico's civilian population residing in cities and towns with 2500+ inhabitants, aged 18-64. Part of a multi-stage, stratified, probability sample, 1935 men and women answered a version of the survey that also included the CES-D depression scale. Analyses addressed the survey's complex design and controlled for income and educational level. The results showed that, among women only, current smokers had twice the odds of elevated depressive symptomatology than never smokers (OR 2.1, 95% CI 1.3-3.5, p = 0.002). For men, only those smoking a pack or more a day had greater odds of depressive symptomatology (OR 5.9, 95% CI 1.6-21.9, p = 0.008). Overall, former smokers who ceased smoking within 6 months had lower odds of depressive symptomatology than current smokers (OR 0.4, 95% CI 0.1-1.0, p = 0.042). These findings add to the accumulating evidence for the association between smoking and depression in different cultures and populations. Benjet, C., Wagner, F.A., Borges, G.G., and Medina-Mora, M.E. The Relationship of Tobacco Smoking with Depressive Symptomatology in the Third Mexican National Addictions Survey. Psychol Med, 34, pp. 881-888, 2004.

Child Maltreatment, Parent Alcohol- and Drug-related Problems, Polydrug Problems, and Parenting Practices: A Test of Gender Differences and Four Theoretical Perspectives

The authors tested how adverse childhood experiences (child maltreatment and parent alcohol- and drug-related problems) and adult polydrug use (as a mediator) predict poor parenting in a community sample (237 mothers and 81 fathers). These relationships were framed within several theoretical perspectives, including observational learning, impaired functioning, self-medication, and parentification-pseudomaturity. Structural models revealed that child maltreatment predicted poor parenting practices among mothers. Parent alcohol- and drug-related problems had an indirect detrimental influence on mothers' parenting practices through self-drug problems. Among fathers, emotional neglect experienced as a child predicted lack of parental warmth and more parental neglect, and sexual abuse experienced as a child predicted a rejecting style of parenting. Locke, T.F. and Newcomb, M.D. Child Maltreatment, Parent Alcohol- and Drug-related Problems, Polydrug Problems, and Parenting Practices: A Test of Gender Differences and Four Theoretical Perspectives. Journal of Family Psychology, 18, pp. 120-134, 2004.

Psychosocial Antecedents of Injection Risk Reduction

This study is based on a collaboration with the Integrated Substance Abuse Program at UCLA. In this study, the authors used the AIDS Risk Reduction Model (ARRM) to test a mediated stage-based longitudinal structural equation model analyzing the impact of intention to change injection risk behaviors on 6-month outcomes in a sample of 294 HIV-negative opiate addicted individuals currently in treatment. The ARRM predicts less occurrence of AIDS risk behaviors through a three-stage process: (1) perceiving one's behavior as risky and recognizing one's skills to reduce the behavior, (2) forming an intention to change behavior, and (3) acting on that intention. Stage 1 ARRM constructs of AIDS knowledge, susceptibility, fear of AIDS and Peer Norms were hypothesized to predict Stage 1 end points of perceived risk, response efficacy, and self-efficacy as well as baseline risk behavior. These constructs predicted Stage 2 (intended risk reduction) which, in turn, predicted the Stage 3 outcome of injection risk behaviors. Prior behavior, continuous participation in treatment, and the effect of gender were also included in the model. Intended risk reduction and continuous participation in treatment significantly predicted less injection risk behavior at Stage 3. Stage 1 constructs of greater self-efficacy, less baseline risk behavior, less susceptibility and greater fear of AIDS predicted intentions to reduce risk as did female gender. Leverage points for change in this highly vulnerable population are discussed in the article. Longshore, D., Stein, J.A. and Conner, B.T. Psychosocial Antecedents of Injection Risk Reduction: A Multivariate Analysis. AIDS Education and Prevention 16, pp. 53-66, 2004.

The Motivation, Skills, and Decision-Making Model of Drug Abuse Prevention

This article summarizes the theoretical basis for targeted prevention programs as they apply to different high-risk groups. The authors explain the advantages and disadvantages of different definitions of risk and discuss strategies for preventing drug use related problems in high-risk youth. Productive prevention programs for many at-risk groups share similar components, including those that address motivation, skills, and decision making. Key aspects of these three components are examined and linked to theories in clinical psychology, social psychology, sociology, and chemical dependence treatment. Among a total of 29 promising targeted prevention programs, the authors describe examples of empirically evaluated, intensive interventions that have made a positive impact on the attitudes and behavior of multiple problem youth. Incorporating the perspectives of multiple disciplines appears essential for progress in drug abuse and o ther problem behavior prevention. Sussman, S., Earleywine, M., Wills, T., Cody, C., Biglan, T., Dent, C. W. and Newcomb, M. D. The Motivation, Skills, and Decision-making Model of Drug Abuse Prevention. Substance Use and Misuse, 39, pp. 1971-2016, 2004.

Estimating Numbers of Injecting Drug Users in Metropolitan Areas

Researchers estimated the population prevalence of current injection drug users (IDUs) in 96 large US metropolitan areas to facilitate structural analyses of its predictors and sequela. They also assessed the extent to which drug abuse treatment and HIV counseling and testing are made available to drug injectors in each metropolitan area. The total number of current IDUs in the US was estimated and the large metropolitan area total was allocated among large metropolitan areas using four different multiplier methods. Mean values were used as best estimates, and their validity and limitations were assessed. Prevalence of drug injectors per 10,000 population varied from 19 to 173 (median 60; interquartile range 42-87). Proportions of drug injectors in treatment varied from 1.0% to 39.3% (median 8.6%); and the ratio of HIV counseling and testing events to the estimated number of IDUs varied from 0.013 to 0.285 (median 0.082). The researchers concluded that, despite limitations in the accuracy of the estimates, they can be used for structural analyses of the correlates and predictors of the population density of drug injectors in metropolitan areas and for assessing the extent of service delivery to drug injectors. In addition, although service provision levels varied considerably, few if any metropolitan areas seemed to be providing adequate levels of services. Friedman, S., Tempalski, B., Cooper, H., Perlis, T., Keem, M., Friedman, R., and Flom, P. Estimating Numbers of Injecting Drug Users in Metropolitan Areas for Structural Analyses of Community Vulnerability and for Assessing Relative Degrees of Service Provision for Injecting Drug Users. J Urban Health, 81, pp. 377-400, 2004.

A New Measure of Linkage Between Two Sub-Networks

In this paper, researchers discuss social networks and links between groups of people with and without certain characteristics, such as people who "link" those with and without HIV infection; or who link injecting drug users with non-injecting drug users.

They propose new measures of this linkage (for individuals and for entire networks) and discuss reasons why their measures are superior to existing measures by providing examples. The authors argue that existing measures of linkage between networks, such as centrality (including closeness centrality and "betweenness" centrality) make no distinction between nodes in different groups, and thus cannot measure which nodes connect the two groups, nor the extent to which they do so. Their new measures, although limited in applicability to binary data and to two groups, have potential for helping to trace HIV infection from networks of drug injectors to the general population. Moreover, they may ultimately help to identify characteristics of individuals in networks that are correlated with linkage to other networks, and thereby suggest how people with those characteristics might be better targeted for HIV prevention interventions. Flom, P., Friedman, S., Strauss, S. and Neaigus, A. A New Measure of Linkage Between Two Sub-Networks. Connections, 26, pp. 62-70, 2004.

Perceived Adverse Consequences Associated with MDMA/Ecstasy Use in Young Polydrug Users

The use of MDMA/Ecstasy has increased among young people in many industrialized nations around the world since the mid-1990s. In this paper, researchers describe how young people characterize perceived long-term consequences associated with Ecstasy. They used three data sources for this work (qualitative interviews, pile sorts, and quantitative data on subjective memory impairment). Contrary to expectations, Ecstasy was classified midway between drugs perceived to be the most and least risky. Risks associated with Ecstasy use included two popular myths implying forms of brain damageÑ"draining spinal fluid" and "creating holes in brains". Qualitative results indicated that some young people are concerned about the potential affects of the drug on memory and as a cause of depression. About 20% (82) of the participants (N =402) "agreed" or "strongly agreed" that Ecstasy has impaired their memories. Public health concerns about the potential adverse consequences of Ecstasy use have increased, along with a growing convergence of findings from neuropsychological studies that indicates a possible relationship between Ecstasy use and memory impairment and/or as contributing to other cognitive problems, but whether MDMA causes damage to serotonergic neurons in humans remains in question. Nonetheless, concern among young users about the adverse consequences of Ecstasy use may provide opportunities for reducing the prevalence of its use and the potential harm that it may cause. Carlson, R., McCaughan, J., Falk, R., Wang, J., Siegel, H., and Daniulaityte, R. Perceived Adverse Consequences Associated with MDMA/Ecstasy Use Among Young Polydrug Users in Ohio: Implications for Intervention. Intl J Drug Policy, 15, pp. 265-274, 2004.

Barriers to Intervention Among Young MDMA/Ecstasy Users

In the past several years, the use of MDMA ("Ecstasy") has increased substantially in the U.S. and in many countries around the world. Although this increase has been associated with the dance club and rave scenes, MDMA use has also expanded into new settings, and the diversity of users has grown. Given the increasing, although as yet unclear, evidence that MDMA is potentially neurotoxic and may lead to adverse psychological consequences, understanding how active users perceive the risks associated with MDMA can help to inform prevention and intervention approaches. Based on audiotaped focus groups and individual interviews conducted with 30 users in Central Ohio, this study found that, beyond the risk of obtaining something potentially deadly instead of MDMA, most users minimize or discount potential risks of neurotoxicity or psychological problems from MDMA use. As more people use MDMA without developing obvious adverse consequences, and others observe their "benign" experiences as meaning that MDMA is not a harmful drug, the more that others may in turn be willing to use it. Participants in this study appeared to want information on the risks associated with MDMA use so they could make their own decisions about future use. Because MDMA is often used among small groups of friends, providing accurate information to peer leaders about MDMA, who can then disseminate the information to their peers, may be a promising approach for discouraging potential users from doing so. Carlson, R., Falck, R., McCaughan, J., and Siegal, H. MDMA/Ecstasy Use Among Young People in Ohio: Perceived Risk and Barriers to Intervention. J Psychoactive Drugs, 36, pp. 181-189, 2004.

Correlates of Sex Trading Among Drug-Using Men Who Have Sex with Men

Researchers examined correlates of trading sex for money, drugs, and shelter, or food among drug-using men who have sex with men (MSM). They used street-based outreach and snowball sampling techniques to recruit 387 MSM in Long Beach, California, as part of a randomized trial of an HIV prevention intervention for MSM

who engage in high-risk sex and drug use. Audio computer-assisted self-interviewing questionnaires were completed by all of the men. The mean age of the participants was 37.8 (SD=8.9); more than half (57.6%) were African American, 29.7% were white, and 12.7% were Latino. The association of predictors with sex trading was assessed with _2 tests and multiple logistic regression. Sex-trading prevalence was 62.5% (95% confidence interval=57.7%, 67.4%), and was associated with crack use, injection drug use, childhood maltreatment, non-gay self-identification, and homelessness (adjusted odds ratios=3.72, 2.28, 2.62, 2.21, and 1.88, respectively). Multiple risk factors are associated with sex trading among MSM, suggesting that interventions that address sex trading among MSM must also target potential use of crack cocaine and injection drug use, as well as homelessness and childhood maltreatment. Interventions are also needed to target non-gay-identified MSM who engage in sex trading. Newman, P., Rhodes, R., and Weiss, R. Correlates of Sex Trading Among Drug-Using Men Who Have Sex with Men. Am J Public Health, 94, pp. 1998-2003, 2004.

HIV Risk Practices Among Needle Exchange Users and Nonusers in Chicago

Researchers sought to assess associations between needle exchange program (NEP) use and drug injection risk practices. Between 1997-2000, they recruited injecting drug users (IDUs) from NEPs and from an area with no NEP, interviewed them about risk practices, and provided counseling and testing for HIV. The risk practices of "regular NEP users" Ñ those who obtained at least half of their needles from an NEP (n = 558) Ñwere compared with those of IDUs who did not use an NEP (n = 175). In multivariate analysis, regular NEP users, compared with NEP nonusers, were less likely to receptively share needles (adjusted odds ratio [AOR], 0.30; 95% CI, 0.19-0.46); lend used needles (AOR, 0.47; 95% CI, 0.31-0.71); share cookers (AOR, 0.39; 95% CI, 0.25-0.61), cottons (AOR, 0.48; 95% CI, 0.32-0.72), or water (AOR, 0.41; 95% CI, 0.27-0.63); or use a needle for >1 injection (0.15; 95% CI, 0.08-0.27). Among those who shared needles, regular NEP users were significantly more likely to do so for a smaller proportion of injections, with fewer partners and persons socially closer, and to have always bleached used needles before injecting. These findings indicate that regular NEP use is associated with less frequent and lower risk HIV injection risk practices. Ouellet, L., Huo, D. and Bailey, S. HIV Risk Practices Among Needle Exchange Users and Nonusers in Chicago. J Acquir Immune Defic Syndr, 37, pp. 1187-1196, 2004.

Hepatitis C Virus Infection Among Injection Drug Users: Survival Analysis of Time to Seroconversion

Time to hepatitis C virus (HCV) seroconversion in initially seronegative IDUs has not been directly measured, and public health planning would benefit from specifying the window of opportunity for prevention of infection, and factors that affect timing of infection. In this study, researchers followed 484 HCV antibody-negative IDUs in Seattle, Washington a median of 2.1 years to observe seroconversion. They examined time to HCV seroconversion in relation to subject characteristics using the Kaplan-Meier method and Cox proportional hazards regression. A weighted-average time to HCV seroconversion was calculated among new injectors (injecting <2 years) using seroprevalence and seroincidence data. There were 134 HCV seroconversions (11.6 per 100 person-years at risk; the 25th percentile of time to seroconversion was 26.2 months). Injection with a syringe used by another injector (adjusted hazards ratio= 1.8; 95% confidence interval=1.3-3.0) and sharing a cooker or cotton (1.8; 1.0 -3.1) were associated with time to HCV seroconversion. Using the estimate of the mean time to seroconversion from first injection in new injectors who were HCV antibodynegative at enrollment (5.4 years), and the midpoint between first injection and study enrollment in new injectors who were HCV antibody-positive at enrollment (0.6 years), the weighted-average time to seroconversion after beginning to inject was estimated to be 3.4 years. These findings indicate that the period of susceptibility to HCV infection in the majority of drug injectors appears to be long enough to justify the allocation of substantial resources toward interventions to reduce injection-related risk behavior in these individuals. Hagan, H., Thiede, H., and Des Jarlais, D. Hepatitis C Virus Infection Among Injection Drug Users: Survival Analysis of Time to Seroconversion. Epidemiology, 15, pp. 543-549, 2004.

HIV Incidence Among High-Risk Puerto Rican Drug Users: A Comparison of East Harlem, New York, and Bayamon, Puerto Rico

Significant differences in HIV-related risk behaviors have been found between Puerto Rican drug users in New York City (NY) and Puerto Rico (PR). Researchers undertook an examination of HIV incidence rates and characteristics of seroconverters in each location. Baseline and follow-up interviewing and HIV testing were conducted in 1998

to 2002 with seronegative PR IDUs and crack smokers from East Harlem, NY (n = 455) and Bayam—n, PR (n = 268). There were a total of 32 seroconverters, 9 in NY and 23 in PR, for seroconversion rates of 0.88/100 person-years at risk (pyr; 95% CI, 0.31-1.45) in NY and 3.37/100 pyr (95% CI, 2.02-4.72) in PR (P < 0.001). In PR, variables significantly related to seroconversion were younger age and using shooting galleries. Being in methadone treatment was protective against seroconversion. In NY, crack use was significantly related to seroconversion. The researchers conclude that the higher seroconversion rate found in PR indicates a need to enhance HIV prevention efforts, including increasing methadone treatment and access to sterile syringes, and to focus on reducing HIV transmission in the Caribbean by targeting the drug use-HIV epidemic and sexual risk behaviors in both locations. Deren, S., Kag, S., Colon, H., Andia, J., and Robles, R. HIV Incidence Among High-Risk Puerto Rican Drug Users: A Comparison of East Harlem, New York, and Bayamon, Puerto Rico. J Acquir Immune Defic Syndr, 36, pp. 1067-1074, 2004.

An HIV Prevalence-Based Model for Estimating Urban Risk Populations of IDUs and MSM

Issues of cost and complexity have limited the study of the population size of men who have sex with men (MSM) and injection drug users (IDUs), two groups at clearly increased risk for human immunodeficiency virus (HIV) and other acute and chronic diseases. In this study, researchers developed a prototypical, easily applied estimation model for these populations and applied it to Miami, Florida. This model combined HIV prevalence estimates, HIV seroprevalence rates, and census data to make plausible estimates of the number and proportion of MSM and IDUs under a number of assumptions. Sensitivity analyses were conducted to test the robustness of the model. The model suggests that approximately 9.5% (plausible range 7.7%-11.3%) of Miami males aged 18 years or older are MSM (point estimate, N = 76,500), and 1.4% (plausible range 0.9%-1.9%) of the total population aged 18 years or older are IDUs (point estimate, N= 23,700). Males may be about 2.5 times more likely than females to be IDUs. The estimates were reasonably robust to biases. The model was used to develop MSM and IDU population estimates in selected urban areas across Florida and should be replicable in other medium-to-large urban areas. Such estimates could be useful for behavioral surveillance and resource allocation, including enhanced targeting of community-based interventions for primary and secondary HIV prevention. Lieb, S., Friedman, S., Zeni, M., Chitwood, D., Liberti, T., Gates, G., Metsch, L., Maddox, L., and Kuper, T. An HIV Prevalence-Based Model for Estimating Urban Risk Populations of IDUs and MSM. J Urban Health, 81, pp. 401-415, 2004.

Adolescent Onset Bipolar Disorder Associated with Risk for Substance Use Disorder

This study further investigated the previously reported elevated risk for substance use disorders (SUD) among children and adolescents with bipolar disorder (BPD), addressing some of the previous methodological weaknesses. The authors compared 57 subjects with early onset BPD with controls of similar age and socioeconomic status. Bipolar disorder was found to constitute a significant risk factor for substance use disorder in adolescence; this relationship held even when conduct disorder (commonly associated with both BPD and SUD) was taken into account. Moreover, as previously reported, adolescent-onset BPD rather than childhood-onset was the greater predictor. Although early onset bipolar disorder is relatively rare among the mental disorders, it is severe; thus, this study points to a potent risk factor that may help identify a high-risk group that could benefit from early intervention for bipolar disorder with possible implications for preventing SUD. Wilens, T.E., Biederman, J., Kwon, A., Ditterline, J., Forkner., P., Moore, H., Swezey, A., Snyder, L., Henin, A., Wozniak, H., and Faraone, S.V. Risk for Substance Use Disorders in Adolescents with Bipolar Disorder. Journal of the American Academy of Child and Adolescent Psychiatry, 43, pp. 1380-1386, 2004.

Age at First Use and Psychopathology as Risk Factors for Substance Use Disorder

This paper explores the issue of early drug use as a risk factor for adolescent substance use disorder (SUD), and the possible role of comorbid conduct problems in explaining this association. Sophisticated statistical tests were applied to longitudinal data from a large population-based sample, the Great Smoky Mountains Study, assessed annually between ages 9 and 16. Of note, drug use before age 13 was a strong predictor of transition to SUD, and early use remained a risk factor even in the absence of conduct disorder. Boys with a history of depression were at increased risk for SUD, and girls with anxiety experienced an increased risk at age 16. Findings from

such large population-based studies can help target populations at higher risk for drug abuse for appropriate preventive interventions. Sung, M., Erkanli, A., Angold, A., and Costello, E.J. Effects of Age at First Substance Use and Psychiatric Comorbidity on the Development of Substance Use Disorders. Drug and Alcohol Dependence, 75, pp. 287-299, 2004.

Relationship Between Early Cannabis Use and Later Use and Abuse of Other Illicit Substances

This study drew on genetic epidemiologic data to assess the relationship between early marijuana use and later use and abuse/dependence of other illicit substances. Several approaches to the data were employed to test whether they better fit the "gateway" model, in which early marijuana use has a causal role in subsequent drug abuse, or a correlated liabilities model, in which early marijuana use and later drug abuse both result from common vulnerability factors. Similar to other studies, they found a strong association between early cannabis use and the later use, abuse, and dependence of other illicit drugs. Further analyses and model-fitting found that one twin's early cannabis use was significantly associated with the second twin's later drug abuse, that genetic factors probably influence both early cannabis use and other drug abuse, and that the correlated liabilities model fit the data well. The authors compare their findings with those of Lynskey and colleagues, noting some differences in methodology and alternative interpretations of the discordant twin findings. These results led the authors to conclude that the relationship between early cannabis use and later drug abuse is largely influenced by correlated genetic and environmental factors, but that a causal influence of early marijuana use cannot be ruled out. Further study of this area, perhaps using prospective data, may further enhance the understanding of this issue, which has important preventive implications. Agrawal, A., Neale, M.C., Gardner, C.O., Prescott, C.A., and Kendler, K.S. A Twin Study of Early Cannabis Use and Subsequent Use and Abuse/Dependence of Other Illicit Drugs. Psychological Medicine, 34, pp. 1227-1237, 2004.

Shared Risks for Different Forms of Drugs

This study used a genetically informative design to investigate whether subjects using different forms of the same drug can appropriately be combined in epidemiologic studies. Drawing on data from a population-based sample of male and female same-sex twin pairs, they compared the genetic, shared environmental, and unique environmental overlap between 1) marijuana and hashish, and 2) intranasal and crack cocaine. Cannabis and cocaine each showed complete overlap in genetic factors between the different forms, and substantial overlap on shared environmental factors. Unique environmental factors were moderately similar for forms of cannabis and only modestly similar for forms of cocaine. These findings suggest that the choice of marijuana vs. hashish, or intranasal cocaine vs. crack, is largely due to unique environmental influences and not familial (inherited) tendencies, and that these different forms of each drug can be appropriately combined in epidemiologic studies. Agrawal, A., Prescott, C.A., and Kendler, K.S. Forms of Cannabis and Cocaine: A Twin Study. American J. Med. Genetics, 129B, pp. 125-128, 2004.

The Epidemiology of Dual Diagnosis

This literature review shows mental disorders to be significantly related to alcohol and drug use disorders. The strongest associations involve externalizing mental disorders and alcohol-drug dependence. Mental disorders are associated with alcohol-drug use, problems among users, dependence among problem users, and persistence among people with lifetime dependence. These dual diagnoses are associated with severity and persistence of both mental and alcohol-drug disorders. A wider range of mental disorders is associated with nicotine dependence. Most people with dual diagnosis report their first mental disorder occurred at an earlier age than their first substance disorder. Prospective studies confirm this temporal order, although significant predictive associations are reciprocal. Analyses comparing active and remitted mental disorders suggest that some primary mental disorders are markers and others are causal risk factors for secondary substance disorders. The article closes with a discussion of ways epidemiologic research can be used to help target and evaluate interventions aimed at preventing secondary substance use disorders by treating early-onset primary mental disorders. Kessler R.C. Biological Psychiatry, 56, pp. 730-737, 2004.

The National Comorbidity Survey Replication (NCS-R): Background and Aims

The National Comorbidity Survey Replication (NCS-R) is a new nationally representative community household survey of the prevalence and correlates of

mental disorders in the US. The NCS-R was carried out a decade after the original NCS. The NCS-R repeats many of the questions from the NCS and also expands the NCS questioning to include assessments based on the more recent Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostics system American Psychiatric Association, 1994). The NCS-R was designed to (1) investigate time trends and their correlates over the decade of the 1990s and (2) expand the assessment of the prevalence and correlates of mental disorders beyond the assessment in the baseline NCS in order to address a number of important substantive and methodological issues that were raised by the NCS. This paper presents a brief review of these aims. Kessler R.C., and Merikangas K.R. International Journal of Methods in Psychiatric Research, 13, pp. 60-68, 2004.

The US National Comorbidity Survey Replication (NCS-R): Design and Field Procedures

The National Comorbidity Survey Replication (NCS-R) is a survey of the prevalence and correlates of mental disorders in the US that was carried out between February 2001 and April 2003. Interviews were administered face-to-face in the homes of respondents, who were selected from a nationally representative multi-stage clustered area probability sample of households. A total of 9,282 interviews were completed in the main survey and an additional 554 short non-response interviews were completed with initial non-respondents. This paper describes the main features of the NCS-R design and field procedures, including information on fieldwork organization and procedures, sample design, weighting and considerations in the use of design-based versus model-based estimation. Empirical information is presented on non-response bias, design effect, and the trade-off between bias and efficiency in minimizing total mean-squared error of estimates by trimming weights. Kessler, R.C., Berglund, P., Chiu, W.T., Demler, O., Heeringa, S., Hiripi, E., Jin, R., Pennell, B.E., Walters, E.E., Zaslavsky, A. and Zheng, H. International Journal of Methods in Psychiatric Research, 13, pp. 69-92, 2004.

Mate Similarity for Substance Dependence and Antisocial Personality Disorder

Substance dependence (SD) and antisocial personality disorder (ASPD) are highly comorbid and aggregate in families. Mating assortment may be an important process contributing to this familial aggregation. Authors hypothesized that symptom counts of substance dependence, antisocial personality disorder, and retrospectively assessed conduct disorder (CD) would be correlated significantly among parents of youth in treatment for substance use and conduct problems and, separately, among parents of community controls. Authors examined SD, ASPD, and CD among 151 pairs of parents of adolescents in treatment for substance use and conduct problems, and in 206 pairs of parents of control subjects. For average dependence symptoms (ADS) (the sum of across-drug substance dependence symptoms divided by the number of substance categories meeting minimum threshold use) mother-father correlations were 0.40 for patients and 0.28 for controls. Mother-father correlations for ASPD symptom count were 0.33 for patients and 0.26 for controls and for CD symptom count were 0.31 for patients and 0.10 for controls. Spousal correlations for ADS and ASPD, suggest substantial non-random mating. Results support gender differences in homogamy for SD. Behavior genetic studies of these disorders need to account for assortment to avoid biases in estimates of genetic and environmental effects. Sakai, J.T., Stallings, M.C., Mikulich-Gilbertson, S.K., Corley, R.P., Young, S.E., Hopfer, C.J. and Crowley T.J. Drug and Alcohol Dependence, 16, pp. 165-175, 2004.

Pharmacogenetics of Nicotine Metabolism in Twins: Methods and Procedures

This article describes a pharmacogenetic investigation of nicotine metabolism in twins. One hundred and thirty-nine twin pairs (110 monozygotic and 29 dizygotic) were recruited and assessed for smoking status, zygosity, and health conditions known or suspected to affect drug metabolism. Participants underwent a 30-minute infusion of stable isotope-labeled nicotine and its major metabolite, cotinine, followed by an 8-hour in-hospital stay. Blood and urine samples were taken at regular intervals for analysis of nicotine, cotinine, and metabolites by gas chromatography-mass spectrometry or liquid chromatography-mass spectrometry and subsequent characterization of pharmacokinetic phenotypes. DNA was genotyped to confirm zygosity and for variation in the primary gene involved in nicotine metabolism, CYP2A6. Univariate and multivariate biometric analyses planned for the future will determine genetic and environmental influences on each pharmacokinetic measure individually and in combination with each other, and in the presence and absence of covariates, including measured genotype. When the analyses are completed, this

study will result in a more complete characterization of the impact of genetic and environmental influences on nicotine and cotinine metabolic pathways than has heretofore been reported. The approach taken, with its use of a quantitative model of nicotine metabolism, highly refined metabolic phenotypes, measured genotype, and advanced tools for biometric genetic analysis, provides a model for the use of twins in next-generation studies of complex drug-metabolism phenotypes. Swan, G.E., Benowitz, N.L., Jacob, P. III, Lessov, C.N., Tyndale, R.F., Wilhelmsen, K., Krasnow, R.E., McElroy, M.R., Moore, S.E., and Wambach, M. Twin Research, 7, pp. 435-448, 2004.

Defining Nicotine Dependence for Genetic Research: Evidence from Australian Twins

The authors used items of the DSM-IV and of the Heaviness of Smoking Index to characterize the nicotine dependence phenotype and to identify salient symptoms in a genetically informative community sample of Australian young adult female and male twins. Phenotypic and genetic factor analyses were performed on nine dependence symptoms (the seven DSM-IV substance dependence criteria and the two Heaviness of Smoking Index (HSI) items derived from the Fagerstrom Tolerance Questionnaire, time to first cigarette in the morning and number of cigarettes smoked per day). Phenotypic and genetic analyses were restricted to ever smokers. Results showed that phenotypic nicotine dependence symptom covariation was best captured by two factors with a similar pattern of factor loadings for women and men. In genetic factor analysis item covariation was best captured by two genetic but one shared environmental factor for both women and men; however, item factor loadings differed by gender. All nicotine dependence symptoms were substantially heritable, except for the DSM-IV criterion of 'giving up or reducing important activities in order to smoke', which was weakly familial. The findings suggest that the salient behavioral indices of nicotine dependence are similar for women and men. DSM-IV criteria of tolerance, withdrawal, and experiencing difficulty quitting and HSI items time to first cigarette in the morning and number of cigarettes smoked per day may represent the most highly heritable symptoms of nicotine dependence for both women and men. Lessov, C.N., Martin, N.G., Statham, D.J., Todorov, A.A., Slutske, W.S., Bucholz, K.K., Heath, A.C., and Madden, P.A. Psychological Medicine, 34, pp. 865-879, 2004.

The Association between Parental Alcoholism and Adolescent Psychopathology: A Systematic Examination of Parental Comorbid Psychopathology

The relationship between parental alcohol dependence (with and without comorbid psychopathology) and adolescent psychopathology was examined in a sample of 665 adolescents (13-17 years old) and their parents. Results indicated that adolescents who had parents diagnosed with alcohol dependence only did not significantly differ from adolescents who had parents with no psychopathology in regard to any of the measures of psychological symptomatology (substance use, conduct disorder, and depression) or clinical diagnoses (alcohol dependence, marijuana dependence, conduct disorder, or depression) assessed. In contrast, adolescents who had parents diagnosed with alcohol dependence and either comorbid drug dependence or depression were more likely to exhibit higher levels of psychological symptomatology. In addition, adolescents who had parents diagnosed with alcohol dependence, depression, and drug dependence were most likely to exhibit psychological problems. These findings underscore the importance of considering parental comorbid psychopathology when examining the relationship between parental alcoholism and offspring adjustment. Ohannessian, C.M., Hesselbrock, V.M., Kramer, J., Kuperman, S., Bucholz, K.K., Schuckit, M.A. and Nurnberger, J.I. Journal of Abnormal Child Psychology 32, pp. 519-533, 2004.

Depression, Suicidal Ideation, and Suicide Attempt in Twins Discordant for Cannabis Dependence and Early-onset Cannabis Use

Previous research has reported both a moderate degree of comorbidity between cannabis dependence and major depressive disorder (MDD) and that early-onset cannabis use is associated with increased risks for MDD. The purpose of this study was to examine whether associations between both lifetime cannabis dependence and early cannabis use and measures of MDD, suicidal ideation, and suicide attempt persist after controlling for genetic and/or shared environmental influences. Drawn from a general population sample of twins (median age, 30 years), 277 same-sex twin pairs discordant for cannabis dependence and 311 pairs discordant for early-onset cannabis use (before age 17 years). The results showed that individuals who were cannabis dependent had odds of suicidal ideation and suicide attempt that were 2.5 to 2.9 times higher than those of their non-cannabis-dependent co-twin.

Additionally, cannabis dependence was associated with elevated risks of MDD in dizygotic but not in monozygotic twins. Those who initiated cannabis use before age 17 years had elevated rates of subsequent suicide attempt (odds ratio, 3.5 [95% confidence interval, 1.4-8.6]) but not of MDD or suicidal ideation. Early MDD and suicidal ideation were significantly associated with subsequent risks of cannabis dependence in discordant dizygotic pairs but not in discordant monozygotic pairs. These findings suggest that the comorbidity between cannabis dependence and MDD likely arises through shared genetic and environmental vulnerabilities predisposing to both outcomes. In contrast, associations between cannabis dependence and suicidal behaviors cannot be entirely explained by common predisposing genetic and/or shared environmental predispositions. Previously reported associations between early-onset cannabis use and subsequent MDD likely reflect shared genetic and environmental vulnerabilities, although it remains possible that early-onset cannabis use may predispose to suicide attempt. Lynskey, M.T., Glowinski, A.L., Todorov, A.A., Bucholz, K.K., Madden, P.A., Nelson, E.C., Statham, D.J., Martin, N.G. and Heath A.C. Archives of General Psychiatry, 61, pp. 1026-1032, 2004.

Neurobehavior Disinhibition in Childhood Predicts Suicide Potential and Substance Use Disorder by Young Adulthood

The objectives of this study were to (1) determine whether two factors that are established components of the risk for substance use disorder (SUD) also impact on the risk for suicide; and (2) evaluate whether SUD manifest by early adulthood predicts suicide propensity. Neurobehavior disinhibition assessed in 227 boys at ages 10-12 and 16 and parental history of SUD were prospectively evaluated to determine their association with the risk for SUD and suicide propensity between ages 16 and 19. The results indicated that neurobehavior disinhibition at age 16 predicts suicide propensity between ages 16 and 19 ($p = .04$). A trend was observed ($p = .08$) for SUD manifest between ages 16 and 19 to predict suicide propensity during the same period. Maternal SUD is directly associated with son's SUD risk but not suicide propensity. Paternal SUD predicts son's neurobehavior disinhibition that, in turn, predisposes to SUD. A direct relation between paternal SUD and son's suicide propensity was not observed. These findings suggest that neurobehavior disinhibition, a component of the liability of SUD, is also associated with suicide risk. These results are discussed within a neurobehavioral framework in which prefrontal cortex dysfunction is hypothesized to underlie the risk for these two outcomes. Tarter, R.E., Kirisci, L., Reynolds, M., and Mezzich, A. Drug and Alcohol Dependence 76, S45-S52, 2004.

Post-traumatic Stress Disorder, Drug Dependence, and Suicidality among Male Vietnam Veterans with a History of Heavy Drug Use

This study examines the roles of post-traumatic stress disorder (PTSD) and drug dependence in non-fatal suicidality (i.e., suicidal ideation and suicide attempt) among Vietnam veterans in their adult years. The sample includes male veterans deployed to Vietnam, including an oversample of those who tested positive for opiates at their return ($N = 642$). PTSD, substance abuse, suicidality, and other psychopathology are analyzed using three waves of survey and military data covering the time period from early adolescence to middle adulthood. Measures include the onset and recency of each of the lifetime DSM-IV PTSD symptom criteria, and yearly symptom measures of DSM-IV dependence for alcohol and eight classes of psychoactive substances. Survival and hazard models are applied to assess the effects of drug dependence, PTSD, and other psychopathology on the duration of suicidality. Longitudinal models estimate the casual relationships among PTSD, drug dependence, and suicidality over a 25-year period. Results show evidence of strong continuity of PTSD, drug dependence, and suicidality over time. The causal role of drug dependence on PTSD and suicidality is limited to young adulthood. Evidence is stronger for self-medication in later adulthood. The results indicate that a life-course perspective is needed for the combined treatment of PTSD and drug dependence for severely traumatized populations. Price, R.K., Risk, N.K., Haden, A.H., Lewis, C.E. and Spitznagel, E.L. Drug and Alcohol Dependence 76, 31-43, 2004.

Making a Structured Psychiatric Diagnostic Interview Faithful to the Nomenclature

Psychiatric diagnostic interviews to be used in epidemiologic studies by lay interviewers have, since the 1970s, attempted to operationalize existing psychiatric nomenclatures. How to maximize the chances that they do so successfully has not previously been spelled out. In this article, the authors discuss strategies for each of the seven steps involved in writing, updating, or modifying a diagnostic interview and its supporting materials: 1) writing questions that match the nomenclature's criteria,

2) checking that respondents will be willing and able to answer the questions, 3) choosing a format acceptable to interviewers that maximizes accurate answering and recording of answers, 4) constructing a data entry and cleaning program that highlights errors to be corrected, 5) creating a diagnostic scoring program that matches the nomenclature's algorithms, 6) developing an interviewer training program that maximizes reliability, and 7) computerizing the interview. For each step, the authors discuss how to identify errors, correct them, and validate the revisions. Although operationalization will never be perfect because of ambiguities in the nomenclature, specifying methods for minimizing divergence from the nomenclature is timely as users modify existing interviews and look forward to updating interviews based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, and the International Classification of Diseases, Eleventh Revision. Robins, L.N., and Cottler, L.B. American Journal of Epidemiology, 15, pp. 808-813, 2004.

The Homeless Supplement to the Diagnostic Interview Schedule: Test-Retest Analyses

This study sought to extend previous work on reliability of self-reported residential history in a homeless population with high rates of drug abuse. The latest version of the Homeless Supplement to the Diagnostic Interview Schedule (DIS/HS) was used to achieve reliability on homelessness experience, use of shelters, transience, and recent residential patterns. Homeless study volunteers were recruited for a test-retest study from a drop-in day centre for mentally ill homeless people (N = 25) and a substance abuse day programme (N = 30). They were administered the instrument approximately one to two days apart. Kappa and intraclass correlation analyses were performed to assess reliability. Overall, the reliabilities of most variables were acceptable, ranging from fair to excellent. Six items were reconstructed to achieve reliability and two were dropped. Substance dependence and adult antisocial behaviour patterns did not affect reliability on most items. This study has developed a reliable self report instrument for measuring residential history that can be used with homeless and drug abusing populations. Replication is needed in larger, more representative samples and comparison of reliability with other psychiatric and cognitive characteristics. North, C.S., Eyrich, K.M., Pollio, D.E., Foster, D.A., Cottler L.B. and Spitznagel E.L. International Journal of Methods in Psychiatric Research, 13, pp. 184-191, 2004.

The Association of Sexual Dysfunction and Substance Use among a Community Epidemiological Sample

This study examines the prevalence of DSM-III sexual dysfunctions and their association with comorbid drug and alcohol use in a community epidemiologic sample. The data for these analyses are based on the Epidemiological Catchment Area Project, a multistage probability study of the incidence and prevalence of psychiatric disorders in the general population conducted in 1981-83. Only the sample of 3,004 adult community residents in the St. Louis area was queried on DSM-III sexual dysfunctions of inhibited orgasm, functional dyspareunia (painful sex), inhibited sexual excitement (i.e., lack of erection/arousal), and inhibited sexual desire. There was a prevalence rate of 11% for inhibited orgasm, 13% for painful sex, 5% for inhibited sexual excitement, 7% for inhibited sexual desire, and 26% for any of these sexual dysfunctions (14% for men and 33% for women). The prevalence of qualifying lifetime substance use among the population was 37%, with males meeting more drug and alcohol use criteria than females. After controlling for demographics, health status variables, and psychiatric comorbidity (depression disorder, generalized anxiety disorder, antisocial personality disorder, and residual disorders), inhibited orgasm was associated with marijuana and alcohol use. Painful sex was associated with illicit drug use and marijuana use. Inhibited sexual excitement was more likely among illicit drug users. Inhibited sexual desire was not associated with drug or alcohol use. Johnson, S.D., Phelps, D.L. and Cottler, L.B. Archives of Sexual Behavior, 33, pp. 55-63, 2004.

Epidemiology of Inhalant Use, Abuse, and Dependence among Youth

Secondary analysis of data on adolescents aged 12-17 from 2000 and 2001 National Household Surveys on Drug Abuse found that inhalant use was common. Results showed that 0.4% of adolescents met DSM-IV inhalant abuse or dependence criteria in the past year. Inhalant abuse and dependence affected adolescents regardless of gender, age, race/ethnicity, and family income. The progression from inhalant use to abuse or dependence was related to early first use, use of multiple inhalants, and weekly inhalant use. Adolescents with inhalant use disorders reported coexisting multiple drug abuse and dependence, mental health treatment, and delinquent behaviors. Adolescents with an inhalant use disorder may represent a subgroup of

highly troubled youth with multiple vulnerabilities. Because early use is associated with progression to abuse and dependence, prevention programs should target elementary school-age children. Wu, L.T., Pilowsky, D.J., and Schlenger, W.E. Inhalant Abuse and Dependence among Adolescents in the United States. J Am Acad Child Adolesc Psychiatry, 43, pp. 1206-1214, 2004.

Alcohol and Marijuana Use and Teen HIV Risk Behavior

While many studies have demonstrated an association between substance use and sexual activity among teens and young adults, few studies have attempted to estimate causal effects. This study employed two complementary research approaches, the bivariate probit regression model and an individual fixed-effects regression model to explore this issue through analysis of data from the 1997 cohort of the National Longitudinal Survey of Youth (NLSY). To test the robustness of their estimates using NLSY data, the authors obtained estimates of the effect of substance use and sexual behavior using a sample of young adults drawn from the National Longitudinal Survey of Adolescent Health (Ad-Health) and found similar results. The authors concluded that the positive associations between substance use and sexual behavior and risky sexual behavior are unlikely to reflect true causal relationships and are more likely to reflect the influence of omitted variables. Grossman, M., Kaestner, R., and Markowitz, S. Get High and Get Stupid: The Effect of Alcohol and Marijuana Use on Teen Sexual Behavior. Review of Economics of the Household, 2, pp. 411-439, 2004.

Males at Greater Risk for Violence, Females Higher Risk of PTSD

This study estimated the cumulative occurrence of traumatic events and posttraumatic stress disorder (PTSD), using fourth edition (DSM-IV) criteria, in a high-risk sample of young people in urban United States. The epidemiological sample (n = 2,311) was recruited in 1985-1986 at entry into first grade of a public school system of a large mid-Atlantic city. Participants were interviewed about history of trauma and PTSD in 2000-2002 when their mean age was 21 years (n = 1,698). The authors found that the lifetime occurrence of assaultive violence was 62.6% in males and 33.7% in females. The risk of assaultive violence in males (but not females) varied by childhood area of residence within the city; the occurrence of other traumas did not vary by area of childhood residence. Females had a higher risk of PTSD than males following assaultive violence (odds ratio = 4.0, 95% confidence interval 2.0-8.3), but not following other traumas. A comparison of the results from this largely inner-city sample with the results from a recent study of a largely suburban sample in another region of the United States in which the same criteria and measures of trauma and PTSD were used suggested the possibility that males' risk for assaultive violence and females' risk for PTSD following exposure to assaultive violence might vary by characteristics of the social environment. Breslau, N., Wilcox, H.C., Storr, C.L., Lucia, V.C., and Anthony, J.C. Trauma Exposure and Posttraumatic Stress Disorder: A Study of Youths in Urban America. J Urban Health, 81, pp. 530-544, 2004.

Early Childhood Misbehavior Associated with Risk of Becoming Tobacco Dependent

In this study, the authors focused on signs of early childhood misbehavior that might be linked to the risk of becoming tobacco-dependent. Standardized teacher ratings of misbehavior were obtained for an epidemiologic sample of first graders entering an urban mid-Atlantic public school system in 1985 and 1986. Fifteen years later, 1,692 of the students were reassessed. As adults, 962 participants indicated that they had tried tobacco at least once; 66% of the 962 had become daily users. Latent class analysis of items on the Fagerstrom Test for Nicotine Dependence gave evidence of three classes pertinent to tobacco dependence syndrome in smokers by young adulthood: one nondependent class of smokers (50% of smokers), a class of smokers experiencing a moderate number of dependence features (31%), and a third class that was more severely affected (19%), as manifest in the need to smoke immediately after waking and smoking when ill. With or without adjustment for covariates, higher levels of teacher-rated childhood misbehavior at entry into primary school were associated with a modest excess risk of becoming tobacco-dependent by young adulthood (risk ratio = 1.6, 95% confidence interval: 1.1, 2.5). Interventions that seek to improve childhood behavior might reduce early onset tobacco smoking and risk of tobacco dependence among smokers. Storr, C.L., Reboussin, B.A., and Anthony, J.C. Am J Epidemiol, 15, 160, pp. 126-130, 2004.

Tobacco Dependence in the First Two Years of Use

This study pursued a line of large-sample epidemiological research on tobacco dependence syndromes that may appear during the first 2 years of tobacco smoking, as clinical features begin to emerge. A specific focus was a possible excess risk of tobacco dependence associated with early-onset smoking. Data came from public use files of the 1995-1998 National Household Surveys on Drug Abuse. Analyses were based on responses from 2,993 smokers, that is, those whose age at onset of tobacco smoking was either equal to the age at the time of the interview (n=1,030) or within 1 year of the age at the interview (n=1,963). Findings from latent class analysis best support a model with three classes of smokers; features of tobacco dependence are prominent in just two of these classes, which in aggregate constitute 29% of the recent-onset smokers. Earlier-onset tobacco smokers may have a modestly higher probability of expressing dependence features within 2 years of smoking onset, compared with later-onset smokers (i.e., those starting after age 20). Clinical features of tobacco dependence emerge within 1-2 years after the onset of smoking. If the three-class model of tobacco dependence is correct, early-onset smoking may confer modest excess risk of becoming tobacco dependent during the first 2 years after smoking onset. Storr, C.L., Zhou, H., Liang, K.Y., and Anthony, J.C. Nicotine Tob Res., 6, pp. 533-545, 2004.

Methodological Advances for Developmental Data

These methodological studies addressed two issues commonly found in human developmental datasets: a failure to capitalize on the measurement of time when using latent class analysis and avoiding the identification of spurious latent classes in structural equation mixture modeling. In one study the authors demonstrate both analytically and empirically that classic techniques for probing interactions in multiple regression can be generalized to LCA. A worked example is presented, and the use of these techniques is recommended whenever estimating conditional LCAs in practice. In another study the authors identify 3 conditions that may lead to the estimation of spurious latent classes in SEMM. They indicate that when the objective of a SEMM analysis is the identification of latent classes, these conditions should be considered as alternative hypotheses and results should be interpreted cautiously. Curran, P.J., Bauer, D.J., and Willoughby, M.T. Testing Main Effects and Interactions in Latent Curve Analysis, Psychol Methods, 9, pp. 220-37, 2004. See also: Bauer, D.J., and Curran, P.J. The Integration of Continuous and Discrete Latent Variable Models: Potential Problems and Promising Opportunities. Psychol Methods, 9, pp. 3-29, 2004.

Pubertal Stage Associated with Substance Use

The aim of this study was to ascertain the association between pubertal development and early adolescent substance use. Students completed questionnaires in school, in a cross-sectional survey of 5769 students age 10- to 15-year-old in the states of Washington, United States, and Victoria, Australia. The odds of lifetime substance use were almost twofold higher in midpuberty (Tanner stage III) and were threefold higher in late puberty (Tanner stage IV/V), after adjustment for age and school grade level. Recent substance use and substance abuse were higher in midpuberty and even more so in late puberty. Reporting most friends as substance users was more likely in the later stages of pubertal development, a relationship that accounted in part for the association found between later pubertal stage and substance abuse. Pubertal stage was associated with higher rates of substance use and abuse independent of age and school grade level. Early maturers had higher levels of substance use because they entered the risk period at an earlier point than did late maturers. The study findings support prevention strategies and policies that decrease recreational substance use within the peer social group in the early teens. Patton, G.C., McMorris, B.J., Toumbourou, J.W., Hemphill, S.A., Donath, S., and Catalano, R.F. Puberty and the Onset of Substance Use and Abuse. Pediatrics, 114, pp. 300-306, 2004.

Comparison of Substance Use in the US and Australia

This study compared risk and protective factors that influence youth substance use in Australia and the United States. The two countries have different policy orientations toward substance use: Australia has adopted harm-reduction policies, and the United States has adopted abstinence-focused policies. Cross-sectional survey data were collected from independent samples of adolescents in the states of Maine (N = 16,861) and Oregon (N = 15,542) in the United States and Victoria in Australia (N = 8442). Study results indicated that more adolescents in Victoria reported using cigarettes and alcohol, whereas more of the U.S. adolescents reported using marijuana. Exposure to risk and protective factors was generally similar in the cross-national samples. Most of the risk and protective factors were strongly associated with substance use to a similar degree in Victoria, Maine, and Oregon. However, among adolescents in Maine and Oregon peer/individual risk and protective factors associated

with social detachment were more strongly related to substance use, and among adolescents in Victoria, family protective factors were less strongly related to alcohol use. Existing differences suggest that the abstinence policy context is associated with higher levels of illicit drug use and stronger relations between individual indicators of social detachment and substance use, whereas the harm reduction policy context is related to more cigarette and alcohol use, possibly from exposure to normative influences that are more tolerant of youth drug use. Beyers, J.M., Toumbourou, J.W., Catalano, R.F., Arthur, M.W. and Hawkins, J.D. A Cross-national Comparison of Risk and Protective Factors for Adolescent Substance Use: The United States and Australia. J Adolesc Health, 35, pp. 3-16, 2004.

Low Parent Involvement Related to Youth Substance Abuse

This study developed a scale-based method for identifying adolescents with low-parent involvement and examined effects on the development and course of alcohol use disorders (AUDs). The participants were 361 adolescents (ages 14 to 17 years) from two-parent families recruited from clinical and community sources. Cluster analysis of questionnaire items describing mother and father involvement identified 75 adolescents with low-parent involvement (i.e., Neglect). Compared with reference adolescents, Neglect adolescents were significantly more likely to be influenced by social pressure to drink alcohol. Among community participants, Neglect adolescents were more likely to develop AUDs. Among adolescents receiving treatment for AUDs, those in the Neglect group showed more improvement during a 1-year follow-up period. The results indicate that inadequate parent involvement may be a form of neglect. Clark, D.B., Thatcher, D.L., and Maisto, S.A. Adolescent Neglect and Alcohol Use Disorders in Two-Parent Families. Child Maltreatment 9, pp. 357-370, 2004.

The Natural History of Alcohol Use Disorders

This study examined clinically relevant research on the development, course and outcomes of adolescence alcohol use disorders (AUDs), using observational studies with adolescent samples selected for inclusion based on systematic assessment of AUDs and clinical relevance. Articles on childhood predictors, characteristics, course, complications and adult outcomes of adolescent AUDs were reviewed. Results indicate that the developmental trajectory toward adolescent AUDs begins with the emergence of childhood mental disorders. These problems are transmitted from parent to child in a developmentally specific fashion, reflect psychological dysregulation dimensions and predict adolescent AUDs. While most DSM-IV AUD diagnostic criterion items are valid for adolescents, tolerance and impaired control items are problematic, and some adolescents with significant alcohol problems are not identified by this diagnostic system. Understanding the psychosocial and biomedical complications that accompany AUDs requires attention to factors other than alcohol involvement itself, including childhood maltreatment and comorbid psychopathology. While some adolescents with AUDs manifest chronic alcohol dependence in adulthood, a substantial proportion overcome alcohol problems and transition to abstinence or normative drinking. While alcohol consumption may be the primary treatment focus, other important consequences, comorbidities and complications need to be addressed for successful developmental outcomes to result. Clark, D.B. The Natural History of Alcohol Use Disorders, Addiction, 99, pp. 5-22, 2004.

Antecedents and Outcomes of Marijuana Use Initiation during Adolescence

This study identified similarities and differences in risk factors for marijuana use initiation from grades 7 to 8, grades 8 to 9, and grades 9 to 10, and examined differences between earlier initiates, later initiates, and nonusers on various problem behaviors at grade 10. Longitudinal data were used to examine predictors and outcomes associated with marijuana initiation from grade 7 (N = 1,955) to grade 10 (N = 909). Participants completed yearly surveys to assess problem behaviors, social influences, and marijuana-related attitudes and behavior. Results showed that earlier initiates were more likely than later initiates to exhibit problem-related marijuana use, hard drug use, polydrug use, poor grades, and low academic intentions at grade 10. Across ages, initiation was predicted by smoking, frequency of marijuana offers, and poor grades. Results provided some evidence for a shift from familial to peer influence on marijuana initiation with increasing age. Marijuana-related beliefs were relatively weak predictors of initiation at all ages after controlling for pro-marijuana social influences and engagement in other types of substance use and delinquent behavior. Results emphasize the importance of early intervention and identify a wide range of potentially modifiable risk factors that may be targeted. Ellickson, P.L., Tucker, J.S., Klein, D.J., and Saner, H. Prev Med., 39, pp. 976-984, 2004.

Pathways From Physical Childhood Abuse To Partner Violence In Young

Adulthood

Analyses investigated several competing hypotheses about developmental pathways from childhood physical abuse and early aggression to intimate partner violence (IPV) for young adult males and females at age 24. Potential intervening variables included: adolescent violence (age 15 to 18), negative emotionality at age 21, and quality of one's relationship with an intimate partner at age 24. At the bivariate level, nearly all variables were associated in the expected directions. However, tests of possible intervening variables revealed only a few significant results. For males, a strong direct effect of abuse on later partner violence was maintained in each model. For females, the quality of one's relationship with an intimate partner did appear to mediate the effect of childhood abuse on later violence to a partner, raising the possibility of gender differences in developmental pathways linking abuse to IPV. Herrenkohl, T.I., Mason, W.A., Kosterman, R., Lengua, L.J., Hawkins, J.D. and Abbott R.D. Violence and Victims, 19, pp. 123-136, 2004.

Adolescent Heavy Drinkers More Likely to be Obese Young Adults

This study examined the association of trajectories of heavy episodic drinking (at least five alcoholic drinks on one occasion) during adolescence with health status and practices at age 24. Data were from a longitudinal panel of 808 youths interviewed between 10 and 24 years of age. Results indicated four distinct trajectories of adolescent heavy episodic drinking were identified: nonheavy drinkers, late onsetters, escalators and chronic heavy drinkers. Overall, young adults who did not engage in heavy episodic drinking during adolescence had the lowest occurrence of health problems and were most likely to engage in safe health behaviors at age 24. Chronic and late-onset heavy episodic drinking during adolescence had negative effects on health status and practices at age 24. Adolescent chronic heavy drinkers were more likely to be overweight or obese and to have high blood pressure at age 24 than those who did not drink heavily in adolescence. Late-onset heavy drinkers were less likely to engage in safe driving practices at age 24 and were more likely to have been ill in the past year than adolescents who did not drink heavily. These health disparities remained even after current frequency of heavy episodic drinking at age 24, other adolescent drug use, ethnicity, gender and family poverty were controlled. Oesterle, S., Hill, K.G., Hawkins, J.D., Guo, J., Catalano, R.F., and Abbott, R.D. Adolescent Heavy Episodic Drinking Trajectories and Health in Young Adulthood. J Stud Alcohol., 65, pp. 204-212, 2004.

Attitudes toward Alcohol and Drug-free Experience among College Students

This study examined prospective relations between attitudes toward alcohol use and drug-free experience and alcohol consumption and problems in 231 undergraduate students (73% women). Attitude toward drug-free experience was hypothesized to moderate the alcohol attitude--behavior relationship. Participants were assessed twice, separated by a 30-day interval. Attitude toward alcohol use at Time 1 was associated with alcohol consumption at Time 2. Time 1 attitude toward alcohol use and the interaction between the attitude variables were associated with problems at Time 2, indicating that attitude toward alcohol use was less associated with alcohol problems among participants with more positive attitudes toward drug-free experience. Attitude toward drug-free experience acted as a protective factor, reducing the relationship between alcohol attitude and alcohol-related problems. Simons, J.S., and Gaher, R.M. Attitudes toward Alcohol and Drug-free Experience among College Students: Relationships with Alcohol Consumption and Problems. Am J Drug Alcohol Abuse, 30, pp. 461-471, 2004.

Racial Identity, Parental Support and Alcohol Use

This study examined racial identity and parental support as predictors of alcohol use in a sample of 488 African American adolescents. Two dimensions of racial identity were investigated: (1) racial centrality (i.e., the significance that one places on race in defining oneself) and (2) private regard (i.e., the extent to which one feels positively about Black people). In addition, perceived support from mothers and fathers was examined. Multivariate results showed that private regard and father support were associated with less self-reported alcohol use after partialling out the effects of age and gender. An interaction between the two racial identity dimensions was also found such that private regard was associated with less alcohol use for adolescents who reported that race was a more central part of their identity. Caldwell, C.H., Sellers, R.M., Bernat, D.H., and Zimmerman M.A. Racial Identity, Parental Support, and Alcohol Use in a Sample of Academically At-risk African American High School Students. Am J Community Psychol, 34, pp. 71-82, 2004.

Religious Activity and Risk Behavior Among African American Adolescents

This study examines how religious activity is associated with risk behaviors, concurrently and developmentally among urban African American adolescents. Seven hundred and five African American youths were interviewed annually during high school. Retention rates for the study exceeded 90%. Frequency of religious activity, sexual intercourse, and alcohol, cigarette, and marijuana use were assessed at each wave. Growth curve analyses found negative concurrent associations between religious activity and each of the four risk behaviors. The developmental effects of religious activity varied by gender. Higher levels of religious activity in 9th grade predicted smaller increases in marijuana use among males and cigarette use among females. In addition, larger decreases in religious activity during high school were associated with greater increases in alcohol use among males and sexual intercourse among females. During high school, religious activity limits the development of certain types of risk behavior among African American youth, even after controlling for reciprocal effects. Steinman, K.J., and Zimmerman M.A. Religious Activity and Risk Behavior among African American Adolescents: Concurrent and Developmental Effects. Am J Community Psychol., 33, pp. 151-161, 2004.

Life Transitions Predict Depression and Alcohol Use

This study examined longitudinally the relationship between depressive symptoms and alcohol use in a sample of black youth. Participants were 458 black males and females interviewed annually during the high school years and then for 3 years during the transition to adulthood. The relationship was examined using growth curves with Hierarchical Linear Modeling. The results suggest that depressive symptoms decrease over time, whereas the use of alcohol increases. The findings also suggest that youths use alcohol as a way to cope with depressive symptoms and that males are more likely to use alcohol as self-medication. The results also indicate that changes in alcohol use do not predict depressive symptoms, but that life changes associated with the transition to adulthood, such as attending college, predict changes in depressive symptoms and alcohol use. Findings highlight the role of depressive symptoms for predicting alcohol use among black youth and the role of significant life transitions in altering the pattern of alcohol use presented previously by these youths. Repetto, P.B., Zimmerman, M.A., and Caldwell, C.H. A Longitudinal Study of the Relationship between Depressive Symptoms and Alcohol Use in a Sample of Inner-city Black Youth. J Stud Alcohol., 65, pp. 169-178, 2004.

Greater Opportunity to Buy Illegal Drugs in Disadvantaged Neighborhoods

This study investigated whether subgroups of people living in disadvantaged neighborhoods may be more likely to come into contact with drug dealers as compared with persons living in more advantaged areas, with due attention to male-female and race-ethnicity differences. The study used standardized survey data collected using stratified, multistage area probability sampling with a nationally representative sample of household residents age 12 or older (n = 25,500). Evidence supports an inference that women are less likely to be approached by someone selling illegal drugs. The study found no more than modest and generally null racial and ethnicity differences, even for residents living within socially disadvantaged neighborhoods, where chances to buy illegal drugs are found to be more common. Limitations of survey data always merit attention, but this study evidence lends support to the inference that physical and social characteristics of a neighborhoods can set the stage for opportunities to become involved with drugs. Storr, C.L., Chen, C.Y., and Anthony, J.C. "Unequal Opportunity": Neighborhood Disadvantage and the Chance to Buy Illegal Drugs. J Epidemiol Community Health, 58, pp. 231-237, 2004.

Cigarette Smoking and Depressive Symptoms: A Longitudinal Study of Adolescents and Young Adults

Cigarette smoking and depressive symptoms have been shown to be related in previous research. This paper examined the relationship between cigarette smoking and depressive symptoms in a longitudinal sample of 688 adolescents and young adults through surveys conducted over 13 years. The results indicate that a history of earlier cigarette smoking in adolescence predicts later depressive symptoms in the late twenties. The study also suggests that depressive symptoms during adolescence predict cigarette smoking in the late twenties but not above and beyond prior smoking. These results help clarify and expand current knowledge on the links between cigarette smoking and depression. The results point to several clinical implications for treatment of both cigarette smoking and depressive symptoms among both adolescents and young adults. Brook, J.S., Brook, D.W., Schuster, E., and Zhang, C. Cigarette Smoking and Depressive Symptoms: A Longitudinal Study of

Adolescents and Young Adults. Psychological Reports, 95, pp. 159-166, 2004.

Tobacco Use and Health in Young Adulthood

This prospective longitudinal study examines the association between lifetime tobacco use and subsequent health problems by age 30. The authors interviewed a community group of 749 participants from upstate New York at mean ages of 14, 16, 22, and 27 years. Daily tobacco use during any of the time periods, as well as the number of periods of daily tobacco use, were significantly associated with increased risk for respiratory ailments, neurobehavioral and cognitive problems, and general malaise. The results suggested that daily tobacco use, either during childhood, adolescence, the early 20s, or a combination of those times, predicted health problems by age 30. Effective smoking prevention programs that begin in childhood are imperative to prevent the occurrence of later health problems. Brook, J.S., Brook, D.W., Zhang, C., and Cohen, P. Tobacco Use and Health in Young Adulthood. Journal of Genetic Psychology, 165, pp. 310-323, 2004.

Smoking Among New Yorican Adolescents

The authors identified longitudinal relationships between early risk and protective factors from the domains of family, personality, and peer influences and later tobacco use in Puerto Rican adolescents living in New York. Aspects of the ethnic minority experience as moderators of familial risk and protective factors were investigated. Participants were 282 female and 276 male Puerto Rican adolescents interviewed twice, 5 years apart. The authors used hierarchical regression analyses to identify a model with direct and indirect paths. Family, personality, peer, and early smoking domains were directly related to later adolescent smoking. Partial mediation occurred. The authors identified risk-protective and protective-protective interactions between variables from the ethnic minority experience and family domains. Interventions to reduce smoking among Puerto Rican adolescents should focus on multiple contexts, including aspects of the ethnic minority experience. Brook, J.S., Pahl, T., Balka, E.B, and Fei, K. Smoking Among New Yorican Adolescents: Time 1 Predictors of Time 2 Tobacco Use. Journal of Genetic Psychology, 165, pp. 324-340, 2004.

Course and Psychosocial Correlates of Personality Disorder Symptoms in Adolescence

Personality disorder symptoms were investigated in a community sample of young people (n=714) to assess their relationship over time with well-being during adolescence and the emergence of intimacy in early adulthood. Drawing on Erikson's theory of psychosocial development, changes in adolescent well-being were conceptualized as indirect indicators of identity consolidation. Cluster B personality disorder symptoms (borderline, histrionic, and narcissistic symptoms) were conceptualized to represent "identity diffusion" - i.e., maladaptive personality traits that usually resolve during the identity crisis of adolescence. Latent growth models were used in two age cohorts to assess (1) interrelationships between Cluster B symptoms, well-being, and intimacy at mean ages 13.8 and 18.6 years; and (2) associations between their developmental trajectories over the next 6 years. As expected, higher personality disorder symptoms were associated with lower well-being during adolescence, and declines in personality disorder symptoms over time were associated with corresponding gains in well-being. Consistent with Erikson's developmental theory, there was an inverse relationship between Cluster B symptoms and intimacy that increased in strength as young people entered adulthood. As an indicator of successful identity consolidation, well-being was significantly associated with intimacy in female adolescents and young adults. Crawford, T.N., Cohen, P., Johnson, J.G., Sneed, J.R., and Brook, J.S. The Course and Psychosocial Correlates of Personality Disorder Symptoms in Adolescence: Erikson's Developmental Theory Revisited. Journal of Youth and Adolescence, 33, pp. 373-387, 2004.

Paternal Psychiatric Symptoms and Early Maladaptive Paternal Behavior

Data from the Children in the Community Study, a community-based longitudinal study were used to investigate associations between paternal psychiatric disorders and child-rearing behaviors. Paternal psychiatric symptoms and behavior in the home were assessed among 782 families during the childhood and adolescence of the offspring. Paternal anxiety, disruptive, mood, personality, and substance use disorders were independently associated with specific types of maladaptive paternal behavior in the home during the child-rearing years after paternal age, education, income, co-occurring paternal psychiatric symptoms, offspring age, sex, intelligence, temperament, and psychiatric symptoms were controlled statistically. Paternal psychiatric disorders that were present by mean offspring age 14 were associated

with elevated risk for maladaptive paternal behavior in the home at mean age offspring 16, after prior maladaptive paternal behavior was controlled statistically. These findings suggest that paternal psychiatric disorder may be an important determinant of maladaptive paternal behavior in the home during the child-rearing years. Improved recognition and treatment of paternal psychiatric disorders may help to reduce the amount of maladaptive parenting behavior than many children and adolescents might otherwise be likely to experience. Johnson, J.G., Cohen, P., Kasen, S., and Brook, J.S. Paternal Psychiatric Symptoms and Maladaptive Paternal Behavior in the Home During the Child Rearing Years. Journal of Child and Family Studies, 13, pp. 421-437, 2004.

Association between Television Viewing and Sleep Problems during Adolescence and Early Adulthood

The purpose of this prospective, longitudinal study was to investigate directional hypotheses regarding the association between television viewing and sleep problems during adolescence and early adulthood. A community-based sample of 759 mothers from upstate New York and their offspring were interviewed during the early adolescence, middle adolescence, and early adulthood of the offspring. Television viewing and sleep problems during adolescence and early adulthood were measured using the Disorganizing Poverty Interview and the age-appropriate versions of the Diagnostic Interview Schedule for Children. Results showed that adolescents who watched 3 or more hours of television per day during adolescence were at a significantly elevated risk for frequent sleep problems by early adulthood. This elevation in risk remained significant after offspring age, sex, previous sleep problems, offspring psychiatric disorders, offspring neglect, parental educational level, parental annual income, and parental psychiatric symptoms were controlled statistically. Adolescents who reduced their television viewing from 1 hour or longer to less than 1 hour per day experienced a significant reduction in risk for subsequent sleep problems. Sleep problems during adolescence were not independently associated with subsequent television viewing when prior television viewing was controlled. Johnson, J.G., Cohen, P., Kasen S., First, M.B., and Brook, J.S. Association between Television Viewing and Sleep Problems during Adolescence and Early Adulthood. Archives of Pediatrics and Adolescent Medicine, 158, pp. 562-568, 2004.

Racial/Ethnic Differences in Cigarette Smoking Initiation and Progression to Daily Smoking

Using data from the National Longitudinal Study of Adolescent Health, this study was designed to identify individual and contextual factors that influence cigarette smoking initiation and progression to daily smoking among non-Hispanic Black, Hispanic, and non-Hispanic White adolescents. Findings confirmed differences in patterns of smoking onset and progression to daily smoking among racial/ethnic groups. Hispanic youth had the highest rates of smoking onset, and White youth had the highest rates of progression to daily smoking. Black youth consistently had the lowest rates for both smoking outcomes. There were more common predictors than ethnic-specific predictors of adolescent smoking and individual factors were much more important predictors than contextual factors. The authors concluded that universal prevention and intervention efforts would reach most adolescents, regardless of race/ethnicity. Kandel, D.B., Kiros, G.E, Schaffran, C., and Hu, M.C. Racial/Ethnic Differences in Cigarette Smoking Initiation and Progression to Daily Smoking: A Multilevel Analysis. American Journal of Public Health, 94, pp. 128-135, 2004.

Substance Abusers' Parenting and Their Children's Externalizing Problems

This study examined associations between substance abusers' (N= 261) parenting and their children's (N=399) rule-breaking, aggressive, and oppositional behavior, and attention problems. Findings suggest that parent monitoring predicted rule-breaking behavior and use of inconsistent discipline predicted ratings of all measured externalizing syndromes (rule-breaking, aggressive/oppositional behavior, and attention problems). Stanger, C., Dumenci, L., Kamon, J. and Burstein, M. Parenting and Children's Externalizing Problems in Substance-Abusing Families. Journal of Clinical Child and Adolescent Psychology, 33, pp. 590-600, 2004.

Trajectories of Substance Use and Dependence from Adolescence to Adulthood

This study describes trajectories of substance use and dependence from adolescence to adulthood. The participants were from a large existing sample from an ongoing study of parental alcoholism. The first assessment occurred when the age of participants ranged from 10.5 to 15.5 years. The follow-up assessments occurred 8

years later when participants were in emerging adulthood. Results suggest that a trajectory of heavy alcohol and drug use was most likely to result in substance dependence and was associated with familial alcoholism and lack of constraint. A trajectory of moderate alcohol use and experimental drug use was associated with some risk for alcohol dependence, although it was less likely to result in comorbid or persistent disorders and had a weaker link with familial alcoholism and personality risk. Chassin, L., Flora, D.B. and King, K.M. Trajectories of Alcohol and Drug Use and Dependence from Adolescence to Adulthood: The Effects of Familial Alcoholism and Personality. Journal of Abnormal Psychology, 113, pp. 483-498, 2004.

Parent Support, Peer Support and Adolescent Substance Use

Using a multi-ethnic sample of adolescents, this study tested comparative effects of parent and peer support (confiding and emotional) on adolescent substance use with data from two assessment points. Results suggest parent support was inversely related to substance use and peer support was positively related to substance use (suppression effect). Effects were mediated through pathways involving self-control and risk-taking tendency. Wills, T.A., Resko, J.A., Ainette, M.G. and Mendoza, D. Role of Parent Support and Peer Support in Adolescent Substance Use: A Test of Mediated Effects. Psychol Addict Behav., 18, pp. 122-134, 2004.

Behavioral Undercontrol and Parenting

This study examined the associations among parental alcoholism, behavioral undercontrol, and parenting in the development of drug use disorders in emerging adulthood. Findings suggest that parental alcoholism is associated with less parental discipline and more adolescent behavioral undercontrol, which in turn raises the risk of later drug disorders. Parent support has a protective buffering effect on the link between undercontrol and drug use disorders, except in cases of high levels of behavioral undercontrol. King, K.M., and Chassin, L. Mediating and Moderating Effects of Adolescent Behavioral Undercontrol and Parenting in the Prediction of Drug Use Disorders in Emerging Adulthood. Psychology of Addictive Behaviors, 18, pp. 239-249, 2004.

Antisocial Parental Behavior, Problematic Parenting and Aggressive Offspring Behaviour During Adulthood

Data from a 25-year community-based prospective longitudinal study were used to investigate the role of problematic parenting in the association between a history of antisocial parental behavior and subsequent offspring aggression during adulthood. Parents with a history of antisocial behavior were significantly more likely than other parents to engage in two or more types of problematic child-rearing behavior. Problematic parenting was associated with offspring aggression during adulthood after a history of antisocial parental behavior was controlled statistically. Antisocial parental behavior was associated with aggressive offspring behavior during adulthood before, but not after, problematic parenting was controlled. These findings support the hypothesis that problematic parenting tends to mediate the association between antisocial parental behavior and subsequent offspring aggression. Johnson, J.G., Smailes, E.M., Cohen, P., Kasen, S., and Brook, J.S. Antisocial Parental Behavior, Problematic Parenting and Aggressive Offspring Behaviour During Adulthood: A 25-year Longitudinal Investigation. British Journal of Criminology Advance Access http://bjc.oupjournals.org doi:10.1093/bjc/ azh041 published June 7, 1-16 pp. 2004.

Surveillance of Drug Use among American Indian Adolescents

This study examined the trends in drug use among American Indian adolescents attending schools on, or near, Indian reservations in the United States, to provide comparisons with non-Indian youth, and to discuss implications for prevention. Reliable and valid school administered drug use surveys have been given every year for 25 years (1975-2000) to representative samples of Indian youth living on reservations, yielding a continuous record of trends in drug use. Comparisons are made with non-Indian youth with data from the Monitoring the Future project. Data were analyzed to obtain measures of lifetime prevalence ("ever tried a drug"), use in the last 30 days, and proportions at high risk and at moderate risk from their drug use. Comparisons utilized difference in proportion tests. Results showed that, from 1975 to 2000, reservation Indian youth show elevated levels of drug use for most illicit drugs compared with non-Indian youth. Despite higher levels of use, the trends showing increases and decreases in use over time mirror those shown by non-Indian youth. Indian youth who use drugs can be divided into moderate and high levels of use. The number of youth in the moderate category varies over time whereas the number in the high category remains relatively constant. These findings indicate a

clear need for intensive efforts to reduce the levels of drug use among Indian youth. Although interventions must be tailored to the social and cultural milieu of Indian reservations, the rates of use vary over time in the same pattern as seen for non-Indian youth. Further, interventions must address the differing characteristics of high and moderate risk users of drugs. Beauvais, F., Jumper-Thurman, P., Helm, H., Plested, B. and Burnside, M. Surveillance of Drug Use among American Indian Adolescents: Patterns Over 25 Years. J Adolesc Health, 34, pp. 493-500, 2004.

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Research Findings - Prevention Ressearch

School-Based Drug Abuse Prevention Program on Adolescent Risky Driving

To determine whether a large-scale randomized trial of a school-based drug abuse prevention program during junior high school led to less risky driving among high school students, researchers examined Department of Motor Vehicles data including the total number of violations on students' driving records as well as the number of "points" that indicate the frequency and severity of the violations. Controlling for gender and alcohol use, students who received the drug prevention program during junior high school were less likely to have violations and points on their driving records relative to control group participants that did not receive the prevention program. Anti-drinking attitudes mediated the effect of the intervention on driving violations but not points. These results suggest that the behavioral effects of competence-enhancement prevention programs can extend to risk behaviors beyond the initial focus of the intervention, such as risky driving. Griffin, K.W., Botvin, G.J. and Nichols, T.R. Long-Term Follow-Up Effects of a School-Based Drug Abuse Prevention Program on Adolescent Risky Driving. Prevention Science, 5(3), pp. 207-212, 2004.

Preventing Substance Use and Disordered Eating

This article assesses the efficacy of a school-based, sport team-centered program to prevent young female high school athletes' disordered eating and body-shaping drug abuse. The ATHENA (Athletes Targeting Healthy Exercise and Nutrition Alternative) curriculum's 8 weekly 45-minute sessions were incorporated into a team's usual practice activities. Content was gender-specific, peer-led, and explicitly scripted. Experimental athletes reported significantly less ongoing and new use of diet pills and less new use of athletic-enhancing substances (amphetamines, anabolic steroids, and sport supplements). Other health-harming actions were also reduced (e.g., riding with an alcohol-consuming driver, failure to use seat belts, and new sexual activity). ATHENA athletes had positive changes in strength-training, self-efficacy and healthy eating behaviors. Thus, sport teams are effective natural vehicles for gender-specific, peer-led curricula to promote healthy lifestyles and to deter disordered eating, athletic-enhancing substance use, and other health-harming behaviors. Elliot, D.L., Goldberg, L., Moe, E.L., DeFrancesco, C.A., Durham, M.B., and Hix-Small, H. Preventing Substance Use and Disordered Eating: Initial Outcomes of the ATHENA (Athletes Targeting Health Exercise and Nutrition Alternatives) Program. Archives of Pediatric Adolescent Medicine, 158, pp. 1043-1049, 2004.

Two Prevention Programs Reduce High Risk Behaviors Among African American Boys

This study was designed to test the efficacy of two programs to reduce high-risk behaviors, including drug use, delinquency, and high risk sexual behavior, among inner-city African-American youth. Students in grades 5 through 8 and their parents and teachers in twelve metropolitan Chicago schools were involved in a cluster randomized trial. The preventive interventions being tested were 1) a social development curriculum, focusing on social competence skills, and 2) a school/community intervention, consisting of the social development curriculum plus a school-wide climate and parent/community intervention. The control group received an attention-placebo. For boys, both programs significantly reduced violent behavior, provoking behavior, school delinquency, drug use, and recent sexual intercourse. The rate of condom use was increased among boys as well. The school/community intervention was significantly more effective than the curriculum-only intervention in

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reducing risk based on examination of a combined behavioral measure. There were no significant effects for girls. Flay, B.R., Gramlich, S., Segawa, E., Burns, J.L., and Holliday, M.Y. Effects of Two Prevention Programs on High Risk Behaviors among African American Youth. Archives of Pediatric and Adolescent Medicine, 158, pp. 377-384, 2004.

One-Year Outcomes of The Coping Power Program

The Coping Power Program randomly assigned at-risk aggressive preadolescent boys during the transition from elementary school to middle school to receive the Coping Power child component, the Coping Power Program parent and child components, or a control condition. Results indicated that both Coping Power intervention conditions produced lower rates of covert delinquent behavior and of parent-rated substance use at the 1-year follow-up compared to the control group. Moreover, the intervention effects were most apparent for the combined Coping Power Program parent and child components. Boys also displayed teacher-rated behavioral improvements in school during the follow-up year, and these effects appeared to be primarily influenced by the Coping Power child component. Lochman, J.E. and Wells, K.C. The Coping Power Program for Preadolescent Aggressive Boys and Their Parents: Outcome Effects at the 1-Year Follow-Up. Journal of Consulting and Clinical Psychology, 72(4), pp. 571-578, 2004.

Comparison of Telephone and In-Person Delivery of Prevention

This study assesses responses to a preventive intervention to reduce HIV risky behaviors and health practices among young people living with HIV (YPLH) in Los Angeles, San Francisco, and New York over 15 months. YPLH aged 16 to 29 years (n = 175; 26% black and 42% Latino; 69% gay men) were randomly assigned to a 3-module intervention involving 18 sessions delivered by telephone, in person, or a delayed-intervention condition. Intention-to-treat analyses found that the in-person intervention resulted in a significantly higher proportion of sexual acts protected by condoms both overall and with HIV-seronegative partners. Pre- and post-analyses of YPLH in the delayed-intervention condition alone found that YPLH tended to have fewer sexual partners, used fewer drugs, reported less emotional distress, and decreased their use of antiretroviral therapies. Prevention programs can be delivered in alternative formats while retaining efficacy. However, when YPLH are using hard drugs, drug treatment may be needed before delivery of preventive interventions. Rotheram-Borus, M.J., Swendeman, D., Comulada, W.S., Weiss, R.E., Lee, M. and Lightfoot, M. Prevention for Substance-Using HIV-Positive Young People: Telephone and In-Person Delivery. JAIDS, 37 (Suppl 2), pp. S68-S77, 2004.

School District Personnel Hold the Keys to Implementation of Effective Prevention

An important issue in drug abuse prevention programming is the relative roles of school district and school-level decision-makers in the implementation of effective substance use prevention curricula. Drawing on a "Site-Based Management" approach to effective decision-making, it was hypothesized that schools whose personnel played active decision-making roles would be more likely to implement effective curricula than those in which decision-making was the prerogative of school district personnel. Study data comprised 1,369 questionnaires completed by a representative national sample of both district-level prevention coordinators and middle school-based lead prevention teachers. From the perspective of the lead prevention teachers, the school district-level prevention coordinator was more influential than school staff in selecting effective prevention curricula. However, they did find some support for their hypothesis from the district-level informants, who indicated that community groups and advisory committees also play a modest role in the selection of such curricula. Ringwalt, C., Ennett, S.T., Vincus, A., Rohrbach, L.A. and Simons-Rudolph, A. Who's Calling the Shots?: Decision-Makers and the Adoption of Effective School-Based Substance Use Prevention Curricula. Journal of Drug Education, 34(1), pp. 19-31, 2004.

Adapting Prevention to Meet Student Needs

This study examines a variety of characteristics associated with schools, teachers, and the prevention curricula implemented to estimate the proportion of the nation's middle school teachers who adapt substance abuse curricula in response to their students' special problems or needs. Data were collected in 1999 from a representative sample of lead substance abuse prevention teachers in the nation's public and private schools. Almost 80% of respondents report adapting their prevention curricula in response to at least one of the dozen specified student

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problems and needs. The problems cited most frequently, (over 50% of respondents) were the needs of students who are sexually active or have discipline problems. The two features associated most strongly with adaptations were the recent training of the teacher in the curricula, and substance abuse prevention lessons that could readily be integrated into the school's overall curriculum. Curriculum developers need to recognize the frequency with which, and reasons for curriculum adaptation and include appropriate optional content that addresses students' needs. Ringwalt, C., Ennett, S.T., Vincus, A. and Simons-Rudolph, A. Students' Special Needs and Problems as Reason for the Adaptation of Substance Abuse Prevention Curricula in the Nation's Middle Schools. Prevention Science, 5(3), pp. 197-206, 2004.

Training Youth to Use Leisure Time Wisely Works

The ÔTimeWise: Learning Lifelong Leisure Skills' curriculum aims to increase positive use of free time, thereby mitigating/preventing the initiation of substance use. The intervention was delivered to 634 middle school youth in a rural area in eastern United States. Self-report data after one year indicate that students who received TimeWise reported less lack of motivation and more identified and subconscious forms of motivation. TimeWise students reported being better able to restructure boring situations into something more interesting; having higher levels of decision making skills, initiative, community awareness; and participating in new interests, sports, and nature-based activities. Caldwell, L.L., Baldwin, C.K., Walls, T., and Smith, E. Preliminary Effects of a Leisure Education Program to Promote Healthy Use of Free Time. Journal of Leisure Research, 36(3), pp. 310-335, 2004.

Effects of Dosage on Outcomes

The present study assessed the ability of the Early Risers "Skills for Success" program to maintain program effects one year post intervention. Participants were kindergarten and first grade children (N=327) who screened positive for aggressive behavior and were randomized to program and control conditions. Program children participated in two continuous years of active intervention followed by one year of no formal intervention activities. Following the active intervention phase, program children, compared to controls, showed significant gains in school adjustment and social competence, but not in academic achievement. At the one-year follow-up program effects were not maintained using intent-to-intervene analyses. Level-of-dosage analyses, however, revealed that there were significant relationships between children's level of participation and measures of their social competence, externalizing problems, and academic achievement. August, G.J., Lee, S.S., Bloomquist, M.L., Realmuto, G.M., and Hektner, J.M. Maintenance Effects of an Evidence-Based Prevention Innovation for Aggressive Children Living in Culturally Diverse, Urban Neighborhoods: The Early Risers Effectiveness Study. Journal of Emotional and Behavioral Disorders, 12(4), 2004.

Early Intervention Reduces Marijuana Use and Psychopathology in Recent Rape Victims

Nearly 700,000 adult women are raped annually although only one in seven reports the assault to police and receive forensic exams and other professional services. The forensic exam, nevertheless, provides a unique opportunity for a preventive intervention to aid women to cope with potential stress related to the rape-exam procedures and address potential post-rape psychopathology. The intervention implemented with 205 adolescent and adult (15 years and older) female rape victims involved a 17-minute videotape that both explains the forensic exam procedures and uses a cognitive-behavioral approach to reduce anxiety and subsequent PTSD versus standard post-rape treatment control. Sixty percent of the women provided 6-week follow up data. Results indicate that at 6-weeks post exam marijuana use was significantly lower in the video intervention group but that there were no significant differences in rates of abusing alcohol or other drugs. The data also found that the video intervention helped women with a prior assault more than those with no prior assault. Resnick, H., Acierno, R., Kilpatrick, D.G. and Holmes, M. Description of an Early Intervention to Prevent Substance Abuse and Psychopathology in Recent Rape Victims. Behavior Modification, 29(1), pp. 1-33, 2005.

Teaching Theory of Drug Action to Elementary School Children

Recent educational and developmental research suggests that children attempt from an early age to understand the world around them by formulating intuitive theories. The current investigation builds on this literature by examining (1) whether school-age children as young as 8 can learn a theory of drug action that explains the brain's role in mediating drug effects, and (2) whether a causally coherent version of the

curriculum is more effective than a less coherent one in changing knowledge and beliefs about alcohol and drug effects, attitudes and intentions toward drug and alcohol use, and actual alcohol use over one year. Participants were 327 grade 3-6 students drawn from 17 classrooms in 3 Catholic schools in an ethnically diverse metropolitan area. Participating schools were chosen on the basis of their socioeconomic and racial diversity. Within each classroom students were randomly assigned to one of 3 groups each of which received one of three curricula developed for this project. Two curricula concerned alcohol and cocaine, and were administered to 110 students each, while the third, a control curriculum about diseases, was administered to 107 children. The "coherent curriculum" was designed to teach the elements of a scientific, brain-mediated theory of drug effects in a causally coherent sequence. The "less coherent curriculum" presented information identical to that in the coherent version; however, sections of the text were reordered so that the consequences of drug use for health and behavior were discussed before the drug's effects. Few differences were found between the two drug and alcohol curricula. However, compared to children receiving the control curriculum both treatment groups demonstrated greater understanding of the circulation of alcohol and cocaine throughout the body, the true long-term effects of these substances, and the stimulant effects of cocaine. Moreover, they had less positive attitudes and intentions toward cocaine. Sigelman, C. K., Rinehart, C. S., Sorongon, A. G., Bridges, L. J., and Wirtz, P. W. Teaching a Coherent Theory of Drug Action to Elementary School Children. Health Education Research, 19, pp. 501-513, 2004.

Infusion-LST Compared to LST as Usual

Findings from the first two years of a study to compare a standard Life Skills Training (LST) program with an infused (I-LST) approach was conducted in 9 small, rural school districts that were randomly assigned to LST, I-LST, or control conditions. Male and female subjects were in grade seven. The LST program significantly reduced alcohol use, binge drinking, marijuana use, and inhalant use after one year for females, and the I-LST program significantly reduced smoking, binge drinking, and marijuana use for females. At the end of the second year the I-LST program continued to impact female smoking, but all other results were non-significant. There were no effects on males at either time point. Smith, E.A. Evaluation of Life Skills Training and Infused-Life Skills Training in a Rural Setting: Outcomes at Two Years. Journal of Alcohol & Drug Education, 48(1), pp. 51-70, 2004.

Cost Comparison of LST and Infusion-LST

A cost-effectiveness comparison of the Life Skills Training (LST) to a LST curriculum infusion approach (I-LST) was conducted. Male and female seventh graders from nine rural schools (2 intervention conditions and control) were followed for two years. After one year, significant effects were observed only for females on alcohol, marijuana, and inhalant use in LST condition and for tobacco, alcohol, and marijuana use for I-LST females. After year two, only the I-LST program affected female smoking. Cost calculations for the two programs included expenditures for training and materials and estimates of teachers' salaries for the project period. Both programs were almost equally effective after one year, but LST was more cost-effective. I-LST cost more to implement, but sustained effects into year two and was therefore more cost-effective overall. Swisher, J. D. A Cost-Effectiveness Comparison of Two Approaches to Life Skills Training. Journal of Alcohol & Drug Education, 48(1) pp. 71-78, 2004.

The Importance of Family-based Prevention Interventions in Rural Areas

There are several reasons to promote the implementation of evidence-based family-focused interventions in rural, small town or micropolitan communities. One key reason is research demonstrating that youth problem behaviors are especially prevalent in rural areas and that these problems can be effectively reduced though family-focused programs. For example, studies have found that rural youth are involved in tobacco, alcohol, and illegal substance use at rates that often exceed those of youth living in urban and suburban communities (America's Children, 2000ÑFederal Interagency Forum on Child and Family Statistics, 2000; National Institute on Drug Abuse, 1997; Johnston, O'Malley, & Bachman, 2000, 2002). Further, earlier program evaluation research has demonstrated the effectiveness of several evidence-based family-focused programs among rural youth, including the reduction of substance use; related economic analyses also have shown that these programs are cost-beneficial. These programs focus on the enhancement of competencies related to reducing risk and increasing protective factors among families and youth. Meek, J., Lillehoj, C.J., Welsh, J. and Spoth, R. Rural Community Partnership Recruitment for an Evidence-based Family-focused Prevention Program: The PROSPER Project, Rural Mental Health, 29(2), pp. 23-28, 2004.

Predicting Marijuana Use Cessation 5 years after Continuation High School

Cessation from marijuana use five years after completion of continuation high school was predicted by social, attitude, intrapersonal, violence-related, drug use, and demographic baseline measures from 339 high risk teenage marijuana users. Young adult social roles were included as additional predictors. Quitting was defined as no use of marijuana in the last 30 days (42% of the sample at follow-up). Results indicate that baseline level of marijuana use, male gender, young adult marital status, and friends' marijuana use (marginal) remained significant direct predictors of quitting. These results suggest the need to reduce psychological dependence on marijuana and increase social unacceptability of marijuana use across genders to increase prevalence of quit attempts. Sussman, S. and Dent, C.W. Five-Year Prospective Prediction of Marijuana Use Cessation of Youth at Continuation High Schools. Addictive Behaviors, 29(6), pp. 1237-1243, 2004.

The Long-Term Negative Impact of High-Risk Peer Group Affiliations

Adolescents' self-identified peer group affiliation is associated with health risk behaviors such as involvement in substance use and violence. This prospective study examined the association between peer group self-identification during high school and psychosocial functioning five years later among a sample of continuation high school students (i.e., students attending alternative public schools). Participants were recruited as part of Project TND, a substance use prevention project conducted in 21 school districts from a five-county region of Southern California. The sample included 532 students, ranging in age from 19 to 24 years most of whom were male (57%) and half were Latino (50%). Participants named the peer group which they felt "most a part of." Responses were collapsed into four general group categories: high-risk youth, jocks-hotshots, regulars, and others. Results indicated that students who self-identified with high-risk peer groups while in continuation high school were most likely to report involvement in drug use and violence during young adulthood, and they were significantly less likely to have graduated from high school or secure stable employment. Sussman, S., Unger, J.B. and Dent, C.W. Peer Group Self-Identification among Alternative High School Youth: A Predictor of Their Psychosocial Functioning Five Years Later. International Journal of Clinical and Health Psychology, 4, pp. 9-25, 2004.

Links Found between Risk-Taking and Aggressive Behavior

This study examined the relationship between risk-taking, general acceptance of aggression, verbal harassment, and aggressive behavior in 7th and 8th grade middle school youth (N=1,440). Results indicated that higher levels of risk-taking predicted higher general acceptance of aggression and verbal harassment. There also was an interaction for aggressive behavior which indicated that except for African American youth, higher risk-taking was related to higher levels of violent behavior; for African American youth the highest levels of aggressive behavior occurred at moderate levels of risk-taking. Thus, the level of risk-taking is an important risk factor that needs to be taken into account both for attitudes toward aggression and aggressive behavior among rural youth. Swaim, R.C., Henry, K.L. and Baez, N.E. Risk-taking, Attitudes toward Aggression, and Aggressive Behavior among Rural Middle School Youth. Violence & Victims, 19, pp. 157-170, 2004.

Adolescent Depression and Suicide Risk Are Associated with Sex and Drug Use Behavior

Although both depression and suicide in adolescents have been associated with drug use and early sexual intercourse, the relationship has not been systematically studied in a nationally representative sample. Sixteen patterns of combined sex and drug use behaviors were obtained through analysis of responses to Wave I of the National Longitudinal Study of Adolescent Health conducted from September 1994 through December 1995. Analyses tested correlations between behavior patterns and current depression, serious suicidal ideation, and previous suicide attempt, controlling for gender, race/ethnicity, family structure, and parent education. Compared to youth who abstain from risk behaviors, involvement in any drinking, smoking, and/or sexual activity was associated with significantly increased chances of depression, suicidal ideation, and suicide attempts. These problems were highest among youth who engaged in illegal drug use. There were few differences between boys and girls who abstain from sex and drug behaviors. Girls were less likely than boys to engage in high-risk behaviors, but those who did tended to be more vulnerable to depression, suicidal ideation, and suicide attempt. Hallfors, D.D., Waller, M.W., Ford, C.A., Halpern, C.T., Brodish, P.H., and Iritani, B. Adolescent Depression and Suicide Risk - Association with Sex and Drug Behavior. Am J of Preventive Med., 27(3), pp. 224-

231, 2004.

Early Screening is Effective for Externalizing Problems

Accurate early screening is a prerequisite for indicated interventions intended to prevent development of externalizing disorders and delinquent behaviors. Using data from the Fast Track longitudinal sample of 396 children from high-risk environments, assumptions about base rates were varied to examine effects of multiple-time-point and multiple-rater screening procedures, and considered the practical import of various levels of screening accuracy in terms of true and false positive rates and their potential costs and benefits. The results indicate that 1st grade single- and multiple-rater screening models effectively predicted externalizing behavior and delinquent outcomes in 4th and 5th grades. Thus while additional research is needed to determine true costs and benefits of early screening, early screening is justified. Hill, L.G., Lochman, J.E., Coie, J.D. and Greenberg, M.T. Effectiveness of Early Screening for Externalizing Problems: Issues of Screening Accuracy and Utility. Journal of Consulting and Clinical Psychology, 72(5), pp. 809-820, 2004.

Effects of Good Inhibitory Control on Negative Emotions and Alcohol Use

Studies on the relation between negative affect and later alcohol use have provided mixed results. To disentangle the diverse elements of negative affect and explain these inconsistent findings some have examined the moderating role of good inhibitory control. This longitudinal investigation examined the independent relationships between three components of negative affect (i.e., depressed mood, fear, and anger) and alcohol use initiation in a sample of aggressive boys, as well as the moderating effect of good inhibitory control. Increased anger and decreased fearfulness were associated with an increased risk for alcohol use initiation only for boys with moderate to low levels of inhibitory control. However, depressed mood predicted alcohol use initiation for boys with good inhibitory control. Pardini, D., Lochman, J. and Wells, K. Negative Emotions and Alcohol Use Initiation in High-Risk Boys: The Moderating Effect of Good Inhibitory Control. Journal of Abnormal Child Psychology, 32(5), pp. 505-518, 2004.

Prediction of Violence Perpetration Among High-Risk Youth

A prospective study examined predictors of violence perpetration in emerging adulthood among high-risk adolescents using problem-behavior theory as a conceptual perspective and self-reported responses to questionnaires administered 5 years apart to 676 participants. Hard drug use, belief that hurting another's property while drunk was acceptable and high-risk group self-identification predicted later violence perpetration independent of baseline violence perpetration. Consistent with problem-behavior theory, personality, perceived environment, and behavior characteristics, beyond baseline violent behavior, predict risk for future violence perpetration in emerging adulthood; the effects of demographic variables are at best indirect. Sussman, S., Skara, S., Weiner, M.D., and Dent, C.W. Prediction of Violence Perpetration Among High-Risk Youth. American Journal of Health Behavior, 28(2), pp. 134-144, 2004.

Drug Use may be Mediated through Low Hostile Anger Control

The relationships among selected predictors of violence, including victimization, low conflict management efficacy, hostile anger and drug use were examined using data on 8th-, 10th-, and 12th-grade adolescents. The secondary analysis used a population-based, cross-sectional survey of health behaviors (N = 3,922). For each grade cohort, it was hypothesized that victimization and low conflict management efficacy would predict low hostile anger control, which would predict gateway drug use, and the subsequent development of hard drug use and violence. Overall model fit and the magnitude of specific paths were expected to increase across grades. Using structural equation modeling (SEM), results indicated acceptable model fit for 8th-grade (CFI = .95), 10th-grade (CFI = .93) and 12th-grade (CFI = .94) cohorts. Results suggest that the influence of relational victimization and conflict management efficacy on hard drug use may be mediated through low hostile anger control and gateway drug use. Weiner, M.D., Pentz, M.A., Skara, S.N., Li, C., Chou, C.P. and Dwyer, J.H. Relationship of Substance Use and Associated Predictors of Violence in Early, Middle, and Late Adolescence. Journal of Child & Adolescent Substance Abuse, 13(4), pp. 97-117, 2004.

Perceived Life Chances and Alcohol Use

The relationship between low perceived chances for success in life and binge drinking was examined in a sample of economically disadvantaged, predominantly black and

Hispanic student, urban adolescents (N = 774) from 13 inner-city schools. Subjects completed confidential questionnaires in the 7th, 8th, and 9th grades. Eight items measured students' estimation of achieving certain adaptive life goals. Students who reported that they typically drink five or more drinks per drinking occasion were identified as binge drinkers. Results indicated that rates of binge drinking increased and perceived life chances decreased for both boys and girls from the 7th to 9th grade. Moreover, higher perceived life chances in the 7th grade predicted less binge drinking in the 8th grade, whereas binge drinking in the 8th grade predicted lower perceived life chances in the 9th grade, controlling for change over time in both variables. Griffin, K.W., Botvin, G.J., Nichols, T.R. and Scheier, L.M. Low Perceived Chances for Success in Life and Binge Drinking among Inner-city Minority Youth. Journal of Adolescent Health, 34, pp. 501-507, 2004.

Self-esteem and Alcohol Use

Prior studies have found inconsistent relationships between measures of self-concept and adolescent alcohol use. This study explored whether the link between various measures of self-concept and alcohol use depends on gender and whether negative rather than positive self-esteem (i.e., self-derogation) might be more useful in predicting alcohol use. Students (N = 1459) attending 22 middle and junior high schools in New York City completed surveys that included measures of efficacy, self-derogation, and alcohol use. Participants completed surveys at baseline, 1-year follow-up, and 2-year follow-up. Findings indicate that lower efficacy was related to greater self-derogation a year later across gender. Increased self-derogation predicted higher alcohol use for girls but not boys. These findings are congruent with a literature highlighting the importance of negative thoughts about the self in drinking behavior for women but not men. Epstein, J.A., Griffin, K.W. and Botvin, G.J. Efficacy, Self-derogation, and Alcohol Use among Inner-city Adolescents: Gender Matters. Journal of Youth & Adolescence, 33, pp. 159-166, 2004.

Influence of Parents on Child Anti-social Behavior

This study examined the unique influence of mothers and fathers on their children's antisocial behavior using a sample of 325 families with sixth grade children. Multiple-group comparisons were conducted to identify differences in the relationships for mothers and fathers with daughters versus sons. Results suggested that, while the relationships were often similar for both parents and for both daughters and sons, mothers and fathers uniquely influenced their child's antisocial behavior depending on the child's gender. Overall, cross-gender influence appeared to be particularly important for fathers' control of their daughters' antisocial behavior. Kosterman, R., Haggerty, K.P., Spoth, R. and Redmond, C. Unique Influence of Mothers and Fathers on their Children's Antisocial Behavior: A Social Development Perspective. Journal of Marriage and Family, 66(3), pp. 762-778, 2004.

Does Perception of Behavior Affect Behavior?

This research examined whether parents' and children's perceptions have reciprocal self-fulfilling prophecy effects on each others' behavior. Mothers, fathers, and their adolescent children completed self-report surveys and engaged in videotaped dyadic interaction tasks. The surveys assessed parents' and children's perceptions of their own and the other's typical hostility and warmth. Observers coded the videotaped interactions to assess the actual hostility and warmth exhibited by mothers, fathers, and children. Data from 658 mother-child dyads were consistent with the conclusion that children had a self-fulfilling effect on their mothers' hostile behavior, but that mothers did not have a reciprocal self-fulfilling effect on their children's hostility. The data did not support the existence of self-fulfilling prophecies among the mother-child dyads with respect to warmth, or among the 576 father-child dyads for either the hostility- or warmth-relevant data. Madon, S., Guyll, M. and Spoth, R. The Self-fulfilling Prophecy as an Intra-family Dynamic, Journal of Family Psychology, 18(3), pp. 459-469, 2004.

Parent Disengagement and Deviant Peers Lead to Premature Adolescent Autonomy

Premature autonomy describes a developmental dynamic where parents of high-risk adolescents reduce their involvement and guidance when confronted with challenges of problem behavior and the influence of deviant friendships. This dynamic was tested on the sample of Oregon Youth Study boys (N = 206), whose family management practices and friendships were observed on videotaped interaction tasks. Latent growth curve modeling identified longitudinal trends between deviant friendship interactions and family management. Direct observations of deviant friendship

process at age 14 were associated with degradation in family management during adolescence. A comparison of antisocial and well-adjusted boys clarified the observation that the parents of antisocial boys began early (i.e., around puberty) and continued to decrease family management compared to parents of well-adjusted boys who maintained high levels of family management through adolescence. In predicting late adolescent problem behavior, there was a statistically reliable interaction between family management degradation and deviant peer involvement in adolescence that supported the premature autonomy hypothesis. Those adolescent males who were involved in deviant friendships and whose parents decreased their family management were most likely to use marijuana and commit antisocial acts at age 18. This suggests developing preventive interventions to arrest the parent disengagement processes during the child's early adolescence. Dishion, T.J., Nelson, S.E. and Bullock, B.M. Premature Adolescent Autonomy: Parent Disengagement and Deviant Peer Process in the Amplification of Problem Behaviour. Journal of Adolescence, 27(5), pp. 515-530, 2004.

Ethnic Identity is Central to Success in Adolescents

This research studied the role of ethnic identity as a protective factor among European American (n = 77) and African American (n = 82) adolescents identified either as high risk or successful. Adolescents participated in a multi-method assessment of depression, internalizing and externalizing behaviors, competence, and academic achievement. The levels of ethnic identity were the same across ethnic groups but were higher among successful adolescents. Bivariate correlations revealed that ethnic identity was significantly associated with all measures of adjustment in the expected directions. As predicted, the associations between ethnicity and depression, total competence, and GPA were statistically higher among African American youth than for European Americans. Similar associations were found when comparing ethnic identity to a construct of socioeconomic disadvantage. These findings suggest that ethnic identity is central to the self-system and motivation for youth who develop in contexts that potentially undermine children's socioemotional adjustment. Yasui, M., Dorham, C.L., and Dishion, T.J. Ethnic Identity and Psychological Adjustment: A Validity Analysis for European American and African American Adolescents. Journal of Adolescent Research, 19(6), pp. 807-825, 2004.

Early Identifiers of Later Risk for Depression

This study examined childhood behavior problems at ages 10 and 11 years as predictors of young adult depression, social phobia, and violence at age 21 years. Data were collected on 808 elementary school students from high-crime neighborhoods of Seattle. Reports of childhood behavior problems were obtained from parents and children in fall 1985 and from teachers in spring 1986. Follow-up reports of violence and DSM-III-R depression and social phobia were collected from 765 respondents using standard survey items and the Diagnostic Interview Schedule in 1996. The past-year prevalence of depressive episodes and social phobias were 20% and 17%, respectively. Several available measures of childhood behavior problems as reported by parents, teachers, and children predicted violence; the strongest positive predictor of young adult violence was self-reported conduct problems, whereas self-reported shyness inhibited later violence. Relatively few child behavioral problems predicted social phobia. Results showed that children who reported higher, relative to lower, levels of conduct problems were nearly four times more likely to experience a depressive episode in early adulthood. Mason, W.A., Kosterman, R., Hawkins, J.D., Herrenkohl, T.I., Lengua, L.J. and McCauley, E. Predicting Depression, Social Phobia, and Violence in Early Adulthood from Childhood Behavior Problems, Journal of the American Academy of Child Psychiatry, 43(3), pp. 307-315, 2004.

A Nonverbal Test of Memory for Alcohol Commercials

There is suggestive evidence that televised alcohol commercials may affect the alcohol consumption of adolescents. However, it has been difficult to assess exposure to and memory of such ads because these complex everyday occurrences have numerous nonverbal, visual features that may not be completely assessed by eliciting verbal responses to them. This study investigated a nonverbal test of memory for alcohol commercials. Participants included 750 adolescents from 6 public middle and 3 public high schools who completed a nonverbal test of memory, tailored to detect prominent visual features of remembered alcohol ads. The results showed that independent judges reliably coded primary features of remembered advertisements along most dimensions, and the test met important criteria for validity in comparisons with other measures. Stacy, A.W., Pearce, S.G., Zogg, J.B., Unger, J., and Dent, C.W. A Nonverbal Test of Naturalistic Memory for Alcohol Commercials. Psychology and Marketing, 21, pp. 295-322, 2004.

Using Virtual Reality to Assess Adolescents' Social Competency

Over the decades many interventions have been aimed at improving adolescents' social competency skills in order to affect outcomes such as interpersonal violence and substance abuse. However, assessment of these skills has been limited to self-ratings or external ratings by teachers and parents and archival records. Responsive virtual human (RVH) technology is a rapidly advancing method for assessing technical and social competency skills. By allowing individuals to engage in seemingly real verbal discourse with virtual characters they are afforded a more realistic social encounter than less interactive paper or computer-based assessments. This study examined the psychometric properties of performance measures for three novel, interactive virtual reality vignette exercises developed to assess social competency skills of at-risk adolescents. Data for 18 performance measures were collected from 117 African-American male 15-17 year olds based on their interactions with a provocative virtual teenage character. Twelve of the 18 performance measures loaded on two factors corresponding to emotional control and interpersonal communication skills, providing support for their factorial validity. Overall, the study findings suggest that the virtual reality vignette exercises may represent a promising approach for assessing adolescents' social competency skills in the context of prevention research. Paschall, M.J., Fishbein, D.H., Hubal, R.C. and Eldreth, D. Psychometric Properties of Virtual Reality Vignette Performance Measures: A Novel Approach for Assessing Adolescents' Social Competency Skills. Health Education Research, 1-10, Advance Access published July 14, 2004.

Operationalizing and Analyzing Media Exposure

The ability of researchers to empirically test theories of media effects and to assess impact of communication campaigns depends on their ability to identify levels of exposure to the media or messages of interest. This paper critically examines strategies used to operationalize and analyze exposure, including some exposures which have not yet been widely used in the communication field. As communication research matures longitudinal designs and field experiments are necessary. In the realm of media campaigns rolling cross-sections and time series analyses also offer researchers the opportunity to evaluate campaign effects with precision previously unattainable and cross-over designs may increase the viability of quasi-experimental studies as approaches preferable to the more traditional cross-sectional surveys and small-scale experiments. Slater M.D., Operationalizing and Analyzing Exposure: The Foundation of Media Effects Research. Journalism & Mass Communication Quarterly, 81(1), pp. 168-183, Spring 2004.

Sensation Seeking, Alienation, and Victimization Moderate the Violent Media Content-Aggressiveness Relation

This study examines whether the relationship between teen use of violent media and aggressiveness is contingent on personality and situational variables. Concurrent effects are modeled in four waves of data from a national sample of students from 20 middle schools using multilevel analyses. Results indicate that the effect of violent media on aggression is more robust among students who report feelings of alienation from school and during times of increased peer victimization. Although overall consumption of violent media is associated with higher levels of aggression, a robust within individual effect also exists; that is, during times when a student is viewing elevated levels of violent media content relative to the student's own norms for use of such media, he or she is also more likely to demonstrate heightened levels of aggression. This relationship is more robust among students who are victimized by their peers and experiencing increased sensation seeking. Thus, socially adjusted youth may indulge in violent media content use with little risk; however, this is not the case for socially and dispositionally vulnerable teens or those going through particularly difficult times. Slater, M.D., Henry, K.L., Swaim, R.C. and Cardador, J.M. Vulnerable Teens, Vulnerable Times: How Sensation Seeking, Alienation, and Victimization Moderate the Violent Media Content-Aggressiveness Relation. Communication Research, 31, pp. 642-668, 2004.

Post-September 11 Increases in Substance Use Persist in Manhattan

Early analyses following the September 11, 2001 terrorist attacks on New York City showed an increase in cigarette, alcohol, and marijuana use. To determine whether these increases would persist, a random-digit dial phone survey was conducted to estimate the prevalence of increased substance use among residents of New York City six to nine months after the attacks. Among 1,570 adults, 9.9% reported an increase in smoking, 17.5% an increase in alcohol use, and 2.7% an increase in marijuana use compared to the month before September 11. These increases were comparable to

increases reported in the first one to two months after September 11. Persons who increased use of cigarettes were more likely than those who did not to report symptoms consistent with posttraumatic stress disorder (PTSD) in the past month (4.3% and 1.2% respectively). Depression was more common among those who increased use of cigarettes (14.6% and 5.2% respectively), alcohol (11.8% vs. 5.2%), and marijuana (34.1% vs. 5.3%). Among residents living in Manhattan below One Hundred Tenth Street, the prevalence of PTSD and depression declined by more than half in the first six months after September 11, while the increase in substance use did not decline substantially. These results suggest that the increase in substance use after a disaster may be a cause for public health concern in the long-term. Vlahov, D., Galea, S., Ahern, J., Resnick, H., Boscarino, J.A., Gold, J., Bucuvalas, M. and Kilpatrick, D. Consumption of Cigarettes, Alcohol, and Marijuana among New York City Residents Six Months After The September 11 Terrorist Attacks. American Journal of Drug and Alcohol Abuse, 30(2), pp. 385-407, 2004.

Manhattan Residents' Substance Abuse Increase Sustained After September 11 Attacks

This study compared reports of increased substance use in Manhattan 1 and 6 months after the September 11, 2001, terrorist attacks. Data from 2 random-digit-dial surveys conducted 1 and 6 months after September 11 showed that 30.8% and 27.3% of respondents, respectively, reported increased use of cigarettes, alcohol, or marijuana. These sustained increases in substance use following the September 11 terrorist attacks suggest potential long-term health consequences as a result of disasters. Vlahov, D., Galea, S., Ahern, J., Resnick, H. and Kilpatrick D. Sustained Increased Consumption Of Cigarettes, Alcohol, And Marijuana Among Manhattan Residents After September 11, 2001. American Journal of Public Health, 94(2), pp. 253-254, 2004.

Director's Report to the National Advisory Council on Drug Abuse - February, 2005

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

Extended Nortriptyline and Psychological Treatment for Cigarette Smoking

Dr. Hall and colleagues at the University of California, San Francisco, conducted a study to determine the effects of long-term antidepressant and psychological treatment for cigarette smoking. One hundred sixty smokers were randomly assigned to one of four treatment conditions in a 2 x 2 (nortriptyline vs. placebo by brief vs. extended treatment) design. All subjects received 8 weeks of a transdermal nicotine patch, five group counseling sessions, and active or placebo treatment. Interventions for subjects in brief treatment ended at this point. Subjects in extended treatment continued taking medication or placebo to week 52 and received an additional 9 monthly counseling sessions, with checkup telephone calls midway through each session. At week 52, point-prevalence abstinence rates with missing subjects imputed as smokers were 30% for placebo brief treatment, 42% for placebo extended treatment, 18% for active brief treatment, and 50% for active extended treatment. With missing subjects omitted, these rates were 32%, 57%, 21%, and 56%, respectively. Comprehensive extended treatments that combine medication and psychological interventions can produce consistent abstinence rates that are substantially higher than those in the literature. Hall, S.M., Humfleet, G.L., Reus, V.I., Munoz, R.F. and Cullen, J. American Journal of Psychiatry, 161, pp. 2100-2107, 2004.

Utilizing Virtual Reality to Standardize Nicotine Craving Research: A Pilot Study

Traditional cue reactivity provides a methodology for examining drug triggers and stimuli in laboratory and clinical settings. However, current techniques lack standardization and generalization across research settings, i.e., the cues may lack ecological validity, tend to be presented out of context, and lack standardization across setting that limit the application of cue exposure practices. Improved methodologies using virtual reality (VR) cue reactivity extend previous research standardizing exposure to stimuli and exploring reactions to drug cues in a controlled VR setting. Improved methodologies include more complex cues involving combinations of social interactions, affective experiences, and physical cues to improve treatment generalization. In a controlled pilot trial, a VR cue exposure system with nicotine-dependent cigarette smokers was tested. It was hypothesized that VR-based smoking cues would elicit increased craving compared to VR neutral cues. Thirteen nicotine-dependent participants were allowed to smoke ad libitum then exposed to VR smoking and VR neutral cues and compared on craving intensity. VR smoking cues significantly increased craving compared to VR neutral cues. On average, craving intensity increased 118% during exposure to VR smoking cues. Implications for substance abuse research and treatment using VR to assess cessation and anticraving medications are discussed. Bordnick, P.S., Graap, K.M., Copp, H., Brooks, J., Ferrer, M. and Logue, B. Addictive Behaviors, 29, pp. 1889-1894, 2004.

Review of the Validity and Significance of Cannabis Withdrawal Syndrome

The authors review the literature examining the validity and significance of cannabis withdrawal syndrome. Converging evidence from basic laboratory and clinical studies indicates that a withdrawal syndrome reliably follows discontinuation of chronic heavy use of cannabis. Common symptoms are primarily emotional and behavioral, although appetite change, weight loss, and physical discomfort are also frequently reported. The onset and time course of these symptoms appear similar to those of other substance withdrawal syndromes. The magnitude and severity of these symptoms

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appear substantial, and these findings suggest that the syndrome has clinical importance. Diagnostic criteria for cannabis withdrawal syndrome are proposed. Budney, A.J., Hughes, J.R., Moore, B.A., and Vandrey, R. American Journal of Psychiatry, 161, pp. 1967-1977, 2004.

Motivational Interviewing With Personalized Feedback: A Brief Intervention for Motivating Smokers With Schizophrenia to Seek Treatment for Tobacco Dependence

This study examined whether motivational interviewing is effective in motivating smokers with schizophrenia or schizoaffective disorder to seek tobacco dependence treatment. Participants (N=78) were randomly assigned to receive a 1-session motivational interviewing intervention (MI), standard psychoeducational counseling (1-session), or brief advice only (5 min.). As hypothesized, a greater proportion of participants receiving the MI intervention contacted a tobacco dependence treatment provider (32%, 11%, and 0%, respectively) and attended the first session of counseling (28%, 9%, and 0%) by the one month follow-up compared with those receiving comparison interventions. Steinberg, M.L., Ziedonis, D.M., Krejci, J.A. and Brandon, T.H. Journal of Consulting and Clinical Psychology, 72, pp. 723-728, 2004.

The Marijuana Check-up: Reaching Users Who Are Ambivalent about Change

A brief intervention called the Marijuana Check-up (MCU) was designed to attract adult marijuana users who were experiencing adverse consequences, but who were ambivalent about change and would be unlikely to seek treatment. The objective of this study was to determine whether the MCU would reach the target population. Comparisons were made between those who enrolled in the MCU vs. those who were screened but failed to enroll based on demographic, drug use and stage of change variables. Comparisons were also made between participants in the MCU and participants in a concurrently offered treatment project that targeted users who wanted to quit. The MCU attracted and enrolled daily users of marijuana who experienced negative consequences but were ambivalent about making changes. The efficacy of the MCU in reducing marijuana use and associated consequences over the 12 months following the feedback sessions will be addressed in future papers. However, this study shows that marketing check-up interventions for marijuana users may help reduce barriers to engagement in drug abuse treatment. This low-burden modality may hold potential for attracting users, screening for problem use, resolving ambivalence and providing information on self-change and treatment options. Stephens, R.S., Roffman, R.A., Fearer, S.A., Willimas, C., Picciano, J.F. and Burke, R.S. Addiction, 99, pp. 1323-1332, 2004.

Improving Contingency Mangement Program for Addiction

Dr. Lamb and colleagues examined whether the effectiveness of contingency management interventions improves when contingencies are arranged in ways that improve the likelihood of all participants experiencing the available reward. In Study 1, smokers not planning to quit, were paid $0, 1, 3, 10, or 30 each day for 5 days for delivery of breath CO levels either < 4 ppm or below half the median of their baseline levels. Higher payment amounts and the easier target criterion resulted in a higher likelihood of participants meeting criterion. Once participants met the 4 ppm criterion, however, they often maintained this behavior even in the absence of payments for reduced breath CO levels. Study 2 examined the effectiveness of percentile schedules at shaping reduced breath CO levels. Percentile schedules shaped lower breath CO levels. The effectiveness of percentile schedules in shaping abstinence was tested in treatment seekers, and percentile schedules were found to be effective in shaping abstinence. Lamb, R.J., Kirby, K.C., Morral, A.R., Galbicka, G. and Iguchi, M.Y. Addictive Behaviors, 29, pp. 507-523, 2004.

Motivational Enhancement Therapy for Nicotine Dependence in Methadone-Maintained Pregnant Women

In this study, Dr. Haug and colleagues compared motivational enhancement therapy (MET) to standard-care practitioner advice for reducing smoking during pregnancy in a 2-group randomized design. Participants were 63 pregnant opioid-dependent smokers seeking substance abuse treatment, methadone maintenance, and prenatal care. At a 10-week follow-up, self-report and biological measures indicated no differences in smoking between the MET and standard-care groups. However, MET participants were more likely to have moved forward on the stage of change continuum than those in standard care. Intensive treatment for nicotine dependence, environmental interventions, and innovative harm reduction strategies are recommended to address the barriers to quitting observed in this population of

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pregnant women. Haug, N.A., Svikis, D.S. and Diclemente, C. Psychol Addict Behav. 18, pp. 289-292, 2004.

Correlates of Motivation to Quit Smoking in Methadone-Maintained Smokers Enrolled in a Smoking Cessation Trial

Investigators examined factors that may be associated with motivation to quit smoking in methadone-maintained persons. A sample of 255 smokers, enrolled in a smoking cessation research protocol, completed measures of their smoking motivation, smoking habit, quitting history, and intent to quit in the future. Analyses indicated that only number of cigarettes smoked per day and expectancies for success with smoking cessation were associated significantly with motivation to quit smoking. These results have implications for understanding motivational processes among methadone-maintained smokers and may help in the design of interventions that will assist this population with quitting smoking. Shadel, W.G., Stein, M.D., Anderson, B.J., Herman, D.S., Bishop, S., Lassor, J.A., Weinstock, M., Anthony, J.L. and Niaura, R. Addictive Behaviors, 20, pp. 295-300, 2005.

Treatment of Tobacco Use in an Inpatient Psychiatric Setting

This study examined delivery of tobacco cessation services in a smoke-free inpatient psychiatric setting. Medical records of 250 psychiatric inpatients were randomly selected and systematically reviewed. A total of 105 patients were identified as current smokers. Smokers evidenced statistically greater agitation and irritability compared with nonsmokers. None of the smokers received a diagnosis of nicotine dependence or withdrawal, and smoking status was not included in treatment planning for any patient. Nicotine replacement therapy was prescribed for 59 smokers. Smokers who were not given a prescription for nicotine replacement therapy were more than twice as likely as nonsmokers and smokers who were given a prescription for this therapy to be discharged from the hospital against medical advice. Only one smoker was encouraged to quit smoking. Psychiatric inpatients smoke at high rates, yet interventions to treat this deadly addiction are rare. Furthermore, not addressing nicotine withdrawal may compromise psychiatric care. Prochaska, J.J., Gill, P. and Hall, S.M., Psychiatric Services, 55, pp. 1265-1270, 2004.

Brief Motivational Intervention at a Medical Clinic Visit Reduces Cocaine and Heroin Use

Dr. Bernstein and colleagues at Boston University examined the effectiveness of a single, structured brief motivational intervention targeting cessation of drug use, conducted between peer educators and out-of-treatment cocaine and heroin users screened in the context of a routine medical visit. A randomized, controlled clinical trial was conducted in inner-city teaching hospital outpatient clinics with 3- and 6-month follow-up by blinded observers. Among the 23, 669 patients screened from 5/98-11/00, 1232 (5%) were eligible, and 1175 enrolled. Enrollees (mean age 38 years) were 29% female, 62% non-Hispanic black, 23% Hispanic, 46% homeless. Among those with drug positive hair at entry, the follow-up rate was 82%. The intervention group was more likely to be abstinent than the control group for cocaine alone (22.3% versus 16.9%), heroin alone (40.2% versus 30.6%), and both drugs (17.4% versus 12.8%), with adjusted OR of 1.51-1.57. Cocaine levels in hair were reduced by 29% for the intervention group and only 4% for the control group. Reductions in opiate levels were similar (29% versus 25%). This study shows that a brief motivational intervention in the medical clinic setting can reduce heroin and cocaine use. Peer interventionist may play an important role as physician extenders in a busy clinical environment, and this approach may enhance the screening, intervention, and referral of patients who use cocaine, heroin, and other drugs. Bernstein, J., Bernstein, E., Tassiopoulos, K., Heeren, T., Levenson, S. and Hingson, R. Drug and Alcohol Dependence, 77, pp. 49-59, 2005.

Computerized Drug Abuse Problem Assessment Helps Screen Older Adults in Primary Care

Dr. Nemes and her colleagues at Danya International, Inc., Silver Spring, Maryland, examined differences in responses of older adults (age 55 and above) and younger adults (ages 18-54) to the Drug Abuse Problem Assessment for Primary Care, (DAPA-PC), a computerized drug and alcohol screening instrument developed for primary care settings. Data were collected from a diverse population of 327 adults presenting for care at the George Washington University Medical Faculty Associates Clinic in Washington, D.C. Results indicated that rates of drug and alcohol abuse were similar in both groups. However, older adults were less likely than younger adults to perceive their drug use as problematic. This finding has serious implications for older adults,

who tend to be underrepresented in treatment programs. There is a need for screening older adults and identifying those who may be at risk for substance abuse problems. Differences in responses to alcohol and drug assessments by age should be taken into consideration when designing screening instruments. The results of this study suggest that the DAPA-PC would provide a useful instrument for screening older adults in a primary care setting. Nemes, S., Rao, P.A., Zeiler, C., Munly, K., Holtz, K.D. and Hoffman, J. American Journal of Drug and Alcohol Abuse, 30(3), pp. 627-642, 2004.

Substance Use Histories in Patients Seeking Treatment for Controlled-Release Oxycodone Dependence

Drs. Potter, Weiss and colleagues at Harvard University, reviewed the medical records of 48 patients abusing Controlled Release oxycodone admitted consecutively to an inpatient detoxification unit to better understand the characteristics of treatment-seeking patients with problematic use of this medication. Patients were categorized according to the manner in which they initially received the drug: illicitly or by prescription legitimately for a medical condition. Fifteen of the 48 patients (31%) initially obtained a CR oxycodone prescription legitimately for a medical condition. While none of these 15 patients had a history of prior opioid misuse, they were more likely than illicit CR oxycodone users to report prior detoxifications as well as lower mean age of first alcohol use and first illicit drug use. These findings support the importance of comprehensive screening for all substance related disorders when opioid therapy for pain is considered. Potter, J.S., Hennessy, G., Borrow, J.A., Greenfield, S.F. and Weiss, R.D. Drug and Alcohol Dependence, 76, pp. 213-215, 2004.

Suicidal Behavior, Drug Use, and Depressive Symptoms

This 2-year prospective study of 470 patients following inpatient detoxification, examined factors associated with drug-related suicidal behavior using multivariable regression analyses. Suicidal behavior included suicidal ideation (SI) and suicide attempt (SA). Lifetime prevalence for SI was 28.5%, and for SA, 21.9%. During the 2-year follow-up, 19.9% of the sample endorsed suicidal ideation, and 6.9% reported a suicide attempt. Correlates of lifetime suicidal behavior included younger age, female, Hispanic, greater depressive symptoms, past sexual abuse, and problem sedative or alcohol use. Factors associated with suicidal behavior at follow-up included past suicidal behavior, more depressive symptoms, and more frequent benzodiazepine and alcohol abuse. These findings highlight the importance of addressing the recurrent suicide risk of patients with substance related disorder and frequent monitoring for changes in depressive symptoms and drug use. Wines, J.D., Saitz, R., Horton, N. J., Lloyd-Travaglini, C. and Samet, J. H. Drug and Alcohol Dependence, 76S, S21-S29, 2004.

Abstinent Unemployed Drug Abusers Taught Work Skills Via Computer That May Translate Into Better Paying Jobs

Participants in the therapeutic workplace program are taught typing and keypad data entry via a computerized self-paced learning program. Most began with few or no computer skills. Overall the eight participants who completed the training had a mean reading level of 9.4 grade years, had been heroin (100%) dependent and 75% also were alcohol and or cocaine dependent (75%). During the past three years 75% had been unemployed. Participants were required to submit a drug free urine test to enter the training program each day. Overall they took 51.48 training hours to acquire typing skills and 31.73 hours to learn keypad typing. Training occurred in one-minute trial blocks and participants were reinforced with pay for correct trials. These findings illustrate that even drug abusers with long histories of employment difficulties and less reading proficiency than a high school graduate could learn skills that could improve their "hireability" through this self-paced program. Dillon, E.M., Wong, C.J, Sylvest, C.E., Crone-Todd, D.E and Silverman, K. Substance Use and Misuse, 39, pp. 2325-2353, 2004.

New Stepped Care Methadone Treatment Combined with Behavioral Reinforcement Improves Employment Outcomes: Preliminary Findings

A new treatment that reinforces participants in methadone treatment for opiate dependence for treatment plan related behaviors including job seeking and job acquisition and which tapers them off methadone and discharges them from the clinic when they fail to engage in job seeking, shows promise for increasing job seeking behavior. Of those judged capable of working (not disabled), 93% achieved some form of employment (75% full time) during the times when the program was in

effect. As this is not a randomized trial, care must be taken in interpreting these findings, but this study suggests that integrating tangible incentives for employment goals may improve employment outcomes in some drug abusers. Kidorf, M., Neufeld, K. and Brooner, R.K. Substance Use and Misuse, 39, pp. 2615-2238, 2004.

New Customized Employment Support Vocational Model Improves Employment Outcomes for Drug Abusers

A new vocational rehabilitation model that pairs drug abusers with a counselor for intense job placement and post-placement support with the goal of rapidly involving them in employment was preliminarily tested in 121 opiate users at two methadone programs. When compared with usual vocational counseling, participants were more likely to be in competitive employment or to have found any employment at all. These preliminary findings suggest this may be a promising new method for moving drug abusers into competitive employment. Staines, G.L., Blankertz, L., Magura, S., Bali, P., Madison, E.M., Spinelli, M., Horowitz, E., Guarino, H., Grandy, A., Fong, C., Gomez, A., Dimun, A. and Friedman, E. Substance Use and Misuse, 39, pp. 2261-2285, 2004.

Behavioral Therapies Can Be Effective in Treating Co-morbid Substance Abuse and Mood Disorders

Dr. Kathleen Carroll of Yale University reviewed the treatment literature regarding two classes of disorders that often co-occur: substance abuse and mood disorders. Focusing on three types of behavioral therapiesÑmotivational interviewing, cognitive-behavioral therapies, and contingency managementÑDr. Carroll evaluated the evidence for these therapies supporting treatment engagement, reduction in substance use, adherence to medications, and relapse prevention. She concludes that while these therapies have not been extensively tested among patients with co-morbid substance abuse and mood disorders, the preliminary evidence suggests that behavioral therapies can effectively treat this co-morbidity. Further, the evidence suggests that certain therapies may be better suited for different points in the treatment process. Given the high rate of co-morbid mood disorders among substance abusers, the positive preliminary results of behavioral treatments should inspire further development and testing of behavioral therapies targeting both disorders. Carroll, K.M. Behavioral Therapies for Co-occurring Substance Use and Mood Disorders. Biological Psychiatry, 56, pp. 778-784, November 2004.

Bipolar Disorder and Substance Abuse

Substance use disorders are over-represented in individuals with bipolar and bipolar spectrum disorders. Although awareness of this phenomenon has increased over the past 20 years, few empirically based treatment strategies have been developed for this challenging patient population. This review examines the relationship between bipolar and substance use disorders and treatment options that have been studied in this patient population. First, to examine the high prevalence rates of substance use disorders in individuals diagnosed with bipolar disorder, the common problems associated with establishing a bipolar disorder diagnosis in individuals who abuse substances, the possible explanations for the frequent coexistence of bipolar and substance use disorders, and the negative effect of substance abuse on the course of and treatment outcomes for bipolar disorder. The review then focuses on treatment approaches for this patient population, including integrated group therapy for co-occurring bipolar and substance use disorders and pharmacotherapies that target both disorders. Finally, it presents suggestions for medications that might be tested for their efficacy in treating both disorders in specific subgroups of patients with bipolar and substance use disorders. Levin, F.R. and Hennessy, G. Bipolar Disorder and Substance Abuse. Biol. Psychiatry, 56, pp. 738-748, 2004.

Treatment of Depression in Patients with Opiate Dependence

Depression is common among opiate-dependent patients and has been associated with worse prognosis. This article reviews the literature on treatment of depressive disorders and symptoms among patients with opiate dependence. Depression bears a complex relationship to opiate dependence and may represent an independent disorder or may be engendered by psychosocial stress or toxic and withdrawal effects of drugs. Primary treatments for opiate dependence (e.g., methadone or buprenorphine maintenance or residential treatment) are associated with substantial improvements in depression. Studies of antidepressant medications have produced mixed results, some positive but more negative. It is not clear what accounts for these differences, and more research is needed to determine how to select opiate-dependent patients most likely to benefit from antidepressants. Fewer studies have

examined psychosocial or behavioral interventions, but some of these also show promise. The data suggest a stepped model of care in which depression is evaluated and observed during the outset of treatment for opiate dependence and if it does not improve, specific psychosocial interventions or antidepressant medications tried. Research is needed on such integrated models of care and treatment algorithms to determine their efficacy and cost effectiveness. Nunes, E.V., Sullivan, M.A. and Levin, F.R. Treatment of Depression in Patients with Opiate Dependence. Biol. Psychiatry, 56, pp. 793-802, 2004.

Treatment of Cocaine-alcohol Dependence with Naltrexone and Relapse Prevention Therapy

This study evaluates whether patients with cocaine-alcohol dependence might benefit from naltrexone (NTX) pharmacotherapy when delivered in conjunction with psychotherapy. Eighty outpatients meeting DSM-IV criteria for alcohol and cocaine dependence were randomly assigned to receive NTX (placebo or 50 mg/d) combined with psychotherapy (Relapse Prevention [RP] or Drug Counseling [DC]) for twelve weeks. It was hypothesized that the skills training focus of RP therapy, in combination with NTX 50 mg/d, would produce greater reductions in cocaine and alcohol use. Outcome measures included self- and objective reports of substance use, treatment retention, medication compliance, and adverse effects. During the first four weeks of treatment, the percentage of cocaine-positive urine screens was significantly lower for those receiving RP therapy (22%) than those receiving DC (47%); however, this difference subsequently diminished. No medication effects were found. All groups reported less alcohol use at the end of treatment. Treatment retention was the same among the groups, with about 33% of the subjects completing all twelve weeks of treatment. The active medication group showed better medication compliance, while the number of adverse events was low overall and not significantly different by group. NTX at 50 mg/d did not reduce cocaine or alcohol use. These findings stand in contrast to previously reported positive findings for NTX and RP in patients with a single diagnosis of cocaine dependence. Schmitz, J.M., Stotts, A.L., Sayre, S.L., DeLaune, K.A. and Grabowski, J. Treatment of Cocaine-alcohol Dependence with Naltrexone and Relapse Prevention Therapy. Am. J Addict, 13, pp. 333-341, 2004.

Director's Report to the National Advisory Council on Drug Abuse - February, 2005

Research Findings - Research on Pharmacotherapies for Drug Abuse

JDTic, a Novel Kappa-Opioid Antagonist, Shows Efficacy in Rat Model of Stress-Induced Relapse to Cocaine

Based on consultant advice, the NIDA Opioid Treatment Discovery Program (OTDP) has pursued the discovery of a developable kappa-opioid antagonist as its #1 goal. JDTic, a highly selective kappa-opioid antagonist that is undergoing DPMC-supported preclinical safety testing, advanced to development from the OTDP. The rationale for the original discovery effort stemmed from the hypothesis that relapse to opiate abuse reflects "self-medication" of an underlying dysphoric state, caused by mu-opioid agonist- (e.g., heroin-) induced sensitization of the brain to dysphoric effects of kappa-opioid agonists (e.g., dynorphin). While this hypothesis is still a reason for NIDA interest in JDTic, recent publications suggesting a role for the kappa-opioid system in mediating certain aspects of the stress response led to an expanded evaluation of JDTic. Within NIDA's highly successful Cocaine Treatment Discovery Program (CTDP), JDTic was sent for evaluation under a contract with Virginia Commonwealth University (Patrick Beardsley, PI) and the compound was found to block footshock-induced reinstatement - but not cocaine prime-induced reinstatement - of lever-pressing in extinguished cocaine self-administration rats. Because any CNS-active compound will impair lever-pressing at a high dose, the demonstrated selectivity of JDTic addresses an important go/no-go decision point within the CTDP and JDTic is viewed as a medication candidate for addressing the stress trigger of relapse to cocaine abuse. Similar findings in the past have generated interest in CRF-1 antagonists as potential addiction treatment medications; unfortunately, development of CRF-1 antagonists has been hampered within multiple pharmaceutical companies by unfavorable safety findings and pharmacokinetics issues. In vitro and in silico predictive safety tests, conducted under CTDP/OTDP contracts, suggest that JDTic is developable and that it may allow NIDA to conduct the type of clinical trials desired for CRF-1 antagonist. A manuscript describing JDTic effects in cocaine relapse models has been submitted by Drs. Carroll and Beardsley; the above mentioned data were presented by Dr. Carroll at a September, 2004 NIDA/AAPS meeting in Bethesda, MD.

A Double-Blind, Placebo-Controlled Trial of Modafinil for Cocaine Dependence

Despite years of active research, there are still no approved medications for the treatment of cocaine dependence. Modafinil is a glutamate-enhancing agent that blunts cocaine euphoria under controlled conditions, and the current study assessed whether modafinil would improve clinical outcome in cocaine-dependent patients receiving standardized psychosocial treatment. This was a randomized, double-blind, placebo-controlled trial conducted at a university outpatient center (from 2002 to 2003) on a consecutive sample of 62 (predominantly African American) cocaine-dependent patients (aged 25-63) free of significant medical and psychiatric conditions. After screening, eligible patients were randomized to a single morning dose of modafinil (400 mg), or matching placebo tablets, for 8 weeks while receiving manual-guided, twice-weekly cognitive behavioral therapy. The primary efficacy measure was cocaine abstinence based on urine benzoylecgonine levels. Secondary measures were craving, cocaine withdrawal, retention, and adverse events. Modafinil-treated patients provided significantly more BE-negative urine samples (p=0.03) over the 8-week trial when compared to placebos, and were more likely to achieve a protracted period (>/=3 weeks) of cocaine abstinence (p=0.05). There were no serious adverse events, and none of the patients failed to complete the study as a result of adverse events. This study provides preliminary evidence, which should be

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confirmed by a larger study, that modafinil improves clinical outcome when combined with psychosocial treatment for cocaine dependence. Dackis, C.A., Kampman, K.M., Lynch, K.G., Pettinati, H.M. and O'Brien, C.P. A Double-Blind, Placebo-Controlled Trial of Modafinil for Cocaine Dependence. Neuropsychopharmacology. 1, pp. 205-211, 2005.

Agonist-like, Replacement Pharmacotherapy for Stimulant Abuse and Dependence

Stimulant abuse and dependence are disproportionately problematic due to the combination of legal and social issues added to the serious behavioral and biological features of the disorders. These problems are compounded by adverse consequences for families and society. Illegality and stigma multiply the consequences of use and difficulties in providing treatment. Specific behavioral interventions have been demonstrated as useful in treatment of substance use disorders (SUDs). Medications also have an important role in treatment. Effective agonist and antagonist pharmacotherapies as well as symptomatic treatments exist for opioid and nicotine dependence. Neither agonists nor antagonists have been approved as uniquely effective for treatment of stimulant abuse or dependence. Still, promising results are emerging for an agonist-like or 'replacement' strategy paralleling that for nicotine and opioid dependence. Supporting data have emerged from both preclinical and clinical research environments. There are scientific, clinical, social, and legal impediments to application of an agonist-like approach to stimulant abuse and dependence. Some resemble past and current concerns about opioid replacement. Others are unique to the stimulant agents, effects, and clinical features. Here, the authors consider (1) agonist and antagonist pharmacotherapy strategies; (2) preclinical research, including methodological approaches, opioid and nicotine replacement, and agonists for stimulant dependence; (3) clinical reports with stimulant medications in cocaine dependence, and the amphetamine replacement strategy for amphetamine dependence; (4) application of agonist-like/replacement strategies, including clinical requirements and risks; and (5) directions for research. Grabowski, J., Shearer, J., Merrill, J. and Negus, S.S. Agonist-like, Replacement Pharmacotherapy for Stimulant Abuse and Dependence. Addict Behav. 29, pp. 1439-1464, 2004.

First Episode Schizophrenia-related Psychosis and Substance Use Disorders: Acute Response to Olanzapine and Haloperidol

Co-occurring substance use disorders, mostly involving alcohol, cannabis or cocaine, occur commonly in patients with schizophrenia and are associated with increased morbidity and mortality. Available but limited data suggest that substance use disorders (especially cannabis use disorders) may also be common in first-episode patients and appear linked to a poor outcome in these patients. Strategies to curtail substance use form an important dimension of the treatment program for both first-episode and chronic patients. This report describes rates of co-occurring substance use disorders in patients within their first episode of schizophrenia-related psychosis from a multi-center, international treatment trial of olanzapine vs. haloperidol. The study involved 262 patients (of 263 who were randomized and who returned for a post-randomization evaluation) within their first episode of psychosis (schizophrenia, schizoaffective disorder or schizophreniform disorder) recruited from 14 academic medical centers in North America and Western Europe. Patients with a history of substance dependence within 1 month prior to entry were excluded. Of this sample, 97 (37%) had a lifetime diagnosis of substance use disorder (SUD); of these 74 (28% of the total) had a lifetime cannabis use disorder (CUD) and 54 (21%) had a lifetime diagnosis of alcohol use disorder (AUD). Patients with SUD were more likely to be men. Those with CUD had a lower age of onset than those without. Patients with SUD had more positive symptoms and fewer negative symptoms than those without SUD, and they had a longer duration of untreated psychosis. The 12-week response data indicated that 27% of patients with SUD were responders compared to 35% of those without SUD. Patients with AUD were less likely to respond to olanzapine than those without AUD. These data suggest that first-episode patients are quite likely to have comorbid substance use disorders, and that the presence of these disorders may negatively influence response to antipsychotic medications, both typical and atypical antipsychotics, over the first 12 weeks of treatment. Green, A.I., Tohen, M.F., Hamer, R.M., Strakowski, S.M., Lieberman, J.A., Glick, I. and Clark, W.S. First Episode Schizophrenia-related Psychosis and Substance Use Disorders: Acute Response to Olanzapine and Haloperidol. Schizophr. Res. 66, pp. 125-135, 2004.

Therapeutic Vaccines for Substance Dependence

Immunotherapies are under development as a new approach to the treatment of substance dependence. The drugs of abuse currently being tested using this new

approach are nicotine, cocaine, phencyclidine and methamphetamine. In laboratory animal models, a range of immunotherapies, including vaccines, monoclonal antibodies and catalytic antibodies, have been shown to reduce drug seeking. In human clinical trials, cocaine and nicotine vaccines have been shown to induce antibody titers while producing few side effects. Studies in humans determining how these vaccines interact in combination with their target drug are underway. Overall, immunotherapy offers a range of potential treatment options: drug treatment, as well as the treatment of overdose, prevention of brain or cardiac toxicity and fetal protection in pregnant drug abusers. Haney, M. and Kosten, T.R. Therapeutic Vaccines for Substance Dependence. Expert. Rev. Vaccines. 3, pp. 11-18, 2004.

Gabapentin Maintenance Decreases Smoked Cocaine-related Subjective Effects, but not Self-administration by Humans

Data from research with laboratory animals indicate that cocaine self-administration can be reduced by GABA agonists. Yet, the effectiveness of GABA agonists to decrease human cocaine self-administration has not been investigated under controlled laboratory conditions. The purpose of this study was to assess the effects of gabapentin, a GABA agonist, on cocaine-related behaviors, including self-administration, in human research participants under controlled laboratory conditions. During this 48-day double-blind, crossover design study, the effects of gabapentin (0, 600, and 1200 mg/d) maintenance on response to cocaine (0, 12, 25, and 50 mg) were investigated in seven cocaine abusers. Active cocaine significantly increased choice to self-administer cocaine, subjective-effect ratings (e.g., "Good Drug Effect"), blood pressure and heart rate (HR). Gabapentin did not reduce cocaine choice or cardiovascular measures, but it did decrease some subjective effects of cocaine (e.g., "Good Drug Effect" and "Anxious"). These data suggest that the cocaine-gabapentin combination was well tolerated, and because some cocaine-related subjective effects were reduced by maintenance on relatively low gabapentin doses, future studies should test higher gabapentin doses. Hart, C.L., Ward, A.S., Collins, E.D., Haney, M. and Foltin, R.W. Gabapentin Maintenance Decreases Smoked Cocaine-related Subjective Effects, but not Self-administration by Humans. Drug Alcohol Depend., 73, pp. 279-287, 2004.

Harm Reduction Approaches to Reducing Tobacco-related Mortality

Tobacco harm reduction approaches are gaining increased attention. Much of this attention is due to a growing concern that significant populations of smokers either do not want to quit or believe they are unable to quit smoking, and to a concern over tobacco-industry attempts to produce tobacco products that claim to result in less toxin exposure. Decreasing tobacco toxin exposure as a method for reducing mortality and morbidity may be a reasonable tobacco control strategy. However, the impact of this strategy must be explored both on individual and population levels. A significant amount of independent research is needed to inform policy decisions. Regulatory authority over potential reduced exposure products is also essential. Hatsukami, D.K., Henningfield, J.E. and Kotlyar, M. Harm Reduction Approaches to Reducing Tobacco-related Mortality. Annu. Rev. Public Health, 25, pp. 377-395, 2004.

Smokeless Tobacco Use: Harm Reduction or Induction Approach?

Smokeless tobacco (ST) substitution for cigarettes as a method to reduce harm has been actively debated. Use of ST as a smoking cessation method or as a means to reduce cigarettes has been proposed. The impact of using ST in these ways is relatively unknown. A review of the different issues and studies related to using smokeless tobacco as a method to reduce tobacco toxin exposure and harm is presented. The toxicity of the product itself varies by brand of ST and across countries. Of the existing studies, comparisons of consequences between cigarettes and ST show that cigarette smoking produces more negative health effects, is likely to have a higher addiction potential and more severe withdrawal, and leads to a higher rate of relapse than ST use. On the other hand, ST use facilitates the use of cigarettes, which is a deadly tobacco product. Additionally, ST is not a harmless product, and a less harmful product, medicinal nicotine, is available as an effective treatment approach. Furthermore, ST products are not under the same regulatory scrutiny as medicinal nicotine products. Considerably more research and product regulation is necessary prior to considering smokeless tobacco as a harm reduction method. Hatsukami, D.K., Lemmonds, C. and Tomar, S.L. Smokeless Tobacco Use: Harm Reduction or Induction Approach? Prev. Med., 38, pp. 309-317, 2004.

Evaluation of Carcinogen Exposure in People Who Used "Reduced Exposure" Tobacco Products

Although tobacco products with reportedly reduced carcinogen content are being marketed, carcinogen uptake in people who use these products has not been assessed systematically. Between June 2001 and November 2002, 54 users of smokeless tobacco and 51 cigarette smokers were randomly assigned to one of two groups. One used test products (Swedish snus for users of smokeless tobacco or OMNI cigarettes for smokers), while the other quit and used medicinal nicotine (the nicotine patch). All participants were assessed for urinary levels of total NNAL [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronide], metabolites of the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. Smokers were also assessed for levels of 1-hydroxypyrene (1-HOP), a biomarker of polycyclic aromatic hydrocarbon uptake. Assessments were made weekly during 2 weeks of baseline normal tobacco use and 4 weeks of treatment. Statistical tests were two-sided. Primary data analyses were conducted on 41 users of smokeless tobacco and 38 cigarette smokers who met the inclusion criteria. Total NNAL levels were statistically significantly lower in users of smokeless tobacco after they switched to snus or to nicotine patch (P<.001 for both groups) than they were before the switch, although the overall mean total NNAL level among subjects who used the nicotine patch was statistically significantly lower than that among those who used snus (mean = 1.2 and 2.0 pmol of NNAL/mg of creatinine, respectively; mean difference = 0.9 pmol of NNAL/mg of creatinine, 95% confidence interval [CI] = 0.2 to 1.5; P =.008). Compared with baseline levels, total NNAL levels (P =.003), but not 1-HOP levels, were statistically significantly reduced in cigarette smokers who switched to the OMNI cigarette, although both total NNAL levels and 1-HOP levels were statistically significantly reduced in smokers who switched to the nicotine patch (P<.001 for both). The overall mean total NNAL levels among smokers who used the nicotine patch was statistically significantly lower than that among smokers who used the OMNI cigarette (mean = 1.2 and 1.9 pmol of NNAL/mg of creatinine, respectively; mean difference = 0.6 pmol of NNAL/mg of creatinine, 95% CI = 0.1 to 1.1; P =.022). Switching to reduced-exposure tobacco products or medicinal nicotine can decrease levels of tobacco-associated carcinogens, with greater reductions being observed with medicinal nicotine. Medicinal nicotine is a safer alternative than modified tobacco products. Hatsukami, D.K., Lemmonds, C., Zhang, Y., Murphy, S.E., Le, C., Carmella, S.G. and Hecht, S.S. Evaluation of Carcinogen Exposure in People Who Used "Reduced Exposure" Tobacco Products. J Natl. Cancer Inst., 96, pp. 844-852, 2004.

Effects of Sustained-release Bupropion Among Persons Interested in Reducing but not Quitting Smoking

The purpose of this study was to determine whether sustained-release bupropion promotes smoking reduction leading to smoking cessation among persons who wish to reduce their amount of smoking, but who are unwilling to quit or who perceive themselves as being unable to quit. Current smokers were assigned randomly to receive either sustained-release bupropion (150 mg twice daily) or matching placebo. During an initial 6-month smoking reduction phase, those who were willing to quit entered a 7-week cessation phase, during which study medication was continued. Four-week continuous abstinence rates were 14% (41/295) in the bupropion group and 8% (25/299) in the placebo group (P = 0.02) during treatment. However, this benefit did not continue after treatment was stopped; subsequent continuous abstinence rates were 7% (20/295) in the bupropion group and 5% (16/299) in the placebo group (P = 0.50). Similar proportions of subjects entered the cessation phase in both treatment groups (38% [n = 113] of those in the bupropion group and 34% [n = 101] of those in the placebo group), although the time until a cessation attempt was shorter for those taking bupropion (median, 64 days vs. 118 days, P = 0.008). The extent of smoking reduction (measured by urinary cotinine concentrations) among the 327 subjects who did not enter the cessation phase was significantly greater (P <0.05) in those treated with bupropion during the reduction treatment phase, but not during the month 12 follow-up visit (P = 0.25). Sustained-release bupropion, when used in smokers initially not willing to make a cessation attempt, can help sustain smoking reduction while subjects are on active medication, reduce the time until the next cessation attempt, and increase short-term abstinence rates. However, these benefits were modest and not sustained after bupropion was discontinued. Hatsukami, D.K., Rennard, S., Patel, M.K., Kotlyar, M., Malcolm, R., Nides, M.A., Dozier, G., Bars, M.P. and Jamerson, B.D. Effects of Sustained-release Bupropion Among Persons Interested in Reducing but not Quitting Smoking. Am. J Med., 116, pp. 151-157, 2004.

A Pilot Trial of Topiramate for the Treatment of Cocaine Dependence

Both GABAergic and glutamatergic neurons appear to be important modulators of the

brain reward system and medications that affect GABA and glutamatergic neurotransmission may reduce the rewarding properties of cocaine and reduce cocaine craving. Topiramate, an anticonvulsant, raises cerebral GABA levels, facilitates GABAergic neurotransmission and inhibits glutamatergic activity at AMPA/kainate receptors. Thus, it may be useful for treating cocaine dependence. The efficacy of topiramate for cocaine dependence was tested in a 13-week, double-blind, placebo-controlled pilot trial (n = 40). Topiramate was titrated gradually over 8 weeks to a dose of 200 mg daily. The primary outcome measure was cocaine abstinence verified by twice weekly urine benzoylecgonine tests (UBT). Eighty-two percent of subjects completed the trial. Analysis of the UBT using a GEE model showed that after week 8, when the dose titration was completed, topiramate-treated subjects were more likely to be abstinent from cocaine compared to placebo-treated subjects (Z = 2.67, P = 0.01). Topiramate-treated subjects were also more likely to attain 3 weeks of continuous abstinence from cocaine (chi2 = 3.9, d.f. = 1, P = 0.05). Topiramate may be effective for the treatment of cocaine dependence. Kampman, K.M., Pettinati, H., Lynch, K. G., Dackis, C., Sparkman, T., Weigley, C. and O'Brien, C.P. A Pilot Trial of Topiramate for the Treatment of Cocaine Dependence. Drug Alcohol Depend., 75, pp. 233-240, 2004.

Cocaine Dependence Severity Predicts Outcome in Outpatient Detoxification from Cocaine and Alcohol

This study compared the effects of alcohol and cocaine dependence severity on the outcome of outpatient detoxification from alcohol and cocaine. Subjects included 84 subjects with both alcohol and cocaine dependence admitted for outpatient detoxification. Fifty-three of the 84 subjects (63%) completed detoxification. Baseline cocaine use, cocaine craving, and cocaine withdrawal symptoms predicted detoxification outcome, whereas alcohol use, alcohol craving, and alcohol withdrawal symptoms did not. Among cocaine- and alcohol-dependent subjects, cocaine dependence severity appears to be a more important predictor of detoxification success than alcohol dependence severity. Kampman, K.M., Pettinati, H.M., Volpicelli, J.R., Oslin, D.M., Lipkin, C., Sparkman, T. and O'Brien, C.P. Cocaine Dependence Severity Predicts Outcome in Outpatient Detoxification from Cocaine and Alcohol. Am. J Addict, 13, pp. 74-82, 2004.

Naltrexone for Heroin Dependence Treatment in St. Petersburg, Russia

Naltrexone may be more effective for treating opioid (heroin) dependence in Russia than in the U.S. because patients are mostly young and living with their parents, who can control medication compliance. In this pilot study in St. Petersburg were 52 randomized consenting patients who completed detoxification to a double blind, 6-month course of biweekly drug counseling and naltrexone, or counseling and placebo naltrexone. Significant differences in retention and relapse favoring naltrexone were seen beginning at 1 month and continuing throughout the study. At the end of 6 months, 12 of the 27 naltrexone patients (44.4%) remained in treatment and had not relapsed as compared to 4 of 25 placebo patients (16%; $p<0.05$). Since heroin dependence is the main vector for HIV transmission in Russia, naltrexone is likely to improve treatment outcome and help reduce the spread of HIV if it can be made more widely available. Krupitsky, E.M., Zvartau, E.E., Masalov, D.V., Tsoi, M.V., Burakov, A.M., Egorova, V.Y., Didenko, T.Y., Romanova, T.N., Ivanova, E.B., Bespalov, A.Y., Verbitskaya, E.V., Neznanov, N.G., Grinenko, A.Y., O'Brien, C.P. and Woody, G.E. Naltrexone for Heroin Dependence Treatment in St. Petersburg, Russia. J Subst.Abuse Treat. 26, pp. 285-294, 2004.

Characteristics of Cigarette Smokers Seeking Treatment for Cessation Versus Reduction

Comparisons were made between cigarette smokers seeking treatment to quit smoking and cigarette smokers seeking treatment to reduce the number of cigarettes they smoke. Potential subjects were recruited from the local metropolitan area by advertisement in the local media. A total of 665 cigarette smokers telephoned seeking treatment for smoking cessation and 565 cigarette smokers telephoned to seek treatment to gradually reduce the number of cigarettes they smoke but not quit smoking. Potential subjects were instructed to call the clinic to find out additional information about the studies, and while on the telephone they were asked questions pertaining to tobacco use and health status. The results show that the two populations are similar in many respects with the following exceptions: smokers seeking treatment to reduce cigarette use tend to smoke more cigarettes per day, are less motivated to quit, make fewer quit attempts, drink more alcoholic beverages per day, and have more health problems (Ps<.05). These results indicate that cigarette smokers seeking treatment for smoking reduction but not cessation may be more

dependent smokers who experience more medical disorders. Lemmonds, C.A., Mooney, M., Reich, B. and Hatsukami, D. Characteristics of Cigarette Smokers Seeking Treatment for Cessation Versus Reduction. Addict Behav. 29, pp. 357-364, 2004.

Impact of Attention-Deficit Hyperactivity Disorder and Other Psychopathology on Treatment Retention Among Cocaine Abusers in a Therapeutic Community

Although there are some data suggesting that individuals with depressive disorders may be more likely to remain in treatment than those without depressive disorders, it is less clear how well other psychiatric subgroups compare to those without psychiatric comorbidity. This sample is a follow-up study of 135 individuals who were admitted into a therapeutic community. Individuals with attention-deficit hyperactivity disorder (ADHD), other Axis I disorders (no ADHD), and no Axis I disorders were compared. Although individuals with other Axis I disorders had a strikingly low early drop-out rate, after a prolonged time in treatment, the drop-out rate increased substantially, such that these individuals were found to complete treatment at a lower rate (17%) than those with no Axis I disorders (29%). Furthermore, individuals with ADHD were less likely to graduate treatment than those with other Axis I or no Axis I disorders (0%, 9%, and 19%, respectively). Future investigations may be useful to determine whether pharmacologic or non-pharmacologic interventions might improve treatment outcome. Levin, F.R., Evans, S.M., Vosburg, S.K., Horton, T., Brooks, D. and Ng, J. Impact of Attention-Deficit Hyperactivity Disorder and Other Psychopathology on Treatment Retention Among Cocaine Abusers in a Therapeutic Community. Addict Behav., 29, pp. 1875-1882, 2004.

Pharmacotherapy for Marijuana Dependence: A Double-blind, Placebo-controlled Pilot Study of Divalproex Sodium

There is a noticeable lack of targeted treatment options for marijuana dependence, in particular pharmacologic approaches. This is the first study evaluating a targeted pharmacologic approach for marijuana dependence. The goals of the study were to determine if such patients would seek pharmacologic treatment, whether these patients could be retained in treatment using a design previously developed for cocaine-dependent patients, and especially whether divalproex sodium showed promise as a treatment agent for marijuana dependence. It was found that marijuana-dependent patients will seek treatment, and such patients can be adequately maintained in a pharmacologic trial. Regardless of treatment group, patients reported a significant reduction in their frequency and amount of marijuana use as well as a reduction in irritability. Given the lack of proven effective treatments for marijuana dependence, pharmacotherapies should be sought. The design of a preliminary clinical trial should include a psychosocial/behavioral intervention emphasizing motivation and medication compliance and a placebo control group. Levin, F.R., McDowell, D., Evans, S.M., Nunes, E., Akerele, E., Donovan, S. and Vosburg, S.K. Pharmacotherapy for Marijuana Dependence: A Double-blind, Placebo-controlled Pilot Study of Divalproex Sodium. Am. J Addict, 13, pp. 21-32, 2004.

A Randomized, Placebo-controlled Trial of Buspirone for the Treatment of Anxiety in Opioid-dependent Individuals

Anxiety symptoms are common among opioid-dependent individuals. Buspirone, a non-benzodiazepine anxiolytic, has been used successfully for the treatment of anxiety in alcoholic patients. Its efficacy in opioid-dependent patients has not been previously examined. A twelve-week, randomized, placebo-controlled trial of buspirone in 36 subjects receiving methadone-maintenance treatment who presented with anxiety symptoms was conducted. Measures of anxiety, depression, and substance use were obtained repeatedly during treatment. Buspirone treatment did not significantly reduce anxiety symptoms in opioid-dependent patients. However, buspirone treatment was associated with trends toward reduction in depression scale scores and a slower return to substance use. McRae, A.L., Sonne, S.C., Brady, K.T., Durkalski, V. and Palesch, Y. A Randomized, Placebo-controlled Trial of Buspirone for the Treatment of Anxiety in Opioid-dependent Individuals. Am. J Addict, 13, pp. 53-63, 2004.

The Blind Spot in the Nicotine Replacement Therapy Literature: Assessment of the Double-blind in Clinical Trials

While clinical trials of medications often use a double-blind procedure, the integrity of the blind and its relationship to treatment outcome is seldom examined. In this review, 73 double-blind, placebo-controlled clinical trials of the nicotine replacement

therapies (NRTs) in smoking cessation were identified. Seventeen articles were found that assessed blindness integrity, demonstrating major variations in the assessment, analysis, and reporting of blindness integrity. Although 12 studies found that subjects accurately judged treatment assignment at a rate significantly above chance, the available literature does not permit definitive conclusions about blindness integrity. Recommendations for the assessment, analysis, and reporting of blindness integrity are made. Mooney, M., White, T. and Hatsukami, D. The Blind Spot in the Nicotine Replacement Therapy Literature: Assessment of the Double-Blind in Clinical Trials. Addict Behav. 29, pp. 673-684, 2004.

A Comparison of Urinary Biomarkers of Tobacco and Carcinogen Exposure in Smokers

Recently, several potential harm reduction strategies, such as reduction in the number of cigarettes smoked and the use of modified cigarette products, have been discussed as possible means by which to reduce tobacco-related disease. To assess any potential reduction in harm by either of these approaches requires an accurate assessment of tobacco toxin exposure. Urine samples were collected at four time points and analyzed for 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), and its glucuronide, 1-hydroxypyrene, anatabine, free nicotine, total nicotine (free plus glucuronidated), free cotinine, total cotinine (free plus glucuronidated), and total trans-3'-hydroxycotinine (free plus glucuronidated). Anatabine is a minor alkaloid that may be useful in assessing tobacco exposure in individuals using nicotine replacement therapies. Urinary anatabine levels were well correlated ($P < 0.0001$) with both free and total nicotine ($r = 0.753$ and 0.773, respectively). Anatabine levels were also correlated with free cotinine ($r = 0.465$; $P < 0.001$), total cotinine ($r = 0.514$; $P < 0.001$), and total NNAL ($r = 0.633$; $P < 0.001$). These data support the role of anatabine as a biomarker of tobacco exposure. 1-Hydroxypyrene is a biomarker of polycyclic aromatic hydrocarbon exposure, but unlike NNAL it is not tobacco specific. Whereas urinary concentrations of 1-hydroxypyrene were consistent across the four visits, the levels were not correlated with NNAL, anatabine, nicotine, or any nicotine metabolites. Murphy, S.E., Link, C.A., Jensen, J., Le, C., Puumala, S.S., Hecht, S.S., Carmella, S.G., Losey, L. and Hatsukami, D.K. A Comparison of Urinary Biomarkers of Tobacco and Carcinogen Exposure in Smokers. Cancer Epidemiol. Biomarkers Prev., 13, pp. 1617-1623, 2004.

Antidepressant Treatment of Co-occurring Depression and Alcohol Dependence

The use of antidepressant pharmacotherapy to treat patients with co-occurring depression and alcohol dependence is controversial. There is a stigma attached to giving medications to alcohol-dependent persons. Also, empirical evidence is sparse and inconsistent, which discourages the use of antidepressants in these patients. Historically, it has been a challenge to accurately diagnose a depressive disorder in the presence of alcohol dependence. In addition, early clinical studies were fraught with methodological problems; however, improved diagnostic assessments are now available, and in the last decade, from well-controlled trials appear to support the use of antidepressants in this patient population in the specific role of relieving depressive symptoms. The majority of these trials also demonstrate that antidepressants have relatively little impact on reducing heavy drinking in this patient population, even though the medications reduce depressive symptoms. Newer approaches to treating patients with co-occurring depression and alcohol dependence suggest adding to the antidepressant a pharmacotherapy that directly impacts drinking. The findings from this review better define the action of antidepressants in patients with co-occurring depression and alcohol dependence as specific to reducing depressive symptoms, and these medications and their action on mood have little impact on treating the co-occurring alcohol dependence. Pettinati, H.M. Antidepressant Treatment of Co-occurring Depression and Alcohol Dependence. Biol. Psychiatry, 56, pp. 785-792, 2004.

Smoking Cessation Services in U.S. Methadone Maintenance Facilities

Most patients in drug treatment smoke cigarettes. This study established the prevalence and types of nicotine dependence services offered in methadone and other opioid treatment clinics in the United States. A cross-sectional survey was conducted of all outpatient methadone maintenance clinics in the United States. One person in a leadership position from each clinic was surveyed. The 20-minute survey was collected by phone, fax, or mail, according to responder preference. Fifty-nine percent of the clinics (408 of 697 clinics) responded. The sample was very similar to all outpatient methadone maintenance clinics in the United States in size, region, and ownership. In the 30 days before the survey, respondents reported that their clinics

provided the following services to at least one patient: 73 percent provided brief advice to quit, 18 percent offered individual or group smoking cessation counseling, and 12 percent prescribed nicotine replacement therapy. However, the services were provided to very few patients. Clinics with written guidelines that required them to address smoking were much more likely to provide services than those without guidelines. Private for-profit clinics were significantly less likely than public or private nonprofit clinics to treat nicotine dependence. Most respondents (77 percent) reported that their staffs were interested in receiving training in nicotine dependence treatment, and more than half (56 percent) had at least one staff member ("champion") with a strong interest in treating nicotine dependence. A vast majority of methadone patients smoke; yet in the 30 days before the survey only one out of three facilities provided counseling to any patients and only one out of ten prescribed nicotine replacement therapy to any patients. A dual strategy of requiring clinics to provide comprehensive nicotine dependence services and training staff to provide these services may provide the incentive and support necessary for the widespread adoption of treatment for nicotine dependence in methadone facilities. Richter, K.P., Choi, W.S., McCool, R.M., Harris, K.J. and Ahluwalia, J.S. Smoking Cessation Services in U.S. Methadone Maintenance Facilities. Psychiatr. Serv., 55, pp. 1258-1264, 2004.

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

A brief telephone-screening interview was conducted with 1759 callers seeking treatment for substance abuse at the Treatment Research Clinic (TRC) over a 16-month period. The purpose of this study was to examine the effectiveness of various recruitment strategies 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 problems were more likely to be eligible for treatment protocols, while those with severe problems in other psychosocial areas (legal, medical, and psychiatric) were more 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 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. Who Gets In?" Recruitment and Screening Processes of Outpatient Substance Abuse Trials. Addict Behav., 29, pp. 389-398, 2004.

A Randomized Controlled Trial of Pemoline for Attention-Deficit/Hyperactivity Disorder in Substance-Abusing Adolescents

In adolescents with substance use disorder (SUD), comorbid attention-deficit/hyperactivity disorder (ADHD) is associated with greater severity of substance abuse, conduct problems, and worse treatment outcomes. Although many controlled trials have established the efficacy of psychostimulants, including pemoline, for ADHD in children and adolescents, none have been conducted in adolescents with SUD. This randomized, placebo-controlled trial, conducted between 1996 and 2000, evaluated the safety and efficacy of pemoline on substance abuse and conduct problems. Sixty-nine adolescents (aged 13-19) with conduct disorder (CD), SUD, and ADHD were recruited from the community and randomly assigned to a 12-week clinical trial of pemoline (n = 35) or placebo (n = 34), titrated over 4 weeks to a single morning dose of 75 to 112.5 mg as tolerated. Pemoline had greater efficacy than placebo for ADHD as determined by significantly more Clinician's Global Impression-Improvement (CGI-I) ratings of 1 (very much improved) or 2 (much improved) at the study endpoint (n = 69; p <.05). There was also greater reduction in ADHD severity on the parent-rated Conners Hyperactivity-Impulsivity scale in pemoline-treated study completers compared to placebo-treated completers (pemoline, n = 17; placebo, n = 16; p <.01), but no difference between groups in the intent-to-treat analysis (n = 68; p <.13). Substance use did not decline in either group, and there was no difference between groups in baseline to study endpoint change in substance use or CD symptoms. Overall, pemoline was well tolerated, demonstrating a good safety profile and no elevation in liver enzyme levels. Pemoline was efficacious for ADHD but did not have an impact on CD or substance abuse in the absence of specific treatment for SUD. Riggs, P.D., Hall, S.K., Mikulich-Gilbertson, S.K., Lohman, M. and Kayser, A. A Randomized Controlled Trial of Pemoline for Attention-Deficit/Hyperactivity Disorder in Substance-abusing Adolescents. J Am. Acad. Child Adolesc.Psychiatry, 43, pp. 420-429, 2004.

Attention-Deficit/Hyperactivity Disorder and the Substance Use Disorders: The Nature of the Relationship, Subtypes at Risk, and Treatment Issues

There is a strong literature supporting a relationship between ADHD and SUD. Clearly, ADHD adolescents with conduct or bipolar disorder as part of their clinical picture are at the highest risk for SUD. ADHD without comorbidity appears to confer an intermediate risk factor for SUD that appears to manifest in young adults and college students. Both family genetic and self-medication influences may be operational in the development and continuation of SUD in ADHD subjects: however, systematic data are lacking. Patients with ADHD and SUD require multi-modal interventions incorporating addiction and mental health treatment. Pharmacotherapy in individuals with ADHD and SUD needs to take into consideration abuse liability, potential drug interactions, and compliance concerns. Although the existing literature has provided important information on the relationship of ADHD and SUD, it also points to a number of areas in need of further study. The mechanism by which untreated ADHD leads to SUD and the risk reduction of ADHD treatment on later SUD, needs to be understood better. The influence of adequateness of treatment of ADHD on later SUD needs to be delineated. Given the prevalence and major morbidity and impairment caused by SUD and ADHD. Prevention and treatment strategies for these patients need to be developed and evaluated further. Wilens, T.E. Attention-Deficit/Hyperactivity Disorder and the Substance Use Disorders: The Nature of the Relationship, Subtypes at Risk, and Treatment Issues. Psychiatr. Clin. North Am., 27, pp. 283-301, 2004.

Impact of ADHD and its Treatment on Substance Abuse in Adults

Attention-deficit/hyperactivity disorder (ADHD) is a risk factor for substance abuse in adults. Additional psychiatric comorbidity increases this risk. ADHD is associated with different characteristics of substance abuse: substance abuse transitions more rapidly to dependence, and lasts longer in adults with ADHD than those without ADHD. Self-medication may be a factor in the high rate of substance abuse in adults with ADHD. While previous concerns arose whether stimulant therapy would increase the ultimate risk for substance abuse, recent studies have indicated that pharmacologic treatment appears to reduce the risk of substance abuse in individuals with ADHD. When treating adults with ADHD and substance abuse, clinicians should assess the relative severity of the substance abuse, the symptoms of ADHD, and any other comorbid disorders. Generally, stabilizing or addressing the substance abuse should be the first priority when treating an adult with substance abuse and ADHD. Treatment for adults with ADHD and substance abuse should include a combination of addiction treatment/psychotherapy and pharmacotherapy. The clinician should begin pharmacotherapy with medications that have little likelihood of diversion or low liability, such as bupropion and atomoxetine, and, if necessary, progress to the stimulants. Careful monitoring of patients during treatment is necessary to ensure compliance with the treatment plan. Wilens, T.E. Impact of ADHD and its Treatment on Substance Abuse in Adults. J Clin. Psychiatry, 65 Suppl 3, pp. 38-45, 2004.

Risk of Substance Use Disorders in Adolescents with Bipolar Disorder

Previous work in adults and youths has suggested that juvenile onset bipolar disorder (BPD) is associated with an elevated risk of substance use disorders (SUD). Considering the public health importance of this issue, the authors now report on a controlled study of adolescents with and without BPD to evaluate the risk of SUD. Probands with DSM-IV BPD (n=57, mean age +/- SD=13.3 +/- 2.4 years) and without DSM-IV BPD (n=46, 13.6 +/- 2.2 years) were studied. Structured psychiatric interviews and multiple measures of SUD were collected. Bipolar disorder was associated with a highly significant risk factor for SUD (32% versus 7%, Z=2.9, p=.004) that was not accounted for by conduct disorder (adjusted odds ratio=5.4, p=.018). Adolescent-onset BPD (> or =13 years) was associated with a higher risk of SUD compared with those with child-onset BPD (chi1=9.3, p=.002). These findings strongly indicate that BPD, especially adolescent onset, is a significant risk factor for SUD independently of conduct disorder. Wilens, T.E., Biederman, J., Kwon, A., Ditterline, J., Forkner, P., Moore, H., Swezey, A., Snyder, L., Henin, A., Wozniak, J. and Faraone, S.V. Risk of Substance Use Disorders in Adolescents with Bipolar Disorder. J Am. Acad. Child Adolesc. Psychiatry, 43, pp. 1380-1386, 2004.

A Clinical Perspective of Attention-Deficit/Hyperactivity Disorder into Adulthood

Attention-deficit/hyperactivity disorder (ADHD) is a common psychiatric disorder that affects all age groups. Recent data on the clinical presentation, comorbidity, neurobiology, and treatment are reviewed. Using the search term ADHD, a selective

PubMed review of the clinical literature was undertaken to evaluate recent data relevant to ADHD with attention to a life span perspective of the disorder. A growing literature indicates that ADHD is more persistent than previously thought and has a developmental variability in its presentation. The disorder impairs academic, social, and occupational functioning and is often associated with comorbidity, including cigarette smoking and substance abuse. Considerable evidence suggests that the disorder has a strong genetic component and a biological underpinning; the pathophysiology includes dysfunction in both noradrenergic and dopaminergic systems. Both psychosocial therapy and pharmacotherapy have been shown effective in the treatment of the disorder throughout the life span. The therapeutic effectiveness of pharmacologic agents in the treatment of ADHD has been attributed to noradrenergic and/or dopaminergic effects. ADHD is associated with impairment and comorbidity throughout the life span. Growing evidence suggests the importance of short- and long-term management of the disorder. While the long-term treatment of ADHD is expected to lessen the individual's impairment, the outcome for adults who have received treatment since childhood requires further research. Wilens, T.E. and Dodson, W. A Clinical Perspective of Attention-Deficit/Hyperactivity Disorder into Adulthood. J Clin. Psychiatry, 65, pp. 1301-1313, 2004.

Methylphenidate Has Some Potential for Abuse

Methylphenidate is used to treat Attention Deficit Hyperactivity Disorder in children and adolescents. However, its abuse potential has not been well characterized, although it produces behavioral effects similar to those observed with other abused stimulants, such as d-amphetamine and cocaine. Investigators at the University of Kentucky, Lexington, KY, aimed to characterize the abuse potential of oral methylphenidate relative to oral d-amphetamine. Ten drug-abusing volunteers were recruited to participate in this study, which consisted of seven dose conditions: methylphenidate (16, 32 and 48 mg), d-amphetamine (8, 16 and 24 mg) and placebo. The reinforcing effects of these drugs were assessed during a self-administration session with a modified progressive-ratio procedure. Subject-rated, performance and physiological effects were assessed concurrently during both the sampling and self-administration sessions. The intermediate dose of methylphenidate and d-amphetamine increased responding significantly above placebo levels. Both methylphenidate and d-amphetamine produced dose-dependent increases in stimulant-like subject ratings (e.g. Active, Alert, or Energetic and High). These findings are consistent with epidemiological data and previous findings from laboratory studies that suggest methylphenidate has at least some abuse potential. Stoops, W.W., Glaser, P.E., Fillmore, M.T. and Rush, C.R. Reinforcing, Subject-rated, Performance and Physiological Effects of Methylphenidate and D-amphetamine in Stimulant Abusing Humans. J Psychopharmacology, 18(4), pp. 534-543, 2004.

Reinforcing Effects of Methylphenidate, Like D-amphetamine and Cocaine, are Influenced by Behavioral Demands

The reinforcing effects of stimulant drugs such as d-amphetamine, caffeine, and cocaine are modulated by behavioral demands following drug administration. Investigators at the University of Kentucky, Lexington, aimed to assess the reinforcing effects of methylphenidate under different behavioral demands using a modified progressive-ratio procedure. The effects of oral methylphenidate (0, 10, 20, and 40 mg) were assessed in seven healthy adult volunteers under both performance and relaxation conditions. Performance sessions required volunteers to complete simple arithmetic problems. Relaxation sessions required volunteers to sit quietly in a semi-reclined position in a darkened room. The results showed that methylphenidate significantly increased break point and number of capsules earned on the modified progressive-ratio procedure as an increasing function of dose under the performance, but not the relaxation, condition. Methylphenidate produced comparable stimulant-like subject ratings under both the performance and relaxation conditions. These findings suggest that the reinforcing effects of methylphenidate, like d-amphetamine and cocaine, are influenced by behavioral demands following drug administration. Stoops, W.W., Lile, J.A., Fillmore, M.T., Glaser, P.E. and Rush, C.R. Reinforcing Effects of Methylphenidate: Influence of Dose and Behavioral Demands Following Drug Administration. Psychopharmacology (Berlin), 177, pp. 349-355, 2005.

Acute Administration of Tiagabine Does Not Alter the Effects of Oral Cocaine

Drugs enhancing central gamma-aminobutyric acid (GABA) systems appear promising in the treatment of cocaine addiction. The investigators from the University of Kentucky, Lexington, KY, examined if tiagabine, a GABA reuptake inhibitor, has an ability to modify the discriminative-stimulus, reinforcing, subjective, performance and cardiovascular effects of oral cocaine in non-treatment seeking cocaine users.

Initially, acute doses of 4 mg tiagabine were tested alone and in combination with oral cocaine in four participants to establish the safety of drug combinations. A higher dose of tiagabine (8 mg) was then tested in 6 patients. Participants learned to discriminate 150 mg of oral cocaine. The effects of cocaine (0-150 mg, p.o.) administered alone and in combination with tiagabine were then determined using the Multiple-Choice Procedure. Cocaine alone produced prototypical behavioral and physiological effects (i.e., functioned as a discriminative and reinforcing stimulus, produced stimulant-like subject-rated effects, improved performance and increased heart rate), but acute administration of tiagabine did not alter these effects. These findings suggest that tiagabine would not be effective at preventing continued cocaine use by blocking its acute, abuse-related effects. Lile, J.A., Stoops, W.W., Glaser, P.E., Hays, L.R. and Rush, C.R. Acute Administration of the GABA Reuptake Inhibitor Tiagabine Does Not Alter the Effects of Oral Cocaine in Humans. Drug and Alcohol Dependence, 76(1), pp. 81-91, 2004.

Ketoconazole, a Cytochrome P450 3A4 Inhibitor Increases Concentrations of Levo-Acetyl-Alpha-Methadol in Opioid-naive Individuals

Levo-acetyl-alpha-methadol (LAAM) exerts most of it mu-agonist activity through the action of its 2 N-demethylation metabolites, norLAAM and dinorLAAM. This reaction is primarily performed by cytochrome P450s (CYP) in the 3A family. Investigators from the University of Utah in Salt Lake City examined the effect of in vivo inhibition of CYP3A on the pharmacokinetics and pharmacodynamics of LAAM. Oral LAAM (5 mg/70 kg) was administered on 2 occasions in a single-blind, randomized crossover design to 13 opioid-naive subjects 1 hour after pretreatment with 400 mg ketoconazole or placebo. Blood and urine samples were collected at defined intervals over 240- and 96-hour periods, respectively; LAAM, norLAAM, and dinorLAAM concentrations were determined by liquid chromatography-tandem mass spectrometry. Physiologic and subjective measures were collected for up to 72 hours. This study showed that a single dose of ketoconazole causes a significant pharmacokinetic drug interaction with a single dose of LAAM that results in increased LAAM concentrations relative to norLAAM and dinorLAAM. Co-administration also results in prolongation of the appearance of its active metabolites and a prolongation of miosis, a sensitive dynamic index of mu-opioid action. The clinically relevant increase in LAAM concentrations and prolongation of plasma LAAM metabolites may affect physiologic function, such as QT intervals, suggesting that co-administration of LAAM and CYP3A4 inhibitors should be contraindicated. Moody, D.E., Walsh, S.L., Rollins, D.E., Neff, J.A. and Huang, W. Ketoconazole, a Cytochrome P450 3A4 Inhibitor, Markedly Increases Concentrations of Levo-Acetyl-Alpha-Methadol in Opioid-naive Individuals. Clinical Pharmacology and Therapeutics. 76(2), pp. 154-166, 2004.

Sex Influences Responses to Disulfiram Treatment in Cocaine-dependent Individuals

Sex and gender influences many physiological and behavioral responses to treatments. Investigators from Yale University and VA Connecticut Health Care System aimed to examine the differential response to disulfiram treatment of cocaine dependence by sex. Sex by treatment interactions from two pooled randomized clinical trials involving 191 cocaine-dependent subjects (36% female) were evaluated. Primary outcomes were days of abstinence and percentage of drug-free urine specimens. Men treated with disulfiram had better outcomes than those who were not. Women had an intermediate outcome regardless of whether they received disulfiram. Sex differences in response to disulfiram treatment may have important clinical and theoretical implications. Reasons for this apparent difference in sex-based response are not clear, but possible mechanisms worthy of greater study include differences in alcohol use by sex as well as differences in dopamine-mediated responses to cocaine and disulfiram. Nich, C., McCance-Katz, E.F., Petrakis, I.L., Cubells, J.F., Rounsaville, B.J. and Carroll, K.M. Sex Differences in Cocaine-dependent Individuals' Response to Disulfiram Treatment. Addictive Behaviors, 29(6), pp. 1123-1128, 2004.

Cocaine Addicts with Conduct Disorder have Altered Secretion of Adrenal Steroids

There is evidence that children with antisocial behaviors have increased plasma levels of the adrenal androgen dehydroepiandrosterone sulfate (DHEA-S) and either a decreased level of cortisol, or a decreased cortisol responsivity to stress. Low levels of cortisol have also been reported in antisocial adults but their levels of DHEA-S have not been studied. The investigators from New York Harbor Healthcare System, NY, assessed blood levels of DHEA-S and cortisol in adult cocaine addicts as a function of

a diagnosis of antisocial personality disorder and of a retrospective diagnosis of conduct disorder (CD). Basal cortisol and DHEA-S were determined in the plasma samples of 40 hospitalized men. The patients' cortisol responsivity was also assessed while they were being exposed to a stressful situation. Patients who had a retrospective CD diagnosis had significantly increased DHEA-S levels and secreted less cortisol when stressed, confirming observations made in children and indicating that mechanisms underlying adrenal steroid alterations in childhood could still be at play in adulthood. Buydens-Branchey, L. and Branchey, M. Cocaine Addicts with Conduct Disorder are Typified by Decreased Cortisol Responsivity and High Plasma Levels of DHEA-S. Neuropsychobiology, 50(2), pp. 161-166, 2004.

Director's Report to the National Advisory Council on Drug Abuse - February, 2005

Research Findings - Research on Medical Consequences of Drug Abuse

Nutritional Status of Hispanic Drug Abusers Co-infected with HIV

Malnutrition in drug abusers has been attributed to poor diet. However, previous studies are conflicting. Many studies have not considered possible concurrent HIV disease. The purpose of this study was to determine the relationship between drug abuse and dietary intake in Hispanic Americans with and without HIV infection. In this study, dietary intake was measured using 3-day food records and 24-hour dietary recalls in three groups: HIV-positive drug abusers, HIV-negative drug abusers and HIV-positive persons who do not use drugs ('non-drug abusers'). The baseline data from a prospective cohort study of the role of drug abuse in HIV/AIDS weight loss and malnutrition conducted in Boston, Massachusetts, USA was examined. The first 284 participants to enroll in the study served as subjects. Results indicated that HIV-positive drug abusers had a body mass index (BMI) that was significantly lower than that of HIV-positive non-drug abusers. Reported energy, fat and fiber intakes did not differ between groups. All groups had median reported intakes of vitamin A, vitamin B6, vitamin B12, selenium and zinc that were in excess of the dietary reference values (DRI). Intakes of alpha-tocopherol were below the DRI, but did not differ from intakes of the general US population. However, increasing levels of drug abuse were associated with lower reported intakes of vitamin B6, vitamin B12, selenium and zinc. Overall, this study does not support the notion that dietary intake can explain the lower BMI of HIV-positive drug abusers. Further studies examining non-dietary determinants of nutritional status in drug abusers are warranted. Forrester, J.E., Tucker, K.L. and Gorbach, S.L. Dietary Intake and Body Mass Index in HIV-positive and HIV-negative Drug Abusers of Hispanic Ethnicity. Public Health Nutr. 7(7), pp. 863-870, 2004.

Immunology of HCV Infection

Persons with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) co-infection are at increased risk for progression to cirrhosis compared with persons with HCV alone, but the reasons for this are unclear. In chronic HCV, the mechanism of liver injury is presumed to be due to HCV-specific T cell destruction of hepatocytes, so it is paradoxical that immunosuppressed hosts have higher rates of fibrosis progression. Intrahepatic cellular immune responses to HCV antigens were assessed to determine whether there were qualitative or quantitative differences in subjects with and without HIV. Expanded, CD4-enriched, liver-infiltrating lymphocytes from 18 subjects with chronic HCV and 12 subjects with HIV/HCV were cultured in the presence of HCV core protein, nonstructural proteins NS3 and NS5, and recall antigens tetanus toxoid and Candida. Secretion of interferon gamma (IFN-gamma), tumor necrosis factor alpha (TNF-alpha), and interleukin (IL) 10 was determined using enzyme-linked immunosorbent spot assay. There were no significant differences in liver biopsy grade or stage for HIV/HCV versus HCV groups. There were no significant differences between groups in the secretion of IFN-gamma or TNF-alpha in response to HCV or recall antigens. However, there was a significant increase in IL-10 secretion in response to NS3 and NS5 in subjects with HCV compared with HIV and HCV co-infection. In conclusion, subjects with co-infection have an alteration of intrahepatic HCV-specific IL-10 cytokine response that may have implications for HCV-related disease progression. Graham, C.S., Curry, M., He, Q., Afdhal, N., Nunes, D., Fleming, C., Horsburgh, R., Craven, D., Sherman, K.E. and Koziel, M.J. Comparison of HCV-specific Intrahepatic CD4+ T Cells in HIV/HCV Versus HCV. Hepatology. 40(1), pp. 125-132, 2004.

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Injection Drug Use and Crack Cocaine Smoking: Independent and Dual Risk Behaviors for HIV Infection

Previous studies have examined the practices of injecting drugs or smoking crack cocaine as high-risk, but independent, factors for HIV transmission. To explore the independent and dual risks of injection practices and crack smoking, this study examined HIV seroprevalence rates among distinct drug user groups, based on patterns of daily administration. A sample of 3,555 drug users and neighborhood controls in urban Miami, FL and rural Belle Glade and Immokalee, FL were partitioned into four mutually-exclusive groups: 1) injection drug users (IDUs); 2) crack-cocaine smokers; 3) dual users who both smoked crack and injected drugs; and 4) non-drug-user controls. HIV seroprevalence rates were 45.1% for IDUs, 30.5% for dual users, 20.1% for crack smokers and 7.3% for controls. Multivariate logistic regression analysis found that when compared with controls, odds ratios for HIV seropositivity were 9.81 for IDUs, 5.27 for dual users, and 2.24 for crack smokers. These findings provide evidence of: 1) behavioral and structural co-factors that influence HIV exposure patterns among drug users; and 2) the substantially higher risk of HIV infection among IDUs compared with other drug users (such as smoking crack). Intervention strategies must be tailored for the specific drug use subpopulations to optimize efficacy. McCoy, C.B., Lai, S., Metsch, L.R., Messiah, S.E. and Zhao, W. Injection Drug Use and Crack Cocaine Smoking: Independent and Dual Risk Behaviors for HIV Infection. Ann Epidemiol. 14(8), pp. 535-542, 2004.

Drug Abuse and Neuropathogenesis

Dendritic cells (DC) are the critical mediators of various immune responses and are the first line of defense against any infection including HIV. They play a major role in harboring HIV and the subsequent infection of T cells and passage of virus through the blood-brain barrier (BBB). The recently discovered DC-specific, CD4-independent HIV attachment receptor, DC-SIGN, and T-cell suppressing factor, indolamine 2,3-dioxygenase (IDO), are known to play a critical role in the immuno-neuropathogenesis of HIV infection. Since brain microvascular cells (BMVEC) express dendritic cell (DC)-specific C type ICAM-3 grabbing nonintegrin (DC-SIGN), it is possible that DC-SIGN may play a critical role in human immunodeficiency virus-type 1 (HIV-1) infection and migration of infected DC across BBB. Matrix metalloproteinases (MMPs) are proteolytic enzymes known to be responsible for maintenance, turnover and integrity of the extracellular matrix. The results show that cocaine upregulates IDO and DC-SIGN expression by DC. Further, cocaine upregulates DC-SIGN and MMPs in BMVEC supporting the hypothesis that cocaine causes membrane permeability facilitating endothelial transmigration of infected DC in to the CNS. Targeting DC-SIGN and IDO with specific monoclonal antibodies, inexpensive synthetic antagonists, antisense oligonucleotides and siRNA may lead to development of novel treatment strategies particularly in high-risk populations such as cocaine users. Nair, M.P., Schwartz, S.A., Mahajan, S.D., Tsiao, C., Chawda, R.P., Whitney, R., Don Sykes, B.B. and Hewitt, R. Drug Abuse and Neuropathogenesis of HIV Infection: Role of DC-SIGN and IDO. J Neuroimmunol., 157(1-2), pp. 56-60, 2004.

Drug Abuse and Progression of HIV Disease

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

Effect of Hard-Drug Use on CD4 Cell Percentage, HIV RNA Level, and Progression to AIDS-Defining Class C Events Among HIV-Infected Women

In vitro and animal studies suggest that cocaine and heroin increase HIV replication

and suppress immune function, whereas epidemiologic studies are inconclusive regarding their effect on HIV infection progression. The authors prospectively examined the association between illicit-drug use and 4 outcome measures (CD4 cell percentage, HIV RNA level, survival to class C diagnosis of HIV infection, and death) in a national cohort of HIV-infected women. Women enrolled between 1989 and 1995 were followed for 5 years and repeatedly interviewed about illicit ("hard")-drug use. Up to 3 periodic urine screens validated self-reported use. Outcomes were compared between hard-drug users (women using cocaine, heroin, methadone, or injecting drugs) and nonusers, adjusting for age, antiretroviral therapy, number of pregnancies, smoking, and baseline CD4 cell percentage. Of 1148 women, 40% reported baseline hard-drug use during pregnancy. In multivariate analyses, hard-drug use was not associated with change in CD4 cell percentage (P = 0.84), HIV RNA level (P = 0.48), or all-cause mortality (relative hazard = 1.10; 95% confidence interval, 0.61-1.98). Hard-drug users did, however, exhibit a higher risk of developing class C diagnoses (relative hazard = 1.65; 95% confidence interval, 1.00-2.72), especially herpes, pulmonary tuberculosis, and recurrent pneumonia. Hard-drug-using women may have a higher risk for nonfatal opportunistic infections. Thorpe, L.E., Frederick, M., Pitt, J., Cheng, I., Watts, D.H., Buschur, S., Green, K., Zorrilla, C., Landesman, S.H. and Hershow, R.C. Effect of Hard-Drug Use on CD4 Cell Percentage, HIV RNA Level, and Progression to AIDS-Defining Class C Events Among HIV-Infected Women. J Acquir Immune Defic Syndr. 37(3), pp. 1423-1430, 2004.

Drug Use and Disease Progression among HIV-Infected Women

Investigators from the Women and Infants HIV Transmission Study (WITS) have examined the relationship between drug use and four outcome measures: two markers of HIV disease progression (CD4 cell percentage, and HIV RNA level), and two clinical outcomes (progression to a first AIDS-defining class C event, and mortality. WITS is a multi-site longitudinal study of the health of HIV-infected mothers and their children, as well as mother-to-child HIV transmission. It is jointly supported by NIAID, NICHD, and NIDA. A woman was categorized as a Ôhard drug' user if she reported use of cocaine, crack, heroin, or other opiates (including methadone), if she reported engaging in injection drug use, or if her urine was positive for any of these drugs. Three time periods were examined for hard drug use (once during pregnancy, and two later points). Each woman was followed for up to five years. Outcomes were compared between hard drug users and nonusers, adjusting for age, antiretroviral therapy, number of pregnancies, smoking, and baseline CD4 cell percentage. Of 1148 women, 40% reported baseline hard drug use during pregnancy. In multivariate analyses, hard drug use was not associated with change in CD4 cell percentage, HIV RNA level, or all-cause mortality. Hard drug users did exhibit a higher risk of developing class C diagnoses, especially herpes, pulmonary tuberculosis, and recurrent pneumonia, leading to a conclusion that HIV-infected women who use hard drugs may be at higher risk for nonfatal opportunistic infections. The investigators consider a number of reasons why a relationship was not found between hard-drug use and CD4 cell percentage or HIV RNA level, given findings of relationships of cocaine and heroin to HIV replication and immune function in animal and in vitro studies, but they also point out that their findings are consistent with most prior epidemiologic evidence. Thorpe, L.E., Frederick, M., Pitt, J., et al. Effect of Hard-Drug Use on CD4 Cell Percentage, HIV RNA Level, and Progression to AIDS-Defining Class C Events among HIV-Infected Women. JAIDS, 37(3), pp. 1423-1430, 2004.

Adult Trauma and HIV Status among Latinas

Latinas have unique cultural factors that can contribute to their health. Recent immigration, documentation status, and language barriers can impact their lives in various ways. Additional stressors and experiencing traumatic events can impact psychological adjustment and substance use. This study tests the differential contribution of adult trauma and other life stressors to psychological adjustment and substance use among Latinas who differ in their HIV status and level of acculturation. A community sample of 121 (87 HIV-positive and 34 HIV-negative) 18 to 50 year old Latinas participated in this study using baseline and one-year follow-up data. Path analyses examined the influence of acculturation, HIV status, and adult trauma, including intimate partner violence (IPV) and sexual assault, on subsequent changes in psychological adjustment (depression) and substance use one year later. Demographic variables of age, education, and relationship status were controlled and further analyses examined the interactive influence of HIV status and acculturation and trauma on the outcomes. Findings indicate that both acculturation and HIV status were related to the outcome variables, but did not influence these over time, emphasizing the developmental stability of these processes. Education was the most

prominent variable in protecting these women from HIV, depression, and intimate partner violence (IPV), but placed them at greater risk for illicit drug use. The primary predictors of change in the outcome variables were domestic and sexual trauma that were exacerbated by HIV positive status. Newcomb, M.D., and Carmona, J.V. Adult Trauma and HIV Status among Latinas: Effects Upon Psychological Adjustment and Substance Use. AIDS and Behavior, 8, pp. 417-428, 2004.

Correlates of Hepatitis C Infection in Homeless Men

This study was conducted as a secondary analysis of data collected by Dr. Adeline Nyamathi and her team of outreach workers in the Los Angeles Skid Row area, where there is a high concentration of homeless people. Homeless individuals are at risk for numerous health problems including Hepatitis C virus (HCV). HCV is primarily caused by sharing of equipment associated with injection drug use (IDU). In the current study, authors assessed differences among HCV-negative and HCV-positive homeless men residing in Los Angeles (N = 198; about 50% HCV positive) on a number of risk factors and behaviors. Findings revealed several significant correlates of HCV-positive status. HCV-positive status was significantly and positively associated with a history of substance use (both IDU and non-IDU), recent risky IDU-related behaviors including equipment sharing, other forms of sharing (e.g., toothbrushes, razors), homelessness severity, tattoos, sexually transmitted diseases, a jail/prison history, and greater age. Lifetime alcohol problems were not associated with HCV. Although associations of HCV with current IDU-related behaviors such as needle-sharing are not surprising, it is particularly alarming that these risky behaviors were recent. Those who work among homeless populations should be aware not only of the high likelihood of HCV infection in this population but also of the transmission risk due to continued IDU sharing behaviors. Substance abuse treatment should be implemented to hinder the spread of HCV in this vulnerable population. Stein, J.A. and Nyamathi, A. Correlates of Hepatitis C Infection in Homeless Men: A Latent Variable Approach. Drug and Alcohol Dependence, 75, pp. 89-95, 2004.

Cross-sectional and Longitudinal Associations in Coping Strategies and Physical Health Outcomes among HIV-positive Youth

This study assessed whether coping styles had an influence on physical health outcomes either concurrently or longitudinally in a sample of HIV-positive youth. In the case of people living with HIV/AIDS, empirical studies have indicated that coping skills buffer stress, have a mental health benefit, increase adherence to medication, and are associated with a better quality of life. Whether this benefit extrapolates to physical health is more questionable. Coping styles were characterized as positive, passive, depressive withdrawal, and escapist. A cross-sectional latent variable analysis (N = 279) assessed associations among environmental stress, self-esteem, social support, coping styles, AIDS symptoms, and CD4 count. A more restricted longitudinal analysis (N = 174) tested associations among earlier environmental stress, self-esteem, coping styles, and AIDS symptoms at follow-up. CD4 count was not associated with coping styles in the cross-sectional analysis. Concurrent AIDS symptoms were significantly predicted by depressive withdrawal and environmental stress. A passive coping style modestly predicted more AIDS symptoms longitudinally. The authors concluded that correlates of perceived health and well-being of persons with HIV/AIDS are important to investigate in addition to more objective measures such as CD4 count that may not be amenable to change through coping style interventions alone. Stein, J.A., and Rotheram-Borus, M.J. Cross-sectional and Longitudinal Associations in Coping Strategies and Physical Health Outcomes Among HIV-positive Youth. Psychology and Health, 19, pp. 321-336, 2004.

The Efficacy of an Integrated Risk Reduction Intervention for HIV-positive Women with Child Sexual Abuse Histories

Child sexual abuse (CSA) is associated with HIV risk behaviors1 and more prevalent among women living with HIV than in the general population2. This randomized Stage II clinical trial tested the impact of a culturally congruent psychoeducational intervention designed to reduce sexual risks and increase HIV medication adherence for HIV-positive women with CSA histories. An ethnically diverse sample of 147 women were randomized to two conditions: an 11-session Enhanced Sexual Health Intervention (ESHI) or an attention control. Results based on "intent to treat" analyses of pre-post changes are reported in the article. Additional analyses explored whether the observed effects might depend on "intervention dose," i.e., number of sessions attended. Women in the ESHI condition reported greater sexual risk reduction than women in the control condition. Although there were no differences between women in the ESHI and control groups on medication adherence, women in the ESHI condition who attended 8 or more sessions reported greater medication

adherence at post-test than control women. The findings provide initial support for this culturally- and gender-congruent psychoeducational intervention for HIV-positive women with CSA, and highlight the importance of addressing the effects of CSA on sexual risk reduction and medication adherence in preventive interventions for women. Wyatt, G.E., Longshore, D., Chin, D., Carmona, J.V., Loeb, T.B., Myers, H.F., Warda, N., Liu, H., and Rivkin, I. The Efficacy of an Integrated Risk Reduction Intervention for HIV-positive Women with Child Sexual Abuse Histories. AIDS and Behavior, 8, pp. 453-462, 2004.

Co-Occurring Hepatitis C, Substance Use, and Psychiatric Illness: Treatment Issues and Developing Integrated Models of Care

Hepatitis C virus (HCV) infection is transmitted by injection drug use and associated with psychiatric conditions. Patients with drug use or significant psychiatric illness have typically been excluded from HCV treatment trials noting the 1997 National Institutes of Health Consensus Statement on HCV that indicated active drug use and major depressive illness were contraindications to treatment of HCV infection. However, the 2002 NIH Consensus Statement recognized that these patients could be effectively treated for HCV infection and recommended that treatment be considered on a case-by-case basis. Treating HCV infection in these patients is challenging, with drug use relapse possibly leading to psychosocial instability, poor adherence, and HCV re-infection. Interferon therapy may exacerbate preexisting psychiatric symptoms. Co-occurring human immunodeficiency virus or hepatitis B virus provide additional challenges, and access to ancillary medical and psychiatric services may be limited. Patients with co-occurring HCV infection, substance use, and psychiatric illness can complete interferon treatment with careful monitoring and aggressive intervention. Clinicians must integrate early interventions for psychiatric conditions and drug use into their treatment algorithm. Few programs or treatment models are designed to manage co-occurring substance use, psychiatric illness, and HCV infection and therapy. The National Institute on Drug Abuse convened a panel of experts to address the current status and the long-range needs through a 2-day workshop, Co-occurring Hepatitis C, Substance Abuse, and Psychiatric Illness: Addressing the Issues and Developing Integrated Models of Care. This conference report summarizes current data, medical management issues, and strategies discussed. Sylvestre, D.L., Loftis, J.M., Hauser, P., Genser, S., Cesari, H., Borek, N., Kresina, T.F., Seeff, L. and Francis, H. Co-occurring Hepatitis C, Substance Use, and Psychiatric Illness: Treatment Issues and Developing Integrated Models of Care. J Urban Health, 81(4), pp. 719-734, 2004.

The Utility of Indirect Predictors of Hepatitis C Viremia

Although the majority of injection drug users (IDUs) have been exposed to hepatitis C (HCV), only 60-85% remain chronically viremic and at risk for HCV-induced progressive liver damage or transmitting HCV to others. Access to direct viral testing to establish the presence or absence of viremia is limited due to its expense. This study of 500 current and former IDUs examines the utility of demographic and biochemical features as a means of indirectly predicting HCV viremia. Retrospective chart and laboratory review were the methods employed for data collection. Overall, 409 (81.8%) were viremic at the time of presentation. HCV viremia did not correlate with the presence of active drug or alcohol use, drug of abuse, duration of drug use, or length of injecting career, but was more common in males and African-Americans. An elevated ALT, found in 36% of patients, was the best biochemical predictor: 95.6% of these patients were viremic. Other predictors of viremia included thrombocytopenia, hypoalbuminemia, elevated GGT, and total bilirubin level, with a stepwise increase in viremia seen as the number of abnormal biochemical predictors increased. The absence of HCV viremia was more difficult to predict. Viremia was found in 66.3% of those lacking all biochemical predictors and even in 43.8% of those in the lowest 10th percentile of ALT. Although indirect demographic and laboratory parameters may be used to help predict viremia in 40% of HCV-exposed IDUs, they are inadequate substitutes for direct viral testing and instead should be used only as an adjunct to education and referrals in high-risk patients. Sylvestre, D.L. and Clements, B.J. The Utility of Indirect Predictors of Hepatitis C Viremia. Drug Alcohol Depend, 74(1), pp. 15-19, 2004.

Risk Factors for Hepatitis C Virus Infection among Blood Donors in Northern Thailand

The epidemiology, virology, and risk factors for hepatitis C virus (HCV) infection among blood donors in northern Thailand have not been extensively evaluated. The researchers performed a prospective matched case-control study of blood donors who tested positive for HCV and were confirmed by recombinant immunoblot assay or nucleic acid testing. Infected donors were matched with one to four HCV-uninfected

donors for sex, age +/- 5 years, and donation at the same site within 15 days of the HCV-positive donor. Married donors were invited to bring their spouse for HCV testing. Among 166 matched sets, a history of intravenous drug use (IDU), reported by 58 HCV infected donors (35.5%) and 2 HCV-negative donors, was strongly associated with HCV infection (odds ratio [OR], 107.6; 95% confidence interval, 14.8-780.7). In multivariate analysis among donors without a history of IDU, significant risk factors included a history of a blood transfusion (OR, 28.8), immediate family with a history of hepatitis/jaundice (OR, 4.4), six or more lifetime sexual partners (OR, 2.7); the frequency of blood donation was negatively associated with HCV infection (OR, 0.89). Six of 45 spouses of HCV-infected donors, and none of 44 spouses of uninfected donors, were HCV positive (p = 0.005). Data indicate that illicit IDU and a history of transfusion are important risk factors for HCV infection in Thailand. Also, these data suggest there may be some risk of transmission by sex or other close contact between spouses. Thaikruea, L., Thongsawat, S., Maneekarn, N., Netski, D., Thomas, D.L. and Nelson, K.E. Risk Factors for Hepatitis C Virus Infection among Blood Donors in Northern Thailand. Transfusion, 44(10), pp. 1433-1440, 2004.

Marijuana Withdrawal

The authors review the literature examining the validity and significance of cannabis withdrawal syndrome. Findings from animal laboratory research are briefly reviewed, and human laboratory and clinical studies are surveyed in more detail. Converging evidence from basic laboratory and clinical studies indicates that a withdrawal syndrome reliably follows discontinuation of chronic heavy use of cannabis or tetrahydrocannabinol. Common symptoms are primarily emotional and behavioral, although appetite change, weight loss, and physical discomfort are also frequently reported. The onset and time course of these symptoms appear similar to those of other substance withdrawal syndromes. The magnitude and severity of these symptoms appear substantial, and these findings suggest that the syndrome has clinical importance. Diagnostic criteria for cannabis withdrawal syndrome are proposed. Budney, A.J., Hughes, J.R., Moore, B.A. and Vandrey, R. Review of the Validity and Significance of Cannabis Withdrawal Syndrome. Am J Psychiatry,161(11), pp. 1967-1977, 2004.

Nuclear Receptor Activation and Interaction with Morphine

Nervous system disease in HIV infection is associated with toxic damage induced by effects from proinflammatory responses and oxidative stress, and such effects may be more prominent among opioid abusers. In these studies, the effects of activating retinoid receptor (retinoic acid receptor (RAR) and retinoid X receptor (RXR)) and peroxisome proliferator activated receptor (PPAR) gamma, which belong to the steroid-lipid nuclear receptor family, on tumor necrosis factor (TNF)-alpha production and inducible nitric oxide synthase (iNOS) gene expression by stimulated U937 and SVG cells, respectively, were examined. Also studied were the effects of morphine on these responses. These studies showed that, in stimulated cells, the observed responses were suppressed by activation of the nuclear receptors as compared to non-stimulated control cells. Moreover, in phytohemagglutinin (PHA)-stimulated U937 cells, morphine reversed the TNF-alpha suppression that was induced by LG101305 and ciglitazone. Preliminary data in SVG cells suggest a tendency for morphine to have a similar effect on LG101305-exposed SVG cells stimulated with a combination of lipopolysaccharide (LPS) and interferon-gamma, whereas this effect was not induced when these cells were incubated with ciglitazone. Therefore, specific nuclear receptor activation may be potentially beneficial in the treatment of neurological disease associated with HIV infection and may show specific interactions with opioids. The mechanisms that underlie these effects require further study. Royal, W. III, Leander, M., Chen, Y.E., Major, E.O. and Bissonnette, R.P. Nuclear Receptor Activation and Interaction with Morphine. J Neuroimmunol., 157(1-2), pp. 61-65, 2004.

Cocaine Use and Renal Disease

Cocaine has anaesthetic, vasoconstrictive and CNS stimulatory effects. Presently, it is used clinically as a local anaesthetic and abused as a recreational drug. It has been implicated in both acute and chronic renal failure and has been reported to affect every aspect of the nephron. This article reviews the spectrum of cocaine-induced kidney disease and attempts to give insight into the pathophysiological mechanisms involved. Gitman, M.D. and Singhal, P.C. Cocaine-Induced Renal Disease. Expert Opin Drug Saf. 3(5), pp. 441-448, 2004.

Gender Differences in Triazolam Pharmacokinetics

Sixty-one healthy men and women, aged 20 to 75 years, received single 0.25-mg doses of triazolam, a cytochrome P450 (CYP) 3A substrate benzodiazepine, and placebo in a double-blind crossover study. Among women, age had no significant effect on area under the triazolam plasma concentration curve (AUC) (Spearman r=0.14, P=.44) or clearance (r =-0.09, P=.62). Among men, AUC increased (r=0.43, P < .02) and clearance declined (r=-0.42, P <.02) with increasing age. Gender differences in triazolam kinetics were not apparent. Compared with placebo, triazolam impaired digit-symbol substitution test performance, increased observer-rated sedation, impaired delayed recall of information learned at 1.5 hours after dosing, and increased electroencephalographic beta amplitude. Among men, mean values of relative digit-symbol substitution test decrement (P <.002) and observer-rated sedation (P <.05) were significantly greater in elderly subjects compared with young subjects. Age-dependent differences among women reached significance for observer-rated sedation (P <.02). A combination of higher plasma levels and increased intrinsic sensitivity explained the greater pharmacodynamic effects of triazolam in elderly subjects. Although the findings are consistent with reduced clearance of triazolam in elderly men, individual variability was large and was not explained by identifiable demographic or environmental factors. Greenblatt, D.J., Harmatz, J.S., von Moltke, L.L., Wright, C.E. and Shader, R.I. Age and Gender Effects on the Pharmacokinetics and Pharmacodynamics of Triazolam, A Cytochrome P450 3A Substrate. Clin Pharmacol Ther., 76(5), pp. 467-479, 2004.

Inhibition of Cytochrome P450 by Ginkgo Biloba

The extraction, isolation and characterization of 29 natural products contained in Ginkgo biloba have been described, which we have now tested for their in-vitro capacity to inhibit the five major human cytochrome P450 (CYP) isoforms in human liver microsomes. Weak or negligible inhibitory activity was found for the terpene trilactones (ginkgolides A, B, C and J, and bilobalide), and the flavonol glycosides. However 50% inhibitory activity (IC50) was found at concentrations less than 10 microg L(-1) for the flavonol aglycones (kaempferol, quercetin, apigenin, myricetin, tamarixetin) with CYP1A2 and CYP3A. Quercetin, the biflavone amentoflavone, sesamin, as well as (Z,Z)-4,4'-(1,4-pentadiene-1,5-diyl)diphenol and 3-nonadec-8-enyl-benzene-1,2-diol, were also inhibitors of CYP2C9. The IC50 of amentoflavone for CYP2C9 was 0.019 microg mL(-1) (0.035 microM). Thus, the principal components of Ginkgo biloba preparations in clinical use (terpene trilactones and flavonol glycosides) do not significantly inhibit these human CYPs in-vitro. However, flavonol aglycones, the biflavonol amentoflavone and several other non-glycosidic constituents are significant in-vitro inhibitors of CYP. The clinical importance of these potential inhibitors will depend on their amounts in ginkgo preparations sold to the public, and the extent to which their bioavailability allows them to reach the CYP enzymes in-situ. von Moltke, L.L., Weemhoff, J.L., Bedir, E., Khan, I.A., Harmatz, J.S., Goldman, P. and Greenblatt, D.J. Inhibition of Human Cytochrome P450 by Components of Ginkgo Biloba. J Pharm Pharmacol., 56(8), pp. 1039-1044, 2004.

Director's Report to the National Advisory Council on Drug Abuse - February, 2005

Research Findings - Services Research

Drug Abuse Treatment Is Cost-effective in Prison

This paper extends previous research that performed a cost-effectiveness analysis (CEA) of the Amity in-prison therapeutic community (TC) and Vista aftercare programs for criminal offenders in southern California. To assess the impact of treatment over time for this unique sample of criminal offenders (N=576), a 5-year follow-up CEA was performed to compare the cost of an offender's treatment-starting with the in-prison TC program and including any community-based treatment received post-parole-and the effectiveness of treatment in terms of days reincarcerated. The average cost of addiction treatment over the baseline and 5-year follow-up period was $7,041 for the Amity group and $1,731 for the control group. The additional investment of $5,311 in treatment yielded 81 fewer incarceration days (13%) among Amity participants relative to controls-a cost-effectiveness ratio of $65. When considering the average daily cost of incarceration in California ($72), these results suggest that offering treatment in prison and then directing offenders into community-based aftercare treatment is a cost-effective policy tool. McCollister, K.E., French, M.T., Prendergast, M.L., Hall, E. and Sacks, S. Long-term Cost Effectiveness of Addiction Treatment for Criminal Offenders. Justice Quarterly, 21(3), pp. 659-679, 2004.

Outcomes and Costs of Day Hospital Versus Community Day Treatment

The purpose of this study was to estimate the outcomes and costs of day hospital and nonmedical community-based day treatment for chemical dependency. A community sample of 271 adults (179 men) dependent on alcohol and/or drugs was recruited and randomized to either a hospital-based (medical) day treatment program or to a community-based (nonmedical) day treatment program. The day hospital (DH) program lasted for 3 weeks. One community-based program (CP2) lasted for 4 weeks, and the other (CP1) lasted for 6 weeks but with shorter treatment days and more criminal justice clients. Because of concerns regarding treatment fidelity, the CP1 was replaced with CP2 as the randomization site for the nonmedical, community-based arm of the trial halfway through the study. Abstinence rates were similar between DH and CP2 subjects, with 53% and 60% of each group, respectively, reporting no drinking for the 30 days preceding both follow-up interviews. DH subjects were less likely than those in either of the nonmedical programs to report medical problems at both follow-ups. Average episode costs per client were significantly ($p < .01$) lower at CP1 ($526) than at DH ($1,274) or CP2 ($1,163). A pattern of weaker effects was observed at the less costly problematic community program (CP1), including less abstinence than was reported at CP2 (only 40% of CP1 subjects were alcohol free at both follow-ups) and worse psychiatric, family/friend and employment outcomes than were reported at DH or CP2. Results demonstrate the clinical diversity that exists between nonmedical, community-based day treatment programs and show that nonmedical programs can compete with DH treatment in cost as well as in most outcomes. Kaskutas, L.A., Witbrodt, J. and French, M.T. Outcomes and Costs of Day Hospital Treatment and Nonmedical Day Treatment for Chemical Dependency. J. Stud. Alcohol, 65(3), pp. 371-82, 2004.

ADHD Status and Relapse In Adolescent Drug Abusers following Treatment

This study examined adolescent drug abusers in treatment (N = 220) to estimate the degree to which probable ADHD status increases the odds of post-treatment alcohol, marijuana, and other drug relapse during 6 months following discharge. Drug abusing youth with probable ADHD status exhibited 2.5 times the risk of post-treatment

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alcohol relapse when compared to youth without probable ADHD status while controlling for demographics, pretreatment conduct-disordered behavior, pretreatment alcohol use frequency, and treatment factors. A significant crude association between probable ADHD status and other drug relapse was not maintained when adjusted for pretreatment conduct-disordered behavior, pretreatment other drug use frequency, or treatment factors. The findings suggest that standard treatment approaches that do not directly address co-morbid disorders may result in elevated post-treatment relapse rates among recovering youth with ADHD. Latimer, W.W., Ernst, J., Hennessey, J., Stinchfield, R.D., and Winters, K.C. Relapse Among Adolescent Drug Abusers Following Treatment: The Role of Probable ADHD Status. Journal of Child and Adolescent Substance Abuse, 13(3), pp. 1-16, 2004.

Marijuana Use Associated with School Dropout and Truancy

This paper explores the relationship between adolescent marijuana use and school attendance. Data were pooled from the 1997 and 1998 National Household Surveys on Drug Abuse to form a sample of 15,168 adolescents, aged 12-18 years, who had not yet completed high school. The analysis determined the role of marijuana use in adolescent school dropout and, conditional on being enrolled, estimated the number of days truant. The potential endogeneity of marijuana use was tested in all specifications. The results indicate that any marijuana use was positively associated with school dropout and truancy in all models. However, when chronic marijuana use (weekly or more frequent) was distinguished from non-chronic marijuana use (less frequent than weekly), chronic marijuana use was found to be the dominant factor in these relationships. The results have important implications for educators, substance abuse treatment providers, and policymakers. Roebuck, M.C., French, M.T., and Dennis, M.L. Adolescent Marijuana Use and School Attendance. Economics of Education Review, 23(2), pp. 133-141, 2004.

Implementation of Managed Care Did Not Affect Receipt of Mental Health Services for Clients in Substance Abuse Treatment

Mental health services affect treatment retention and outcomes for many clients in substance abuse treatment programs. This natural experiment assessed whether converting Medicaid from a fee-for-service program to a capitated, prepaid managed care program affected access to mental health services among clients treated for substance abuse. Medicaid enrollees who were being treated for substance abuse in Oregon were interviewed before treatment and after six months of service. One cohort (N=53) was interviewed one to six months before the implementation of managed care, a second (N=66) was interviewed two years after implementation, and a third (N=49) was interviewed three to four years after implementation. Logistic regression analyses were used to identify whether the implementation of managed care, the psychiatric need of the client, and other client characteristics affected the receipt of mental health services during the first six months of substance abuse treatment. Clients in all three cohorts had similar characteristics. The implementation of managed care did not affect whether clients received mental health services. Baseline psychiatric score derived from the Addiction Severity Index was the only client characteristic that predicted receipt of mental health services. Bigelow, D.A., McFarland, B.H., McCamant, L.E., Deck, D.D., and Gabriel, R.M. Effect of Managed Care on Access to Mental Health Services among Medicaid Enrollees Receiving Substance Treatment. Psychiatric Services, 55(7), pp. 775-779, 2004.

Substance Abuse Treatment Needs and Access in the USA: Interstate Variations

This study investigated interstate substance abuse treatment needs and access in the USA. After assessing the validity of recently developed survey and indicator measures, the study analyzed the geographic distribution and nature of state substance abuse treatment needs. Substance abuse treatment utilization index scores were regressed on the need measurements to identify differences among state populations in treatment access. Treatment needs clustered in stable, distinct geographic patterns. The most severe problems, primarily reflecting alcoholism, were in the West. Drug and alcohol substance use disorders and related problems were not significantly correlated at this level of aggregation. There was evidence of regionalization of the drug-of-choice mix in treatment admissions. Only 21% of the variations in state treatment utilization rates stemmed from the prevalence of substance use disorders and related problems. The biggest treatment gaps were in the South and South-West, regions with large minority populations. Development of interstate survey and indicator measures of treatment needs has created new opportunities to broaden our understanding of substance abuse epidemiology and

Staff Highlights

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In Memoriam

treatment access in the USA. The nature and severity of drug and alcohol problems vary from state to state, but the interstate disparities in treatment services remain even after variations in treatment need have been discounted. Further research is needed to understand the causes of these differences in treatment access. McAuliffe, W.E., and Dunn, R. Substance Abuse Treatment Needs and Access in the USA: Interstate Variations. Addiction, 99(8), pp. 999-1014, 2004.

Mixed Results for Step Down Continuing Care in the Treatment of Substance Abuse

This study examined the predictors of participation in step down continuing care (i.e., contiguous episode of care at a lower level of intensity) in publicly funded substance abuse treatment programs, and the relation between participation in step down care and alcohol and crack cocaine use outcomes over a 36-month follow-up. The sample included patients in residential/inpatient programs (IP; N = 134) and intensive outpatient programs (IOP; AT = 370). About one-third of IP patients received step down continuing care; fewer than 25% of IOP patients received step down continuing care. Patients who received step down continuing care following IP had greater social support at intake and were more likely to be female and White than those who did not receive continuing care. Patients who received continuing care following IOP were more likely than those who did not to be female and employed, and were older, had higher self-efficacy, and shorter lengths of stay in IOP. Participation in step down care was not associated with other factors assessed at intake. In the IP sample, receiving step down continuing care was not associated with better alcohol or crack cocaine use outcomes over the 36-month follow-up. In the IOP sample, there were no main effects favoring continuing care for either alcohol or crack cocaine use outcomes. However, patients who received continuing care had less crack cocaine use in the first six months of the follow-up. These findings suggest that new models of continuing care are needed that are more acceptable to patients, produce better outcomes, and are cost-effective. McKay, J.R., Foltz, C., Leahy, P., Stephens, R., Orwin, R.G., and Crowley, E.M. Step Down Continuing Care in the Treatment of Substance Abuse: Correlates of Participation and Outcome Effects. Evaluation and Program Planning, 27(3), pp. 321-331, 2004.

Alcohol and Marijuana Use Among College Students

Previous research has shown that the recent tightening of college alcohol policies has reduced college students' drinking. Over the period in which these stricter alcohol policies have been put in place, marijuana use among college students has increased. This raises the question of whether current policies aimed at reducing alcohol consumption are inadvertently encouraging marijuana use. This paper addressed this question by investigating the relationship between the demands for alcohol and marijuana for college students using data from the 1993, 1997, and 1999 waves of the Harvard School of Public Health's College Alcohol Study (CAS). Researchers found that alcohol and marijuana are economic complements and that policies that increase the full price of alcohol are associated with decreased participation in marijuana use. Williams, J., Pacula, R.L., Chaloupka, F.J., and Wechsler, H. Alcohol and Marijuana Use Among College Students: Economic Complements or Substitutes? Health Economics, 13(9), pp. 825-843, 2004.

To What Extent Are Key Services Offered in Treatment Programs for Special Populations?

Many substance abuse treatment (SAT) facilities offer programs tailored for special populations such as women, adolescents, gays/lesbians and others. Previous research shows that there are specific services that are integral to the successful treatment of these populations (e.g., family therapy for adolescents, childcare and transportation assistance for women, and HIV testing and counseling for gays/lesbians). This study examines whether facilities that report having programs for special populations actually offer the recommended services. The data come from the 2000 National Survey of Substance Abuse Treatment Services, which contains information on service offerings, special programs and other characteristics for all SAT facilities in the USA. The results indicate that facilities with special programs are more likely to offer the recommended key services. However, often less than half of these facilities provide the key services. There are consistent differences by ownership status, with for-profit facilities less likely to offer many of the key services. To What Extent are Key Services Offered in Treatment Programs for Special Populations? Olmstead, T. and Sindelar, J.L. Journal of Substance Abuse Treatment, 27(1), pp. 9-15, 2004.

Screening Behavioral Risks in Populations

The concept of behavioral risk refers to health behaviors that increase the likelihood of a variety of illness conditions. With increased scientific research, it has become clear that this concept is useful in understanding the linkage between behavior and health. This paper reviews scientific, conceptual, and practical issues related to the identification of health risk behaviors in primary care. It includes both a literature review and an analysis of the feasibility of screening and health risk appraisal from a public health perspective, giving special attention to four behavioral risk factors: cigarette smoking, alcohol misuse, physical inactivity, and unhealthy diet. The review indicates that there are a wide variety of acceptable screening tests that can be used for population screening programs, and a large number of health risk appraisal instruments to employ in medical and work settings where preventive health services are available. Given the variety of available assessment procedures, the choice of a given instrument will depend on the target population, the purpose of the program, the time available for assessment, and a number of other practical considerations, such as cost. Multiple risk factor screening is feasible, but there is no single instrument or procedure that is optimal for all risk factors or populations. Based on the results of this review, the specific test or combination of tests is less important than the use of screening to make both patients and healthcare providers more aware of the critical importance of monitoring behavioral risk factors on a routine basis. We conclude that while further research and development work needs to be done, sufficient progress has been made to warrant a more ambitious effort that would bring behavioral risk factor screening into the mainstream of preventive medicine and public health. (with Robert Wood Johnson) Babor, T.F., Sciamanna, C.N., Pronk, N.P. Assessing Multiple Risk Behaviors in Primary Care: Screening Issues and Related Concepts. American Journal Preventive Medicine. 27(2 Suppl.), pp. 42-53, 2004.

Effectiveness of Commonly Available Substance Abuse Treatment

Strong efficacy research has been conducted on novel treatment approaches for adolescent substance abusers, yet, little is known about the effectiveness of the substance abuse treatment approaches most commonly available to youths, their families, and referring agencies. This report compares the 12-month outcomes of adolescent probationers (N = 449) who received either Phoenix Academy, a therapeutic community for adolescents that uses a treatment model that is widely implemented across the U.S., or an alternative probation disposition. Across many pretreatment risk factors for relapse and recidivism, groups were well matched after case-mix adjustment. Repeated measures analyses of substance use, psychological functioning, and crime outcomes collected 3, 6, and 12 months after the baseline interview demonstrated that Phoenix Academy treatment is associated with superior substance use and psychological functioning outcomes over the period of observation. As one of the most rigorous evaluations of the effectiveness of a traditional community-based adolescent drug treatment program, this study provides evidence that one such program is effective. Implications of this finding for the dissemination of efficacious novel treatment approaches are discussed. Morral, A.R., McCaffrey, D.F. and Ridgeway, G. Effectiveness of Community-Based Treatment for Substance-Abusing Adolescents: 12-Month Outcomes of Youths Entering Phoenix Academy or Alternative Probation Dispositions. Psychology of Addictive Behaviors. 18(3), pp. 257-268, 2004.

Out of Touch or on The Money: Do the Clinical Objectives of Addiction Treatment Coincide with Economic Evaluation Results?

Previous economic studies have examined the association between substance abuse treatment and reduced costs to society, but it remains uncertain whether the economic measures used in cost and benefit-cost analyses of treatment programs correspond in direction and magnitude with clinical outcomes. In response to this uncertainty, the present study analyzed a longitudinal data set of addiction treatment clients to determine the statistical agreement between clinical and economic outcomes over time. Data were collected from 1,326 clients in the Chicago cohort of the Persistent Effects of Treatment Study. These individuals were interviewed at baseline and at 6-, 24-, 36-, and 48-month follow-up periods (92% follow-up). Correlations between clinical and economic measures were generally small (rho = 0.1 to 0.3) and often became non-significant when controlling for baseline severity. The results demonstrate that although some associations exist, outcomes should be evaluated along both clinical and economic dimensions. Dismuke C.E., French M.T., Salome H.J., Foss, M.A., Scott, C.K., and Dennis, M.L. Out of Touch or on the Money: Do the Clinical Objectives of Addiction Treatment Coincide with Economic Evaluation Results? Journal of Substance Abuse Treat, 27(3), pp. 253-263, 2004.

Cost Estimation of Drug Abuse Treatment

The Drug Abuse Treatment Cost Analysis Program (DATCAP) was designed in the early 1990s as a research guide to collect and analyze financial data from addiction treatment programs. This paper introduces the Brief DATCAP and presents some preliminary findings. Initial feedback from respondents in four adult and one adolescent treatment programs suggests that the Brief DATCAP is understandable, and easier and quicker to complete than the DATCAP. More importantly, preliminary results indicate that cost estimates from the Brief DATCAP differ from those of the longer DATCAP by less than 2%. These results have important research and policy implications because a shorter yet reasonably accurate cost instrument will enhance the feasibility and precision of future economic evaluations of addiction interventions. French, M.T., Roebuck, M.C., and McLellan, A.T. Cost Estimation When Time and Resources are Limited: The Brief DATCAP. Journal of Substance Abuse Treat, 27(3), pp. 187-193, 2004.

Gender Differences in Older Adult Treatment Outcomes For Alcohol Dependence

This study examined clinical characteristics and treatment outcomes of older alcohol-dependent men and women in a mixed-age private outpatient chemical dependency program. The sample comprised 92 patients aged 55 to 77 (63 men and 29 women). The measures consisted of demographic characteristics, alcohol and drug use and dependence, drinking history, health status, psychiatric symptoms, length of stay in treatment, use of Alcoholics Anonymous and 6-month treatment outcomes. Results showed that women reported later initiation of heavy drinking (5+ drinks per occasion) than the men, but had similar drinking levels at the treatment intake interview. At the 6-month follow-up, 79.3% of women reported abstinence from alcohol and drugs in the prior 30 days versus 54.0% of men ($p = .02$). Greater length of stay in treatment predicted abstinence at 6 months. Among those who were not abstinent, none of the women reported heavy drinking in the 30 days prior to follow-up, whereas non-abstinent men reported a mean (SD) of 4.0 (9.2) heavy drinking days ($p = .025$). The results suggest that older women may have better drinking outcomes compared with older men, following treatment for alcohol dependence. Satre, D.D., Mertens, J.R., and Weisner, C. Gender Differences in Older Adult Treatment Outcomes for Alcohol Dependence. Journal of Studies on Alcohol, 65(5), pp. 638-642, 2004.

Five-Year Treatment Outcomes Favorable to Older Adults

This study compared 5-year treatment outcomes of older adults to those of middle-aged and younger adults in a large managed care chemical dependency program. Investigators examined age group differences in individual, treatment and extra-treatment factors, which may influence long-term outcome. Seventy-seven per cent of original study participants completed a telephone interview 5 years after outpatient chemical dependency treatment at Kaiser Permanente. This sample (N = 925) included 65 patients aged 55-77, 296 patients aged 40-54 and 564 patients aged 18-39 (age at baseline). Measures at follow-up included alcohol and drug use, Addiction Severity Index (ASI), Alcoholics Anonymous Affiliation Scale, social resource and self-reported health questions. Mortality data were obtained from contact with family members of patients as well as automated health plan records. Older adults were less likely to be drug-dependent at baseline than younger and middle-aged adults, and had longer retention in treatment than younger adults. At 5 years, older adults were less likely than younger adults to have close family or friends who encouraged alcohol or drug use. Fifty-two per cent of older adults reported total abstinence from alcohol and drugs in the previous 30 days versus 40% of younger adults. Older women had higher 30-day abstinence than older men or younger women. Among participants dependent only on alcohol, there were no significant age differences in 30-day abstinence. In logistic regression analysis, age group was not significant. Variables associated with greater age that independently predicted 30-day abstinence in the logistic regression model included longer retention in treatment and having no close family or friends who encouraged alcohol or drug use at 5 years; female gender was also significant. Results indicate that older adults have favorable long-term outcome following treatment relative to younger adults, but these differences may be accounted for by variables associated with age such as type of substance dependence, treatment retention, social networks and gender. Age differences in these characteristics inform intervention strategies to support long-term recovery of older adults and provide direction for investigation of how age affects outcome. Satre, D.D., Mertens, J.R., Arean, P.A and Weisner, C. Five-year Alcohol and Drug Treatment Outcomes of Older Adults Versus Middle-aged and Younger Adults in a Managed Care Program. Addiction, 99(10), pp. 1286-1297, 2004.

Limitation in DSM-IV Cannabis Tolerance as Indicator of Dependence in Adolescents

The usefulness of the Diagnostic and Statistical Manual's (4th ed.; DSM-IV; American Psychiatric Association, 1994) tolerance criterion as an indicator of dependence has been debated. The authors of this study evaluated the performance of the DSM's cannabis tolerance criterion, operationally defined as a percentage increase in quantity needed to get high, in distinguishing adolescents with and without cannabis dependence. Two samples of adolescent cannabis users (ages 12-19) provided data (ns = 417 and 380). Tolerance, defined as a percentage increase (median increase = 300% and 175%, respectively, in the samples), had only moderate overall sensitivity and specificity in distinguishing those with and without cannabis dependence. Results suggest limitations of the DSM-IV's change-based operational definition of tolerance in adolescents. Chung, T., Martin, C.S., Winters, K.C., Cornelius, J.R., and Langenbucher, J.W. Limitations in the Assessment of DSM-IV Cannabis Tolerance as an Indicator of Dependence in Adolescents. Experimental and Clinical Psychopharmacology, 12(2), pp. 136-146, 2004.

Predicting Incentives to Change among Adolescents with Substance Abuse Disorder

This study assessed the degree and nature of motivation and treatment readiness among adolescents admitted to substance abuse services, and whether such factors vary across subgroups of youth based on their social, legal, or clinical profiles. Data come from interviews with 249 youth, 12-18 years of age, who have been admitted to inpatient, residential, or outpatient substance abuse treatment. Measures are adapted from an instrument developed to assess multiple domains of motivation to change (e.g., intrinsic and extrinsic motivation, treatment readiness). Results suggest that the incentive to change among adolescents with substance-abusing behavior is modest at best, regardless of dimension. Nonetheless, ethnicity, type of substance use, and psychopathology significantly predict incentives to change, though the predictors depend on which dimension is considered. The most robust predictor of incentives is the severity of negative consequences associated with youth's substance use-the greater the severity, the greater the incentives. Breda, C., and Heflinger, C.A. Predicting Incentives to Change Among Adolescents with Substance Abuse Disorder. American Journal of Drug and Alcohol Abuse, 30(2), pp. 251-267, 2004.

Effects of Family Background and Pre-incarceration Socio-environmental Factors on Post-release Drug Use for Prisoners

This study compared the effects of family background and pre-incarceration socio-environmental variables on post-release drug use for prison-based drug treatment participants in order to explain observed disparities in rates of 3-year post-release drug use between African Americans and whites. The sample (279 African Americans, 512 whites) comprised male treatment participants who were supervised by a U.S. probation officer following incarceration. Researchers used event history analysis to model time to first drug use during post-release supervision. Results indicated that none of the family background or socio-environmental factors predicted post-release drug use. Variables predictive of drug use for one or both racial groups were socio-demographic characteristics and pre-incarceration behaviors such as age at release, prior incarcerations, and pre-incarceration employment. There were no significant between-group differences for these predictors. Researchers conclude that future study of the effects of socio-environmental variables on post-release drug use will require evaluation of post-release social environment at time of release. Rounds-Bryant, J., Motivans, M.A., and Pelissier, B.M.M. Correlates of Drug Treatment Outcomes for African American and White Male Federal Prisoners: Results from the TRIAD Study, 30(3), pp. 495-514, 2004.

Boosting, a Modern Statistical Technique, Can Overcome Many Obstacles in Causal Effect Modeling

Causal effect modeling with naturalistic rather than experimental data is challenging. In observational studies participants in different treatment conditions may also differ on pretreatment characteristics that influence outcomes. Propensity score methods can theoretically eliminate these confounds for all observed covariates, but accurate estimation of propensity scores is impeded by large numbers of covariates, uncertain functional forms for their associations with treatment selection, and other problems. This paper demonstrates that boosting, a modern statistical technique, can overcome many of these obstacles. Authors illustrate this approach with a study of adolescent probationers in substance abuse treatment programs. Propensity score weights estimated using boosting eliminate most pretreatment group differences, and

substantially alter the apparent relative effects of adolescent substance abuse treatment. McCaffrey, D.F., Ridgeway,G,. and Morral, A.R. Propensity Score Estimation with Boosted Regression for Evaluating Causal Effects in Observational Studies. Psychological Methods, 9, 2004.

Social Context of HIV Risk Behaviours Among Male-to-Female Transgenders of Colour

To explore the social context of drug use and sexual behaviours that put male-to-female (MTF) transgenders at risk for HIV, focus groups were conducted consisting of African American, Latina and Asian and Pacific Islander MTF transgenders (N=48) who reside or work in San Francisco, California. Participants were likely to report having unprotected sex with primary partners to signify love and emotional connection, as well as to receive gender validation from their partners. In contrast, viewing sex work with customers as a business encouraged intentions to use condoms. Safer sex intentions with customers were frequently undermined by urgent financial needs, which stemmed from transphobia, employment discrimination and costly procedures associated with gender transition. Participants reported using drugs as a way to cope with or escape life stresses associated with relationships, sex work, transphobia and financial hardship. Interventions with at-risk MTF transgenders should address the interpersonal and social context of unsafe sex and drug use, particularly the unique roles of relationship issues with male partners, stigma, discrimination and community norms regarding sex work and drug use. Nemoto, T., Operario, D., Keatley, J. and Villegas, D. Social Context of HIV Risk Behaviours among Male-to-Female Transgenders of Colour. AIDS Care, 16(6), pp. 724-735, 2004.

HIV Risk Behaviors Among Male-to-Female Transgender Persons of Color in San Francisco

The authors examined HIV risk behaviors among African American, Asian/Pacific Islander (API), and Latina male-to-female (MTF) transgender persons in order to improve HIV prevention programs. Individual survey interviews with MTF transgender persons of color (n = 332; 112 African Americans, 110 Latinas, and 110 APIs) were conducted. Prevalence and correlates of receptive anal sex and unprotected receptive anal sex (URAS) varied by type of partner (primary, casual, or commercial sex partners). URAS with primary partners was associated with drug use before sex; URAS with casual partners was associated with HIV-positive status and drug use before sex; and URAS with commercial sex partners was associated with African American ethnicity and low income. Findings on current risk behaviors among MTF transgender persons provided meaningful implications for HIV prevention interventions. Nemoto, T., Operario, D., Keatley, J., Han, L., and Soma, T. HIV Risk Behaviors Among Male-to-Female Transgender Persons of Color in San Francisco. American Journal of Public Health, 94(7), pp. 1193-1999, 2004.

An HIV Prevalence-based Model for Estimating Urban Risk Populations of Injection Drug Users and Men Who Have Sex with Men

Issues of cost and complexity have limited the study of the population sizes of men who have sex with men (MSM) and injection drug users (IDUs), two groups at clearly increased risk for human immunodeficiency virus (HIV) and other acute and chronic diseases. Authors developed a prototypical, easily applied estimation model for these populations and applied it to Miami, Florida. This model combined HIV prevalence estimates, HIV seroprevalence rates, and census data to make plausible estimates of the number and proportion of MSM and IDUs under a number of assumptions. Sensitivity analyses were conducted to test the robustness of the model. The model suggests that approximately 9.5% (plausible range 7.7%-11.3%) of Miami males aged 18 years or older are MSM (point estimate, N =_76,500), and 1.4% (plausible range 0.9%-1.9%) of the total population aged 18 years or older are IDUs (point estimate, N=_23,700). Males may be about 2.5 times more likely than females to be IDUs. The estimates were reasonably robust to biases. The model was used to develop MSM and IDU population estimates in selected urban areas across Florida and should be replicable in other medium-to-large urban areas. Such estimates could be useful for behavioral surveillance and resource allocation, including enhanced targeting of community-based interventions for primary and secondary HIV prevention. Lieb, S., Friedman, S.R., Zeni, M.B., Chitwood, D.D., Liberti, T.M., Gates, G.J., Metsch, L.R., Maddox, L.M., and Kuper, T. Comprehensive Model of Substance Abuse Treatment Processes Introduced. Journal of Urban Health: Bulletin of the New York Academy of Medicine, 81(3), pp. 401-415, 2004.

Case Management Does Not Appear to Improve Outcomes for HIV/AIDS Substance Abuse Patients

A recent clinical trial at San Francisco General Hospital examined the effects of extended-contact case management (52 weekly contacts extending beyond hospital discharge) compared to typical brief-contact (one or two contacts prior to hospital discharge) sessions prior to hospital discharge) for general-medical (44%), outpatient detoxification (25%), and emergency department patients (22%). Case management emphasized education about unsafe drug use and sexual practices related to HIV transmission. Results after 18 months showed no between-condition differences for substance abuse, HIV transmission risk, physical or mental health, service use, nor perceived quality of life. Death from AIDS-related causes (16% of the sample) were the same for both groups. Results demonstrate the importance of using control groups to assess intervention effect levels. Findings call into question claims by several demonstration projects lacking control conditions that case management can improve patient outcomes for substance abuse and HIV risk. Sorensen, J.L., and Masson, C.L. Case Management for Substance Abusers with HIV/AIDS: Lessons from a Clinical Trial. Directions in Rehabilitation Counseling, 15, pp. 193-201, 2004.

Use of a SAMHSA Standard to Guide Change Efforts Can Increase General Medical Use of Buprenorphine among Rural Physicians

The Opiate Medication Initiative for Rural Oregon Residents trained physicians and counselors in Central and Southwestern Oregon to use buprenorphine and develop service models that supported patient participation in drug abuse counseling. The Change Book from Addiction Technology Transfer Centers was used to structure the change process. Fifty-one individuals (17 physicians, 4 pharmacists, 2 nurse practitioners, and 28 drug abuse counselors and administrators) from seven counties completed the training and contributed to the development of community treatment protocols. A pre-post measure of attitudes and beliefs toward the use of buprenorphine suggested significant improvements in attitude after training, especially among counselors. Eight months after training, 10 of 17 physicians trained had received waivers to use buprenorphine and 29 patients were in treatment with six of the physicians. The Change Book facilitated development of county change teams and structured the planning efforts. The initiative also demonstrated the potential to concurrently train physicians, pharmacists, and counselors on the use of buprenorphine. McCarty, D., Rieckmann, T., Green, C. Gallon, G. and Knudsen, J. Training Rural Pactitioners to Use Buprenorphine: Using the Change Book to Facilitate Technology Transfer. Journal of Substance Abuse Treatment, 26, pp. 203-208, 2004.

Addiction Severity Associated with Increased Inpatient & Ambulatory Care Treatment

Research examining managed care in a large urban hospital found that addiction severity was associated with both inpatient and ambulatory care treatment. The study also found that homelessness and substance abuse exacerbate the health care needs of HIV-infected patients, increasing their use of emergency department and inpatient services. The study indicates that substance abuse treatment is likely to reduce the utilization of general medical public health services, especially among addicts with HIV-infections. Masson, C.L, Sorensen, J.L., Phibbs, C.S., and Okin, R.L. Predictors of Medical Service Utilization Among Individuals with Co-occurring HIV Infection and Substance Abuse Disorders. AIDS Care, 16, pp. 744-755, 2004.

Director's Report to the National Advisory Council on Drug Abuse - February, 2005

Research Findings - Research in the Clinical Trials Network (CTN)

Two large-scale clinical trials, **CTN 0006 - Motivational Incentives for Enhanced Drug Abuse Recovery: Drug Free Clinics and CTN 0007 - Motivational Incentives for Enhanced Drug Abuse Recovery: Methadone Clinics**, were conducted in the CTN in Community-based Treatment Programs and completed in 2004. The studies replicated prior small-scale research studies conducted in university-affiliated clinics. These studies, carried out in both methadone programs and psychosocial counseling treatment programs, demonstrated that incentive-based interventions using tangible incentives (vouchers that can be exchanged for retail good or onsite-prizes) that can be earned upon submission of drug-free urine samples, are highly efficacious in increasing treatment retention and promoting abstinence from drugs. These results suggest that incentive programs are effective and should be more widely utilized at community clinics in order to improve the outcome of drug abuse treatment.

CTN 0011 A Feasibility Study of a Telephone Enhancement Procedure (TELE) to Improve Participation in Continuing Care Activities - This study was a CTN multi-site clinical trial to investigate the feasibility and efficacy of telephone calls to support compliance with discharge plans from short-term inpatient treatment facilities. The results of the pilot study attest to the feasibility of this intervention, which was initially developed and implemented at the Betty Ford Center in Community-based Treatment Programs, as well as to a positive effect of the intervention based on subjects' attendance in community outpatient programs to which they were referred and drug abstinence at follow-up.

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Director's Report to the National Advisory Council on Drug Abuse - February, 2005

Research Findings - Intramural Research

Development and Plasticity Section, Cellular Neurobiology Research Branch

Dopaminergic Differentiation of Human Embryonic Stem Cells In this manuscript IRP scientists report that human embryonic stem cells (hESCs) differentiated into dopaminergic neurons when cocultured with PA6 cells. After 3 weeks of differentiation, approximately 87% of hES colonies contained tyrosine hydroxylase (TH)-positive cells, and a high percentage of the cells in most of the colonies expressed TH. Differentiation was inhibited by exposure to BMP4 or serum. TH-positive cells derived from hESCs were postmitotic, as determined by bromodeoxyurindine colabeling. Differentiated cells expressed other markers of dopaminergic neurons, including the dopamine transporter, aromatic amino acid decarboxylase, and the transcription factors associated with neuronal and dopaminergic differentiation, Sox1, Nurr1, Ptx3, and Lmx1b. Neurons that had been differentiated on PA6 cells were negative for dopamine-beta-hydroxylase, a marker of noradrenergic neurons. PA6-induced neurons were able to release dopamine and 3,4-dihydroxphe-hylacetic acid (DOPAC) but not noradrenalin when depolarized by high K(+).When transplanted into 6-hydroxydopamine-treated animals, hES-derived dopaminergic cells integrated into the rat striatum. Five weeks after transplantation, surviving TH-positive cells were present but in very small numbers compared with the high frequency of TH-positive cells seen in PA6 coculture. Larger numbers of cells positive for smooth muscle actin, but no undifferentiated ES cells, were present after transplantation. Therefore, hESCs can be used to generate human dopaminergic cells that exhibit biochemical and functional properties consistent with the expected properties of mature dopaminergic neurons. Zeng, X., Cai, J., Chen, J., Luo, Y., You, Z.B., Fotter, E., Wang, Y., Harvey, B., Miura, T., Backman, C., Chen, G.J., Rao, M.S. and Freed, W.J. Stem Cells, 22, pp. 925-940, 2004.

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

Sigma-1 Receptors at Galactosylceramide-Enriched Lipid Microdomains Regulate Oligodendrocyte Differentiation In the brain, myelin is important in regulating nerve conduction and neurotransmitter release by providing insulation at axons. Myelin is a specialized yet continuous sheet structure of differentiated oligodendrocytes (OLs) that is enriched in lipids, specifically galactosylceramides (GalCer) originated at the endoplasmic reticulum (ER). GalCer are known to affect OL differentiation. However, the mechanism whereby GalCer affect OL differentiation is not well understood. Sigma-1 receptors (Sig-1Rs), shown by IRP researchers to exist in detergent-insoluble lipid microdomains at lipid-enriched loci of ER in NG108 cells, are important in the compartmentalization/transport of ER-synthesized lipids and in cellular differentiation. In this study, authors used rat primary hippocampal cultures and found that Sig-1Rs form GalCer-enriched lipid rafts at ER lipid droplet-like structures in the entire myelin sheet of mature OLs. In rat OL progenitors (CG-4 cells), levels of lipid raft-residing Sig-1Rs and GalCer increase as cells differentiate. Sig-1Rs also increase in OLs and myelin of developing rat brains. Sig-1R, GalCer, and cholesterol are colocalized and are resistant to the Triton X-100 solubilization. Treating cells with a Sig-1R agonist or targeting Sig-1Rs at lipid rafts by overexpression of Sig-1Rs in CG-4 cells enhances differentiation, whereas reducing Sig-1Rs at lipid rafts by transfection of functionally dominant-negative Sig-1Rs attenuates differentiation. Furthermore, Sig-1R siRNA inhibits differentiation. These findings indicate that, in the brain, Sig-1Rs targeting GalCer-containing lipid microdomains are important for OL differentiation and that Sig-1Rs may play an important role in the pathogenesis of certain demyelinating diseases. Hayashi, T. and

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Su, T.P. Proceedings National Academy of Sciences USA, 101, pp. 14949-14954, 2004.

A Perspective on the New Mechanism of Antidepressants: Neuritogenesis Through Sigma-1 Receptors Sigma receptors were first described as one of the opiate receptor subtypes. Now it is well established that sigma receptors, existing as subtypes sigma-1 and sigma-2, are unique non-opioid receptors which are implicated in higher-ordered brain functions. Sigma-1 receptors have high to moderate affinities for (+)benzomorphans and also many psychotrophic drugs and neurosteroids. Sigma-1 receptor agonists and certain neurosteroids such as dehydroepiandrosterone sulfate (DHEA-S) have antidepressant-like effects in animal behavioral models of depression. The antidepressant-like effect induced by sigma-1 receptor agonists may involve intracellular Ca (2+) mobilization such that sigma-1 receptor agonists modulate Ca (2+) release from endoplasmic reticulum (ER) in a cytoskeletal protein-dependent manner. In addition, growth factor-induced neurite outgrowth is mediated through sigma-1 receptors, suggesting a role of antidepressants in neuroplasticity. Igmesine (JO1783), OPC-14 523 and SA4503, have recently been developed as sigma-1 agonists and are found to have antidepressant-like activity perhaps with fewer side effects. This article reviews the new potential use of sigma-1 receptor ligands in the treatment of mood disorder. Takebayashi, M., Hayashi, T., and Su, T.P. Pharmacopsychiatry, 37, pp. 208-213, 2004.

Delta Opioid Peptide (d-ala 2, d-leu 5) Enkephalin: Linking Hibernation and Neuroprotection Hibernation is a potential protective strategy for the peripheral, as well as for the central nervous system. A protein factor termed hibernation induction trigger (HIT) was found to induce hibernation in summer-active ground squirrels. Purification of HIT yielded an 88-kD peptide that is enriched in winter hibernators. Partial sequence of the 88-kD protein indicates that it may be related to the inhibitor of metalloproteinase. Using opioid receptor antagonists to elucidate the mechanisms of HIT, it was found that HIT targeted the delta opioid receptors. Indeed, delta opioid (D-Ala 2, D-Leu 5) enkephalin (DADLE) was shown to induce hibernation. Specifically, HIT and DADLE were found to prolong survival of peripheral organs, such as the lung, the heart, liver, and kidney preserved en bloc or as a single preparation. In addition, DADLE has been recently demonstrated to promote survival of neurons in the central nervous system. Exposure to DADLE dose-dependently enhanced cell viability of cultured primary rat fetal dopaminergic cells. Subsequent transplantation of these DADLE-treated dopaminergic cells into the Parkinsonian rat brain resulted in a two-fold increase in surviving grafted cells. Interestingly, delivery of DADLE alone protected against dopaminergic depletion in a rodent model of Parkinson s disease. Similarly, DADLE blocked and reversed the dopaminergic terminal damage induced by methamphetamine (METH). Such neuroprotective effects of DADLE against METH neurotoxicity was accompanied by attenuation of mRNA expressions of a tumor necrosis factor p53 and an immediate early gene c-fos. In parallel to these beneficial effects of DADLE on the dopaminergic system, DADLE also ameliorated the neuronal damage induced by ischemia-reperfusion following a transient middle cerebral artery occlusion. In vitro replication of this ischemia cell death by serum-deprivation of PC12 cells revealed that DADLE exerted neuroprotection in a naltrexone-sensitive manner. These results taken together suggest that DADLE stands as a novel therapeutic agent. In this review paper, IRP scientists present laboratory evidence supporting the use of DADLE for protection of peripheral and central nervous system. Borlongan, C.V., Wang, Y. and Su, T.P. Frontiers in Bioscience, 9, pp. 3392-3398, 2004.

Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Tetracycline-Inducible Expression Systems for the Generation of Transgenic Animals: A Comparison of Various Inducible Systems Carried in a Single Vector The most often used tetracycline-regulated transgenic mice system requires the generation of two transgenic strains, one carrying an inducible promoter and the other a transactivator. In this study, IRP investigators report the design of a universal and simplified regulatory gene delivery vector to facilitate the generation of conditional transgenic animals that integrate both the tetracycline regulatory and response elements in a single vector. The newly developed tetracycline reversed transactivator rtTA-M2 was used in all our constructs, based on its highly improved properties with respect to specificity, stability and inducibility. To minimize interference between the different tetracycline-inducible promoters used in this study (tetracycline-responsive element (TRE), TRE-tight, or Tk-tetO) and the rtTA-M2 transactivator, both elements were cloned in opposite directions and separated by a 5kb human p53 intron. The functionality of this system was confirmed after in vitro transfection in a mammalian cell line. Overall induction by the tetracycline-responsive element promoter was significantly higher than that induced by the newly developed

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TRE-tight promoter. However, the TRE-tight promoter showed a significantly tighter expression with minimal background, and still maintained high induction levels. The minimal Tk-tetO promoter showed a very weak induction capacity. This study demonstrates that this combination of elements, placed in a single vector is sufficient for delivering a functional tetracycline-inducible system to a mammalian cell line. Moreover, additional modifications to this regulatory gene delivery system, such as the introduction of specific cloning sites and selection markers, have been designed with the idea of creating a simplified and universal inducible system to facilitate the generation of conditional transgenic, knock-out, and knock-in animals. Backman, C.M., Zhang, Y., Hoffer, B.J. and Tomac, A.C. Journal Neuroscience Methods, 139, pp. 257-262, 2004.

MALDI Matrices for Biomolecular Analysis Based on Functionalized Carbon Nanomaterials When used in small molar ratios of matrix to analyte, derivatized fullerenes and single wall nanotubes are shown to be efficient matrices for matrix-assisted laser desorption/ionization (MALDI) mass spectrometry. The mixing of an acidic functionalized fullerene with a solution of bioanalyte, depositing a dried droplet, and irradiating with a pulsed nitrogen laser yields protonated or cationized molecular ions. Derivatized fullerenes could offer several advantages over conventional MALDI matrices: a high analyte ionization efficiency, a small molar ratios (less than 1) of matrix/analyte, and a broader optical absorption spectrum, which should obviate specific wavelength lasers for MALDI acquisitions. The major disadvantage to the use of fullerenes is the isobaric interference between matrix and analyte ions; however, it is overcome by using MALDI-ion mobility time-of-flight (IM-oTOF) mass spectrometry to preseparate carbon cluster ions from bioanalyte ions prior to TOF mass analysis. However, an alternative to the dried droplet preparation of fullerene MALDI samples is the aerosolization of matrix-analyte solutions (or slurries) followed by impacting the aerosol onto a stainless surface. We also demonstrate that the fullerene matrices can be used to acquire spectra from rat brain tissue. Ugarov, M.V., Egan, T., Khabashesku, D.V., Schultz, J.A., Peng, H., Khabashesku, V.N., Furutani, H., Prather, K.S., Wang, H.W., Jackson, S.N. and Woods, A.S. Analytic Chemistry, 76, pp. 6734-6742, 2004.

Analysis of Phosphorylated Peptides by Ion Mobility-Mass Spectrometry An ion mobility-mass spectrometry technique for rapid screening of phosphopeptides in protein digests is described. A data set of 43 sequences (ranging in mass from 400 to 3000 m/z) of model and tryptic peptides, including serine, threonine, and tyrosine phosphorylation, was investigated, and the data support previously reported observation (Ruotolo, B.T., Verbeck, G.F., IV, Thomson, L.M., Woods, A.S., Gillig, K.J., Russell, D.H. J. Proteome Res. 303, 2001) that the drift time-m/z relationship for singly charged phosphorylated peptide ions is different from that for nonphosphorylated peptides. The data further illustrate that a combined data-dependent IM-MS/MS approach for phosphopeptide screening would have enhanced throughput over conventional MS/MS-based methodologies. Ruotolo, B.T., Gillig, K.J., Woods, A.S., Egan, T.F., Ugarov, M.V., Schultz, J.A. and Russell, D.H. Analytic Chemistry, 76, pp. 6727-6733, 2004.

Modulation of Physiological Brain Hyperthermia by Environmental Temperature and Impaired Blood Outflow in Rats To study the role of ambient temperature and brain blood outflow in modulating physiological brain hyperthermia, temperatures in two brain structures (nucleus accumbens or NAcc and hippocampus or Hippo) and a non-locomotor head muscle (musculus temporalis) were monitored in rats exposed to three arousing stimuli (placement in the cage or environmental change, 3-min social interaction with a female rat, 3-min innocuous tail-pinch) under three conditions (intact animals at 23 degrees C or control, intact animals at 29 degrees C, animals with chronically occluded jugular veins at 23 degrees C). While each stimulus in each condition induced hyperthermia, with more rapid and stronger changes in brain structures than muscle, there were significant differences between conditions. At 29 degrees C, animal placement in the cage resulted in stronger temperature increase and larger brain-muscle differentials, while basal temperatures in Hippo and muscle (but not in NAcc) were higher than control. At 29 degrees C, hyperthermia during social interaction was smaller but more prolonged, while the response to tail-pinch was similar to that seen at normal environmental temperatures. Animals with chronically occluded jugular veins had similar basal temperatures but showed much weaker hyperthermia than intact animals during each stimulus presentation; temperature increases in brain structures, however, were much stronger than in the muscle. These data suggest that the brain is able to decrease neural activation induced by environmental challenges under conditions of impaired blood outflow and restricted heat dissipation to the external environment. Kiyatkin, E.A., and Brown, P.L. Physiology and Behavior, 83, pp. 467-474, 2004.

Electrophysiology Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Marijuana and Cannabinoid Regulation of Brain Reward Circuits The reward circuitry of the brain consists of neurons that synaptically connect a wide variety of nuclei. Of these brain regions, the ventral tegmental area (VTA) and the nucleus accumbens (NAc) play central roles in the processing of rewarding environmental stimuli and in drug addiction. The psychoactive properties of marijuana are mediated by the active constituent, Delta(9)-THC, interacting primarily with CB1 cannabinoid receptors in a large number of brain areas. However, it is the activation of these receptors located within the central brain reward circuits that is thought to play an important role in sustaining the self-administration of marijuana in humans, and in mediating the anxiolytic and pleasurable effects of the drug. Here IRP scientists describe the cellular circuitry of the VTA and the NAc, define the sites within these areas at which cannabinoids alter synaptic processes, and discuss the relevance of these actions to the regulation of reinforcement and reward. In addition, the authors compare the effects of Delta(9)-THC with those of other commonly abused drugs on these reward circuits, and discuss the roles that endogenous cannabinoids may play within these brain pathways, and their possible involvement in regulating ongoing brain function, independently of marijuana consumption. The authors conclude that, whereas Delta(9)-THC alters the activity of these central reward pathways in a manner that is consistent with other abused drugs, the cellular mechanism through which this occurs is likely different, relying upon the combined regulation of several afferent pathways to the VTA. Lupica, C.R., Riegel, A.C. and Hoffman, A.F. British Journal of Pharmacology, 143, pp. 227-234, 2004.

Differential Effects of Endogenous and Synthetic Cannabinoids on Alpha7-Nicotinic Acetylcholine Receptor-Mediated Responses in Xenopus Oocytes The effects of endogenous and synthetic cannabinoid receptor agonists, including 2-arachidonoylglycerol (2-AG), R-methanandamide, WIN55,212-2 [4,5-dihydro-2-methyl-4(4-morpholinylmethyl)-1-(1-naphthalenylcarbonyl)-6H-pyrrolo[3,2,1ij]quinolin-6-one], and CP 55,940 [1alpha,2beta-(R)-5alpha]-(-)-5-(1,1-dimethyl)-2-[5-hydroxy-2-(3-hydroxypropyl) cyclohexyl-phenol], and the psychoactive constituent of marijuana, Delta9-tetrahydrocannabinol (Delta9-THC), on the function of homomeric alpha7-nicotinic acetylcholine (nACh) receptors expressed in Xenopus oocytes was investigated using the two-electrode voltage-clamp technique. The endogenous cannabinoid receptor ligands 2-AG and the metabolically stable analog of anandamide (arachidonylethanolamide), R-methanandamide, reversibly inhibited currents evoked with ACh (100 microM) in a concentration-dependent manner (IC50 values of 168 and 183 nM, respectively). In contrast, the synthetic cannabinoid receptor agonists CP 55,940, WIN55,212-2, and the phytochemical Delta9-THC did not alter alpha7-nACh receptor function. The inhibition of alpha7-mediated currents by 2-AG was found to be non-competitive and voltage-independent. Additional experiments using endocannabinoid metabolites suggested that arachidonic acid, but not ethanolamine or glycerol, could also inhibit the alpha7-nACh receptor function. Whereas the effects of arachidonic acid were also noncompetitive and voltage-independent, its potency was much lower than 2-AG and anandamide. Results of studies with chimeric alpha7-nACh-5-hydroxytryptamine (5-HT)3 receptors comprised of the amino-terminal domain of the alpha7-nACh receptor and the transmembrane and carboxyl-terminal domains of 5-HT3 receptors indicated that the site of interaction of the endocannabinoids with the alpha7-nAChR was not located on the N-terminal region of the receptor. These data indicate that cannabinoid receptor ligands that are produced in situ potently inhibit alpha7-nACh receptor function, whereas the synthetic cannabinoid ligands, and Delta9-THC, are without effect, or are relatively ineffective at inhibiting these receptors. Oz, M., Zhang, L., Ravindran, A., Morales, M. and Lupica, C.R. Journal of Pharmacology and Experimental Therapeutics, 310, pp. 1152-1160, 2004.

Differential Effects of Endogenous and Synthetic Cannabinoids on Voltage-Dependent Calcium Fluxes in Rabbit T-Tubule Membranes: Comparison with Fatty Acids The effects of cannabinoid receptor ligands including 2-arachidonoylglycerol, R-methanandamide, Delta9-THC (Delta9-tetrahydrocannabinol), WIN 55,212-2 [4,5-dihydro-2-methyl-4(4-morpholinylmethyl)-1-(1-naphthalenylcarbonyl)-6H-pyrrolo[3,2,1ij]quinolin-6-one], CP 55,940 ([1alpha,2beta-(R)-5alpha]-(-)-5-(1,1-dimethyl)-2-[5-hydroxy-2-(3-hydroxypropyl) cyclohexyl-phenol]) and a series of fatty acids on depolarization-induced Ca2+ effluxes mediated by voltage-dependent Ca2+ channels were investigated comparatively in transverse tubule membrane vesicles from rabbit skeletal muscle. Vesicles were loaded with 45Ca2+ and membrane potentials were generated by establishing potassium gradients across the vesicle using the ionophore valinomycin. Endocannabinoids, 2-

arachidonoylglycerol and R-methanandamide (all 10 microM), inhibited depolarization-induced Ca2+ effluxes and specific binding of [3H]PN 200-110 (isradipine) to transverse tubule membranes. On the other hand, synthetic cannabinoids, including CP 55,940, WIN 55,212-2, and Delta9-THC (all 10 microM), were ineffective. Additional experiments using endocannabinoid metabolites suggested that whereas ethanolamine and glycerol were ineffective, arachidonic acid inhibited Ca2+ effluxes and specific binding of [3H]PN 200-110. Further studies indicated that only those fatty acids containing two or more double bonds were effective in inhibiting depolarization-induced Ca2+ effluxes and specific binding of [3H]PN 200-110. These results indicate that endocannabinoids, but not synthetic cannabinoids, directly inhibit the function of voltage-dependent calcium channels (VDCCs) and modulate the specific binding of calcium channel ligands of the dihydropyridine (DHP) class. Oz, M., Tchugunova, Y. and Dinc, M. European Journal of Pharmacology, 502, pp. 47-58, 2004.

MRI Physics Unit, Neuroimaging Research Branch

Simultaneous MRI Acquisition of Blood Volume, Blood Flow and Blood Oxygenation Information during Brain Activation IRP investigators have developed a new functional MRI technique that is able to achieve concurrent acquisition of three hemodynamic images based primarily on the changes of cerebral blood volume, blood flow and blood oxygenation, respectively, associated with brain activation. The feasibility and efficacy of the new technique were assessed by brain activation experiments with visual stimulation paradigms. Experiments on healthy volunteers showed that this technique provided efficient image acquisition and thus higher contrast-to-noise ratio (CNR) per unit time, compared with conventional techniques collecting these functional images separately. In addition, it was demonstrated that the proposed technique was able to be utilized in event-related functional MRI experiments, with potential advantages of obtaining accurate transient information of the activation-induced hemodynamic responses. This new technique allows for efficient measurement of three complementary functional signals associated with brain activation, and provides a valuable tool to assist with data interpretation and functional transduction mechanisms. Yang, Y., Gu, H. and Stein, E.A. Magnetic Resonance Medicine, 52, pp. 1407-1417, 2004.

Mapping the Orientation of Intravoxel Crossing Fibers Based on the Phase Information of Diffusion Circular Spectrum IRP scientists have developed a new method to map the orientation of intravoxel crossing fibers by using the phase of the diffusion circular spectrum harmonics. In a previous paper, we demonstrated that the magnitude of the 4th order harmonic of the diffusion circular spectrum can be used to identify the existence of fiber crossings. However, the orientation of the intravoxel crossing fibers remained unknown. This study extends the previous approach so that it is able to identify the orientation of the intravoxel crossing fibers by utilizing the phase information of the circular spectrum. In general, the phase of the circular harmonic determines the rotation of the apparent diffusion coefficient (ADC) profile on the sampling circle that is spanned by the major and medium eigenvector of the diffusion tensor and thus can be used to determine the orientation of the crossing fibers. Results of simulations and in vivo experiments indicated that the estimated intravoxel crossing fibers are consistent with the orientations of the single fibers in surrounding tissues, significantly reducing the discontinuity of the fiber orientation field given by the conventional major eigenvector method. The proposed method provides important information on the white matter tracts in the fiber crossing area, and would be useful for improving accuracy in tractography. Zhan, W., Stein, E.A. and Yang, Y. NeuroImage, 23, pp. 1358-1369, 2004.

Molecular Neuropsychiatry Section, Molecular Neuropsychiatry Research Branch

Substituted Amphetamines That Produce Long-Term Serotonin Depletion in Rat Brain ("Neurotoxicity") Do Not Decrease Serotonin Transporter Protein Expression Administration of high-dose d-fenfluramine (d-FEN) or parachloroamphetamine (PCA) produces 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 few studies have measured SERT protein levels. Thus, in the present study IRP scientists 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 d-FEN- and PCA-induced decreases in tissue 5-HT and SERT binding sites reflect neuroadaptive changes rather than neurotoxic effects. Rothman, R.B., Jayanthi, S., Cadet, J.L., Wang, X., Dersch, C.M. and Baumann, M.H. Annals of the New York Acadamy of Science, 1025, pp. 151-161, 2004.

Abnormal Brain Activity in Prefrontal Brain Regions in Abstinent Marijuana Users IRP investigators used PET (15)O and a modified version of the Stroop task to determine if 25-day abstinent heavy marijuana (MJ) users have persistent deficits in executive cognitive functioning (ECF) and brain activity. Performance on a modified version of the Stroop task and brain activity was compared between 25-day abstinent, heavy marijuana users (n = 11), and a matched comparison group (n = 11). The 25-day abstinent marijuana users showed no deficits in performance on the modified version of the Stroop task when compared to the comparison group. Despite the lack of performance differences, the marijuana users showed hypoactivity in the left perigenual anterior cingulate cortex (ACC) and the left lateral prefrontal cortex (LPFC) and hyperactivity in the hippocampus bilaterally, when compared to the comparison group. These results suggest that marijuana users display persistent metabolic alterations in brain regions responsible for ECF. It may be that marijuana users recruit an alternative neural network as a compensatory mechanism during performance on a modified version of the Stroop task. These differences in brain activity may be a common denominator in the evolution of maladaptive behaviors such as substance abuse and other neuropsychiatric disorders. Eldreth, D.A., Matochik, J., Cadet, J.L. and Bolla, K.I. Neuroimage 23, pp. 914-920, 2004.

Role of Dietary Iron Restriction in a Mouse Model of Parkinson's Disease There is a growing body of evidence suggesting that iron chelation may be a useful therapy in the treatment of Parkinson's Disease (PD). Experiments were designed to test the impact of dietary iron availability on the pathogenic process and functional outcome in a mouse model of PD. Mice were fed diets containing low (4 ppm) or adequate (48 ppm) amounts of iron for 6 weeks before the administration of MPTP, a mitochondrial toxin that damages nigrostriatal dopaminergic neurons and induces Parkinson-like symptoms. Low dietary iron increased serum total iron binding capacity ($P < 0.001$). Consistent with neuronal protection, iron restriction increased sphingomyelin C16:0 and decreased ceramide C16:0. However, there was a 35% decrease in striatal dopamine (DA) in iron-restricted mice. Motor behavior was also impaired in these animals. In vitro studies suggested that severe iron restriction could lead to p53-mediated neuronal apoptosis. Administration of MPTP reduced striatal DA ($P < 0.01$) and impaired motor behavior in iron-adequate mice. However, in iron-restricted mice, striatal dopamine levels and motor behavior were unchanged compared to saline-treated mice. Thus, while reduced iron may provide protection against PD-inducing insults such as MPTP, the role of iron in the synthesis of DA and neuronal survival should be considered, particularly in the development of iron-chelating agents to be used chronically in the clinical setting. Levenson, C.W., Cutler, R.G., Ladenheim, B., Cadet, J.L., Hare, J. and Mattson, M.P. Experimental Neurology, 190, pp. 506-514, 2004.

Clinical Psychopharmacology Section, Medications Discovery Research Branch

N-Substituted Piperazines Abused by Humans Mimic the Molecular Mechanism of 3,4-Methylenedioxymethamphetamine (MDMA, or 'Ecstasy') 3,4-Methylenedioxy-methamphetamine (MDMA, or 'Ecstasy') is an illicit drug that stimulates the release of serotonin (5-HT) and dopamine (DA) from neurons. Recent evidence reveals that drug users are ingesting piperazine analogs, like 1-benzylpiperazine (BZP, or 'A2') and 1-(m-trifluoromethylphenyl)piperazine (TFMPP, or 'Molly'), to mimic psychoactive effects of MDMA. In the present study, IRP scientists compared the neurochemistry of MDMA, BZP, and TFMPP in rats. The effects of MDMA, BZP, and TFMPP on transporter-mediated efflux of [(3)H]5-HT and [(3)H]MPP(+) (DA transporter substrate) were determined in synaptosomes. The effects of drugs on extracellular levels of 5-HT and DA were examined using in vivo microdialysis in conscious rats. MDMA evoked transporter-mediated release of

[(3)H]5-HT and [(3)H]MPP(+). BZP released [(3)H]MPP(+), whereas TFMPP was a selective releaser of [(3)H]5-HT. MDMA (1-3 mg/kg, i.v.) increased dialysate 5-HT and DA in a dose-related fashion, with actions on 5-HT being predominant. BZP (3-10 mg/kg, i.v.) elevated dialysate DA and 5-HT, while TFMPP (3-10 mg/kg, i.v.) elevated 5-HT. Administration of BZP plus TFMPP at a 1:1 ratio (BZP/TFMPP) produced parallel increases in dialysate 5-HT and DA; a 3 mg/kg dose of BZP/TFMPP mirrored the effects of MDMA. At a 10 mg/kg dose, BZP/TFMPP increased dialysate DA more than the summed effects of each drug alone, and some rats developed seizures. Results show that BZP/TFMPP and MDMA share the ability to evoke monoamine release, but dangerous drug-drug synergism may occur when piperazines are coadministered at high doses. Baumann, M.H., Clark, R.D., Budzynski, A.G., Partilla, J.S., Blough, B.E. and Rothman, R.B. Neuropsychopharmacology, online publication 20 November 2004.

Intracerebroventricular Administration of Anti-endothelin-1 IgG Selectively Upregulates Endothelin-A and Kappa Opioid Receptors Endothelin (ET) type A receptor antagonists enhance morphine-induced antinociception and restore morphine analgesia in morphine tolerant rats [Peptides 23 (2002) 1837; Peptides 24 (2003) 553]. These studies suggest that the central ET and opioid systems functionally interact. To explore this idea further, IRP researchers determined the effect of i.c.v. administration of anti-ET-1 IgG (rabbit) on brain opioid receptor and ET receptor expression. Three days after implanting cannula into the lateral ventricle, male Sprague-Dawley rats were administered 10 mul (i.c.v.) of either control rabbit IgG (2.5 mug/mul) or anti-ET IgG (2.5 mug/mul) on day 1, day 3, and day 5. On day 6, animals were killed and the caudate and hippocampus collected. Anti-ET IgG had no significant effect on expression, measured by Western blots, of mu, delta or ET-B receptors, but increased kappa opioid (59%) and ET-A (33%) receptor protein expression in the caudate. [(35)S]-GTP-gamma-S binding assays demonstrated that anti-ET IgG decreased [d-Ala(2)-MePhe(4), Gly-ol(5)]enkephalin efficacy, but not potency in the caudate. Control experiments showed that there was no detectable rabbit IgG in caudate and hippocampal samples. These results suggest that ET in the CSF negatively regulates kappa opioid and ET-A receptors in certain brain regions. These findings support the hypothesis that CSF neuropeptides have regulatory effects and further demonstrate a link between ET and the opioid receptor system. Wang, X., Xu, H. and Rothman, R.B. Neuroscience, 129, pp. 751-756, 2004.

Medicinal Chemistry Section, Medications Discovery Research Branch

Novel Azido- and Isothiocyanato- Analogues of [3-(4-phenylalkyl-piperazin-1-yl)propyl]-bis-(4-fluorophenyl)amines as Potential Irreversible Ligands for the Dopamine Transporter Potential irreversible ligands were prepared, based on a series of 3(1-piperazinyl)propyl-N,N-bis(4-fluorophenyl)amines, as molecular probes for the dopamine transporter (DAT). Both azido- and isothiocyanato-substituted phenyl alkyl analogues were synthesized and evaluated for displacement of [3H]WIN 35,428 in rat caudate-putamen tissue. All of the analogues showed moderate binding potencies at the DAT. One azido analogue was radioiodinated and used to photolabel human DAT transfected HEK 293 cell membranes. [125I]JJC 3-024 irreversibly labeled an ~80 kDa band corresponding to the DAT detected using SDS-PAGE. This radioligand provides a novel addition to the growing arsenal of structurally diverse irreversible ligands that are being used to identify binding domains on the DAT. Characterizing points of attachment of these irreversible probes to the DAT protein will ultimately help elucidate 3D- arrangement of the transmembrane domains, identify individual binding sites of the DAT inhibitors and direct future drug design. Cao, J., Lever, J.R., Kopajtic, T., Katz, J.L., Holmes, M.L., Justice, J.B. and Newman, A.H. Journal of Medicinal Chemistry, 47, pp. 6128-6136, 2004.

Behavioral Neuroscience Section, Behavioral Neuroscience Research Branch

Unconditional Hyperactivity and Transient Reinforcing Effects of NMDA Administration into the Ventral Tegmental Area in Rats The dopaminergic projection from the ventral tegmental area (VTA) to the nucleus accumbens plays an important role in positive reinforcement and locomotion. Intra-VTA administration of many drugs capable of activating these neurons has been shown to be reinforcing and induce locomotion. Administration of the excitatory amino acid NMDA (N-methyl-D-aspartate) into the VTA may likewise be positively reinforcing, because it stimulates the meso-accumbens dopamine system and locomotion. Locomotor-rearing experiments were conducted to pinpoint the range of NMDA concentrations that induce significant locomotion and rearing, and to determine whether co-administration of the glycine binding site agonist d-serine would enhance the effects of NMDA administration into the VTA. Reinforcing effects of NMDA were assessed by intracranial self-administration procedures: a lever-press delivered a 75-nl infusion

containing NMDA (0.1, 0.3 or 1.0 mM) plus serine into the VTA or an adjacent region, the supramammillary nucleus. Co-administration of serine slightly enhanced rearing induced by NMDA administration. Administration of NMDA at concentrations of 0.3 or 1.0 mM (500 nl) induced vigorous locomotion and rearing. NMDA (0.3 mM) was self-administered into the VTA slightly more than vehicle in the first or second sessions, yet this small reinforcing effect became irregular in subsequent sessions. The rats did not learn to self-administer NMDA into the supramammillary nucleus. Authors concluded that ventral tegmental NMDA injections, in the concentration range that induced marked unconditional hyperactivity, supported only marginal and transient self-administration. Ikemoto, S. Psychopharmacology, 172, pp. 202-210, 2004.

Mapping of Chemical Trigger Zones for Reward Addictive drugs are thought to activate brain chemistry that normally mediates more natural rewards such as food or water. Drugs activate this circuitry at synaptic junctions within the brain; identifying the junctions at which this occurs provides clues about the neurochemical and anatomical characteristics of the circuitry. One approach to identifying the junctions at which drugs interact with this circuitry is to determine if animals will lever-press for site-specific microinjections of addictive drugs. This approach has identified GABAergic, dopaminergic, glutamatergic, and cholinergic trigger zones within meso-corticolimbic circuitry important for natural reward function. Ikemoto, S. and Wise, R.A. Neuropharmacology, 47, pp. 190-201, 2004.

Rewarding Effects of AMPA Administration into the Supramammillary or Posterior Hypothalamic Nuclei But Not the Ventral Tegmental Area IRP scientists examined whether injections of the excitatory amino acid AMPA are rewarding when injected into the posterior hypothalamus and ventral tegmental area. Rats quickly learned to lever-press for infusions of AMPA into the supramammillary or posterior hypothalamic nuclei but failed to learn to lever-press for similar injections into the ventral tegmental areas. AMPA injections into the supramammillary nucleus, but not the ventral tegmental area, induced conditioned place preference. The rewarding effects of AMPA appear to be mediated by AMPA receptors, because coadministration of the AMPA antagonist CNQX blocked the rewarding effects of AMPA, and administration of the enantiomer R-AMPA did not mimic the rewarding effects. AMPA injections into the supramammillary nucleus, but not the ventral tegmental area, also increased extracellular dopamine concentrations in the nucleus accumbens. Pretreatment with the D1 dopamine antagonist SCH 23390 [R-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzaz epine] led to extinction of AMPA self-administration. These findings implicate posterior hypothalamic regions in reward function and suggest that reward mechanisms localized around the ventral tegmental area are more complex than has been assumed recently. Ikemoto, S., Witkin, B. M., Zangen, A. and Wise. R.A. Journal of Neuroscience, 24, pp. 5758-5765, 2004.

Cocaine-induced Fos Expression in Rat Striatum is Blocked by Chloral Hydrate or Urethane Anesthetics used in electrophysiological studies alter the effects of cocaine and amphetamine on neural activity in the striatum. However, the mechanism underlying this alteration has not been established. In the present study, IRP scientists examined the effects of anesthetics on cocaine-induced neural activity in the striatum. Authors first assayed the ability of 20 mg/kg cocaine to induce Fos expression in the striatum following pretreatment with 400 mg/kg chloral hydrate or 1.3 g/kg urethane, two of the most commonly used anesthetics for in vivo electrophysiology. Chloral hydrate blocked, while urethane strongly attenuated cocaine-induced Fos expression without affecting basal levels of expression. The investigators then examined dopaminergic and glutamatergic mechanisms for anesthetic effects on cocaine-induced Fos expression. Chloral hydrate and urethane did not attenuate basal or cocaine-induced increases of dopamine levels as assessed by microdialysis in dorsal striatum. In contrast, chloral hydrate attenuated glutamatergic neurotransmission as assessed by microdialysis in the presence of the glutamate transport blocker l-trans-pyrrolidone-2,4-dicarboxylic acid. Chloral hydrate attenuated basal levels of glutamate by 70%, while cocaine had no effect on glutamate levels. Since glutamate levels were tetrodotoxin-sensitive, the majority of glutamate measured in this assay was by synaptic release. To assess a causal role for a reduction of glutamatergic neurotransmission in anesthetic effects on cocaine-induced Fos expression, the investigators injected the glutamate receptor agonists AMPA and NMDA into the dorsal striatum of chloral hydrate-anesthetized rats. The glutamate receptor agonists partially reinstated cocaine-induced Fos expression in anesthetized rats. Authors conclude that anesthetics attenuate cocaine-induced neuronal activity by reducing glutamatergic neurotransmission. Kreuter, J.D., Mattson, B.J., Wang, B., You, Z-B. and Hope, B.T. Neuroscience, 127, pp. 233-242, 2004.

Sensitization of Psychomotor Stimulation and Conditioned Reward in Mice: Differential Modulation by Contextual Learning Incentive motivation theory ascribes a critical role to reward-associated stimuli in the generation and maintenance of goal-directed behavior. Repeated psychomotor stimulant treatment, in addition to producing sensitization to the psychomotor-activating effects, can enhance the incentive salience of reward-associated cues and increase their ability to influence behavior. In the present study, IRP scientists sought to investigate this incentive sensitization effect further by developing a model of conditioned reinforcement (CR) in the mouse and investigating the effects of a sensitizing treatment regimen of amphetamine on CR. Furthermore, these investigators assessed the role of contextual stimuli in amphetamine-induced potentiation of CR. They found that mice responded selectively on a lever resulting in the presentation of a cue previously associated with 30% condensed milk solution, indicating that the cue had attained rewarding properties. Prior treatment with amphetamine (4 x 0.5 mg/kg i.p.) resulted in psychomotor sensitization and enhanced subsequent responding for the CR. Furthermore, this enhancement of responding for the cue occurred independent of the drug-paired context, whereas the sensitized locomotor response was only observed when mice were tested in the same environment as that in which they had received previous amphetamine. These results demonstrate that the CR paradigm previously developed in the rat can be successfully adapted for use in the mouse, and suggest that behavioral sensitization to amphetamine increases the rewarding properties (incentive salience) of reward-paired cues, independent of the drug-paired context. Mead, A.N., Crombag, H.S. and Rocha, B.A. Neuropsychopharmacology, 29, pp. 249-258, 2004.

Dopamine, Learning and Motivation The hypothesis that dopamine is important for reward has been proposed in a number of forms, each of which has been challenged. Normally, reward stimuli such as food, water, lateral hypothalamic brain stimulation and several drugs of abuse become ineffective as rewards in animals given performance-sparing doses of dopamine antagonists. Dopamine release in the nucleus accumbens has been linked to the efficacy of these unconditioned reward, but dopamine release in a broader range of structures is implicated in the Ôstamping-in' of memory that attaches motivational importance to otherwise neutral environmental stimuli. Wise, R.A. Nature Review Neuroscience, 5, pp. 483-494, 2004.

Neurobiology of Relapse Section, Behavioral Neuroscience Research Branch

A Role of Ventral Tegmental Area Glutamate in Contextual Cue-induced Relapse to Heroin Seeking The environmental context previously associated with opiate use plays an important role in human relapse, but the neuronal mechanisms involved in context-induced drug relapse are not known. Using a rat relapse model, IRP researchers determined the effect of a group II metabotropic glutamate receptor agonist, LY379268, on contextual cue-induced reinstatement of heroin seeking. LY379268, which acts centrally to reduce evoked glutamate release, was injected systemically or directly into the ventral tegmental area (VTA), a brain area involved in opiate reward and conditioned drug effects. Rats were trained to self-administer intravenous heroin for 12 days; drug infusions were paired with a discrete tone-light cue. Subsequently, lever pressing was extinguished in the presence of the discrete cue in a context that differed from the drug self-administration context in terms of visual, auditory, tactile, and circadian cues. After extinction of lever responding, LY379268 was injected systemically or into the VTA, and non-reinforced responding was determined in the extinction context or the drug context. Exposure to the heroin-associated context induced robust reinstatement of drug seeking, and this effect was attenuated by systemic or intra-VTA injections of LY379268. Results indicate that glutamate transmission in the VTA plays an important role in contextual cue-induced relapse to heroin seeking. Bossert, J.M., Liu, S., Lu, L. and Shaham, Y. The Journal of Neuroscience, 24, pp. 10726-10730, 2004.

Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch

Adenosine Receptor-mediated Modulation of Dopamine Release in the Nucleus Accumbens Depends on Glutamate Neurotransmission and N-methyl-D-aspartate Receptor Stimulation Adenosine, by acting on adenosine A(1) and A(2A) receptors, exerts opposite modulatory roles on striatal extracellular levels of glutamate and dopamine, with activation of A(1) inhibiting and activation of A(2A) receptors stimulating glutamate and dopamine release. Adenosine-mediated modulation of striatal dopaminergic neurotransmission could be secondary to changes in glutamate neurotransmission, in view of evidence for a preferential colocalization of A(1) and A(2A) receptors in glutamatergic nerve terminals. By using in vivo microdialysis techniques, local perfusion of NMDA (3, 10 microm), the selective A(2A)

receptor agonist 2-p-(2-carboxyethyl)phenethylamino-5'-N-ethylcarboxamidoadenosine (CGS 21680; 3, 10 microm), the selective A(1) receptor antagonist 8-cyclopentyl-1,3-dimethylxanthine (CPT; 300, 1000 microm), or the non-selective A(1)-A(2A) receptor antagonist in vitro caffeine (300, 1000 microm) elicited significant increases in extracellular levels of dopamine in the shell of the nucleus accumbens (NAc). Significant glutamate release was also observed with local perfusion of CGS 21680, CPT and caffeine, but not NMDA. Co-perfusion with the competitive NMDA receptor antagonist dl-2-amino-5-phosphonovaleric acid (APV; 100 microm) counteracted dopamine release induced by NMDA, CGS 21680, CPT and caffeine. Co-perfusion with the selective A(2A) receptor antagonist MSX-3 (1 microm) counteracted dopamine and glutamate release induced by CGS 21680, CPT and caffeine and did not modify dopamine release induced by NMDA. These results indicate that modulation of dopamine release in the shell of the NAc by A(1) and A(2A) receptors is mostly secondary to their opposite modulatory role on glutamatergic neurotransmission and depends on stimulation of NMDA receptors. Furthermore, these results underscore the role of A(1) vs. A(2A) receptor antagonism in the central effects of caffeine. Quarta, D., Borycz, J., Solinas, M., Patkar, K., Hockemeyer, J., Ciruela, F., Lluis, C., Woods, A.S., Goldberg S.R. and Ferre, S.J. Neurochemistry, 91, pp. 873-880, 2004.

Rimonabant, a CB1 Antagonist, Blocks Nicotine-conditioned Place Preferences The effects of Rimonabant (SR141716), an antagonist at cannabinoid CB1 receptors, were evaluated in animal models for subjective and rewarding effects of nicotine. Acute administration of 1 or 3 mg/kg SR141716 blocked expression of nicotine-induced conditioned place preferences. SR141716 (0.3-3 mg/kg) was also studied in rats trained to discriminate nicotine from saline under a fixed-ratio schedule of food delivery. In contrast to nicotine replacement therapy and bupropion, SR141716 did not have nicotine-like discriminative effects and did not alter the dose-response curve for nicotine discrimination. These findings support the proposed use of SR141716 for smoking cessation and indicate that it would selectively reduce the influence of environmental stimuli that contribute to persistent smoking behavior, without affecting subjective responses to nicotine. LeFoll, B, and Goldberg, S.R. Neuroreport, 15, pp. 2139-2143, 2004.

Combining Mass Spectrometry and Pull-down Techniques for the Study of Receptor Heteromerization. Direct epitope-epitope Electrostatic Interactions Between Adenosine A2A and Dopamine D2 Receptors Previous results from FRET and BRET experiments and computational analysis (docking simulations) have suggested that a portion of the third intracellular loop (I3) of the human dopamine D(2) receptor (D(2)R) and the C-tail from the human adenosine A(2A) receptor (A(2A)R) are involved in A(2A)R-D(2)R heteromerization. The results of the present studies, using pull-down and mass spectrometry experiments, suggest that A(2A)R-D(2)R heteromerization depends on an electrostatic interaction between an Arg-rich epitope from the I3 of the D(2)R ((217)RRRRKR(222)) and two adjacent Asp residues (DD(401-402)) or a phosphorylated Ser (S(374)) residue in the C-tail of the A(2A)R. A GST-fusion protein containing the C-terminal domain of the A(2A)R (GST-A2A(CT)) was able to pull down the whole D(2)R solubilized from D(2)R-tranfected HEK-293 cells. Second, a peptide corresponding to the Arg-rich I3 region of the D(2)R ((215)VLRRRRKRVN(224)) and bound to Sepharose was able to pull down both GST-A2A(CT) and the whole A(2A)R solubilized from A(2A)R-tranfected HEK-293 cells. Finally, mass spectometry and pull-down data showed that the Arg-rich D(2)R epitope binds to two different epitopes from the C-terminal part of the A(2A)R, containing the two adjacent Asp residues or the phosphorylated Ser residue ((388)HELKGVCPEPPGLDDPLAQDGAVGS(412) and (370)SAQEpSQGNT(378)). The present results are the first example of epitope-epitope electrostatic interaction underlying receptor heteromerization, a new, expanding area of protein-protein interactions. Ciruela, F., Burgueno, J., Casado, V., Canals, M., Marcellino, D., Goldberg, S.R., Bader, M., Fuxe, K., Agnati, L.F., Lluis, C., Franco, R., Ferre, S. and Woods, A.S. Analytical Chemistry, 76, pp. 5354-5363, 2004.

Beta-endorphin Elevations in the Ventral Tegmental Area Regulate the Discriminative Effects of Delta-9-tetrahydrocannabinol beta-Endorphin is an endogenous opioid that produces behavioral effects similar to heroin and morphine and is released in the nucleus accumbens by cocaine, amphetamine and ethanol, suggesting a general involvement in the reinforcing effects of abused drugs. Here IRP researchers show that, in rats, Delta-9-tetrahydrocannabinol (THC), the main psychoactive ingredient in cannabis, produces large increases in extracellular levels of beta-endorphin in the ventral tegmental area and lesser increases in the shell of the nucleus accumbens. Authors then used a two-lever choice THC-discrimination procedure to investigate whether THC-induced changes in endogenous levels of beta-

endorphin regulate the discriminative effects of THC. In rats that had learned to discriminate injections of THC from injections of vehicle, the opioid agonist morphine did not produce THC-like discriminative effects but markedly potentiated discrimination of THC. Conversely, the opioid antagonist naloxone reduced the discriminative effects of THC. Bilateral microinjections of beta-endorphin directly into the ventral tegmental area, but not into the shell of the nucleus accumbens, markedly potentiated the discriminative effects of ineffective threshold doses of THC but had no effect when given alone. This potentiation was blocked by naloxone. Together these results indicate that certain psychotropic effects of THC related to drug abuse liability are regulated by THC-induced elevations in extracellular beta-endorphin levels in brain areas involved in opiate reward and reinforcement processes. Solinas, M., Zangen, A., Thiriet, N. and Goldberg, S.R. European Journal of Neuroscience, 19, pp. 3183-3192, 2004.

Chlormethiazole Potentiates the Discriminative Stimulus Effects of Methamphetamine in Rats Chlormethiazole is a positive modulator of gamma-aminobutyric acid (GABA)(A) receptors used in the treatment of alcohol withdrawal seizures. It recently has been reported to attenuate seizures engendered by acute and repeated exposure to cocaine in mice and neurotoxic effects of methamphetamine in rats. The aim of the present study was to determine whether chlormethiazole could also attenuate the discriminative stimulus effects of methamphetamine, a behavior predictive of the subjective effects of methamphetamine in humans. In Sprague-Dawley rats trained to discriminate 1.0 mg/kg methamphetamine [intraperitoneally (i.p.)] from saline under a fixed-ratio schedule of food delivery, the ability of chlormethiazole (i.p.) to (1) substitute for methamphetamine, (2) antagonize effects of methamphetamine and to (3) shift the methamphetamine dose-effect function was investigated. Chlormethiazole (18 and 30 mg/kg, i.p.) partially substituted for the discriminative stimulus effects of methamphetamine when administered alone (maximum group average, 60% responses on the methamphetamine-appropriate lever). Chlormethiazole did not attenuate effects of methamphetamine when coadministered with the training dose of methamphetamine. Instead, chlormethiazole potentiated the discriminative stimulus effects of methamphetamine as demonstrated by a significant (about 2.5-fold) leftward and upward shift in the methamphetamine dose-effect function in the presence of chlormethiazole (10 mg/kg). In conclusion, the present findings suggest that there is a behavioral interaction between methamphetamine and chlormethiazole. The profile of this interaction is qualitatively different from that of methamphetamine and classical GABAergic drugs (i.e., benzodiazepines and barbiturates), suggesting the involvement of non-GABAergic mechanisms in the effects produced by chlormethiazole. Gasior, M., Witkin, J.M., Goldberg, S.R. and Munzar, P. European Journal of Pharmacology, 94, pp. 183-189, 2004.

Neuropsychopharmacology Section, Behavioral Neuroscience Research Branch

Dopamine D3 Receptor Antagonists as Potential Anti-Addiction, Anti-Craving and Anti-Relapse Medications for the Treatment of Addiction IRP scientists have previously found that SB277011A, a high-potency high-selectivity dopamine D3 receptor antagonist dose-dependently inhibits nicotine-enhanced brain-stimulation reward. Now, these researchers have extended these findings to include two additional putative D3 receptor antagonists - NGB2904 and BP897. It was found that both NGB2904 and BP897 blocked (within critical dose ranges) nicotine's enhancing effect on brain reward. However, while SB277011A and NGB2904 had no significant effect on brain-stimulation reward by themselves, BP897 dose-dependently attenuated brain-stimulation reward by itself. These findings are congruent with other data suggesting that SB277011A and NGB2904 are highly selective dopamine D3 receptor antagonists, while BP897 interacts with many receptors - including, most importantly for the present results - the dopamine D2 receptor. As drug-enhanced brain reward is believed to be a neural substrate for addiction, these findings suggest that dopamine D3 receptor antagonists are worthy of further investigation as potential anti-addiction, anti-craving, and anti-relapse medications for the treatment of drug abuse. These findings also suggest a specific utility for dopamine D3 antagonists - to assist cigarette smokers in breaking their nicotine dependence and to quit smoking. These findings further suggest that NGB2904 should be added to SB277011A as a highly selective dopamine D3 receptor antagonist with possible anti-addiction clinical utility. Campos, A.C., Xi, Z.-X., Gilbert, J., Ashby, C.R. Jr., Heidbreder, C.A., Newman, A.H. and Gardner, E.L., Poster, 2004. Society for Neuroscience Annual Meeting, San Diego, CA, October 23-27, 2004.

Dopamine D3 Receptor Antagonists as Potential Anti-Addiction, Anti-Craving

and Anti-Relapse Medications for the Treatment of Addiction IRP scientists have previously found that acute blockade of the dopamine D3 receptor in the rat brain (which is neuroanatomically restricted to the mesolimbic dopamine system, implicated in drug-induced reward and drug-seeking behavior) dose-dependently attenuates cocaine-enhanced brain-stimulation reward, acquisition of cocaine-induced conditioned cue preference, expression of cocaine-induced conditioned cue preference, acquisition of heroin-induced conditioned cue preference, expression of heroin-induced conditioned cue preference, cocaine-triggered relapse to cocaine-seeking behavior in animals pharmacologically detoxified and behaviorally extinguished from their intravenous cocaine-taking behavior, and stress-triggered relapse to cocaine-seeking behavior. Now, these researchers have extended these studies, and have found that SB277011A and NGB2904, high-potency high-selectivity dopamine D3 receptor antagonists, inhibit environmental cue-induced relapse to cocaine-seeking behavior in animals pharmacologically detoxified and behaviorally extinguished from their intravenous cocaine-taking behavior. The environmental cues found capable of triggering relapse to drug-seeking behavior were sights and sounds previously associated with intravenous cocaine-taking behavior. These findings suggest that dopamine D3 receptor antagonists are worthy of further investigation as potential anti-addiction, anti-craving, and anti-relapse medications for the treatment of drug abuse. Gilbert, J.G., Xi, Z.-X., Campos, A.C., Peng, X., Ashby, C.R. Jr., Heidbreder, C.A., Newman, A.H. and Gardner, E.L., Poster, 2004. Society for Neuroscience Annual Meeting, San Diego, CA, October 23-27, 2004.

Gamma-vinyl GABA (GVG; Vigabatrin) as a Potential Anti-Addiction, Anti-Craving and Anti-Relapse Medication for the Treatment of Addiction IRP scientists working in collaboration with scientists at the Brookhaven National Laboratory and Saint John's University in New York have previously found that gamma-vinyl GABA (GVG; Vigabatrin), an inhibitor of GABA transaminase which pharmacologically boosts synaptic levels of the neurotransmitter gamma-aminobutyric acid (GABA) in the reward circuitry of the brain, dose-dependently attenuates cocaine-enhanced synaptic levels of the neurotransmitter dopamine in brain-reward circuits (measured by in vivo brain microdialysis and positron emission tomography), cocaine-enhanced brain-stimulation reward, cocaine-induced conditioned place preference, cocaine self-administration, cocaine-induced behavioral sensitization, nicotine-enhanced synaptic levels of the neurotransmitter dopamine in brain-reward circuits (measured by in vivo brain microdialysis and positron emission tomography), nicotine-induced conditioned place preference, and heroin-induced conditioned place preference. Now, these researchers have extended those findings, and have found that GVG - but not gabapentin - dose-dependently attenuates cocaine-triggered relapse to cocaine-seeking behavior in animals pharmacologically detoxified and behaviorally extinguished from their intravenous cocaine-taking behavior. The additional new findings with GVG suggest that GVG, but not necessarily other GABAmimetic medications, is worthy of further investigation as an anti-addiction, anti-craving, and anti-relapse medication for the treatment of drug abuse. Its effectiveness against cocaine, nicotine, and opiates suggests a broad efficacy against drug addiction. Peng, X., Xi, Z.-X., Gilbert, J., Campos, A.C., Dewey, S.L., Schiffer, W.K., Brodie, J.D., Ashby, C.R. Jr. and Gardner, E.L., Poster, 2004. Society for Neuroscience Annual Meeting, San Diego, CA, October 23-27, 2004.

Glutamate mGluR5 Receptor Antagonists as Potential Anti-Addiction, Anti-Craving and Anti-Relapse Medications for the Treatment of Addiction IRP scientists have found that acute blockade of the glutamate mGluR5 receptor in the rat brain (which is neuroanatomically linked to the mesolimbic dopamine system, implicated in drug-induced reward and drug-seeking behavior) dose-dependently lowers the progressive-ratio break-point (a measure of incentive motivation to self-administer drugs) during intravenous cocaine self-administration, and also attenuates cocaine-triggered relapse to cocaine-seeking behavior in animals pharmacologically detoxified and behaviorally extinguished from their intravenous cocaine-taking behavior. However, the same acute blockade of the glutamate mGluR5 receptor does not attenuate either stress-triggered or environmental cue-triggered relapse to cocaine-seeking behavior. These findings suggest that medications which produce acute blockade of the glutamate mGluR5 receptor are worthy of further investigation as potential anti-addiction, anti-craving, and anti-relapse medications for the treatment of drug abuse. Further, these findings confirm that the brain mechanisms underlying drug-triggered relapse to drug-seeking behavior is mediated by different brain mechanisms than stress-triggered or environmental cue-triggered relapse to cocaine-seeking behavior, a finding previously reported by IRP scientists. Xi, Z.-X., Gilbert, J., Campos, A.C., Peng, X., Ashby, C.R. Jr. and Gardner, E.L., Poster, 2004. Society for Neuroscience Annual Meeting, San Diego, CA, October 23-27, 2004.

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

Neonatal Abstinence Syndrome in Methadone-exposed Infants is Altered by Level of Prenatal Tobacco Exposure Maternal tobacco consumption during pregnancy has been associated with lower birth weight infants, preterm births, intrauterine growth retardation, smaller head circumference and increase in morbidity, yet few studies have examined the role tobacco has on the opiate neonatal abstinence syndrome (NAS). This study examined the effect of prenatal tobacco exposure on NAS for infants born to mothers maintained on methadone during gestation. Twenty-nine pregnant women and their newborn infants participated in this study. Tobacco exposure was based on maternal self-report with 16 women reporting cigarette consumption of 10 or less per day and 13 reporting smoking 20 cigarettes or more a day. The onset, peak, and duration of NAS were examined. Results showed that infants born to mothers who reported smoking 20 or more cigarettes per day had significantly higher NAS peak scores of 9.8 versus 4.8, and took longer to peak (113.0 h versus 37.8 h), than light smokers of 10 or fewer cigarettes per day. Investigators concluded that tobacco use in conjunction with methadone plays an important role in the timing and severity of NAS in prenatally exposed infants. Choo, R.E., Huestis, M.A., Schroeder, J.R., Shin, A.S. and Jones, H.E. Drug and Alcohol Dependence, 75, pp. 253-260, 2004.

Methamphetamine and Amphetamine Concentrations in Meconium of Neonates of Women Enrolled in the IDEAL Study of In Utero Methamphetamine Exposure The Infant Development, Environment, and Lifestyle (IDEAL) study is a multi-center, longitudinal investigation of the effects of prenatal methamphetamine exposure. Meconium, a useful matrix for identifying in utero drug exposure, was employed to identify gestational drug use. Of the 13,808 mothers screened, 1631 were consented and 176 enrolled. MA exposed mothers (n=84) were identified by self-report of gestational MA use and/or GC/MS confirmation of MA, AMP, and/or MDMA in infant meconium. Comparison participants (n=92) were matched by race, birth weight, maternal education and type of insurance, denied amphetamines use and had negative meconium results. Among the 1631 mothers, self-reported use rates were 5.2% (amphetamines), 25% (tobacco) and 5.9% (cannabis). Positive meconium screening rates were 3.6% for any amphetamine, 20% cotinine and 11.2% cannabis. For specimens that screened positive, 40.7% of amphetamines and 20.2% of cannabis specimens were confirmed. On average, 68% of the meconium from neonates whose mothers reported 3rd trimester use had detectable MA, while detection rates were ²10% for self-reported use during the 1st and/or 2nd trimesters. Mean ± SD, median and range of MA concentrations were 3674 ± 3406, 2623, 479 to 13,431 ng/g meconium and AMP 569 ± 543, 403, 30 to 2000 ng/g meconium in infants whose mothers reported 3rd trimester use. However, the highest MA (19,376 and 16,976 ng/g) and AMP (2765 ng/g) concentrations were found in offspring born to women who reported MA use only in the 1st or 1st and 2nd trimesters, raising questions about the self-report. The log transformed meconium MA concentrations significantly correlated with the frequency of MA use in the 3rd trimester (r=0.645, P=0.004), although variability prevents prediction of frequency of use for an individual mother. AMP was always detected in MA positive meconium. In 55% of the GCMS positive samples, the ratios of amphetamine to MA were 0.1 to 0.2; 14% were less than 0.1 and 18% were 0.2 to 0.3. Meconium analysis for MA is a useful adjunct to self-report for identification of MA exposure; however, the greatest sensitivity was achieved with specimens collected from offspring of women who reported use in the 3rd trimester. Further research is needed to determine if there are additional MA metabolites in meconium that could improve the identification of MA-exposed infants. Zhao, Z., Liu, J., LaGasse, L.L., Derauf, C., Grant, P., Shah, R., Arria, A., Haning, W., Smith, L.M., Lester, B. and Huestis, M.A., Poster, 2004. Joint Meeting of the Society of Forensic Toxicologists and The International Association of Forensic Toxicologists, Washington, DC, August 28-September 3, 2004.

A Validated Gas Chromatographic-Negative Chemical Ionization Mass Spectrometric Method for delta-9-tetrahydrocannabinol (THC) in Sweat A sensitive gas chromatography-negative ion chemical ionization-mass spectrometry (GC/MS-NICI) method was developed and validated for the measurement of D9-tetrahydrocannabinol (THC) in human sweat patches. THC-d0 and THC-d3 were spiked onto worn blank sweat patches (PharmChekª, PharmChem Incorporated) and extracted with 3 mL methanol/0.2 M sodium acetate buffer (pH 5.0, 3:1, v/v) on a reciprocating shaker at ambient temperature for 30 min. Two mL of extracted solution was diluted with 8 mL 0.1 M sodium acetate buffer, pH 4.5 and extracted using solid phase extraction columns (CleanScreen¨, ZSTHC020, UCT). Dried extracts were derivatized with trifluoroacetic acid (TFAA) and analyzed using an Agilent 6890 GC

interfaced with an Agilent 5973 mass selective detector operated in NICI- selected ion monitoring mode. The lower limits of detection and quantification for THC in human sweat were 0.2 and 0.4 ng/patch, respectively. The standard curve was linear from 0.4 to 10 ng/patch (r2>0.995). Overall recovery of THC from blank worn patches spiked with 0.6, 4.0 and 8.0 ng THC was 44 to 46%. Assay imprecision, expressed as coefficient of variation, was less than 10.3%, for 0.6, 4.0 and 8.0 ng/patch quality control (QC) samples. Twenty-one potential interfering compounds (50 ng/patch) spiked into low QC samples (0.6 ng/patch) did not influence THC quantitation. This GC/MS-NICI assay for THC in human sweat provides adequate sensitivity and performance characteristics for analyzing THC in sweat patches and meets the requirements of the proposed Substance Abuse and Mental Health Administration's guidelines for sweat testing. Saito, T., Wtsadik, A., Scheidweiler, K., McCain, M., Fortner, N., Takeichi, S. and Huestis, M.A. Clinical Chemistry, 50, pp. 2083-2090, 2004.

Urinary Pharmacokinetics of Methamphetamine and Its Metabolite, Amphetamine Following Controlled Oral Administration to Humans
Methamphetamine is widely abused for its euphoric effects. The objectives of the investigators were to characterize the urinary pharmacokinetics of methamphetamine and amphetamine after controlled methamphetamine administration to humans and to improve the interpretation of urine drug test results. Participants (n=8) received four daily 10 mg (low) oral doses of sustained release (d)-methamphetamine hydrochloride within 7 days. After 4 weeks, five participants received four daily 20 mg (high) oral doses. All urine specimens were collected during the study. Methamphetamine and amphetamine were measured by GC-MS/PCI. Maximum excretion rates ranged from 403-4919 µg/h for methamphetamine and 59-735 µg/h for amphetamine with no relationship between dose and excretion rate. The mean molar % of dose in the urine as total methamphetamine and amphetamine were 57.5 ± 21.7% (low dose) and 40.9 ± 8.5% (high dose). Mean urinary terminal elimination half-lives across doses were 23.6 ± 6.6 h for methamphetamine and 20.7 ± 7.3 h for amphetamine. Methamphetamine renal clearance across doses was 175 ± 102 mL/min. The mean amphetamine/methamphetamine % ratio based on the area under the urinary excretion-time curve increased over time from 13.4 ± 6.5 to 35.7 ± 26.6%. Slow urinary excretion results in drug accumulation and increases in detection time windows. These findings also support the presence of an active renal excretion mechanism for methamphetamine. Kim, I., Oyler, J.M., Moolchan, E.T., Cone, E.J. and Huestis, M.A. Therapeutic Drug Monitoring, 26, pp. 664-672, 2004.

Imagery-induced Tobacco Craving: Duration and Lack of Assessment Reactivity Bias Little is known about the natural history of tobacco craving, including the intensity, frequency, and duration of craving episodes during various phases of the addictive process. In this study, IRP scientists investigated the duration of imagery-induced tobacco craving and whether craving responses are biased by repeated assessment, a phenomenon known as reactivity bias. Nonabstinent smokers (n = 40) either imagined a scene describing smoking urges or rested. They then either completed the Tobacco Craving Questionnaire (TCQ) every minute for 15 minutes or completed it after imagery or rest (minute 1) and 15 minutes later. TCQ scores were greater after imagery compared with rest and remained significantly elevated at minute 15. There was no evidence that TCQ responses were affected by repeated measurement. These data suggest that imagery-induced craving can persist for at least 15 minutes and that craving responses are not biased by assessment reactivity. Heishman, S.J., Saha, S. and Singleton, E.G. Psychology of Addictive Behaviors, 18, pp. 284-288, 2004.

Director's Report to the National Advisory Council on Drug Abuse - February, 2005

Program Activities

New NIDA PAs and RFAs

On November 3, 2004, NIDA issued an RFA entitled **Lapse or Relapse to Drug Abuse and Other Chronic Conditions (RFA-DA-05-004)**. This RFA invites applications in which a behavioral, cognitive, social cognitive or neurobiological approach is used to advance our understanding of the causes, consequences and treatment of drug abuse relapse. The purpose of this RFA is to stimulate research that will lead to an improved understanding of the relapsing nature of drug addiction. This RFA particularly encourages interdisciplinary research that fosters collaboration between basic and applied researchers, between those studing humans in laboratory settings and those studying clinical populations. In addition, researchers who study other chronic relapsing conditions (e.g., obesity, depression, anxiety disorders) are encouraged to apply their research approaches or paradigms to the problem of drug abuse and addiction. Letter of Intent Receipt Date for this RFA was December 27, 2004; Application Receipt Date was January 25, 2005.

On January 3, 2005, NIDA issued an RFA entitled **Neurobiology of Behavioral Treatment: Recovery of Brain Structure and Function (RFA-DA-05-006)**. Through this RFA NIDA invites exploratory/developmental, interdisciplinary research applications to investigate the human central nervous system effects of behavioral therapies, alone or in combination with pharmacotherapies, used for the treatment of drug abuse/addiction. Major advances have been made in understanding how drugs of abuse alter various brain processes and systems both structurally and functionally. Likewise, after a course of treatment the brain is also changed in some way. Further, many of these changes can be very persistent, even after long-term abstinence from drugs. Through the use of clinical neurobiological approaches, such as brain imaging (e.g., PET, MRI, MRS, EEG) and other related neurobiological methodologies (e.g., ERP, neuropsychological testing, genetics) considerable information is now being amassed that reveals how acute and chronic drug abuse alters brain structure and/or function. However, relatively little is yet known of the brain's specific response to detoxification/withdrawal and protracted abstinence, and even less is known of how treatment (both behavioral and/or pharmacological) might affect brain structure and function. A critical question that remains to be addressed is how drug addiction therapies, particularly behavioral treatments, might affect the structure and/or function of a brain altered by drugs of abuse with specific implications for consequential behavior change. Therefore, it is important to understand the specific role of various treatments in the recovery of neurobiological systems altered by extended drug exposure and behavioral therapy. Exploratory studies that will detect and characterize neurobiological mechanisms predictive of treatment outcome and efficacy are especially encouraged. Letter of Intent Receipt Date for this RFA is February 21, 2005; Application Receipt Date is March 21, 2005.

On January 21, 2005, NIDA issued an RFA entitled **HIV and Drug Abuse Interventions among Pregnant Women in Drug Abuse Treatment (RFA-DA-05-008)**. The purpose of this RFA is to encourage research on HIV prevention and risk reduction interventions among pregnant women in drug abuse treatment. (For the purposes of this RFA, drug abuse treatment refers to behavioral or combined behavioral and pharmacological treatment of drug abuse and/or dependence.) Pregnancy is a time of increased risk for HIV infection, both for drug-using women and for their infants through mother-to-child transmission. Behavioral HIV prevention and risk reduction interventions have shown promise in reducing HIV risk behaviors with a wide variety of drug-using populations, including drug-abusing pregnant women. For HIV-infected pregnant women, evidence suggests that proper HIV

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intervention care, including the use of certain antiretroviral medications, can reduce the maternal transmission of HIV to the child and can reduce other maternal and fetal complications. This RFA invites applications for studies to prevent or reduce HIV risk among pregnant women in drug abuse treatment through: 1) targeted behavioral HIV prevention and risk reduction interventions; and 2) behavioral interventions aimed at improving adherence to prenatal care among HIV-positive, pregnant drug-abusers. Letter of Intent Receipt Date for this RFA is February 21, 2005; Application Receipt Date is March 21, 2005.

PAs and RFAs Issued With Other NIH Components/Agencies

On September 29, 2004, NIDA, in conjunction with numerous other NIH components, the FDA and the CDC issued a Program Announcement (PA) entitled **Manufacturing Processes of Medical, Dental, and Biological Technologies (SBIR/STTR)**. Through this PA the NIH, CDC, and FDA encourage research related to advanced processing in the manufacture of biomedical products and the implementation of new technologies in medical care. New methods, procedures, measures, and controls are needed for manufacturing a broad range of technologies and products with unsurpassed quality and to lower manufacturing costs for existing and/or new processes. Research is also encouraged that can contribute to the containment and reduction of health care costs and that can improve the cost effectiveness, quality, and accessibility of the health care system.

On October 20, 2004, NIDA, in conjunction with a number of other NIH components, issued a PA entitled **The Effect of Racial and Ethnic Discrimination/Bias on Health Care Delivery (PA-05-006)**. The purposes of this PA are: (1) to improve the measurement of racial/ethnic discrimination in health care delivery systems through improved instrumentation, data collection and statistical/analytical techniques; (2) to enhance understanding of the influence of racial/ethnic discrimination in health care delivery and its association with disparities in disease incidence, treatment and outcomes among disadvantaged racial/ethnic minority groups; and (3) to reduce the prevalence of racial/ethnic health disparities through the development of interventions to reduce the influence of racial/ethnic discrimination in health care delivery systems in the United States. For the purposes of this PA, health care delivery is defined as the provision or receipt of a broad range of health-related services including preventive, primary, ambulatory and in-patient, emergency, specialty and long-term care. Health care delivery systems are defined as insurance plans, hospitals, clinics, private physician offices, or public and community health facilities that provide or finance health care delivery.

On October 20, 2004, NIDA in conjunction with NIMH and NIAAA, issued a PA entitled **Co-Occurring Mental Illness, Alcohol and/or Drug Abuse and Medical Conditions (PA-05-007)**. Through this PA, NIDA, NIMH, and NIAAA invite research grant applications to conduct services research on co-occurring mental illness, alcohol and/or drug abuse, and commonly co-occurring medical conditions. A significant number of individuals simultaneously suffer from mental illness, problem alcohol and/or drug use, and other medical or physical disorders, such as mood disorders compounded with substance abuse, chronic pain with depression and/or alcohol abuse, schizophrenia with heroin use and hepatitis C. This PA encourages innovative and theory-driven empirical research to examine the organization, management, integration, dissemination and implementation, and financing of services for co-occurring mental illness, alcohol and/or drug abuse, and commonly co-occurring medical conditions, as well as the impact of these factors on the quality, cost, access, utilization, outcomes, and cost and cost effectiveness of care.

On November 22, 2004, NIDA in collaboration with NCI and NIAAA, issued a PA entitled **Decision Making in Health: Behavior Maintenance (PA-05-016)**. The purpose of this initiative is to invite applications for research projects that will expand our knowledge of basic decision-making processes underlying initiation and long-term maintenance of healthy lifestyle behaviors that may reduce one's risk of cancer and other chronic diseases, such as cardiovascular disease, diabetes, and addiction. The NCI, NIDA, and NIAAA encourage collaborations between basic judgment and decision-making researchers, and applied cancer control or addiction researchers that will elucidate the basic cognitive and affective processes involved in decisions that are made repeatedly over time, such as adhering to weight-loss programs or smoking cessation programs.

On December 2, 2004, NIDA, in collaboration with other components of the NIH and DHHS, issued a PA entitled **Community Participation in Research (PAR-05-026)**. The goal of this PAR is to support research on health promotion, disease prevention, and health disparities that is jointly conducted by communities and researchers. This

PAR invites NIH research project grant (R01) and exploratory/developmental grant (R21) award mechanisms. Community-based participatory research (CBPR) is defined as scientific inquiry conducted in communities and in partnership with researchers. The process of scientific inquiry is such that community members, persons affected by the health condition, disability or issue under study, or other key stakeholders in the community's health have the opportunity to be full participants in each phase of the work (from conception - design - conduct - analysis - interpretation - conclusions - communication of results). CBPR is characterized by substantial community input in the development of the grant application.

On December 10, 2004, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Research on Mind-Body Interactions and Health (PA-05-027)**. Through this PA, the participating Institutes, Centers, and Offices invite applications in support of research on mind-body interactions and health. "Mind-body interactions and health" refers to the relationships among cognitions, emotions, personality, social relationships, and health. A central goal of this program is to encourage interdisciplinary collaboration and innovation towards understanding the processes underlying mind-body interactions and health as well as towards the application of such basic knowledge to interventions and clinical practice in the promotion of health and the prevention or treatment of disease and disabilities.

On December 21, 2004, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Social and Cultural Dimensions of Health (PA-05-029)**. The ultimate goal of this PA is to encourage the development of health research that integrates knowledge from the biomedical and social sciences. This involves the further development of health-related social science research relevant to the missions of the NIH Institutes and Centers (ICs) and the development of multi- or inter-disciplinary research that blends the theories and approaches of the social and biomedical sciences. Within the broad spectrum of research identified in this announcement, applicants are encouraged (but are not required) to employ multiple (i.e., biological, behavioral, and/or social) levels of analysis. This announcement invites applications to (a) elucidate basic social and cultural constructs and processes used in health research, (b) clarify social and cultural factors in the etiology and consequences of health and illness, (c) link basic research to practice for improving prevention, treatment, health services, and dissemination, and (d) explore ethical issues in social and cultural research related to health. On January 24, 2005, NIDA, in conjunction with numerous other NIH components, issued a PA entitled Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) to Improve The Chemistry and Targeted Delivery of RNAi Molecules (PA-05-041). Through this PA the participating institutes of the NIH invite the small business community to apply cutting edge-technology to develop new approaches and chemical modifications that will increase the long term stability, delivery and targeting of siRNAs in cells and tissues for laboratory and therapeutic applications.

On October 26, 2004, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **International Cooperative Biodiversity Groups (ICBG) (RFA-TW-04-004)**. The unifying theme underlying the ICBG program is the concept that the discovery and development of pharmaceutical and other useful agents from natural products can, under appropriate circumstances, promote economic opportunities and enhanced research capacity in developing countries while conserving the biological resources from which these products are derived. This RFA calls for the development of interdisciplinary programs through the establishment of International Cooperative Biodiversity Groups (ICBGs), with active and substantial participation by U.S. and developing country scientists and institutions. It is the intent of this RFA to promote the conservation of biological diversity through the discovery of bioactive agents from natural products, and to ensure that benefits accruing from both the research process and any discoveries are shared with the country of origin. The RFA is seeking applications that will build institutional relationships with developing countries that will continue to grow beyond the life of the RFA and will serve as effective models for others to develop similar relationships.

On November 19, 2004, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Leadership for HIV/AIDS Clinical Trials Networks (RFA-AI-05-001)**. The objective of this RFA is to establish the Leadership of three to six HIV/AIDS Clinical Trials Networks to carry out the NIAID research agenda in the following areas: (1) Vaccine Research and Development; (2) Translational Research/Drug Development; (3) Optimization of Clinical Management, Including Co-Morbidities; (4) Microbicides; (5) Prevention of Mother-to-Child Transmission (MTCT) of HIV; and (6) Prevention of HIV Infection. Each Network Leadership will consist of three components: (1) a Coordinating and Operations Center (CORE) to provide

scientific and administrative leadership, central operations, and communications; (2) a Statistical and Data Management Center (SDMC) to provide biostatistical leadership and central data management; and (3) a Network Laboratory Structure to provide the laboratory services necessary to conduct the clinical research. These Network Leadership components may be combined in a single application or in separate, but linked applications. Resulting Networks may be funded through one to three Cooperative Agreements (U01). Clinical Trial Units will be solicited in a subsequent, linked RFA titled " Units for HIV/AIDS Clinical Trials Networks ". The resulting combination of a Network Leadership and affiliated Clinical Trial Units will constitute an HIV/AIDS Clinical Trials Network. Each Network will give high priority to collaborations with other NIH HIV/AIDS clinical research programs, the other Networks funded through this RFA and other HIV research entities in order to effectively develop and implement a clinically relevant, interdisciplinary and cost-efficient research program.

On November 24, 2004, NIDA, NIMH and NICHD jointly issued an RFA entitled **Adolescent Medicine Trials Network for HIV/AIDS Interventions (RFA-HD-04-025)**. Through this RFA participating institutes invite applications from investigators willing to participate with NICHD under a cooperative agreement to sustain the Adolescent Medicine Trials Network (ATN). This network will have the capacity for developing and conducting selected behavioral, community-based translational, prophylactic, therapeutic, and vaccine trials based on and adding to the information developed through the Adolescent Medicine HIV/AIDS Research Network (1994-2001) and the current Adolescent Trials Network for HIV/AIDS Interventions (2001-2006). The primary mission of the Adolescent Medicine Trials Network (ATN) for HIV/AIDS Interventions will be to conduct research, both independently and in collaboration with existing research networks and individual investigators, in HIV-infected and HIV-at-risk pre-adolescents, adolescents, and young adults up to age 25 years. The objective of this RFA is to continue and expand the infrastructure required for a network of 14-17 clinical sites, one data and operations center, and one scientific leadership group with discipline-specific subgroups. This network will design, develop, and conduct multiple common clinical trials as well as pertinent formative and translational research studies collaboratively or independently when needed. This network will bring the required numbers of subjects into rigorously designed common protocols and thus address pressing research questions in youth more quickly than could individual centers acting alone.

On November 24, 2004, NIDA, in collaboration with other NIH components and the Agency for Healthcare Research and Quality (AHRQ), issued an RFA entitled **Building Interdisciplinary Research Careers in Women's Health (RFA-OD-05-002)**. The cosponsors of this RFA invite institutional career development award applications for Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Career Development Programs, hereafter termed "Programs." Programs will support research career development of junior faculty members, known as Interdisciplinary Women's Health Research (IWHR) Scholars, who have recently completed clinical training or postdoctoral fellowships, and who are commencing basic, translational, behavioral, clinical and/or health services research relevant to women's health. The goal of this initiative is to promote the performance of interdisciplinary research and transfer of findings that will benefit the health of women, including sex/gender similarities or differences in biology, health or disease. The programs will accomplish these goals by bridging advanced training with research independence, as well as bridging scientific disciplines or areas of interest. This will increase the number and skills of investigators at awardee institutions through a mentored research and career development experience leading to an independent interdisciplinary scientific career addressing women's health.

On December 3, 2004, NIDA, in collaboration with several other NIH components, issued an RFA entitled **Pediatric HIV/AIDS Cohort Study (PHACS) (RFA-HD-05-018)**. Through this RFA, participating Institutes invite applications from investigators willing to participate with the Institutes under a cooperative agreement (U01) to address two critical pediatric HIV research questions: the long term safety of fetal and infant exposure to prophylactic antiretroviral chemotherapy, and the effects of perinatally acquired HIV infection in adolescents. This effort will include refocus of a currently ongoing NIH-funded project (the Women and Infants Transmission Study [WITS]) and may include merger with data from other U.S.-based pediatric HIV cohort studies. This joint effort will take the form of the Pediatric HIV/AIDS Cohort Study (PHACS). The objective of this RFA is to create a body of data to understand more fully the effect of HIV on sexual maturation, pubertal development, and socialization of perinatally HIV-infected pre-adolescents and adolescents, and to acquire more definitive information regarding long-term safety of antiretroviral agents

when used during pregnancy and in newborns.

On December 22, 2004, NIDA and NIAAA issued an RFA entitled **Secondary Analysis of the NESARC and NSPY Datasets (RFA-DA-05-005)**. This RFA requests applications to support the secondary analysis of data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) or the National Survey of Parents and Youth (NSPY) to study the epidemiology and etiology of alcohol and drug abuse, as well as the utilization of alcohol and drug abuse services and the prevention of these behaviors. The purpose of this RFA is to take advantage of these rich data sets and to provide support for innovative research using state of the art analytical strategies. Findings from these studies are expected to provide context for the development of prevention and treatment interventions that are likely to have a direct impact on public health outcomes.

On January 10, 2005, NIDA, in conjunction with the National Human Genome Research Institute (NHGRI) and the NIH Office of Rare Diseases issued an RFA entitled **K23 with Emphasis on Therapeutic Interventions Employing Genomic or Proteomic Technologies (RFA-HG-05-013)**. The purpose of the Mentored Patient-Oriented Research Career Development Award (K23) is to support the career development of translational researchers in genomics. The program will support clinicians who propose an integrated clinical research and bench research project that applies genomics and proteomics tools to the study of human patients whose disease has a genetic component. For the purpose of this award, genomics and proteomics are being broadly interpreted to include the application of increasing knowledge of the genome and the proteome to the development and implementation of novel therapeutic strategies as applied to genetic diseases and complex diseases with a genetic component. Priority will be given to projects that have a near-term objective that will lead to the development of effective therapeutic interventions. This award will provide support for three to five years of supervised study and research for clinically trained professionals who plan to become independent, productive clinical investigators focusing on patient-oriented research.

On February 2, 2005, NIDA and NIAAA jointly issued an RFA entitled **Consequences of Drug Abuse and Alcohol Exposure on Brain and Behavioral Development (RFA-DA-05-007)**. The purpose of this RFA is to support research to further our understanding of the consequences of drug use, abuse, and addiction on the human brain and behavior during development. Research has demonstrated adverse consequences of drugs of abuse across multiple domains, however little is understood about the effects of drugs of abuse on development per se. The rapid advancement and refinement of new technologies offer unprecedented opportunities to characterize the neurobiological consequences of drugs of abuse on the developing human brain, and to address the relationships between the neurobiological aspects of development and the behavioral consequences of drug exposure. For example, advances in behavioral assessment, neuroimaging technologies, and statistical methods have the potential to define the effects of abused drugs on the human brain and behavior, effects that are very likely to be strongly influenced by the developmental state of the nervous system at the time that exposure occurs and, importantly, by a wide variety of environmental factors. This RFA calls for research that addresses the effects of drug exposure on neurobiological and behavioral development, spanning the continuum of human development through the transition to adulthood with a focus on the following areas: (1) documentation of the effects of exposure on development, (2) examination of the effect of timing of exposure on development, (3) examination of mechanisms that link exposure to adverse consequences, and (4) determination of the role of environmental context on the effects of exposure.

Other Program Activities

Cooperative Research and Development Agreement with IVAX Research to Test an AMPA Antagonist (Talampanel) for the Treatment of Cocaine Dependence

The Division of Pharmacotherapies and Medical Consequences of Drug Abuse has successfully negotiated a Cooperative Research and Development Agreement (CRADA) to test talampanel, a unique proprietary inhibitor of the amion-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) subtype of glutamate excitatory amino acid receptors as a treatment for cocaine dependence. Talampanel is already in Phase II clinical studies as a potential treatment for epilepsy so a substantial amount of preclinical and clinical data will be available to shorten the lead time necessary to test the hypotheses (prevention of locomotor sensitization, blockade of cocaine-cue induced drug seeking behavior, and blockade of cocaine-primed reinstatement in animal models of cocaine self-administration) generated by NIDA grantees that this

class of compound may be useful as a treatment for cocaine dependence.

Ondansetron Shows Effect in Clinical Trial

Ondansetron a 5-HT3 antagonist, has been shown to modulate the behavioral effects of cocaine in animals and to block some of the subjective effects of cocaine in humans. In a pilot dose ranging double blind phase II study of ondansetron the highest dose of 8mg/day was superior to placebo and the lower two doses in reducing cocaine use. This study will be followed up by a larger confirmatory study.

NIDA Medications Development Program Expands Capabilities for Preclinical Safety Testing

On September 30, 2004, NIDA contract N01DA-4-8841, entitled "Toxicological Evaluations of Potential Medications to Treat Drug Addiction," was awarded to Gene Logic Laboratories, Inc., of Gaithersburg, MD. The Principal Investigator is Dr. Eias Zahalka. This contract not only allows the NIDA Medications Development Program to continue it's support of the standard preclinical safety tests required for IND and NDA filings, but it also expands NIDA's capability to conduct predictive toxicology testing during the medications discovery process. Predictive toxicology, exemplified by the in vitro HERG assay to predict QT prolongation problems, the Spot Ames test to predict genotoxicity, etc., first became incorporated into NIDA's medication discovery programs in 2000. With the advent of gene expression profiling techniques, the field of toxicogenomics has played an important role in developing new predictive toxicology assays, and Gene Logic has been a pioneer in this area of research. With the new award, NIDA's medications discovery programs immediately have access to in vitro assays that are predictive of hepatotoxicity, a common finding that terminates many drug development projects. By addressing safety issues such as hepatotoxicity during the drug discovery process, development candidates have a better chance of succeeding in preclinical development.

NIDA Medications Development Program Renews and Expands Contract to Support Test Compound Evaluation in Relapse Models

Dating back to the inception of the NIDA Cocaine Treatment Discovery Program (CTDP) in 1992, it has been recognized that different stages of the cocaine addiction cycle must be targeted with different types of medications. Initially, the CTDP's focus was limited to the discovery of potential "agonist therapies" for initiation of abstinence (analogous to the use of mu-opioid agonists in opiate addiction) and "antagonist therapies" to prevent relapse in abstinent addicts (analogous to naltrexone's use in opiate addiction). In 1997, NIDA staff began efforts to expand CTDP testing to include animal models that focus on relapse triggers such as stress and conditioned cues. The first related RFP was released in early 1999 but it did not yield any acceptable proposals (as judged by the peer review process). Persistence and the reissue of a revised RFP resulted in a contract award to Virginia Commonwealth University (Patrick Beardsley, PI) September, 2000. At that time, VCU staff did not have hands-on experience conducting stress- or cue-induced relapse studies; however, over the course of their first contract, the laboratory evolved into an experienced and productive group (e.g., see discussion of JDTic studies under "Research Findings", above). The contract, entitled "Medication Discovery using Rat Models of Relapse to Drug Self-Administration," went through the competitive renewal process during FY 2004 and on September 30, VCU was again selected as NIDA's contractor. The new contract (number N01DA4-8848) provides an expanded level of support for test compound evaluation in relapse models and will give NIDA the additional flexibility to address relapse to methamphetamine, nicotine, and perhaps cannabinoids.

NIDA Medications Development Program Awards Contract for Discovery of Medications to Treatment Methamphetamine-Induced Cognitive Impairment

Building on the concept that different stages of the addiction process should be targeted with different types of medications, the NIDA MDP has expanded its focus to address an important long-term consequence of methamphetamine abuse, cognitive impairment. Two different consultant meetings, held in 2000 and 2003, helped shape NIDA's planning for this new contract. During the 2000 meeting, clinicians stressed the fact that methamphetamine addicts are more cognitively impaired than cocaine addicts and they argued that restoration of normal cognitive function would facilitate behavioral therapy. Although animal models of methamphetamine-induced cognitive impairment did not exist in 2000, the field progressed rapidly and by 2003, consultants concluded that the state of the science was sufficient to support the development of relevant models under a NIDA contract. An RFP was released in early 2004 and the resulting contract (N01DA-4-8849; "Animal Models of Methamphetamine-Induced Cognitive Impairment") was awarded September 29, 2004 to the U.C. Irvine (John Marshall, PI). During the life of this contract, consultants with pharmaceutical company and/or neurotoxicology backgrounds will

assist NIDA staff and the contract PI in developing models and establishing appropriate protocols for evaluation of test compounds. To this end, a contract kickoff meeting was held at UCI on October 20, 2004. NIDA attendees were Mr. Hirsch Davis (Project Officer), Dr. David McCann, and Dr. Jane B. Acri. UCI attendees included Dr. John Marshall and Dr. Steven O'Dell. NIDA's consultants were Dr. Rex Denton (Bristol-Myers Squib), Dr. Mary Jeanne Kallman (Lilly Research Laboratories) and Dr. Victoria Luine (Hunter College of the City University of New York).

NIDA/Portland VA Medical Center IAG is Expanded in Scope to Address Abuse Liability Testing as well as Medications Discovery

Over the past several years, NIDA's Cocaine Treatment Discovery Program (CTDP) has shifted away from a major emphasis on Biogenic Amine Transporter- (BAT-) directed "agonist medications" and toward the evaluation of compounds that target common triggers of relapse, such as stress (see above). This has resulted in a decreased need for BAT-directed testing, supported until August 2004 through an IAG with the Portland VA Medical Center (Aaron Janowsky, PI). At the same time, the DEA has increased its requests to NIDA for abuse liability testing of new street drugs, which primarily show mixed hallucinogen/psychostimulant properties. NIDA has an obligation to provide data to support DEA scheduling recommendations for these compounds, in vitro testing is part of the requirement, and assays targeting BATs are essential. To accommodate the small but remaining needs of the CTDP for BAT-directed testing, as well as NIDA's increased need for in vitro data relevant to abuse liability testing, a new IAG (Y1DA 5007 "In Vitro Receptor, Transporter, and Release Assays for NIDA Medications Discovery and Abuse Liability Testing") was established with the Portland VA Medical Center in December 2004. Assays are being expanded in scope to include 5-HT2a receptors, PCP receptors, and other targets relevant to abuse liability.

The PA, "Collaborative Clinical Studies in Drug Abuse" has resulted in the funding of a Multi-Site Clinical Trial entitled "Maternal Opioid Treatment Human Experimental Research" (MOTHER) to six domestic and two international sites

Promising preliminary data from a double-blind randomized trial at the Johns Hopkins School of Medicine suggest that buprenorphine results in improved birth outcomes and less neonatal abstinence syndrome (NAS) relative to methadone. The current randomized parallel group study will be the first multi-site trial to assess the efficacy of buprenorphine for reducing NAS relative to methadone in opioid dependent pregnant women. Overall, this study will provide pivotal data to support an indication for the use of both methadone and buprenorphine during pregnancy and for establishing efficacy of buprenorphine for reducing NAS relative to methadone. The Kickoff Meeting for the MOTHER Project was held December 15 - 17, 2004, in Washington, D.C.

Translationally Oriented Approaches, Devices and Strategies (TOADS) work-group

The Translationally Oriented Approaches, Devices and Strategies (TOADS) work-group, co-chaired by Dr. Nemeth-Coslett, DCNDBT, has set aside money to support up to 8 junior researchers to attend the 11th International Conference on Human-Computer Interaction. Researchers who have an interest in using state-of-the-art technologies as an investigative tool in drug abuse research, prevention and treatment were invited, via fliers at Neuroscience and through several ListServes, to submit proposals.

Update on the National Drug Abuse Treatment Clinical Trials Network (CTN)

The proposals for the Request for Applications (RFA) DA-05-001 for the fourth solicitation for the CTN were received October 14, 2004. This RFA includes both new applications (new Nodes) and competing continuations. The anticipated award date is July 2005.

Two new Requests for Proposal (RFPs) were issued: DA-5-2207 for the Data and Statistics Center for the CTN, and DA-5-2208 for the Clinical Coordinating Center for the CTN. Responses were due in January 2005. Both contracts are to be awarded in April 2005.

Nine protocols have completed enrollment since 2001. These studies enrolled 2,692 patients who were randomized in 53 community treatment programs located in 16 states. Twelve additional protocols are currently recruiting & enrolling patients. These protocols will enroll 4,674 patients across 88 Community Treatment Programs when completed. Highlights of the active protocols include:

- Protocol CTN 0003 (Bup/Nx: Comparison of Two Taper Schedules) began

enrollment June 30, 2003. The study involves 11 sites across 8 nodes; the targeted enrollment is 480 participants. Participation has reached 2/3 of the targeted enrollment.

- Protocol CTN-0004 (Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome in Subjects Seeking Treatment for Substance Abuse) closed enrollment August 9, 2004 and has a target for study completion in early 2005.
- Protocol CTN 0010 (Buprenorphine/Naloxone Facilitated Rehabilitation for Opioid Dependent Adolescents/Young Adults) began enrollment in July 2003. This is the first protocol in the CTN that targets adolescent substance abusers. Enrollment is at 1/3 of the projected target of 240 adolescents.
- Protocol CTN 0011 (A Feasibility Study of a Telephone Enhancement Procedure to Improve Participation in Continuing Care Activities) has completed enrollment and follow-up and is now at the analysis stage.
- Protocol CTN 0013 (Motivational Enhancement Therapy to Improve Treatment Utilization and Outcome In Pregnant Substance Abusers.) This protocol has recently begun enrollment and has reached 1/3 of the projected target of 200 pregnant substance-abusing women.
- Protocol CTN 0014, Brief Strategic Family Therapy for Adolescent Drug Abusers (BSFT), is in the final stages of provider training and will involve three phases of implementation. The first wave of sites has finished protocol training and moved to patient enrollment in August 2004. BSFT will be implemented at 8 sites across 6 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) began in March 2004. This study is being carried out at 8 sites across 7 Nodes and targeted enrollment is 480. The study has reached nearly 50% of the targeted patient enrollment.
- Protocol CTN 0017 (HIV and HCV Intervention in Drug Treatment Settings). The study has recently begun enrollment in November 2004. It will be carried out at 8 CTP sites across 5 nodes.
- CTN 0018 (Reducing HIV/STD Risk Behaviors: A Research Study for Men in Drug Abuse Treatment) began enrolling in April 2004. This study will be carried out at 14 CTP sites across 11 nodes. The enrollment has reached 25% of the target of 560 patients.
- CTN 0019 (Reducing HIV/STD Risk Behaviors: A Research Study for Women in Drug Abuse Treatment) began enrollment in April 2004. This study will be carried out at 12 CTP sites across 7 nodes. The targeted enrollment is 480 patients for each study. The enrollment has reached nearly 1/3 of the target goal.
- CTN 0020 (Job Seekers Training for Substance Abusers). The protocol recently began enrollment in October 2004. It will be conducted at 12 CTP sites across 7 nodes. The targeted enrollment is 624 patients.
- Protocol CTN 0021(Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome for Spanish-Speaking Individuals Seeking Treatment for Substance Abuse) began enrollment in November 2003. This is the first Spanish only protocol in the CTN. It will be conducted at 6 bi-lingual sites across 5 nodes and has a target enrollment of 480 patients. The study has reached nearly 50% of the target goal.
- In addition to the primary CTN trials, there are 12 studies supported by independent grants or as supplements that use CTN studies as a platform.
- New Collaborative Study: Starting Treatment with Agonist Replacement Therapies (START) Study: The CTN will participate with the Division of Pharmacotherapies & Medical Consequences of Drug Abuse on a multi-centered trial to compare the effect of buprenorphine/naloxone (Bup/Nx) and methadone (MET) on liver function in the outpatient setting. This is a randomized, open-label, multi-center, Phase 4 study in participants entering opioid agonist treatment programs at community centers (methadone centers) throughout the country. It is anticipated that 1,000

patients will be entered into the trial starting second quarter of 2005.

3 Additional Protocols to begin enrollment in FY 05.
Three new studies will address emerging needs of ADHD in adolescents, ADHD in smoking adults, and the problem of treatment for prescription opiate abuse. In addition, a genetics component will be tested in the START Bup/Nx study.

The NIH Summer Internship Program (SIP) and the Minority Recruitment & Training Program (MRTP)
The NIH Summer Internship Program (SIP) and the Minority Recruitment & Training Program (MRTP) are now accepting applications for the Summer, 2005. Both programs provide training opportunities for students who are interested in the scientific basis of drug abuse. In these programs, students gain basic science and/or clinical laboratory experience, attend student seminars, and participate in a summer poster presentation. The goal of the programs is to expose students to the realities of research, from experimental design to data analysis, interpretation and presentation. For information and an application for the SIP, go to www.training.nih.gov or contact Dr. Stephen Heishman (sheish@intra.nida.nih.gov). For an application or to receive information about the MRTP, contact Christie Brannock (cbrann@intra.nida.nih.gov)

NIDA's New and Competing Continuation Grants Awarded Since September 2004

Alemagno, Sonia A. -- University of Akron
HIV Prevention For Community-Based Drug-Using Offenders

Anokhin, Andrey P. --Washington University
Neurocognition, Genetics and Adolescent Substance Abuse

August, Gerald J. -- University of Minnesota Twin Cities
Early Risers Multi-Site Implementation Study

Bauman, Laurie J. -- Yeshiva University
Reducing Risk Among Highly Vulnerable Youth

Beaston-Blaakman, Aaron -- Brandeis University
A Conceptual and Empirical Analysis of Cost Analysis

Bellack, Alan S. -- University of Maryland Baltimore Professional School
Behavioral Treatment for Drug Abuse In SPMI Patients

Bergman, Jack -- Mc Lean Hospital, Belmont, MA
CB-1 Antagonists for Cannabis Addiction

Blankenship, Kim M. --Yale University
Criminal Justice, Race and HIV Risk In CT Drug Users

Block, Robert I. -- University of Iowa
Brain Development of Adolescent Marijuana Users

Bohn, Laura M. -- Ohio State University
Physiological Implications of Opioid Receptor Regulation

Bolland, John M. -- University of Alabama In Tuscaloosa
Decision Making & Substance Abuse Among Inner-City Youth

Botvin, Gilbert J. -- Weill Medical College of Cornell University
Enhancing Implementation Fidelity In A Multi-Site Trial

Bowen, Scott -- Wayne State University
A Preclinical Model of Adolescent Toluene Abuse In Rats

Boyd, Carol J. -- University of Michigan at Ann Arbor
Prescription Abuse and Diversion By Secondary Students

Brody, Gene H. -- University of Georgia
Preventing Drug Use In Rural African Americans

Broner, Nahama -- Research Triangle Institute
HIV/AIDS and Diverted Offenders

Brown, Richard A. -- Butler Hospital, Providence, RI
MI For Teen Substance Abuse With Psychiatric Comorbidity

Bryan, Angela -- University of Colorado at Boulder

Marijuana Use, Gender and Adolescent HIV Sexual Risk

Burstein, Sumner H. -- University of Massachusetts Medical School Worcester
Endocannabinoid Analogs As Anti-Inflammatory Agents

Casey, Betty J. -- Weill Medical College of Cornell University
Development of Basic Components of Decision Making

Chawarski, Marek C. -- Yale University
Brief Introductory Therapy For Opioid Dependence

Choi, Kyung-Hee -- University of California San Francisco
Asian Men's Health Study

Conklin, Cynthia A. -- University of Pittsburgh at Pittsburgh
Extinction In Smokers: Renewal and Spontaneous Recovery

Cornelius, Jack R. -- University of Pittsburgh at Pittsburgh
Fluoxetine For MDD/Cannabis Disorder In Young People

Coscia, Carmine J. -- St. Louis University
Opioid Modulation of Astrocyte Proliferation

Cottler, Linda B. -- Washington University
Deconstructing HIV Interventions For Female Offenders

Cozzi, Nicholas V. -- Physiogenix, Inc.
Amphetamine-Related Photoaffinity Probes

Crits-Christoph, Paul F. -- University of Pennsylvania
The Process of Group Therapy For Cocaine Dependence

Dahl, Ronald E. -- University of Pittsburgh at Pittsburgh
Pubertal Maturation & Drug Use Vulnerability

D'Amico, Elizabeth J. -- Rand Corporation
Brief Youth Substance Use Intervention For Primary Care

Daughters, Stacey B. -- University of Maryland at College Park
Distress Tolerance and Drug Treatment Drop-Out

Dimmitt Champion, Jane -- University of Texas Health Science Center, San Antonio
Behavioral Invervention For Minority Adolescent Women

Dow-Edwards, Diana L. -- Suny Downstate Medical Center
THC Affects the Development of Executive Function

Ehlers, Cindy L. -- Scripps Research Institute
Adolescent Marijuana Use In Native Americans

Faraone, Stephen V. -- Upstate Medical University
Validating Novel Familial Phenotypes of Drug Abuse

Fava, Maurizio -- Massachusetts General Hospital
Drug Discovery Group for Nicotine Dependence Treatment

Ferris, Craig F. -- University of Massachusetts Medical School Worcester
Neurobehavioral Effects of MDMA In Adolescent Monkeys

Fischer, Gabriele -- Medical University of Vienna
Maternal Opioid Treatment: Human Experimental

Forman, Robert F. -- University of Pennsylvania
Group Drug Counseling Toolkit

Frank, Deborah A. -- Boston Medical Center
Prenatal Cocaine Exposure: Adolescent Follow-Up

Gabbay, Frances H. -- Henry M. Jackson Foundation for the Adv. of Military Medicine
Inhibitory Control: Toward A Vulnerability Phenotype

Gerzanich, Vladimir V. -- University of Maryland Baltimore Professional School
Nicotinic ACH Receptors In Cerebrovascular Endothelium

Gibbons, Frederick X. -- Iowa State University
Social-Cognitive Model of Adolescent Substance Use

Gibson, Laura E. -- University of Vermont & State Agricultural College
Smoking Cessation and PTSD

Green, Alan I. -- Dartmouth College
Cannabis & Schizophrenia: fMRI Reward Circuit Biomarker

Gwaltney, Chad J. -- Brown University
Effect of Mood on Impulsivity Among Adolescent Smokers

Halpern, John H. -- Mc Lean Hospital, Belmont, MA
Neurocognitive Consequences of Long-Term Ecstasy Use

Haney, Margaret -- New York State Psychiatric Institute
Medication Development For Marijuana Relapse

Hart, Carl L. -- New York State Psychiatric Institute
Drug Effects on Behavior: Workplace Implications

Hasin, Deborah S. -- New York State Psychiatric Institute
Phenotypes For Drug Abuse: Epidemiologic-Genetic Approach

Heil, Sarah H. -- University of Vermont & State Agricultural College
Maternal Opioid Treatment: Human Experimental Research

Hester, Robert -- University of Dublin Trinity College
Executive Functions In Cannabis Dependence

Huber, Robert -- Bowling Green State University at Bowling Green
Ethopharmacological Characterization of Reward Systems

Hurd, Yasmin L. -- Karolinska Institute
Neurodevelopmental Effects of Adolescent Cannabis Use

Hurt, Hallam -- Children's Hospital of Philadelphia
Adolescent Drug Use: Exploring Neurocognitive Precursors

Itzhak, Yossef -- University of Miami-Medical School
Adolescent Exposure To Psychostimulants: Role of Nnos

Jacobsen, Leslie K. -- Yale University
Brain Functional Correlates of MDMA Use In Adolescence

Jainchill, Nancy -- National Development & Research Institutes
Integrated Continuity of Care for Adolescent Drug Users

Johnson, Knowlton -- W Pacific Institute For Research and Evaluation
A Community Trial To Prevent Inhalant Use In Alaska

Jones, Hendree E. -- Johns Hopkins University
Maternal Opioid Treatment: Human Experimental Research

Jones, Sara R. -- Wake Forest University Health Sciences
Voltammetry In Freely Moving Mice

Juliano, Laura M. -- American University
Disentangling Pharmacological and Expectancy Effects

Kelleher, Kelly J. -- Children's Research Institute
Trial of Automated Risk Appraisal for Adolescents

Kelley, Michelle L. -- Old Dominion University
Effect of Treatment for Drug-Abusing Fathers on Children

Kirby, Kimberly C. -- Treatment Research Institute, Inc. (TRI)
Craft Behavior Therapy Phase 2 Study: Tx Entry Component

Knight, John R. -- Children's Hospital, Boston, MA
Screening and Brief Advice to Reduce Teen Substance Use

Kobilka, Brian K. -- Stanford University
Biophysical Analysis of Opioid Receptor Structure

Konradi, Christine -- Mc Lean Hospital, Belmont, MA
Adolescent Drug Exposure and Adult PFC Function

Kosten, Thomas R. -- Yale University

Heroin Addiction Treatment: Naltrexone and Lofexidine

Kuhn, Cynthia M. -- Duke University
Dopamine Function During Adolescence

Landry, Charles F. -- University of Wisconsin, Madison
Nicotine and Gene Expression in Adolescent Brain

Law, Ping-Yee -- University of Minnesota Twin Cities
Neuronal Regulation of Opioid Receptor Trafficking

Lee, Christine M. -- University of Washington
Personalized Feedback Intervention For Marijuana Use

Leonard, Noelle R. -- National Development & Research Institutes
HIV Risk and Substance Use In Adolescent Couples

Leslie, Frances M. -- University of California, Irvine
Mechanisms of Adolescent Vulnerability to Drugs of Abuse

Lester, Barry M. -- Women and Infants Hospital-Rhode Island
Maternal Opioid Treatment: Human Experimental Research

Levin, Frances R. -- New York State Psychiatric Institute
Marijuana Abusing ADHD Teens: Atomoxetine Treatment

Lopez-Zetina, Javier -- California State University Long Beach
Comparison of Drug Use In the US/Mexico Border

Lukas, Scott E. -- Mc Lean Hospital, Belmont, MA
Cannabis Dependence: Imaging and Medication Development

Lundahl, Leslie H. -- Wayne State University
Cue Reactivity Model/Pharm. Intervention In Cannabis Use

Lynch, Thomas R. -- Duke University
Developing Computer Based Treatments For Addiction

Lynskey, Michael T. -- Washington University
Cannabis Use, Abuse and Dependence: Exploring Phenotypes

Lysle, Donald T. -- University of North Carolina, Chapel Hill
Behavioral Factors In Heroin's Effect On Nitric Oxide

Mackenzie, Robert G. -- Wayne State University
Metabolic Regulation of Midbrain Dopamine Neurons

Mains, Richard E. -- University of Connecticut School of Medicine/ Dentistry
Constructing A Conditional Kalirin Null Mouse

Maldonado, Rafael -- Pompeu Fabra University
Vulnerability To Nicotine Addiction

Malow, Robert M. -- Florida International University
HIV Prevention Groups For AOD Using SMI Women

Marsch, Lisa A. -- National Development & Research Institutes
Science-Based Treatment For Opioid-Dependent Adolescents

Martin, Peter R. -- Vanderbilt University
Maternal Opioid Treatment: Human Experimental Research

McCance-Katz, Elinore F. -- Virginia Commonwealth University
Opioids & HIV Medications: Interactions In Drug Abusers

McMahon, Lance R. -- University of Texas Health Sciences Center, San Antonio
Treatment of Cannabinoid Withdrawal In Rhesus Monkeys

Mendelson, John E. -- California Pacific Medical Center-Pacific Campus
Clinical Pharmacology Of 3,4-Methylenedioxy Amphetamines

Meucci, Olimpia -- Drexel University College of Medicine
Cellular and Molecular Mechanisms of HIV Neuropathology

Milligan, Erin D. -- University of Colorado at Boulder
Pain Control Via Spinal Interleukin-10 Gene Therapy

Milner, Teresa A. -- Weill Medical College of Cornell University
Estrogen-Opioid Interactions In Hippocampus

Moore, Brent A. -- Yale University
Selegiline for Treatment of Cannabis Dependence

Murphy, Susan A. -- University of Michigan at Ann Arbor
Methodology For Adaptive Treatment Strategies

Nair, Madhavan P. -- State University of New York at Buffalo
Cocaine/Immuno and Neuropathogenesis of HIV-1 Infection

Neale, Michael C. -- Virginia Commonwealth University
Psychometric and Genetic Assessments of Substance Use

Patten, Christi A. -- Mayo Clinic College of Medicine, Rochester NY
Intervention For Support Persons To Help Smokers Quit

Paulus, Martin P. -- University of California, San Diego
Stimulant Dependence: Neural Mechanisms of Relapse

Peck, James -- University of California, Los Angeles
Behavioral Therapy Development for Methamphetamine Abuse

Penetar, David M. -- Mc Lean Hospital, Belmont, MA
Bupropion Effects On Marijuana Withdrawal Symptoms

Petry, Nancy M. -- University of Connecticut School of Medicine/Dentistry
Group-Based Contingency Management/Outpatient Treatment

Pillay, Srinivasan S. -- Mc Lean Hospital, Belmont, MA
fMRI of Pain In Cannabis Dependence

Prado, Guillermo -- University of Miami-Medical
Ecodevelopmental Classes of Youth Drug Use/Risky Sex

Prendergast, Michael L. -- University of California, Los Angeles
Gender-Responsive Treatment for Women Offenders

Reich, Warren A. -- Family Center, Inc.
Images of Self and Others In AIDS-Orphaned Youth

Rivkees, Scott A. -- Yale University
CB1 Receptor Action on the Developing Hippocampus

Sadee, Wolfgang -- Ohio State University
Polymorphisms In Regulatory Regions of Addiction Genes

Salina, Doreen D. -- Northwestern University
Integrated Health Treatment for Women Drug Users

Sanders-Bush, Elaine -- Vanderbilt University
Hallucinogens and Serotonin Signal Transduction

Selby, Peter L. -- St. Joseph's Health Centre
Maternal Opioid Treatment: Human Experimental Research

Sharp, Burt M. -- University of Tennessee Health Sciences Center
Opiate Receptor-Mediated Effects of Stress on Immunity

Simoni-Wastila, Linda J. -- University of Maryland Baltimore Professional School
Prescription Drug Abuse In Adolescents and Young Adults

Sinha, Rajita -- Yale University
Lofexidine To Prevent Stress-Related Opiate Relapse

Sowell, Elizabeth R. -- University of California, Los Angeles
Longitudinal MRI In Prenatal Methamphetamine or Alcohol

Spear, Linda P. -- State University New York, Binghamton
Adolescence: Natural Incentives, Motivation and Affect

Staley, Julie K. -- Yale University
Tobacco Smoking & Nicotinic Acetylcholine Receptors

Stein, Lynda A. -- Brown University

Motivation and Skills For THC/Etoh+ Teens In Jail

Stein, Michael D. -- Rhode Island Hospital, Providence, RI
A Brief Marijuana Intervention For Adolescent Women

Stine, Susan M. -- Wayne State University
Maternal Opioid Treatment: Human Experimental Research

Strain, Eric C. -- Johns Hopkins University
Medications Development for Drug Abuse Disorders

Swartzwelder, H. Scott -- Duke University
Developmental THC Sensitivity In Male and Female Rats

Taylor, Palmer -- University of California, San Diego
Nicotinic Receptor Template-Guided Drug Design

Thomas, Brian F. -- Research Triangle Institute
Analogs: Unique Probes for Cannabinoid Receptors

Tompkins, Christopher P. -- Brandeis University
Adolescent Primary Care Adoption of Substance Use SBI

Tsuang, Ming T -- University of California, San Diego
Alternate Phenotypes of Substance Abuse

Unger, Jennifer B. -- University of Southern California
Acculturation and Drug Use in Family and Peer Contexts

Unterwald, Ellen M. -- Temple University
Cocaine-Induced Opioid, Dopamine & Behavioral Changes

Vanyukov, Mcihael M. -- University of Pittsburgh at Pittsburgh
Substance Use Disorder Liability: Candidate Gene System

Wang, Gene-Jack -- Brookhaven Science Associates-Brookhaven National Lab
PET In Obese Monkeys

Watson, Donnie W. -- Friends Research Institute, Inc.
Substance Use and HIV Prevention

Wells, Gregg B. -- Texas A&M University Health Science Center
Bacterial Proteins in the Nicotinic/GABA Receptor Family

Wenzel, Suzanne L. -- Rand Corporation
Prevention for Impoverished Young Women In Shelters

Werch, Chudley E. -- University of Florida
Brief Positive Image Communications for Adolescents

Werch, Chudley E. -- University of Florida
A Selective Prevention Program For High School Seniors

Wetter, David W. -- University of Texas MD Anderson Cancer Center
Group Therapy for Nicotine Dependence

Wigdahl, Brian -- Drexel University College of Medicine
High Specificity HIV-1 Markers Predictive of Neuro-AIDS

Winder, Danny G. -- Vanderbilt University
Periadolescent Noradrenergic Regulation In the BNST

Windle, Michael T. -- University of Alabama at Birmingham
Parenting, Adolescent Substance Use and Delinquency

Wood, Evan -- University of British Columbia
Evaluating the Natural History of Injection Drug Use

Yacoubian, George S. -- Pacific Institute for Research and Evaluation
Preventing Club Drug Use Among Rave Attendees

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Extramural Policy and Review Activities

Receipt, Referral, and Review

NIDA received 1020 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 712 applications.

OEA arranged and managed 18 grant review meetings in which 238 applications were evaluated. OEA's reviews included applications in chartered, standing review committees and Special Emphasis Panels (SEPs). In addition, OEA's Contracts Review Branch (CRB) arranged and managed 2 contract proposal reviews and 3 concept reviews.

NIDA's chartered committees consist of NIDA-E (Treatment Review Committee), NIDA-F (Health Services Review Committee), NIDA-L (Medications Development Committee), and NIDA-K (Training Committee). In addition to meetings of each of these committees, OEA staff held 14 Special Emphasis Panels for a variety of reasons:

Conflicts with the chartered committees
The Minority Institutions' Drug Abuse Research Development Program (MIDARP)
Center Grant Applications
Program Project Grant applications
Behavioral Science Track Award for Rapid Transition (B/START)
Cutting Edge Basic Research Awards (CEBRA)
Imaging Science Track Awards for Research Transition (I/START)
Conference Grants (R13)
1 Special Emphasis Panel that reviewed RFA submissions.

OEA managed the following RFA reviews:

- DA05-002: Enhancing State Capacity to Foster Adoption of Science-based Practices

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

Non-R&D Contract Reviews

- N01DA-5-1122: Research Dissemination to the Entertainment Industry

R&D Contract Reviews

- N01DA-5-7746: Production Analysis & Distribution of Cannabis & Marijuana Cigarettes and Related Compounds

R&D Concept Reviews

- N01DA-5-8857: Clinical Data Management - Support for Clinical Trials
- N01DA-5-8855: Statistical Support - Support for Clinical Trials
- N01DA-5-5532: Data Archiving, Analyses and Management for the NSPY

Extramural Outreach

Dr. Levitin, Director, OEA, continues her work as the NIDA Research Integrity Officer

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Grantee Honors

In Memoriam

and representative to the NIH on these matters. She also has agreed to serve on the NIH Director's Pioneer Award (NDPA) Evaluation Advisory Committee.

Dr. Levitin served as an evaluator for the Science Service INTEL competition to identify the best science projects from high school students throughout the United States.

Dr. Levitin joined Arnold Mills from NIDA/DESPR and a CSR representative to present a workshop at the University of Wisconsin for faculty from all of their campuses on the NIH and the review and funding process at NIH and NIDA.

Dr. Levitin continues to serve on several subcommittees of the Extramural Program Management Committee (EPMC), which is an NIH-wide committee of senior NIH staff that advises the Director, NIH on matters concerning extramural policy.

Dr. Khursheed Asghar, Chief of the Basic Sciences Review Branch in OEA, gave a talk at the NIDA Research Development Seminar held on November 18-19, 2004, entitled "Review Process for NIDA Research Grant Applications". The workshop was sponsored by the NIDA Special Populations Office and the seminar was specifically designed for new investigators.

Dr. Khursheed Asghar participated in the annual meeting of the Society for Neuroscience, attending the NIDA mini convention, and participating in the NIDA booth, fielding questions from the visitors, introducing NIDA programs to young investigators and students, and recruiting grantees for service on NIDA review committees.

Loretta Beuchert, OEA, attended the annual meeting of the Society for Neuroscience, attending the NIDA mini convention, and participating in the NIDA booth to provide information and materials to potential applicants.

Mr. Lyle Furr, OEA, attended the 55th AALAS National meeting October 17-21, 2004.

Mr. Richard Harrison, OEA, attended the American Indian Science and Engineering Society (AISES) Annual Conference in Anchorage, AK, November 11-14, 2005.

Dr. Rita Liu, OEA, co-organized, along with Dr. David Shurtleff, DBNBR, and Dr. Cathrine Sasek, OSPC, the NIDA Mini-convention: Frontiers in Addiction Research, which took place on October 22, 2004 at the San Diego Convention Center in conjunction with the annual meeting of the Society for Neuroscience. This included 4 scientific symposia, 1 poster session for young investigators, and the Keynote speech was given by Dr. Antonello Bonci, the recipient of the 2004 Jacob P. Waletzky Memorial Award.

Dr. Rita Liu co-edited with Dr. David Shurtleff and Dr. Cathrine Sasek, a special Neuropharmacology issue entitled "Frontiers in Addiction Research: Celebrating the 30th Anniversary of the NIDA". The issue, published in Neuropharmacology, Vol 47, Supplement No. 1, 2004, included 30 contributors. Most of them are NIDA senior grantees, center directors, MERIT (Method to Extend Research In Time) awardees, PECASE (Presidential Early Career Award in Science and Education) awardees or NIDA Intramural Research Scientists.

Dr. Rita Liu is working with NIMH and NINDS to co-organize a monthly seminar series in 2005 on Neuroimaging. The topics will encompass structural MRI, computational tools, DTI (diffuse tensor imaging) and tract tracing, image guided surgery, imaging developing brain, and ethics in neuroimaging. The series is meant to educate NIH staffers to this rapidly growing field.

Dr. Rita Liu attended the American Society for Cell Biology (ASCB) meeting as a NIDA representative for the ASCB Conversation with NIH: Strategies for New Investigators.

Staff Training and Development

The OEA Symposium Series, a forum for staff training and sharing of ideas and information, continued through the fall and winter. Topics addressed have included extramural policy updates, the Extramural Scientist Administrator Training Program, model organism training, the NIH Guide Notice on implementation of recent OHRP guidance on research involving coded private information and biological specimens, the new (2004) version of PHS 398, updated criteria for evaluating research grant applications, centralized receipt of Progress Reports beginning October 1, 2004, and special emphasis PAs.

Director's Report to the National Advisory Council on Drug Abuse - February, 2005

Congressional Affairs (Prepared February 7, 2005)

APPROPRIATIONS FY 2005

The fiscal year 2005 spending bill for the Departments of Labor, Health and Human Services, and Education, which includes funding for the National Institutes of Health (NIH), cleared the Senate on November 20, 2004, as part of the year-end omnibus appropriations package (HR 4818). The President signed the bill December 8, 2004. [PL 108-447]

The House passed its version of the bill in September with $142.5 billion in discretionary spending. It proposed increases of $727 million for the NIH, mirroring the Administration's request. The Senate Appropriations Committee approved a more generous measure that included $2.8 billion more than the House bill, mainly for Title I, NIH and other health and education programs. The Senate Appropriations Committee recommended an appropriation of $1,026,200,000 for the NIDA. The President's request was $1,019,060,000. The fiscal year 2004 appropriation was $990,953,000.

The final bill provided $28.6 billion for NIH, a 3 percent increase over fiscal 2004 and about the same as the Administration and the House wanted but $300 million less than in the Senate bill. All figures are subject to the government wide 0.83% reduction (by contrast, last year's was 0.59%). NIH also is subject to a 2.4% Public Health Service Program Evaluation Transfer tap, which is a 0.2% increase over last year. The effect of these reductions is that the gross FY 2005 appropriations increase for NIH of about $800 million becomes a net increase of about $612 million. The total NIH appropriation will be about $27.9 billion, rather than the $28.5 billion shown in the congressional gross NIH budget tables. NIDA originally received an increase of 2.4 percent, but after the across the board cut and Labor/HHS/ED rescission, the final 2005 appropriations figure for NIDA is $1,006,419, a 1.6 percent increase over 2004.

108TH CONGRESS - Public Laws of interest

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

HR 5213 (PL 108-427) The Research Review Act of 2004 was introduced October 5, 2004, by Representative Bilirakis (R-FL). The bill expands research information regarding multidisciplinary research projects and epidemiological studies. It was signed by the President on November 30, 2004.

S 1194 (PL 108-414) The Mentally Ill Offender Treatment and Crime Reduction Act of 2004 was introduced by Senator DeWine (R-Ohio) on June 5, 2004 [A companion measure, HR 2387, was introduced June 5, 2003 by Rep. Strickland (D-Ohio)]. It was signed by the President on October 30, 2004. The measure is intended to facilitate collaboration among the criminal justice, juvenile justice, mental health treatment, and substance abuse systems to improve public safety. It will establish grants of up to $75,000 to create and expand mental health courts and programs that offer specialized training to officers and employees of criminal and juvenile justice agencies to identify mental illness. As amended, it would authorize $50 million for 2005 and such sums as are necessary for fiscal 2006 through 2009.

S 2195 (PL 108-647) The "Anabolic Steroid Control Act of 2004," was introduced to amend the Controlled Substances Act to clarify the definition of anabolic steroids and to provide for research and education activities relating to steroids and steroid precursors. Introduced by Senator Biden (D-DE) on March 11, 2004, the bill was a companion bill to HR 3866. The Senate passed S 2195 by unanimous consent on

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October 6, 2004, and the House cleared it October 8, 2004, by voice vote. It was signed into law on October 22, 2004.

S 2195 expands the types of steroids banned for general distribution under federal law. The law classifies as a controlled substance any product "chemically and pharmacologically related to testosterone" with exception of estrogens, progestins, corticosteroids, and dehydroepiandrosterone. The law outlines more than 50 specific substances that qualify a product for controlled substance status. The law authorizes $90 million over six years beginning in fiscal 2005 for the DHHS to conduct education programs in elementary and secondary schools to highlight the harmful effects of anabolic steroids. The law also authorizes $6 million over six years beginning in fiscal 2005 for HHS to conduct a survey on the use of anabolic steroids. One supplement targeted by the bill is androstenedione, known as "andro." The Food and Drug Administration (FDA) barred this particular steroid precursor from sale on March 11, 2004.

Of particular interest, the new law enables the Secretary of Health and Human services to award grants to public and nonprofit private entities to enable them to carry out science-based education programs in elementary and secondary schools to highlight the harmful effects of anabolic steroids. In awarding these grants, HHS is to give preference to applicants that intend to use grant funds to carry out programs based on the Athletes Training and Learning to Avoid Steroids (ATLAS) program; the Athletes Targeting Healthy Exercise and Nutrition Alternatives (ATHENA) program, and other programs determined to be effective by the NIDA.

108TH CONGRESS - Other bills of interest

NIDA staff will monitor Congressional activity to keep abreast of whether any of these bills are re-introduced in the 109th Congress.

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 September 30, 2003, the measure, as amended, passed in the House by voice vote, under suspension of the rules (two-thirds vote required). On October 1, 2003, it was received in the Senate and referred to the Senate Judiciary Committee. No further action. (Related Bills: S1860).

HR 2256 - On May 22, 2003, Representative Ramstad (R-MN) introduced HR 2256, the Help Expand Access to Recovery and Treatment (HEART) Act of 2003. This bill would amend the Employee Retirement Income Security Act of 1974, Public Health Service Act, and the Internal Revenue Code of 1986 to provide parity with respect to substance abuse treatment benefits under group health plans and health insurance coverage. The bill was referred to the House Energy and Commerce Committee, Ways and Means Committee, and Education and the Workforce Committee. There was no further action after committee referrals. The companion bill in the Senate was S.1138, introduced on May 22, 2003 by Senator Norm Coleman (R-MN). That bill was referred to the Committee on Health, Education, Labor and Pensions, with no further action.

HR 3634 - On November 21, 2003, Representative Souder (R-IN) introduced HR 3634, a measure similar to S 1887. Both bills would have amended the Controlled Substance Act to lift the patient limitation on prescribing drug addiction treatments by medical practitioners in group practices. The House bill was referred to the House Energy and Commerce and the House Judiciary Committees. No further action.

HR 3866 - On March 1, 2004, Judiciary Chairman F. James Sensenbrenner Jr., (R-WI) introduced H.R. 3866,"the Anabolic Steroid Control Act of 2004." H.R. 3866 passed the House on June 3, 2004, by a vote of 408-3. The measure went to the Senate, where a similar bill (S. 2195) was pending before the Judiciary Committee. No further action. Related bills: S1780, S2195 [PL 108-647]

HR 3922, the "Drug-Impaired Driving Enforcement Act of 2004," introduced by Representative Portman (R-OH). The bill would have provided assistance and guidance to states to address the growing problem of drug-impaired driving, including offering model legislation and grants to states to enforce the law. The bill called on the U.S. Secretary of Transportation to develop a model state drug impaired driving law that would in part call for evaluation, counseling, treatment, and supervision for persons convicted; enhance training of police; fund research to develop field tests to identify drug-impaired drivers. The bill was referred to the House Committee on Transportation and Committee on Judiciary. No further action.

HR 4883 - On July 21, 2004, Representative Graves (R-MO) introduced H.R. 4883, "the Terrorism Against Animal-Use Entities Prohibition Improvement Act of 2004." Provisions would have amended the Animal Enterprise Protection Act by including economic disruption of an animal enterprise as an offense. It also increases fines and prison terms for certain offenses. Additionally, the bill included a wiretapping provision. The bill was introduced with no co-sponsors and was referred to the House Committee on the Judiciary. No further action.

HR 4888/S 2718 - On July 21, 2004, Representative Lucille Roybal-Allard (D-CA) and four bipartisan colleagues introduced H.R. 4888, "the Sober Truth on Preventing Underage Drinking Act." On July 22, 2004, Senators Mike DeWine (R-OH) and Chris Dodd (D-CT) introduced an identical bill, S. 2718. Title II, Section 201 of the legislation would create an Interagency Committee, which would include NIAAA and NIDA, focused on underage drinking. H.R. 4888 was referred to the House Committee on Energy and Commerce. S. 2718 was referred to the Senate Committee on Health, Education, Labor and Pensions. No further action.

HR 5429 - On December 6, 2004, Representative Mark Souder (R-IN) introduced the Safe and Effective Drug Act, a bill to require the National Institute on Drug Abuse to develop a meta-analysis of the available scientific data regarding the safety and health risks of smoking marijuana and the clinically-proven effectiveness of smoking marijuana for medicinal purposes, and to require the Food and Drug Administration to promptly disseminate the meta-analysis. The bill was referred to the House Energy and Commerce Committee.

S 1780, the "Anabolic Steroid Control Act of 2003," is a bill to amend the Controlled Substances Act to clarify the definition of anabolic steroids and to provide for research and education activities relating to steroids and steroid precursors. It was introduced October 23, 2003, by Senator Joseph Biden (D-DE). The bill was referred to the Senate Judiciary Committee. No further action. [Related bills: HR 3866 and S 2195 (PL 108-647)].

S 1860 - On November 14, 2003, S 1860, the "Office of National Drug Control Policy Reauthorization Act of 2003," was introduced in the Senate by Senator Hatch, R-Utah. The measure was referred to the Senate Judiciary Committee. No further action. (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. The Senate bill was referred to the Senate Judiciary Committee. No further action. (Related bills: HR 3634). (See S. 45 in the 109th Congress, below.)

S 2741 - On July 22, 2004, Senator Tom Daschle (D-SD) introduced S. 2741,"the Advancing FASD Research, Prevention, and Services Act," to extend the Fetal Alcohol Syndrome prevention and services program. The bill would require the Director of NIH to establish a research agenda for Fetal Alcohol Spectrum Disorders (FASD) involving award grants, contracts, or cooperative agreements. S. 2741 was referred to the Senate Committee on Health, Education, Labor and Pensions. No further action.

109th Congress - Bills of Interest

S. 45 - On January 24, 2005, Senator Carl Levin (D-MI), with Senators Orrin Hatch (R-UT) and Joe Biden (D-DE) introduced S. 45, to amend the Controlled Substances Act to lift the patient limitation on prescribing drug addiction treatments by medical practitioners in group practices, and for other purposes. The bill has been referred to the Committee on the Judiciary. (This is a reintroduction of S.1887 from the 108th Congress).

Note: Several methamphetamine-related bills have been introduced. All focus completely or mostly on the law enforcement aspects of this problem.

109th Congress - Committees of Jurisdiction

Several different Senate and House committees hold some jurisdiction over NIDA's work, or on other organizations (e.g. Office of National Drug Control Policy) important to NIDA's work.

Senate: In the Senate, primary focus has traditionally been on the

- Committee on Appropriations (Subcommittee on Labor, Health and

Human Services, and Education; and Subcommittee on Transportation, Treasury and General Government);

- Committee on Health, Education, Labor, and Pensions (HELP)(and most recently the Subcommittee on Substance Abuse and Mental Health Services);
- Committee on the Judiciary (Subcommittee on Crime, Corrections, and Victims' Rights); and the
- Caucus on International Narcotics Control (this is an officially recognized Caucus, established by law in 1985).

The HELP Committee has seen significant change, in membership and subcommittee structure. HELP Committee members, 109th Congress:

Mike Enzi (R-WY), Chair
Edward Kennedy (D-MA), Ranking Member
Judd Gregg (R-NH)
Chris Dodd (D-CT)
Bill Frist (R-TN)
Tom Harkin (D-IA)
Lamar Alexander (R-TN)
Barbara Mikulski (D-MD)
Richard Burr (R-NC)
James Jeffords (I-VT)
Johnny Isakson (R-GA)
Jeff Bingaman (D-NM)
Mike DeWine (R-OH)
Patty Murray (D-WA)
John Ensign (R-NV)
Jack Reed (D-RI)
Orrin Hatch (R-UT)
Hillary Rodham Clinton (D-NY)
Jeff Sessions (R-AL)
Pat Roberts (R-KS)

HELP Subcommittees:

Bioterrorism Preparedness and Public Health (Chair: Burr)
Education and Early Childhood Development (Chair: Alexander)
Retirement Security and Aging (Chair: DeWine)
Employment and Workplace Safety (Chair: Isakson)

Of the above, Mr. Burr's Subcommittee would pay the most attention to the NIH. Members of the Bioterrorism Preparedness and Public Health Subcommittee:

Richard Burr (R-NC), Chair
Edward Kennedy (D-MA), Ranking Member
Bill Frist (R-TN)
Chris Dodd (D-CT)
Lamar Alexander (R-TN)
Tom Harkin (D-IA)
Mike DeWine (R-OH)
Barbara Mikulski (D-MD)
John Ensign (R-NV)
Jeff Bingaman (D-NM)
Orrin Hatch (R-UT)
Patty Murray (D-WA)
Pat Roberts (R-KS)
Jack Reed (D-RI)
Mike Enzi (R-WY, ex officio)

Judiciary Committee members, 109th Congress:

Arlen Specter (R-PA), Chair
Patrick Leahy (D-VT), Ranking Member
Orrin Hatch (R-UT)
Edward Kennedy (D-MA)
Charles Grassley (R-IA)
Joe Biden (D-DE)
John Kyl (R-AZ)
Herb Kohl (D-WI)

Mike DeWine (R-OH)
Dianne Feinstein (D-CA)
Jeff Sessions (R-AL)
Russell Feingold (D-WI)
Lindsey Graham (R-SC)
Charles Schumer (D-NY)
John Cornyn (R-TX)
Richard Durbin (D-IL)
Sam Brownback (R-KS)
Tom Coburn (R-OK)

At this writing, we await final word as to the agreed-upon subcommittee structure and/or the membership under each of the other committees and subcommittees.

House: In the House, primary focus has traditionally been on the

- Committee on Appropriations (Subcommittee on Labor, Health and Human Services, Education, and Related Agencies; and Transportation, Treasury, and Independent Agencies);
- Committee on Energy and Commerce (Subcommittee on Health); and the
- Committee on Government Reform (Subcommittee on Criminal Justice, Drug Policy, and Human Resources).

At this writing, we await final word as to the agreed-upon subcommittee structure and/or the membership under each of these committees and subcommittees.

Congressional Briefings and Visits

October 14, 2004 -- At the request of the American Society of Addiction Medicine, Dr. Volkow was the lead speaker at a Congressional Briefing focusing on addiction research and the application of that research to clinical practice.

January 7, 2005 -- At the request of Congressman Patrick Kennedy, Dr. Volkow met with him to discuss NIDA's research priorities and recent advances in imaging and brain research.

February 1, 2005 - Congressman Patrick Kennedy and his staff followed up the January 7 meeting with a visit to NIDA's Intramural Research Program. They received a briefing on a few topics currently under investigation at the IRP: Molecular Genetics of Addiction Vulnerability; Preclinical Research on Relapse to Heroin and Cocaine: Implications for Treatment; Brain Imaging Studies of Human Drug Abuse; and Drug Testing: Technological Advances and New Biomarkers. This briefing was followed by a tour of the facility, spending time in the brain imaging center (fMRI and PET labs) as well as the toxicology lab. Mr. Kennedy continues his interest especially in the brain imaging work, and was quite curious and engaged with all of the topics covered.

Director's Report to the National Advisory Council on Drug Abuse - February, 2005

International Activities

Administrative Supplements
In September 2004, the NIDA International Program concluded a very successful administrative supplement program with the awarding of 16 international supplements to existing NIDA grants. The intent of the international supplement announcement is to stimulate collaborative research between current NIDA grantees and researchers in other countries. Funds were made available for administrative supplements to existing NIDA-supported research projects to take advantage of opportunities to establish collaborative relationships with scientists conducting research, or with a potential to conduct research in other countries. The 16 awards were made for research in 10 countries including China, France, Spain, Australia, Hungary, South Africa, Russia, New Zealand, Georgia and Scotland.

Administrative Supplements for U.S. - Netherlands Collaborative Research
On November 9, 2004, the NIDA International Program and The Netherlands Organization for Health Research and Development (ZonMw) announced the availability of administrative supplements to support collaborative research in the United States and The Netherlands (NOT-DA-05-002). Current NIDA grantees may request funding to expand existing NIDA-supported research projects, within the scope of the original grant, to take advantage of the unique opportunities offered by binational drug abuse research. Priority will be given to research projects that emphasize the following areas: 1) the effect of exposure to marijuana on the developing brain; 2) prevention and treatment strategies related to marijuana use in children and adolescents; 3) prevention strategies/interventions for other abused drugs with emphasis on adolescents and young adulthood. Only existing R01 and R21 grants supported by NIDA with at least one year of support remaining at the time of the supplemental award are eligible for support under this notice. Supplements may be requested for up to two years of support, but extend no longer than the parent grant, with funding beginning no later than September 30, 2005. NIDA anticipates that up to three projects will be funded under this initiative. NIDA and ZonMw will collaboratively fund the awards through the 1999 Exchange of Letters between the two organizations.

IP Meeting Identifies Drugged-Driving Research Needs and Opportunities
NIDA-supported a workshop on drugged-driving research needs that was held prior to the August 2004 International Council on Alcohol, Drugs and Traffic Safety meeting in Glasgow, Scotland. During the NIDA pre-conference, IP Director Dr. Steven W. Gust discussed the Institute's international programs and collaborative research goals with 22 international experts in drugged driving. The participants, representing 13 nations, identified primary research questions about drugged driving and suggested mechanisms to establish and support international research collaboration on those questions. The experts suggested that NIDA develop a five-year plan for international collaborative research on drugged driving areas including: epidemiology of drugged driving, new technology for drug detection, identification techniques, policy studies, and prevention and treatment research. The participants also requested that NIDA assist researchers in standardizing data collection variables to facilitate cross-site comparison of research results.

Distinguished International Scientist Collaboration Awards (DISCA)
The NIDA 2004 Distinguished International Scientists have completed their research visits to the United States. The competitive DISCA awards provide support to senior scientists during research exchange visits of one to three months so that applicants and their partners can cooperate on drug abuse research.

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- Dr. Helena Barros, Fundacao Faculdade Federal Ciencias Medicas Porto Alegre, Brazil, and NIDA grantee, Dr. Klaus Miczek, Tufts University, have filed an R01 grant application to investigate the critical behavioral, physiological and corticolimbic features of different stress experiences that play a significant role in promoting escalation of cocaine self-administration in female rats. The binational research team proposes to document changes to the GABAergic system and the efficacy of GABAA and GABAB agonists after repeated stress and drug experiences. Drs. Barros and Miczek hope to identify predictors that influence the transition from drug experimentation to an intense and dysregulated pattern of cocaine use, particularly among females, which could potentially allow treatment providers to implement preventive measures or treatments that are specifically designed for each individual. After her return to Brazil, Dr. Barros began conducting experiments to adapt the methods Dr. Miczek uses in his laboratory and collect preliminary data.
- Dr. Ivan Berlin, Groupe Haspitalier Universitaire Pitie-Salpetriere, France, and Dr. Lirio S. Covey, New York State Psychiatric Institute, analyzed data about the mood, coping, personality traits, and genetic markers compiled for 600 smokers motivated to quit smoking during a multi-site therapeutic trial. Based on their analysis, the researchers submitted an abstract for presentation at the 2005 Society for Research on Nicotine and Tobacco and began preparing an article for submission to scientific journals. Drs. Berlin and Covey also prepared a second manuscript that addresses the relationship of the ability to quit smoking with the dopamine receptor D2 (DRD2) polymorphism and the Dopamine Transporter polymorphism (DAT). During Dr. Berlin's two-month visit to the United States, he presented his research to scientific audiences at the New York State Psychiatric Institute, Brookhaven National Laboratory, and the NIDA Intramural Research Program in Baltimore.
- Dr. Richard Isralowitz, Ben Gurion University, Israel; Dr. Lala Straussner, New York University; and Dr. Andrew Rosenblum, National Development and Research Institutes, New York, collaborated on research about drug use among Former Soviet Union (FSU) immigrants in the United States. The team prepared an annotated bibliography on immigrants, immigration, acculturation and drug use; translated five data collection instruments in Russian to simplify data collection for future research projects among FSU immigrants; prepared a concept paper and recommendations for future research on using drug treatment programs to deliver infectious disease services to drug-using FSU immigrants; and submitted a scientific paper for publication.

INVEST Drug Abuse Research Fellowship

NIDA has selected two INVEST Drug Abuse Research Fellows: Dr. Tsafrir Loebl, Israel; and Dr. Maciej Stasiak, Poland.

- Dr. Loebl will work with Dr. David R. Gastfriend, Massachusetts General Hospital, to investigate treatment modalities and outcomes using the American Society for Addiction Medicine (ASAM) Patient Placement Criteria (PPC). They will compare the effects of long-acting Risperidone with the effects of a placebo by assessing emotional, behavioral, and cognitive conditions (PPC Dimension 3) and continued use and relapse potential (PPC Dimension 5). Results will be correlated with functional imaging studies of cocaine-cue stimuli. Drs. Loebl and Gastfriend will also test the effects of a 12-week Motivational Enhancement Therapy (MET) program on readiness to change among non-treatment seeking, active cocaine-dependent individuals, by administering the PPC Dimension 4 assessment and conducting functional imaging studies at baseline and endpoint of the MET program. A psychiatrist specializing in addiction treatment, Dr. Loebl has just completed his residency at the Geha Mental Health Center in Petah-Tiqva, Israel, where he studied changes in gene expression following exposure to Delta9-THC.
- Dr. Stasiak will work with Dr. Nicholas E. Goeders, Louisiana State University - Shreveport to determine which combinations of pharmacological and behavioral therapies are most effective in reducing cocaine seeking by rats. The researchers will investigate pharmacotherapies derived from benzodiazepines, corticosterone synthesis inhibitors, and CRH receptor antagonists along with conditioned cue reinforcement to better understand the complex

mechanism through which stress alters vulnerability to cocaine seeking. Dr. Stasiak holds a Ph.D. and a D.Sc. in neurophysiology and is an adjunct professor at the Nencki Institute of Experimental Biology in Warsaw. His research has been published in *Behavioural Brain Research, Acta Neurobiologiae Experimentalis* and he earned the 2001 award from The Polish Academy of Sciences and the Polish Neuroscience Society for the best work in neurobiology.

Hubert H. Humphrey Drug Abuse Research Fellowship

NIDA Humphrey Fellow Makes News Worldwide

In an internationally distributed interview, current NIDA Hubert H. Humphrey Drug Abuse Research Fellow, Dr. Arun Kumar Sharma, India, described how the **NIDA Humphrey Fellowship** is changing his perspective and approach to issues in research and community medicine by providing a global context for the connection between drug abuse and HIV/AIDS. Dr. Sharma discussed his studies of individual dynamics and social network analysis to design science-based interventions to prevent HIV in drug-using populations. He also talked about the need to disseminate this perspective and new approaches among scientists, politicians, and the media in India. Washington File, an international news service provided by the U.S. Department of State, released the interview December 1, 2004.

IP Hosts Orientation for Humphrey Fellows

NIDA staff discussed the Institute's drug abuse research activities and priorities when the Hubert H. Humphrey Drug Abuse Research Fellows attended an orientation session at NIDA headquarters on Friday, September 23, 2004. Presenters included: Drs. Steven W. Gust and M. Patricia Needle, IP; and Drs. Betty Tai and Jacques Normand, CCTN; Dr. Richard Hawks, DPMCDA; Dr. David Shurtleff, DBNBR; Dr. Laurence Stanford, DCNDBT and Dr. Jack Stein, DESPR. Dr. Needle and Ms. Dale Weiss, IP, also met with each Humphrey Fellow individually in November to discuss plans for the Fellows' research affiliations with NIDA grantees. NIDA and the U.S. Department of State support the Fellowship program, which includes academic courses at Johns Hopkins University, a minimum of six weeks in a research affiliation with a NIDA grantee, and professional development activities to help Fellows establish personal relationships with NIDA grantees and staff. The 2004-2005 Humphrey Fellows are:

- Dr. Luis Alfonzo Bello, Public Health Physician, Ministry of Public Health, Caracas, Venezuela;
- Ms. Snezana Rosic, Elementary School Psychologist, Novi Sad, Serbia & Montenegro;
- Dr. Irena Jakovljevic, Psychiatrist, Montenegro, Serbia & Montenegro;
- Dr. Venera Zakirova, Assistant Professor, Moscow Humanitarian University, and Family Service Counselor, Ufa, Russia;
- Dr. Khola Iram, AIDS Prevention Project Manager, Peshwar, Pakistan;
- Dr. Charlton Easton Collie, Pulmonologist and Medical Lecturer, Kingston, Jamaica;
- Dr. Arun Kumar Sharma, Community Medicine Faculty, University College of Medical Sciences, Delhi, India; and
- Dr. Nael Mostafa Hasan, Psychiatrist, Behman Hospital, Cairo, Egypt.

Former Humphrey Fellow Appointed to Bangladesh Government Post

1993-1994 Hubert H. Humphrey Drug Abuse Research Fellow A.K.M. Abdul Awal Mazumder, Bangladesh, has been appointed to the Prime Minister's staff.

Travel Support

NIDA supported a November 17-21, 2004, workshop to train Thai scientists in using DENS-ASI assessment tools by providing travel assistance to Dr. Deni Carise, Treatment Research Institute, Philadelphia, Pennsylvania.

NIDA sponsored a symposium on **"Drug Abuse and HIV/AIDS in the Asia Region"** at the XVIII World Congress of the World Association for Social Psychiatry, Globalization and Diversity: Challenges for Social Psychiatry, which was held October 24 - 27, 2004, in Kobe, Japan. Shridhar D. Sharma, M.D., Institute of Human Behavior & Allied Sciences (India), chaired the session, which was designed for practitioners and researchers attempting to better understand and respond to the epidemics of drug abuse and HIV/AIDS. The presenters discussed emerging trends and consequences of drug use, including methamphetamine and opiates, which are the region's primary drugs of abuse; reviewed effective, evidence-based practices for

prevention interventions; and outlined the implications of drug abuse treatment for prevention of HIV/AIDS. The panelists also offered practical approaches to overcoming the gap between research and practice and addressed cultural differences within and across countries in the region. Presenters included former Hubert H. Humphrey Drug Abuse Research Fellow M. Suresh Kumar, M.D., D.P.M., M.P.H., Institute of Mental Health and SAHAI Trust (India); Martin Lutterjohann, Diph. Psych., National Authority for Combating Drugs (Cambodia); NIDA grantee Wayne Wiebel, Ph.D., University of Illinois, Chicago and Family Health International (Indonesia); and Zunyou Wu, M.D., Ph.D., National Center for AIDS/STD Control & Prevention, Center for Disease Control and Prevention (China).

NIDA supported the participation of 11 researchers at the **Frontiers in Addiction Research** meeting, held October 22, 2004, in San Diego, California, in conjunction with the Society for Neuroscience Annual Meeting to discuss future directions in the neuroscience of drug abuse and related areas. Travel support was awarded to: Ms. Laurie Sellings, McGill University, Canada; Dr. Miriam Melis, University of Cagliari, Italy; Dr. Patricia DiCiano, University of Cambridge, United Kingdom; Dr. Tie-Yuan Zhang, McGill University, Canada; Ms. Parisa Zarnegar, Karolinska Institute, Sweden; Mr. Paulo J. Cunha, University of Sao Paulo, Brazil; Ms. Stefania Fasano, San Raffaele University, Italy; Dr. Alexander Zharkovsky, University of Tartu, Estonia; Mr. Enrique Rodriguez Borrero, University of Puerto Rico; Mr. Ravid Doron, Bar-Ilan University, Israel; and Ms. Camilla Bellone, University of Geneva, Switzerland.

NIDA supported the participation of 14 drug abuse researchers from Colombia, Mexico, Spain, and the United States, at a one-day preconference workshop on **International Scientific Research Collaborations**, which was held in conjunction with the National Hispanic Science Network on Drug Abuse (NHSN) conference on October 11 - 14, 2004, in San Antonio, Texas. NHSN is dedicated to improving the health of Hispanics by 1) increasing the amount and quality of interdisciplinary translational research on drug abuse; and 2) fostering the development of Hispanic scientists in drug abuse research. Dr. Steven Gust opened the meeting by discussing NIDA's efforts to promote international collaboration on drug abuse research by supporting research, training, exchange opportunities, and international meetings. NIDA-supported participants included:

- From Colombia: Agusto Pérez-G—mez, Ph.D., visiting scientist, Robert Wood Johnson Medical School.
- From Mexico: former NIDA INVEST Fellow Silvia Cruz, Ph.D., CINESTAV; Emilia Figueroa Guillen, M.D., Clinica Integral de Tratamiento; Eduardo Lazcano Ponce, Instituto Nacional de Salud Publica; Jazmin Mora Rios, Ph.D., Instituto Nacional de Psiquiatr'a Ram—n de la Fuente; and Ricardo Sanchez-Huesca, Ph.D., Centros de Integracion Juvenil.
- From Spain: Maria Angeles Luengo-Martin, Ph.D., Universidad de Santiago de Compostela; Miguel Angel Mu–oz, Universidad de Granada; Francisco Javier Romero, M.D., Ph.D., Universidad Cardenal Herrera-CEU; and Vicent M. Villar, Ph.D., Universidad Cardenal Herrera-CEU.
- From the United States: James Anthony, Ph.D., Michigan State University; Elena Bastida, Ph.D.,University of Texas-Pan American; Kathleen Kantak, Ph.D., Boston University; and Monica Sequeira Malta, Ph.D. John Hopkins University.

NIDA supported the participation by Dr. A. Thomas McLellan, Treatment Research Institute, Philadelphia, Pennsylvania, at the **Regional Meeting of the Royal College of Psychiatrists in the Middle East**, which was held in Cairo October 3-4, 2004. NIDA, UNODC, Cairo University, Behman Hospital, and Merck co-sponsored the meeting.

NIDA supported the participation of two researchers at the **Central/East European Collegium Internationale Neuropsychopharmacologicum Regional Meeting**, which was held in conjunction with Masaryk University September 9-12, 2004, in Brno, Czech Republic. Dr. Robert J. Malcolm, Jr., Medical University of South Carolina, discussed the psychostimulant modafinil and its implications for treating cocaine dependency. Dr. Barbara J. Mason, The Scripps Research Institute, LaJolla, California, discussed the use of acamprosate to treat alcohol dependence with and without comorbid substance abuse.

NIDA supported the participation of three researchers at the **International Congress on Addiction**, held September 8-10, 2004, in Vienna, Austria. Travel support was awarded to Dr. Claire Sterk, Emery University; Dr. Sandro Galea, New York Academy of Medicine; and Dr. Lawrence Scheier, New Mexico Behavioral Health

Research Center.

NIDA supported the participation of five researchers at the **University of Miami Drug Abuse and AIDS Research Center International Conference**, held August 25-27, 2004, in Miami, Florida. Travel support was awarded to: Dr. Javier Bustos, Helios Salud, Argentina; Dr. Frank Mora Rodriguez, University of Costa Rica; Dr. Rosario Achi Araya, University of Costa Rica; Dr. Catalina Mejia, Yanhaas and Associates, Columbia; and former NIDA INVEST Fellow Dr. Zhao Min, Shanghai Mental Health Center, China.

Dr. Steven Gust, IP, attended the annual progress review of the **Rosita** project in Santiago de Compostela, Spain in November 2004. The Rosita project is an international research study to assess the feasibility of using roadside testing for illicit drug use. Six countries in Europe and four U.S. States are participating in this multi-site effort.

Publications

Brochures Describe NIDA International Research Training and Exchange Programs

Three new brochures describe the program components, eligibility requirements, application procedures, deadlines, and award notification dates for the research training and exchange programs supported by the NIDA International Program. The brochures will be distributed at NIDA-supported meetings and mailed to target audiences. They may be downloaded in PDF format from the IP Web site, www.international.drugabuse.gov. The three brochures are:

- **INVEST Drug Abuse Research Fellowships** provide one year of training with a NIDA grantee in the United States for scientists from any other country who have at least two years of postdoctoral research experience.
- **NIDA Hubert H. Humphrey Drug Abuse Research Fellowships** offer academic course work and professional affiliations for mid-career professionals from eligible countries who hold a doctoral or master's degree and have substantial professional or research experience in drug abuse.
- **NIDA Distinguished International Scientist Collaboration Program Awards (DISCA) and NIDA Distinguished International Scientist Collaboration Awards for U.S. Citizens and Permanent Residents (USDISCA)** support one- to three-month exchange visits for NIDA grantees and their foreign research partners. Both scientists must have at least seven years of postdoctoral experience. The applicants may choose to have the foreign drug abuse researcher visit the United States by applying for a DISCA award, or have the NIDA grantee travel to the foreign country by applying for a USDISCA award.

International Visitors

Dr. Lula Beatty, SPO, and Dr. Jacques Normand, OD, met with two visitors from Venezuela on September 22, 2004. The U.S. Department of State International Visitor Leadership Program sponsored the visit. The discussions focused on HIV/AIDS and issues concerning special populations in the United States and Venezuela.

The President of the Mongolian Anti-Drug Education Promotion Foundation, Mr. Erdene-Ochir Dashnyam visited NIDA on October 5, 2004. Drs. Liz Ginexi and Larry Seitz, DESPR, and Dr. Ivan Montoya, DPMCDA, met with Mr. Dashnyam. The informative discussion centered on the extent of the drug abuse and HIV/AIDS problems in Mongolia.

Dr. Timothy Condon, OD, met with Dr. Didier Jayle, the French National Coordinator for Drugs and Drug Addiction on October 13, 2004. Accompanying Dr. Jayle was Mrs. Daniéle Dupraz, the Diplomatic Advisor at the Inter-Departmental Mission, Dr. Jacques Drucker, the Counselor for Health Affairs at the Embassy of France, and Ms. Terry Gay, International Health Officer, DHHS.

On November 12, 2004, Dr. Jag Khalsa, DPMCDA, and Ms. Dale Weiss, IP, met with Dr. Galina Trastanetskaya, the Deputy Director of the Department of Youth Policy and Support for Children, Russia. The National Peace Foundation sponsored Dr. Trastanetskaya's visit. Accompanying Dr. Trastanetskaya was Dr. Olga Bessolova, Ms. Sarah Harder, and Ms. Jeanne Whitney Smith of the National Peace Foundation.

Ms. Dale Weiss, IP, met with Dr. Marie Haring Sweeney, Health Attaché to Vietnam, and Mr. Bruce Ross, Deputy Director of the HHS Global AIDS Program in Bangkok, Thailand. The meeting was sponsored by the Fogarty International Center. Ms. Weiss discussed NIDA's past and current programs in Vietnam and Thailand. Dr. Sweeny and Mr. Ross discussed their roles as the Health Attaché and Deputy Director of the HHS Global AIDS Program respectively.

Ms. Dale Weiss participated in a presentation to a delegation from Thailand on November 16, 2004. The presentation was part of the delegation's study visit to the United States on Substance Abuse Surveillance Systems. Also participating in the presentation were Dr. Erin Artigiani, University of Maryland, Center for Substance Abuse Research; Dr. Stephan Sherman, University of Maryland, Bureau of Government Research; and Dr. Susanna Nemes, Danya International, Inc. The Thai Delegation included Dr. Vichai Poshyachinda, Ms. Abha Sirivongs Na Ayudhya, Dr. Sawetri Assanangkornchai, Dr. Apinun Aramrattana, Dr. Manop Kanato and Ms. Naramon Chuangrungsi.

On December 15, 2004, Ms. Dale Weiss met with Dr. Craig Shapiro, DHHS Health Attaché in Beijing, China. The meeting took place at, and was sponsored by, the Fogarty International Center. Discussions included NIDA's past and current work in China, and the role of Dr. Shapiro as the Health Attaché.

Other International Activities

Drs. Frank Vocci and Ahmed Elkashef participated in symposia at Cairo University, Ain Shams University, Behman Hospital and the UNODC training on drug abuse and clinical studies while in Cairo from September 24- October 1, 2004. Drs. Richard Rawson and David Farrabee of UCLA and Drs. Deni Carise and Tom McLellan of University of Pennsylvania also participated in the symposia and trainings.

Dr. Frank Vocci presented at the ICAA meeting in Venice, Italy on Medications for the Management of Cocaine Dependence on November 4, 2004.

Dr. Frank Vocci presented at the World Psychiatry Association meeting in Florence, Italy on the Neurobiology of Addiction on November 11, 2004. Dr. Ivan Montoya presented the results of a study of buprenorphine for the treatment of concurrent cocaine and heroin dependence at the Italian Congress of Drug Abuse, October 17-21, 2004.

Dr. Jag Khalsa of DPMC, at the invitation of the U.S. Embassy in Mexico City, participated in a Mexican Government-U.S. Embassy-co-sponsored meeting on Drug Abuse in Children and gave a talk on Medical and Health Consequences of Marijuana, December 1-3, 2004. He also met with several drug abuse authorities in Mexico who were very appreciative of the technical support they have received from NIDA and other US Government agencies.

Drs. Wilson Compton, and Kevin P. Conway, DESPR, co-chaired the 10th International Federation of Psychiatric Epidemiology symposium on **Life Course Epidemiology of Substance Use Disorders**, in Bristol and Bath, England, September 10-13, 2004. Invited talks were delivered by Drs. Robert Zucker, Kenneth Sher, Michael Lynskey, and Stephen Gilman.

Dr. Elizabeth Robertson, DESPR, briefed Veronica Colondam director of Yayasan Cinta Anak Bangsa for a drug-free Indonesia on prevention programming and research on November 10, 2004.

Dr. Larry Seitz, of the Prevention Research Branch met with Dr. Didier Jayle and other representatives of the French government regarding prevention issues on October 13, 2004.

Dr. Yonette Thomas, DESPR and Gabriele Fischer, Medical University Vienna, co-chaired the 16th International Congress on Addiction on The Epidemiology of Drug Abuse: Linking Environment, Culture, and Genes, in Vienna Austria, September 7-10, 2004. Invited talks were delivered by Drs. Claire Sterk, Sandro Galea, Lawrence Scheier, and Yonette Thomas.

Drs. Yonette Thomas, DESPR, Patricia Needle, NIDA International Program, and Petra Exnerova Jacobs, Academia Medica Pragensis, co-chaired the Seminar on Substance Abuse Prevention and Treatment Research: Possibilities for International Collaboration, in Prague, Czech Republic, September 13, 2004. Invited talks were delivered by Drs. Lawrence Scheier, Geoffrey Hunt, Patricia Needle, and Yonette Thomas.

Ana Anders, Senior Advisor on Special Populations, presented on NIDA's National Hispanic Science Network on Drug Abuse at the "Science Week" Conference, November 8-11, 2004 in Valencia, Spain.

Dr. Marilyn Huestis, IRP, was the plenary lecturer for the annual meeting of the Japanese Association of Forensic Toxicologists in Akita, Japan. Her lecture, Quality Assurance and Quality Control in Forensic Toxicology Laboratories in the United States, was specifically requested by the association in an effort to improve quality assurance and method validation criteria in Japan.

Dr. Marilyn Huestis was a co-host of the FBI/SOFT/TIAFT meeting in Washington, D.C. in September 2004. This was the largest forensic toxicology meeting ever held with representation from over 60 countries.

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Meetings/Conferences

On September 13-14 and November 18-19, 2004, NIDA convened the final two meetings of the **Minority Health Disparities Work Group** in Bethesda, Maryland. These meetings were coordinated by Dr. Denise Pintello, OSPC, and chaired by Dr. Jose Szapocznik, who is a member of the National Advisory Council on Drug Abuse. The purpose of this Work Group was to review NIDA's Minority Health Disparities Program and to make recommendations to effectively address research needs and priorities, research training, collaborations, and outreach and dissemination activities for racial/ethnic minority populations. Based on their findings and recommendations, the Work Group members prepared a report for the National Advisory Council on Drug Abuse.

On December 13, 2004, NIDA sponsored a symposium at the Annual Meeting of the American College of Neuropsychopharmacology entitled **Substance Abuse in the 21st Century: What Problems Lie Ahead for the Baby Boomers?** The meeting was organized by Drs. Timothy Condon, Susan Weiss and Gayathri Dowling. Speakers included Drs. Timothy Condon, Deputy Director, NIDA, Susan Resnick, National Institute on Aging, David Oslin, University of Pennsylvania, and Frederic Blow, University of Michigan. Among the topics discussed were: the potential impact of substance abuse in the baby boomer generation, the changes the brain undergoes across the lifespan and how drug abuse may impact these changes, the impact of substance abuse and psychiatric co-morbidity in older adults, and the misuse and abuse of prescription drugs and alcohol in elderly populations. The purpose of this symposium was to increase awareness, begin discussion, encourage interest, and help generate a research agenda in this area.

A NIDA-Sponsored Meeting on **Developing Efficacious Behavioral Therapies for Criminal Justice Involved Populations**, was organized and co-chaired by Drs. Cece McNamara, Lisa Onken, and Melissa Racioppo of the Behavioral and Integrative Treatment Branch, Division of Clinical Neuroscience, Development and Behavioral Treatment. This meeting was held on December 1-2, 2004 at the Washingtonian Marriott in Gaithersburg, MD.

A two-day FNRB/DBNBR Workshop, entitled **Mechanisms of Brain Resiliency and Repair** was held in the Neuroscience Center Building, October 7-8, 2004. Its purpose was to help NIDA determine the optimal strategy regarding brain resiliency and repair research directed towards the neurotoxic consequences of drug abuse. Speakers were drawn primarily from leaders in their fields of neural protection and recovery (spontaneous, physiological recovery as well as interventions to enhance recovery) for the broad range of neurodegenerative diseases in general. In addition, a brief (4 invited speakers) symposium of the same name was held October 22, 2004 as part of the NIDA "Mini-Convention" at the annual Society for Neuroscience Convention in San Diego.

NIDA organized a Satellite Symposium Workshop at the American Association of Pharmaceutical Scientists' (AAPS) Annual Meeting, November 5-7, 2004, on the topic of Natural Products and Nutraceuticals. The Workshop was entitled **Naturceuticals (Natural Products), Nutraceuticals, Herbal Botanicals, and Psychoactives: Drug Discovery and Drug-Drug Interactions**. The workshop was organized by Dr. Rao S. Rapaka and the co-sponsors from the AAPS were the DDD Section, Drug Metabolism Focus Group (DFG) and the Nutraceutical Focus Group. Approximately 30 speakers presented talks at one of the workshop's six sessions. This workshop was attended by a large number of researchers from academe and industry. The proceedings of the workshop will be edited by Dr. Rapaka and will appear as a special

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volume of Life Sciences.

Drs. David Shurtleff, DBNBR, Rita Liu, OEA and Cathrine Sasek, OSPC, organized the **NIDA Mini-Convention, Frontiers in Addiction Research**, a Satellite Symposium at the 2004 meeting of the Society for Neuroscience in San Diego CA. Following introductory remarks by Dr. Timothy Condon, NIDA Deputy Director, more than 600 attendees to this third consecutive mini-convention, attended a day-long series of six scientific sessions devoted to the latest NIDA supported drug abuse research. The mini-convention featured a "young investigators" poster session during the lunch break and a keynote address by the Jacob P. Waletzky Award Recipient, Dr. Antonello Bonci. The scientific sessions and their chairs/organizers included:

- **Behavioral Neuroscience of Nicotine Addiction**
Chaired and organized by Drs. Paul Schnur, DBNBR, and Bill Corrigall
- **The Role of Glutamate in Drug Addiction**
Organized and chaired by Dr. David Shurtleff (with the assistance of Dr. Minda Lynch, DBNBR)
- **Creative Directions in Imaging**
Organized and chaired by Drs. Tom Aigner, DBNBR, Steven Grant, DCNDBT, and Nathan Appel, DPMCDA
- **Mechanisms of Brain Resiliency and Repair**
Organized and chaired by Drs. Jerry Frankenheim, Nancy Pilotte, Geraline C. Lin and Yu (Woody) Lin, DBNBR
- **Young Investigators Poster Session**
Organized by Dr. Susan Volman, DBNBR

Drs. Yonette Thomas and Meyer Glantz, DESPR, co-chaired the **NIDA Science Workshop on Drug Abuse: A Workshop on Behavioral and Economic Research**, October 18-20, 2004. This was a multi-disciplinary science meeting that DESPR collaborated on with the Division of Clinical Neuroscience, Development, and Behavioral Treatment (DCNDBT) and the Division of Basic Neuroscience and Behavioral Research (DBNBR).

The **CTN Data and Safety Monitoring Board (DSMB)** met November 16-17, 2004, in Gaithersburg, MD. The DSMB group reviewed ongoing protocols, focusing on their data and safety monitoring plans, progress to date, and feasibility. This is the first meeting in which the studies Lead Investigators (LI) have been invited to address the DSMB. The study LIs from four protocols attended this meeting to report on trial enrollment status and targets.

A **CTN symposium** chaired by Dr. Kathleen Brady (South Carolina Node) and Dr. Jack Blaine (NIDA CCTN Special Consultant) was held at the 2004 annual meeting of the American Academy of Addiction Psychiatry on December 10th in San Juan, Puerto Rico. CTN Presenters included Dr. Kathleen Brady on Update of CTN including new initiatives for 2005, Dr. Denise Hien (Long Island Node) on Implementing Interventions for Women with Trauma in Community Drug Treatment Settings: Research Update and Clinical Challenges, Dr. Robert Hubbard (North Carolina Node) on Preliminary Findings from A Feasibility Study of a Telephone Enhancement of Long-Term Engagement (TELE) to Improve Participation in Continuing Care Activities after Discharge from Residential Treatment, and Dr. Jack Blaine on Motivational Incentives: Effects on Retention and Stimulant Drug Use in Community Treatment Clinics.

Several CTN researchers and community treatment providers presented at the American Association for the Treatment of Opioid Dependence Conference (AATOD) on October 17, 2004, in Orlando, FL. The objectives of this session were to provide an overview of the CTN, to present preliminary CTN findings, to discuss the challenges encountered when blending research and practice, and to discuss plans for further disseminating CTN protocol results.

A National Recruitment and Retention Workshop was conducted on September 13-14, 2004 in Albuquerque, NM. The focus of the workshop was strategies for recruitment in drug abuse treatment clinical trials, as well as, plans for retention and follow-up of patients.

The **CTN Training Subcommittee** met on September 15-16, 2004 in Albuquerque, NM.

The **CTN National Steering Committee Meeting** was held September 28-30, 2004, in Detroit, Michigan. The SC discussed new studies for initiation in 2005 and the status of ongoing efforts.

Staff Highlights

Grantee Honors

In Memoriam

The CTP Caucus and the newly formed PI Caucus met on September 28, 2004. Dr. Volkow was able to meet with the group.

The CTN Executive Committee met on September 29-30, 2004. The committee reviewed plans for prioritization of trials and protocols under development.

The *Portfolio Coordinating Committee* (PCC) met on September 29, 2004, at the Detroit Meeting.

The *Operations Coordinating Committee* (OCC) met on September 29, 2004, at the Detroit Meeting.

The *External Affairs Coordinating Committee* (EACC) met on September 29, 2004, at the Detroit Meeting.

The following Interest Groups (IG) met during the Detroit Steering Committee Meeting: Adolescent IG, Co-Occurring IG, Gender IG, Nicotine Treatment Research IG, Pharmacotherapy IG, and Spirituality IG, Treatment Matching IG.

Dr. Arnaldo Quinones organized a meeting of the **CTN Prescription Opioid Treatment Study** group. The meeting was held on December 3, 2004 in New York City, and was chaired by Dr. Quinones. The purpose of the meeting was to discuss the research hypothesis for the "Prescription Opioid Treatment Study" with experts on the field of addiction to prescription medications, identify a "core group" of CTN members who will continue to move this project forward, determination of CTP selection criteria, and establishing the process for external review. As a result of the meeting, a "core group" of CTN researchers has been charged with the mission of developing the study; a timeline for protocol development was established. An initial protocol draft has been completed. Subsequent telephone conference calls with the "core group" will take place on a weekly basis with the purpose of moving the project forward.

The **CTN Genetics Special Interest Group** held a workshop on September 26, 2004 before the NIDA Blending Meeting in Detroit. The meeting addressed the following: Can genes predict who does well and who doesn't in clinical trials? How are genetics studies done? What will they look like in the CTN? Will they help us understand addiction? Will they point to new treatments? Will they change the stigma against our patients/clients? What will CTPs do in genetics studies? How will CTPs be involved in decision-making?

Several CTN researchers and community treatment providers presented at the **Addiction Health Services Research Conference** October 6-8, 2004, in Philadelphia, PA. The aim of this symposium was to acquaint participants with the Clinical Trials Network (CTN), provide examples of health services research within the CTN, and stimulate interest in additional opportunities for health services research with the CTN.

Dr. Timothy Condon, Deputy Director, NIDA, presented "Methamphetamine: The Science of Addiction" at the National Conference of State Legislatures National Health Conference in Savannah, Georgia on December 9, 2004.

Dr. Timothy Condon presented "Research Advances in Neuroscience" at the NIDA 30th Anniversary Symposium, Society for Neuroscience in San Diego, California on October 22, 2004.

Dr. Timothy Condon presented "Addiction as a Brain Disease: Blending Research & Practice" at the TASC Leadership Learning Conference in St. Charles, Illinois on October 20, 2004.

Dr. Timothy Condon presented "Research to Practice: Using Evidence-Based Methods in Community Treatment and Drug Court Settings" at the American Association for the Treatment of Opioid Dependence 20th Anniversary National Conference in Orlando, Florida on October 19, 2004.

Dr. Timothy Condon presented "Substance Abuse in the Elderly--an Overview" at a conference entitled Drug Abuse in the 21st Century--What Problems Lie Ahead for the Baby Boomers? in Bethesda, Maryland on September 16, 2004.

Dr. Timothy Condon briefed Senate staff on "Methamphetamine and Marijuana: Abuse and Addiction" in Washington, D.C. on August 13, 2004.

Drs. Timothy Condon, Cindy Miner, and Denise Pintello, OSPC, presented a poster entitled, "Assessing NIDA's Public Health Information Publications: Methods and Preliminary Findings from a Study Targeting Public Health Officials and Policymakers" at the American Public Health Association in Washington, D.C. on November 9, 2004.

Dr. Cindy Miner, Deputy Director, OSPC, moderated a session at the Frontiers in Science: Drug Addiction-From Basic Research to Therapies Conference in Bethesda, MD on September 9, 2004.

Dr. Cindy Miner, Deputy Director, OSPC, chaired a Grantwriting Workshop at the American Academy of Child & Adolescent Psychiatry Conference in Washington, D.C. on October 21, 2004.

Dr. Betty Tai, Director, CCTN, presented at the Annual Meeting of the Association for Medical Education and Research in Substance Abuse (AMERSA) November 11-13, 2004 in Washington, D.C. Dr. Tai presented on "NIDA CTN 5 Years Later: Lessons Learned".

Dr. Lula Beatty, Chief, Special Populations Office, attended the meeting of the Committee on the Psychology of Women, American Psychological Association, October 1, 2004 in Crystal City, VA.

Dr. Lula Beatty participated in the Special Population's Office research development technical assistance workshops held November 18-19, 2004 in Bethesda, MD.

Dr. Lula Beatty chaired the meeting entitled "HIV and Criminal Justice Involvement in African Americans as a Consequence of Drug Abuse" on October 12-13, 2004 in Bethesda, MD.

Dr. Lula Beatty held a round table at the American Public Health Association's meeting on November 8, 2004 in Washington, DC.

Ana Anders, Senior Advisor on Special Populations, participated in the planning of the Latino Behavioral Health Institute conference held in Los Angeles on September 21-24, 2004.

Ana Anders participated in the annual conference of the National Hispanic Science Network on October 11-14, 2004 in San Antonio, TX.

Ana Anders participated as a member of the CSAP Hispanic/Latino Expert Panel meeting on January 12 -13, 2005 in Washington, D.C.

Dr. Joseph Frascella, Director, Division of Clinical Neuroscience, Deveopment and Behavioral Treatment (DCNDBT), participated in the National Hispanic Science Network annual meeting and co-chaired and presented in the Grant-Writing Workshop within the meeting held in San Antonio, Texas October 12-15, 2004.

Dr. Joseph Frascella attended the Society for Neuroscience meeting in San Diego, October 23-28th, 2004.

Dr. Joseph Frascella presented on the division's programs at the NIDA Research Development Seminar Series and gave a talk on the grant process, November 18-19, 2004 in Bethesda, Maryland.

Dr. Joseph Frascella attended the annual meeting of the American College of Neuropsychopharmacology and co-chaired a panel entitled "The Neurobiology of Obesity: Relations to Addiction", December 12-16, 2004 in San Juan, Puerto Rico.

Drs. Joseph Frascella and Steven Grant, DCNDBT, participated in a workshop entitled "Detection and Disclosure of Incidental Findings in Neuroimaging Research", co-sponsored by NIDA, NINDS, NIMH, NIBIB, NIA, NICHD and Stanford University that was held in Bethesda, Maryland on January 6 and 7, 2005.

Dr. Joseph Frascella presented on the division's programs at the Native American and Alaskan Native Researchers and Scholars Workgroup Meeting, January 24-25, 2005 in Bethesda, Maryland.

Dr. Steven Grant co-chaired the session on "Neuroeconomics" at the NIDA workshop on "Drug Abuse: A Workshop on Behavioral and Economic Research" held in Bethesda, MD on October 18-20, 2004. The speakers in the session were Drs. Hans Breiter, Massachusetts General Hospital, Kevin McCabe, George Mason University, Julie Stout, Indiana University, P. Read Montague, Baylor College of Medicine, Gregory Berns, Emory University, and Paul Glimcher, New York University.

Dr. Steven Grant co-chaired a symposium titled " Predictors of Treatment Response and Relapse: Neurobiological Markers" at the annual meeting of the American College of Neuropsychopharmacology in San Juan, Puerto Rico on December 12-16, 2004. The speakers were Drs. Steven Forman, University of Pittsburgh, Martin Paulus, University of California, San Diego, Linda Porrino, Wake Forest University, and Efrat Aharonovich, Columbia University.

Dr. Steven Grant co-chaired a study group with Dr. Celeste Napier of Loyola University titled "Is a Wider Brain Circuitry Needed To Account for Drug Abuse? Implications for Psychiatry of Addiction and Addiction Therapy" at the annual meeting of the American College of Neuropsychopharmacology held in San Juan, Puerto Rico on December 12-16, 2004. The speakers were Drs. Gary Aston-Jones, University of Pennsylvania, Christell Baunez, CNRS, Marseille, Phillip Winn, University St. Andrews, Celeste Napier, Loyola University, and Thomas Insel, NIMH.

Dr. Steven Grant participated in the trans-NIH Workshop on "PET and SPECT Imaging Consortium: Safety Assessment of Novel, High Specificity, Low Mass Radiotracers for Use in Research and Drug Discovery" held in Bethesda, MD on January 27, 2005. The meeting addressed ways to accelerate the development of PET and SPECT radiotracers for human imaging studies. The topics included current guidelines and practices for preclinical pharmacology, toxicity, and safety assessment, and preclinical dosimetry needed for RDRC approval or for an investigational IND to evaluate the in vivo characteristics of high specificity, low mass, PET and SPECT radiotracers in human studies.

Dr. Melissa W. Racioppo, DCNDBT, presented several workshops on grant-writing and behavioral treatment research at the annual meeting of the American Association of Marriage and Family Therapy in Atlanta, GA on September 9 - 11, 2004.

Dr. Nicolette Borek, DCNDBT, participated as a scientific staff collaborator in the Network Meeting of the Adolescent Trials Network for HIV/AIDS Interventions in Washington, DC, October 20-22, 2004. The ATN is a collaborative network cosponsored by NICHD, NIDA, NIMH, and NIAAA.

Dr. Nicolette Borek, DCNDBT, presented a talk on NIDA's research priorities at the NIMH/NIDA Early Investigators Workshop during the American Academy of Child and Adolescent Psychiatry annual meeting in Washington, DC, October 19-23, 2004.

Drs. Nicolette Borek and Larry Stanford, DCNDBT, represented NIDA's Behavioral Development program in DCNDBT at the Society for Neuroscience meeting in San Diego, October 23-28th, 2004.

Dr. Laurence Stanford served on the planning committee for a workshop entitled Detection and Disclosure of Incidental Findings in Neuroimaging Research, co-sponsored by NIDA, NINDS, NIMH, NIBIB, NIA, NICHD and Stanford University, held in Bethesda on January 6 and 7, 2005. Dr. Stanford also co-chaired the working group on Institutional Review Board issues attendant to incidental findings.

NIDA staff (Drs. Weiss and Vocci) gave presentations at Demand Treatment! Partners II Lessons Learned Institute in Chicago, Illinois on October 17-20, 2004. Dr. Weiss spoke on Addiction as a Brain Disease: Blending Research and Practice. Dr. Vocci, along with NIDA grantees Richard Rawson and Martin Doot, conducted a session on Buprenorphine, Physician Practice and Your Community.

Dr. Frank Vocci, Director, Division of Pharmacotherapies and Medical Consequences of Drug Abuse (DPMCDA), spoke on Progress in Addiction Treatment: Insights from the Clinic and the Laboratory Bench at the California Society of Addiction Medicine meeting in San Diego on October 8, 2004.

Dr. Frank Vocci spoke on the Implementation of Buprenorphine Therapy at the Join Together Meeting in Chicago, Illinois on October 18, 2004.

Dr. Ivan Montoya, DPMCDA, was a keynote speaker at the Best Practices conference in New Brunswick, New Jersey. He discussed the relationship between smoking and mental disorders, October 7-8, 2004.

Dr. Ivan Montoya participated in the National Hispanic Science Network on Drug Abuse and the Latino Mental Health meetings held in San Antonio Texas. October 11-16, 2004.

Dr. Cora Lee Wetherington, DBNBR and NIDA's Womens' Health Research Coordinator chaired the session entitled Substance Abuse at the NIH Office of Research on Women's Health meeting, Women's Health Interdisciplinary Research Symposium,

October 4-5, 2004, in Bethesda, MD.

Dr. Cora Lee Wetherington chaired Session II: Interdisciplinary SCOR Presentation at the NIH Office of Research on Women's Health, Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health: Center Directors Meeting, October 6, 2004, in Bethesda, MD.

On November 20, 2004, Dr. David Shurtleff, Director, DBNBR, was invited to and presented an overview of NIDA research opportunities at the annual 2004 meeting of the Society for Judgment and Decision Making in Minneapolis, MN.

On December 15, 2004, Drs. David Shurtleff and Glen Hanson presented a poster entitled NIDA's Division of Basic Neuroscience and Research: Overview of Current and Future Research Opportunities at the annual 2004 meeting of the America College of Neuropharmacology in San Juan, PR.

Dr. Joni Rutter, DBNBR, chaired NIDA Genetics Consortium Bi-Annual meeting, November 30-December 1, 2004.

Dr. Joni Rutter attended the American Society of Human Genetics, 54th Annual meeting, Toronto, Canada. October 26-30th, 2004.

Dr. Jonathan D. Pollock, DBNBR, with Dr. Solomon Snyder organized a panel, entitled, Glia and Astrocytes As Modulators of Synaptic Function " at the 43rd Annual Meeting of the American College of Neuropsychopharmacology, San Juan, PR, December 13, 2004.

Dr. Jonathan D. Pollock, DBNBR, with Dr. George Uhl, IRP, organized a panel, entitled, "Molecular Genetics of Addiction Vulnerability and Treatment" at the 43rd Annual Meeting of the American College of Neuropsychopharmacology, San Juan, PR, December 14, 2004.

Dr. Yonette Thomas, DESPR, was the featured speaker at the Third Program of the 71st Season of The District of Columbia Sociological Society, at the American Sociological Association in Washington, D.C. on November 17, 2004. The presentation was entitled "Social Epidemiology in Drug Abuse Research."

Drs. Arnold Mills, DESPR, Teri Levitin, OEA and Yvette Davis, CSR, conducted a research seminar for faculty from the University of Wisconsin Comprehensive Universities System, December 3, 2004. Mills' presentation focused on the research opportunities available at NIDA.

Dr. Arnold Mills, DESPR, participated in the "Research Development for the Career Scientist" seminar sponsored by the Special Populations Office, November 18-19, 2004. Mills reviewed and commented on concept papers submitted by participants and served as a resource for participants who wanted to learn more about research opportunities available through DESPR.

Dr. Arnold Mills, DESPR, chaired the DESPR-sponsored meeting "Drug Abuse Research in Rural Communities: Current Knowledge and Future Directions" at the North Bethesda Marriott on December 7-8, 2004. This meeting focused on advances in rural area research and recommendations for expanding NIDA's research program in this scientific area.

Dr. Peter Hartsock, DESPR, participated in the Senior Working Group on Health and Security of the Chemical and Biological Arms Control Institute (CBACI) in a special meeting on "HIV/AIDS and Global Peacekeeping Operations," September 21, 2004, Washington, D.C. The meeting was led by Dr. Ulf Kristoffersson, Director of the UNAIDS Office on AIDS, Security, and Humanitarian Response, and Dr. Kenneth Schor, U.S. Public Health Service Director for Humanitarian Assistance, Disaster Response, and International Health Policy.

Dr. Peter Hartsock, DESPR, participated in the Senior Working Group on Health and Security of the Chemical and Biological Arms Control Institute (CBACI) in a special meeting on "Health as a Diplomatic Tool," September 28, 2004, Washington, D.C. The meeting was led by Dr. Margaret Hamburg, former Health Commissioner for New York City and current Vice President of Biological Programs, Nuclear Threat Initiative.

Dr. Peter Hartsock, DESPR, participated in the Senior Working Group on Health and Security of the Chemical and Biological Arms Control Institute (CBACI) in a special meeting on the "Current and Future Potential Impact of HIV/AIDS Orphans on Global Security," October 29, 2004. The meeting was led by Dr. Anne Peterson, the Assistant Administrator for the Bureau of Global Affairs at USAID.

Dr. Peter Hartsock, DESPR, delivered the Woodrow Wilson Lecture on the "Health and Demography of Russia," at the Kennan Institute for Advanced Russian Studies, Woodrow International Center for Scholars, October 6, 2004, Washington, D.C.

Dr. Peter Hartsock, DESPR, participated in a meeting, sponsored by HHS Secretary Tommy Thompson, honoring the 45th meeting of the Directing Council of the Pan American Health Organization, September 29, 2004, Washington, D.C.

Dr. Peter Hartsock, DESPR, organized and conducted a trip by Surgeon General Richard Carmona to Galveston, Texas, November 3-4, 2004. Part of the trip was to meet with the dean and faculty of the University of Texas Medical Branch (UTMB) in Galveston. This is the University's oldest medical school and health science center. Discussions dealt with federal/academic cooperation in research that is essential to the security of the U.S. A second part of the trip was for Dr. Carmona to deliver the keynote address at the National Board Meeting of the U.S. Lifesaving Association (USLA), the meeting coinciding with the 40th Anniversary of the founding of the USLA. In his address, the Surgeon General emphasized physical fitness, especially among youth.

Dr. Peter Hartsock, DESPR, participated in an HIV/AIDS Forum hosted by the Chair of China Studies at the Center for Strategic and International Studies, November 17, 2004, Washington, D.C. The forum dealt with health planning and the role of civil society and foreign organizations involved in the fight against HIV/AIDS in China.

Dr. Peter Hartsock, DESPR, participated in a meeting on "The Next Agenda: AIDS and the Way Forward," Woodrow Wilson International Center for Scholars, November 30, 2004, Washington, D.C. The meeting was chaired by Peter Piot, Executive Director, UNAIDS and Randall Tobias, U.S. Global AIDS Coordinator.

Dr. Peter Hartsock, DESPR, participated in a meeting on "Eurasia's HIV Security Challenge: Presenting a Collaborative Research Strategy", U.S. Capitol Building, December 1, 2004. The meeting was sponsored by Women in International Security (WIIS) and the U.S. Civilian Research and Development Foundation for the former Soviet Union (CRDF).

Drs. Kevin P. Conway, DESPR, William Corrigall, and Frank Vocci, DPMCDA, held a meeting on Tobacco Dependence: Measurement and Characterization on November 9-10, 2004, in Bethesda, MD.

Dr. Kevin P. Conway, DESPR, participated in the NIJ workshop entitled "What Have We Learned from Recent Longitudinal Studies of Crime and Delinquency." The workshop was held on October 18-19, 2004, in Washington, D.C.

Dr. Kevin P. Conway, DESPR, presented a paper at the American Society of Criminology, in Nashville, TN, on November 19, 2004. The paper was entitled "Co-offending Networks in Philadelphia."

Dr. Elizabeth Lambert, DESPR and Jacques Normand, OD, met with Dr. Richard Rothenberg, Department of Medicine, Emory University School of Medicine, on October 26, 2004 in Atlanta, Georgia. The meeting served to welcome Dr. Rothenberg as the new Chair of the Steering Committee on the Cooperative Agreement on Sexual Acquisition and Transmission of HIV (SATHCAP) and to review the entire SATHCAP program. They were joined by the Principal Investigator and Co-investigator of the SATHCAP Coordinating Center, Dr. Martin Iguchi and Ms. Sandy Berry of RAND.

Moira O'Brien, DESPR, chaired the 8th Border Epidemiology Work Group Meeting (BEWG), September 16-17, in Albuquerque, New Mexico, and gave a presentation on, "Methamphetamine Abuse in the United States: Findings from the Community Epidemiology Work Group." Participants included representatives from the Mexican Ministry of Health, Border areas in 5 Mexican States and in 4 U.S. States, the Hispanic Science Network, National Institute of Justice and Drug Enforcement Administration. The most recent available data on patterns and trends in drug abuse in border areas were presented with an emphasis on methamphetamine abuse. Indicator data show that methamphetamine abuse continues at high levels in western border areas near the Pacific Ocean and that abuse of the drug is increasing in central and western border areas. Methamphetamine abuse indicators remain at low levels in eastern areas along the Texas-Mexico border, but show some signs of increasing.

Moira O'Brien, DESPR, co-chaired the New Mexico State Epidemiology Work Group held September 14-15, 2004, in Albuquerque, New Mexico. The meeting was held in collaboration with the New Mexico Department of Health, Office of Epidemiology.

Dr. Beverly Pringle, Services Research Branch, DESPR, presented a paper as part of a symposium on Health Services Research in NIDA's Clinical Trials Network at the annual Addictions Health Services Research Conference, Philadelphia, PA, October 7, 2004.

Dr. William Cartwright, Services Research Branch, DESPR, co-chaired a session on behavioral economics with DBNBR at the meeting, Drug Abuse: Workshop on Behavioral and Economic Research, Bethesda, October 18-20, 2004. Dr. Dionne Jones, Services Research Branch, DESPR, served as faculty advisor to potential grantees participating in the NIDA Research Development Seminar Series, Hyatt Regency, Bethesda, MD, November 18-19, 2004.

Dr. Dionne Jones facilitated a Round Table Discussion on Funding Opportunities at NIDA/NIH at the American Public Health Association Annual Meeting, Convention Center, Washington, DC, November 7-10, 2004.

Dr. Dionne Jones was part of the planning committee that organized a 2-day meeting for NIDA's African American Initiative, "Reducing HIV and Criminal Justice Involvement in African Americans as a Consequence of Drug Abuse," and she moderated a panel on "Treatment and Services," at the Residence Inn by Marriott, Bethesda, MD, October 12-13, 2004.

Dr. Dionne Jones represented NIDA/DESPR/SRB at the Addiction Health Services Research Conference, Downtown Club, Philadelphia, PA, October 6-8, 2004.

Dr. Dionne Jones made a presentation on "Identifying Risk Behaviors for HIV/AIDS Among African Americans." for the Henry Cornwell Distinguished Scholar Lecture Series at Lincoln University, Lincoln, PA, September 21, 2004.

Dr. Tom Hilton, Service Research Branch, DESPR, addressed the Society for Occupational Health Psychology steering committee at their October 22, 2004 meeting at the American Psychological Association in Washington, DC, regarding NIDA research support opportunities.

Dr. Ning-sheng Cai, IRP, presented "Serial Analysis of Gene Expression in the Rat Striatum following Acute Methamphetamine Administration" at SAGE 2004 conference at Boston on October 2, 2004.

Dr. Ron Herning, IRP, presented a poster entitled "EEG of MDMA Abusers during Abstinence" at the 6th Annual Meeting of the EEG and Clinical Neuroscience Society in Irive California on September 29-October 2, 2004.

Dr. Ron Herning gave a talk entitled "Neuropsychiatric Alterations in MDMA Abusers" at the Seventh International Conference on Neuroprotective Agents in Aisilomar, California on November 14-19, 2004.

Dr. Yihong Yang in the Neuroimaging Branch, IRP, attended the Frontiers of Biomedical Imaging Symposium - The MRI Nobel Celebration and Future Directions, November 8-10, 2004 in Urbana-Champaign, IL. He was invited to speak in the Banquet and MRI Nobel Celebration as a former student of Dr. Paul Lauterbur, the winner of Nobel Prize in Medicine or Physiology 2003.

Dr. Marilyn Huestis, IRP, attended a NIDA Science, Policy and Communications Division meeting of the state of the science supporting driving under the influence of drugs. It was determined that NIDA would consider supporting the National Highway Traffic Safety Administration initiative to collect information and biological specimens from drivers to determine the extent of the drugged driving problem and the relationship between drug concentrations in biological specimens and impaired driving.

Dr. Marilyn Huestis presented the "Effects of Cannabis on Performance" at Indiana University to an international audience of toxicologists, attorneys, and criminal justice personnel.

Dr. Marilyn Huestis presented a seminar to the Pharmacology, Toxicology, and Pharmaceutics departments of the University of Illinois. Her presentation was on the antagonism of smoked cannabis effects by oral rimonabant, a CB1 cannabinoid receptor antagonism.

Dr. Eric Moolchan, IRP, gave a talk on "Addressing Health Disparities Throughout the Cycle of Tobacco Addiction" at the University of Texas, MD Anderson Cancer Center, Houston, TX on October 18, 2004.

Dr. Eric Moolchan presented Pediatrics Rounds on "Treating Adolescent Tobacco Addiction" at Johns Hopkins University School of Medicine in October 2004.

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Media and Education Activities

Press Releases

September 28, 2004 - **NIDA Research Identifies Factors Related to Inhalant Abuse, Addiction**.
A recent study showed that young people who have been treated for mental health problems, have a history of foster care, or who already abuse other drugs, have an increased risk of abusing or becoming dependent on inhalants. In addition, adolescents who first begin using inhalants at an early age are more likely to become dependent upon them. The study by Dr. Li-Tzy Wu and her colleagues was published in the October 2004 issue of the *Journal of the American Academy of Child and Adolescent Psychiatry*.

September 30, 2004 - **NIDA NewsScan #33**

- Hostility Personality Trait Predicts Brain Metabolic Response to Nicotine
- PET Scans Show Cocaine Addicts Have Generalized Decrease in D2 Receptors Throughout Striatum
- In Treating Co-Occurring Disorders, Target Both Depression and Substance Abuse
- Long-Lasting Craving for Cocaine
- Study Finds Communities Will Provide Support for MI Programs
- Complex Genetics Tied to High Cost of Brain Disorders; Majority of Costs Related to Addiction
- NIDA Grantees Receive AACE Award

October 13, 2004 - **NIH Announces New Funding for Transdisciplinary Tobacco Use Research Centers**.
The National Institutes of Health (NIH) announced new funding for the Transdisciplinary Tobacco Use Research Centers' (TTURC) initiative, which originally awarded grants to seven research centers in 1999. This new investment, totaling almost $12 million, will be funded over the next five years by the National Institute on Drug Abuse (NIDA), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the National Cancer Institute (NCI).

October 15, 2004 - **NIDA Sponsors Mini-Convention in Conjunction With Annual Society for Neuroscience Meeting in San Diego**.
The National Institute on Drug Abuse (NIDA) sponsored the mini-convention, *Frontiers in Addiction Research*, on October 22, 2004, in conjunction with the 34th Annual Meeting of the Society for Neuroscience (SfN), in San Diego. *Frontiers in Addiction Research* brought together outstanding scientists from a wide array of research disciplines to share advances and discuss future directions in the neuroscience of drug abuse and addiction. The symposium, which coincided with NIDA's 30th anniversary, included 20 speakers and 72 poster presentations.

November 1, 2004 - **NIDA Study Finds High School Program Yields Health Benefits for Female Athletes**.
New research that focuses on a health promotion program supported by the National Institute on Drug Abuse (NIDA), shows the program decreased the abuse of stimulant medications and other substances believed to enhance body image or performance among female high school athletes, while encouraging healthy behaviors. The study, led by Drs. Diane Elliot and Linn Goldberg at Oregon Health & Science University, was

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published in the November 2004 issue of the *Archives of Pediatrics and Adolescent Medicine*.

November 8, 2004 - **NIDA Researchers Develop New Genetic Strain of Mice To Study Nicotine Addiction**.
A team of investigators, supported by the National Institute on Drug Abuse (NIDA), has created a strain of mice that scientists can use to study nicotine addiction and its associated behaviors. This research, led by Dr. Henry Lester of the California Institute of Technology, and his colleagues at the Institute of Behavioral Genetics at the University of Colorado, was published in the November 5, 2004, issue of the journal *Science*.

November 17, 2004 - **NIDA Joins Forces With Perlegen To Research Nicotine Addiction**.
The National Institute on Drug Abuse (NIDA) has awarded a $2.1 million contract to Perlegen Sciences, Inc., to investigate the human genome for DNA variations and candidate genes associated with nicotine addiction. "This partnership, which combines NIDA support and cutting-edge private-sector technology, will help us better understand the significance of genetic influences in smoking," says NIDA Director, Dr. Nora D. Volkow. "As we learn more about genetic influences on nicotine addiction and treatment response, we will be able to individually tailor the treatments for people who are addicted to this powerful drug."

December 8, 2004 - **NIDA Study Offers New Clues About Connection Between Cocaine Abuse, Thinking, and Decision-making**.
New research, funded in part by the National Institute on Drug Abuse (NIDA), shows that chronic cocaine abuse is directly related to dysfunction in areas of the brain involved in higher thought and decision-making. The scientists who performed the study suggest that the resulting cognitive deficits may help explain why abusers persist in using the drug or return to it after a period of abstinence. The study, published in the December 8, 2004, issue of the Journal of Neuroscience, was conducted by Dr. Robert Hester of Trinity College in Dublin, Ireland, and Dr. Hugh Garavan of Trinity College and the Medical College of Wisconsin in Milwaukee.

December 21, 2004 - **Teen Drug Use Declines 2003-2004** - *But Concerns Remain About Inhalants and Painkillers*.
According to the Department of Health and Human Services, results from the annual Monitoring the Future (MTF) survey indicate an almost 7 percent decline of any illicit drug use in the past month by 8th, 10th, and 12th graders combined, from 2003 to 2004. Trend analysis from 2001 to 2004 revealed a 17 percent cumulative decline in drug use, and an 18 percent cumulative drop in marijuana past month use. "These positive findings demonstrate the commitment by many, including researchers, federal agencies, states, parents, teachers, local communities, and teens themselves, to work together to reduce drug use among our youth," HHS Secretary Tommy G. Thompson said. "We need to continue our efforts to educate parents and teens about the consequences of drug abuse."

Dr Frank Vocci was interviewed by Browyn Sloan on the methamphetamine epidemic in Cambodia.

Dr. Frank Vocci was interviewed by Ms. Alla Katsnelson of Nature Medicine regarding the cocaine vaccine.

Dr. Frank Vocci. was interviewed by Ms. Shannon Kile for a story on therapeutic vaccines that was posted at betterhumans.com

Dr. Frank Vocci was interviewed by Ms. Arline Kaplan of Psychiatric Times for an article on analgesic drug abuse and new analgesic development.

Dr. Marilyn Huestis was invited by the Office of the National Drug Control Policy to participate in a media roundtable in New York in October on the effects of marijuana use in adolescents.

Articles of Interest

October 5, 2004, *The Wall Street Journal*Ñ"Vaccine to Combat Addictions Shows Promise"ÑInterview with Frank Vocci, Ph.D.

November 2004, *Addiction Professional*Ñ"The Future of Addiction Services: It's in the Science"ÑInterview with Nora D. Volkow, M.D.

November/December 2004, *Psychology Today*Ñ"Pay Attention to This"ÑInterview with Nora D. Volkow, M.D.

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January 2005, *Readers Digest*Ñ"Virtual Cures for Real-World Phobias"ÑInterview with Dave Thomas, Ph.D.

Educational Activities

"Brain Power! The NIDA Junior Scientist Program" for grades K-1 is now available both in hard copy and on line. The curriculum is designed for classroom use and includes a teacher's guide, a parent newsletter, a video, and a poster. It includes five modules which examine what it means to be a scientist, as well as what the brain is and how to keep it healthy and protect it.

Conferences/Exhibits

Community Anti-Drug Coalitions of America -- January 11-13, 2005

Winter Conference on Brain Research -- January 22-28, 2005

American Association for the Advancement of Science 171st Annual Meeting -- February 17-21, 2005

Council on Social Work Education and National Gerontological Social Work Joint Conference -- February 26-March 1, 2005

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Planned Meetings

National CTN Steering Committee Meetings are planned for the following dates and locations: February 7-9, 2005, San Francisco, California; and April 11-13, 2005, Raleigh-Durham, North Carolina.

A National AE/SAE Workshop will focus on reporting of adverse events in CTN trials will be held on February 11, 2005, following the Steering Committee meeting in San Francisco, CA.

The CTN Data and Safety Monitoring Board will meet March 10-11, 2005 in Rockville, Maryland. The group will review the continuing progress of the CTN's protocols.

An invited session has been organized for the annual meeting of the Society for Clinical Trials, May 22-25, 2005, Portland, Oregon. The topic is on special design challenges in multi-site trials involving behavioral interventions. Paul Wakim, Ph.D., CCTN senior statistician, is chairing the symposium. Planned speakers are: Daniel Feaster, University of Miami School of Medicine; Paula Schnurr, VA National Center for PTSD and Dartmouth Medical School; Rickey Carter, Medical University of South Carolina; and Ellen Hodnett, University of Toronto Faculty of Nursing.

A three-day CIDI (Composite International Diagnostic Interview) Train the Trainer program will be held February 10-12, 2005, in San Francisco, CA.

Dr. Jag Khalsa of DPMC will present a mini-symposium on "Management of Hepatitis C Infection in Drug Users" at the Annual Conference of the American Society of Addiction Medicine (ASAM), Dallas, TX, April 15-17, 2005. Drs. Richard Garfein (CDC), Ramesh Ganju (Harvard), Charles Hinkin (UCLA), and Diana Sylvestre (UCSF) will present epidemiology, pathogenesis, psychiatric consequences, and treatment complications of HCV among IDUs.

Dr. Jag Khalsa of DPMC will present a mini-symposium on "The Role of Drugs of Abuse in AIDS Disease Progression" at the Annual Meeting of the Society of NeuroImmune Pharmacology (SNIP), April 8, 2005, Clear Water, FL. Drs. Maria Prins (Amsterdam, The Netherlands), Dr. Robert Muga (Spain), and Dr. David Vlahov (USA) will present data from their AIDS/IDU cohorts and discuss the impact of drug abuse on HIV/AIDS disease progression.

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Publications

NIDA Publications

Epidemiologic Trends in Drug Abuse - Community Epidemiology Work Group - Volume I
Executive Summary June 2004
NIH Pub. No.: 05-5364A
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
Meeting Proceedings June 2004
NIH Pub. No. 05-5365A
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 utilize this volume to identify potential areas for further research.

NIDA Notes

NIDA Notes, Volume 19 Issue 3
NIH Pub. No. 04-3478
In the Director's Column, Dr. Nora D. Volkow discusses the role of NIDA research in illuminating the problem of teen vulnerability to drug abuse and addiction. NIDA's ongoing initiatives to understand and combat the problem include a new three-pronged focus: to explore how developmental changes in the adolescent brain increase vulnerability to drugs; to find more effective ways to dissuade teens from abusing drugs; and to study the period of emerging adulthood and identify ways to prevent initiation or escalation of drug abuse during this life transition. Research approaches will range from animal studies on the effects of nicotine and cocaine on the developing brain, to human studies that explore how teens perceive risk and make decisions on matters such as drug abuse that involve risk.

The lead article describes a recent NIDA-supported study finding that a compound that elevates glutamate levels in the brain may help reduce vulnerability to relapse in patients recovering from cocaine addiction. The study found that in rats, reduced glutamate concentrations in the nucleus accumbens (NAc) as a result of cocaine use persist for a considerable time after access to the drug is removed; however, when rats were injected with n-acetylcysteine to increase glutamate concentration before receiving a dose of cocaine, they returned to self-administering the drug at much lower levels than did rats simply injected with cocaine alone. Other Research Findings report:

- Extinction training in rats addicted to cocaine increased quantities of glutamate receptors in the brain, which made them less likely to resume self-administering the drug than rats not exposed to the behavioral modification.
- A NIDA-sponsored clinical trial on a combination buprenorphine-naloxone medication for opiate addiction capped a 25-year NIDA initiative that led to the development of a take-home treatment that can be prescribed in a doctor's office.
- Researchers have tested a sustained-release injectable form of buprenorphine that substantially blocked heroin's effects and relieved

craving and withdrawal for up to six weeks.

- Cocaine and amphetamine intake in rats stimulates the growth of dendrites in the brain, causing a type of structural plasticity that impedes the brain's subsequent ability to change and adapt to novel situations.

Research News covers the proceedings of a conference on prenatal exposure to drugs held in Bethesda, Maryland, in March 2004, which was co-sponsored by NICHD and the National Institute of Health's Office of Research on Women's Health; and the meeting of the CTN Dissemination Subcommittee, which discussed ways to better convey innovations from researchers to practitioners. The Bulletin Board features the new NIDA display "The Science of Addiction," part of the DEA Museum's exhibit "Target America: Opening Eyes to the Damage Drugs Cause," in Times Square in New York City; and Dr. Mary Jeanne Kreek, principal investigator and scientific director of a NIDA Research Center in New York City, who was awarded the Alumni Gold Medal for Distinguished Achievements in Medicine from the Columbia College of Physicians & Surgeons. The Tearoff article focuses on the Web-based training program *Prevention Connection: Substance Abuse Prevention Training for Health Promotion Practitioners*, which was developed and tested under a NIDA-supported Small Business Innovation Research Grant. It uses an interactive, multimedia approach to train wellness professionals to integrate substance abuse prevention materials and messages into health promotion programs.

NIDA Notes, Volume 19 Issue 4
NIH Pub. No. 04-3478
In the Director's Column, Dr. Nora D. Volkow discusses drug-related damage in unborn children, which includes reduced weight in newborns, behavioral disorders in toddlers, cognitive deficits in young children, and increased vulnerability to drugs in adolescents. The lead article reports that methamphetamine abusers who remain abstinent for nine months or more can partially recover from damage to motor skills, memory, and thalamic metabolism. Other research findings report that brain imaging studies may point to reasons why cocaine addiction and recovery are different for men and women in some aspects, including the reasons for seeking rehabilitation, response to treatment, and vulnerability to relapse. In another story, findings that a schizophrenia treatment weakens some of the effects of cocaine on rodents have been confirmed and extended by investigators in NIDA's Intramural Research Program. The final research article describes a large prospective study examining the rates of tobacco addiction in adults who were prenatally exposed to tobacco. Research News gives an update on drug treatment studies in NIDA's Clinical Trials Network, where researchers and practitioners collaborate in design and execution of the studies. It also includes a report on a conference in which behavioral health professionals are committed to improving treatment systems for people with coexisting disorders. A related story describes new evidence that adults with co-occurring disorders benefit from depression treatment. The Bulletin Board reports on the 2003 National Survey on Drug Abuse and Health finding that in 2003, prescription drug abuse increased and hallucinogen abuse sharply dropped. The Tearoff article describes NIDA's new communication products in print and on the web.

NIDA Notes, Volume 19 Issue 5
NIH Pub. No. 04-3478
In the Director's Column, Dr. Nora D. Volkow discusses the increase in misuse and abuse of prescription medications by adolescents and adults. The lead article reports on two recent studies showing that the age of initiation and the pleasure of response to marijuana in adolescence foreshadow adult outcomes. This issue also reports on The National Survey on Drug Use and Health, which has found that inhalant abuse by teenagers is on the rise. In another story, NIDA-supported economists are offering drug treatment program administrators the comprehensive Drug Abuse Treatment Cost Analysis Program, which features a method to put dollar values on the full range of treatment resources. In the final research article, a recent NIDA study provides no confirmation for previous findings that MDMA (Ecstasy) abusers develop problems recalling words, but suggests that heavy use of the drug does cause persistent deficits in mental processing speed and problem solving. Research News covers a NIDA-sponsored conference on lipids, the messenger molecules crucial for the regulation and control of biological processes, including those influencing the effects of drugs on cell function. The Bulletin Board reports on the eighth annual PRISM Awards, sponsored by NIDA in recognition of the entertainment industry's serious treatment of destructive social issues surrounding drug abuse in film and television. This feature also highlights the appointment of six new members to the National Advisory Council on Drug Abuse. The Tearoff article describes NIDA's latest *Research Report* on MDMA abuse, part of the continuing effort to provide science-based information to the public.

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Upcoming NIDA Publications

Community Drug Alert Bulletin - Prescription Drug Abuse
This publication will summarize current information about the consequences that can result from the abuse of some prescription and over-the-counter (OTC) medications. Classes of drugs to be discussed include benzodiazepines, opiates, sedative/hypnotics, and stimulants. The medicinal value as well as some of the potential health problems that can result from abuse of these drugs will also be discussed. Some data will be presented from what we currently know about who is abusing and how they are accessing these medications. Information will be provided on what can be done to reduce prescription/OTC drug abuse, and how to diagnose and treat individuals who have become addicted to these drugs.

Community Drug Alert Bulletin - Inhalants
This publication will summarize key information on the toxicity of inhalants and the serious health consequences of abusing inhalants. The household and other common sources of these psychoactive vapors will be discussed, as well as the three general classifications of inhalants. Trends showing an increase in use among young teens, based on data from SAMHSA's NSDUH, and NIDA's MTF will be included, as will guidance on where to find further information on health effects of prevention and treatment of inhalants and other drugs.

CTN-Related Publications

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

A patient recruitment brochure for CTN Protocol - 0017 Reducing the Risk of HIV and Hepatitis-C Infection: A Research Study was published and distributed throughout the CTN.

Other Publications

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Rutter, J.L., Bromley, C.M., Goldstein, A.M., Elder, D.E., Holly, E.A., Guerry, D. IV, Hartge, P., Struewing, J.P., Hogg, D., Halpern, A., Sagebiel, R.W., and Tucker, M.A. Heterogeneity of Risk for Melanoma and Pancreatic and Digestive Malignancies: A Melanoma Case-control Study. Cancer, 101, pp. 2809-2816, 2004.

Drs. David Shurtleff, Rita Liu and Cathrine Sasek served as guest editors for a special issue of Neuropharmacology, (Volume 47, Supplement 1, Pages 1-367, 2004) "Frontiers in Addiction Research: Celebrating the 30th Anniversary of the National Institute on Drug Abuse." The special issue featured research papers from 30 neuroscientists including NIDA's Director, Dr. Nora Volkow. Almost all of the contributing authors were NIDA-supported, as Research Center Directors, MERIT (Method to Extend Research In Time) or PECASE (Presidential Early Career Award in Science and Education) Awardees, Senior Scientists, or NIDA-Intramural Research Scientists. All are leaders in their respective fields, providing important insights into this complex problem from various perspectives and at multiple levels of analysis.

Drug Abuse and Suicidal Behavior (ed. Lynda Erinoff, Wilson Compton, Nora Volkow). Drug Alcohol Depend, 76, pp. S1-S105, 2004. This supplement resulted from a March, 2003 workshop sponsored by NIDA. The supplement consists of two editorials, one an overview of the workshop and another highlighting the need for further research on drug abuse and suicidal behavior. There are six papers reporting new data: use of children of twins design to study familial effects; neurobehavior disinhibition as a predictor of substance use and suicidal behavior; a longitudinal study of suicidal behavior in school children; an empirical review of the association between completed suicide and substance use disorders; a longitudinal study of PTSD, drug dependence, and suicidality among Vietnam veterans; and a prospective study of suicidal behavior in a clinical population who had been detoxified. There are

also two review articles, one on conceptual issues in understanding suicidal behavior and substance use in adolescents and the other on impulsivity in suicidal behavior and substance abuse.

Womack S., Compton W.M., Dennis M., McCormick S., Fraser J., Horton J.C., Spitznagel E.L., and Cottler L.B. American Journal of Addiction, 13, 295-304, 2004. Early identification of patients with comorbid depression and their subsequent enrollment in an enhanced psychiatric case management (PCM) intervention were examined as an effective way to engage depressed substance abuse patients into psychiatric treatment. Depression was screened using the Global Appraisal of Individual Needs (GAIN) and a DSM-IV checklist. Patients positive on both evaluations were assigned to PCM (n = 10) or to no case management, or treatment as usual (TAU) (n = 10). An examination of outcomes at six weeks indicated that PCM services are feasible and appear to be effective in encouraging use of psychiatric referral by depressed substance abusers.

Compton, W., Horton, J., Cottler, L., Booth, R., Leukefeld, C. and Singer, M., Cunningham-Williams, R., Reich, W., Corsi, K., Staton, M., Fink, J., Stopka, T. and Spiznagel E. A Multi-State Trial of Pharmacy Syringe Purchase. J Urban Health, 81, pp. 661-670, 2004. Although pharmacies have long been recognized for their potential as sites for access to sterile syringes to prevent HIV, little is known about types of pharmacies and the extent to which they may actually be utilized. Researchers identified four states in which attempts to purchase syringes from pharmacies had been documented, and hypothesized that Connecticut would have the highest rate of purchase followed by Colorado, Missouri, and Kentucky. They also hypothesized that minority research assistants would have lower rates of purchase of syringes than white research assistants; that males would have lower rates than females; and that urban rates of purchase would differ significantly from rural. They conducted a standardized, multi-state study in urban and rural areas of the four states, and found that, of 1,600 overall purchase attempts, 35% were refused. Regarding ordering of purchase rates, their hypothesis was partly supported: Kentucky had the most restrictive regulatory environment, in which positive identification was often required for syringe purchase, but the rates in Kentucky (41%) were not significantly different from those in Missouri (47%). On the other extreme, Connecticut, which had the most permissive regulatory environment, had rates of purchase slightly lower (28%) than Colorado (25%). Significant variation in pharmacy syringe purchase was found for urban (40%) vs rural (31%) pharmacies ($P<.01$). There was no consistent pattern of ethnic or gender bias in rates of syringe purchase. The researchers conclude that, despite numerous potential advantages of pharmacies as sites for access to sterile syringes to complement needle exchange programs, pharmacy purchase of syringes faces significant obstacles.

Grant, B.F., Stinson, F.S., Dawson, D.A., Chou, S.P., Dufour, M.C., Compton, W.M., Pickering, R.P. and Kaplan, K. Prevalence and Co-occurrence of Substance Use Disorders and Independent Mood and Anxiety Disorders: Results From the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry. 61, pp. 807-816, 2004. To address uncertainties in the prevalence and comorbidity of substance use disorders and independent mood and anxiety disorders, this study presented nationally representative data on the prevalence and comorbidity of DSM-IV alcohol and drug use disorders and independent mood and anxiety disorders (including only those that are not substance induced and that are not due to a general medical condition). Participants were adult (age 18+) household and group quarters' residents in the United States in 2001-2002. Results were that the prevalences of 12-month DSM-IV independent mood and anxiety disorders in the US population were 9.21% (95% confidence interval [CI], 8.78%-9.64%) and 11.08% (95% CI, 10.43%-11.73%), respectively. The rate of substance use disorders was 9.35% (95% CI, 8.86%-9.84%). Only a few individuals with mood or anxiety disorders were classified as having only substance-induced disorders. Associations between most substance use disorders and independent mood and anxiety disorders were positive and statistically significant. The authors concluded that substance use disorders and mood and anxiety disorders that develop independently of intoxication and withdrawal are among the most prevalent psychiatric disorders in the United States. Associations between most substance use disorders and independent mood and anxiety disorders were overwhelmingly positive and significant, suggesting that treatment for a comorbid mood or anxiety disorder should not be withheld from individuals with substance use disorders.

Compton, W.M. and Pringle, B. (2004). Services Research on Adolescent Drug Treatment: Commentary on Dennis (et al.) The Cannabis Youth Treatment (CYT) Study: Main Findings from Two Randomized Trials. Journal of Substance Abuse

Treatment, 27, pp. 195-196, 2004.

Sussman, S., Stacy, A.W., Johnson, C.A., Pentz, M.A. and Robertson, E. A Transdisciplinary Focus on Drug Abuse Prevention: An Introduction. Substance Use & Misuse, 39(10-12), pp.1441-1456, 2004.

Delany, P.J., Fletcher, B.W., Shields, J.J. and Conway, K.P. Creating A Collaborative Model for Treating Substance Abusing Offenders. In D. Fishbein (Ed.), The Science, Treatment, and Prevention of Antisocial Behaviors: Evidence-based Practices, Vol. II. (Chapter 13, pp. 1-13): Civic Research Institute: Kingston, NJ, 2004.

Pringle, B. and Flanzer, J. Substance Abuse Treatment Services. In R. G. Steele, & M. C. Roberts (Eds.), Handbook of Mental Health Services for Children, Adolescents, and Families. New York: Kluwer/Plenum, 2004.

Director's Report to the National Advisory Council on Drug Abuse - February, 2005

Staff Highlights

Honors and Awards

The following NIDA staff members received awards at a ceremony held at the Neuroscience Center in September 2004:

NIDA DIRECTOR'S AWARD OF MERIT

Individual Awards:
Ming L. Shih, Ph.D., CCTN
Redonna Chandler, Ph.D., DESPR
Kevin Conway, Ph.D., DESPR
Elizabeth Ginexi, Ph.D., DESPR
Larry A. Seitz, Ph.D., DESPR
Joni Rutter, Ph.D., DBNBR
Paul Schnur, Ph.D., DBNBR
Hirsch D. Davis, M.A., DPMCDA
Steven R. Oversby, Psy.D., DPMCDA
Moo Park, Ph.D., DPMCDA
Amy Hauck Newman, Ph.D., IRP
Loretta Beuchert, OEA
Lyle K. Furr, OEA
Diana K. Souder, OEA
Nancy A. Hurd, OPRM
Gloria J. Lester, OPRM
Mary C. Mayhew, OSPC
Lucinda L. Miner, Ph.D., OSPC
Denise Pintello, M.S.W., Ph.D., OSPC
Ana B. Staton, MPA, OSPC

Group Awards:
DESPR Administrative Staff
Ann R. Hutzler
Roxie A. Brown
Debra L. Yarrick
Elaine Solano
Elizabeth Cooper

DESPR Health Disparities Workgroup:
Aria Crump, Sc.D.
Arnold Mills, M.S.W.
James Colliver, Ph.D.
William Cartwright, Ph.D.

Co-Chairs NIDA's Neuroscience Consortium:
Rita Liu, Ph.D., OEA
Cathrine Sasek, Ph.D., OSPC

DBNBR's Support Group:
Christie L. Baxter
Amira H. Debbas
Douglas M. Janes
Jessica E. Webster
Joyce Williams

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Staff Highlights

Grantee Honors

In Memoriam

Management Analysis and Services Branch:
Suzanne Cole
David Daubert
Chanvadey Nhim
Traci Pelan
Donna Tolson
Bridget McDonald
Montrue Nelson
Sharon Goon
Davey Jones

NIDA APA Planning Committee:
Timothy P. Condon, Ph.D., OD/OSPC
Wilson M. Compton, Ph.D., DESPR
Dorynne J. Czechowicz, Ph.D., DCNDBT
Joseph Frascella, Ph.D., DCNDBT
Meyer D. Glantz, M.D., DESPR
Steven J. Grant, Ph.D., DCNDBT
Jagjitsingh H. Khalsa, Ph.D., DPMCDA
Ivan D. Montoya, Ph.D., DPMCDA
Lisa S. Onken, Ph.D., DCNDBT
Nancy S. Pilotte, Ph.D., DBNBR
Jonathan D. Pollock, Ph.D., DBNBR
David Shurtleff, Ph.D., DBNBR
Vincent L. Smeriglio, Ph.D., DCNDBT
Elliot A. Stein, Ph.D., IRP
Jack B. Stein, Ph.D., DESPR
Betty Tai, Ph.D., CCTN
Donald R. Vereen, Jr., M.D., OD
Francis J. Vocci, Jr., Ph.D., DPMCDA
Naimah Z. Weinberg, M.D., DESPR
Cora L. Wetherington, Ph.D., DBNBR
Michelle M. Person, OSPC
Jan W. Lipkin, OSPC
Joan D. Nolan, OSPC
Beverly Y. Jackson, OSPC
Robin M. Mackar, OSPC
Lucinda L. Miner, Ph.D., OSPC
Jane Smither-Holland, OSPC
Susan R.B. Weiss, Ph.D., OSPC

NIDA DEA Museum Exhibit Group:
Jan W. Lipkin, OSPC
Joan D. Nolan, OSPC
Beverly Jackson, OSPC
Sheryl A. Massaro, OSPC
Susan R. B. Weiss, Ph.D., OSPC
Cathrine A. Sasek, Ph.D., OSPC
Robin M. Mackar, OSPC
Lucinda L. Miner, Ph.D., OSPC
Gayathri J. Dowling, Ph.D., OSPC

NIDA Extramural Support Staff:
Nancy B. Sorrell, CCTN
Roxie A. Brown, DESPR
Elaine Solano, DESPR
Elizabeth Cooper, DESPR
Debra L. Yarrick, DESPR
Ann R. Hutzler, DESPR
Margaret A. Montgomery, DBNBR
Douglas M. Janes, DBNBR
Jessica E. Webster, DBNBR
LaJuan B. Whitten, DPMCDA
Grace E. Anochie, DPMCDA
Harriet McGregor, DPMCDA
Heidi E. Lawrenz, DPMCDA
Veronica Holland-Lawrence
Charlotte S. Annan, OD
Annie Joseph, OEA
Vivian G. Chiu, OEA

Marilyn D. Thomas, OEA
Sandy I. Solomon, OEA
Angela Y. Benjamin, OEA
Mark S. Lombardi, OPRM
Tu C. Phan, OPRM

NIDA EEO Staff:
Rosemary C. Pettis
Pamela L. Oliver

NIDA DIRECTOR'S AWARD OF MERIT FOR EEO, DIVERSITY, AND QUAITY OF WORKLIFE AWARD

Gary P. Fleming, J.D., OPRM

COMMISSIONED CORP AWARDS

Janice Carico, IRP
Paul Na, IRP
Barton Weick, IRP
Ahmed Elkashef, M.D., DPMCDA
Edwina Smith, DPMCDA
Kesinee Nimit, M.D., OEA

Other Staff Honors and Awards

Dr. Rao S. Rapaka, Ph.D, was the recipient of the 2004, Research Achievement Award for DRUG DESIGN and DISCOVERY. This award is given once in every two years and includes a plaque and $2000 cash award (which Dr. Rapaka, as a NIDA employee could not accept). The award is given to researchers who have made fundamental contributions in the specified area. Dr. Rapaka's citation reads:

> Dr. Rao S. Rapaka, Ph.D, Chief, Chemistry & Physiological Systems Research Branch, NIDA, National Institutes of Health. Dr. Rapaka made seminal contributions in several areas of pharmaceutical research, including the design of novel peptide analogues and peptidomimetics, the development of angiotensin analogues, the design of peptides derived from collagen and elastin, conformational studies of peptides, the establishment of structure-activity relationships, the development of strategies for the synthesis of racemization-free peptides, and studies on structural aspects of drug-receptor interactions and enzyme-substrate interactions. He is the author of over 100 publications and of over 20 research monographs and workshop proceedings, and has organized over 70 national and international scientific symposia and workshops. He promoted research on the discovery of neuronal, endogenous ligands and on their medicinal chemistry, with particular emphasis on neuropeptides, opioid peptides and cannabinoids. He is an AAPS Fellow and has participated in a number of activities related to the AAPS, including serving as Chair of the MNPC Section and as an associate editor for "Pharmaceutical Research" for the medicinal and natural products chemistry section. He received a number of national and international awards, including several NIDA and NIH awards and the Michael J. Morrison Award for Best Research Administrator. Dr.Rapaka also promotes the development of emerging areas of research and of novel technologies such as proteomics, metabolomics/metabonomics, pharmacogenomics and toxicokinetics. He is currently promoting the "Lipidomics" area and organized the first meeting on this important, emerging field in Washington DC and the Second International Meeting on Lipidomics, held in Paestum, Italy.

Ahmed Elkashef, M.D., Chief, Clinical Medical Branch, Division of Pharmacotherapies and Medical Consequences of Drug Abuse received the Public Health Service Commendation Medal for his work in establishing a relapse prevention paradigm for clinical trials.

Pat Smith, RNBC, M.S., Clinical Trials Specialist-Nurse in the Clinical Medical Branch, Division of Pharmacotherapies and Medical Consequences of Drug Abuse received the Public Health Service Commendation Medal for managing the Methamphetamine Clinical Trials Group.

Elizabeth Lambert of DESPR's Epidemiology Research Branch is the new Chair of DESPR's HIV/AIDS Workgroup.

Dr. Amy Newman was invited to be a member of the Editorial Board of Current Medicinal Chemistry.

Dr. Amy Newman was invited to present at the NIH Technology Showcase, UMD System, Shady Grove Hospital in October 2004.

Dr. Amy Newman was elected Chair of the NIDA Equal Opportunity, Diversity and Quality of Life Advisory Committee.

Dr. Peter Grundt, IRP, received an NIH FARE Travel Award for FY05.

Dr. Marilyn Huestis, IRP, serves on the US Anti-doping Research Advisory Board, which oversees research projects and grants on new analytical methods, ethics in sport, and establishment of anti-doping policy.

Staff Changes

Dr. Jacques Normand has been selected as the Director of AIDS Research, in the Office of the Director, NIDA. Dr. Normand's selection follows an extensive national search and the assistance of a committee of outside experts. Since joining NIDA in 1997, Dr. Normand has served as Acting Chief, Community Research Branch in the Division of Epidemiology, Services and Prevention Research (DESPR), Acting Chief, Epidemiology Research Branch in DESPR, and more recently, Chief, Population Based Health Intervention (PBHI) Unit in the Center on AIDS and Other Medical Consequences of Drug Abuse (CAMCODA). As Chief of the PBHI Unit, Dr. Normand was responsible for planning, developing, and administering a national and international research program focusing on behavioral, social, and health consequences of drug abuse related to HIV/AIDS and other medical consequences. Prior to joining NIDA, he served as a Senior Associate with CSR and a Study Director with the National Academy of Sciences. Dr. Normand received his Ph.D. in psychology from the Illinois Institute of Technology in 1982 and has a long-standing interest in epidemiology, prevention and HIV/AIDS research.

Ruben Baler, Ph.D. joined the Science Policy Branch in the Office of Science Policy and Communications in October 2004 as a Health Science Administrator. He received his Ph.D. in Microbiology and Molecular Biology from the University of Miami in 1993. Before arriving at NIDA, he worked at the National Institute of Mental Health as a Principal Investigator in the Unit on Temporal Gene Expression, conducting basic research on the molecular basis of circadian gene expression in vertebrates. His publications have focused on gene promoter architecture and the determination of tissue and temporal specificity afforded by discrete clusters of cis-acting elements.

Geoffrey Laredo joined the Office of the Director, Office of Science Policy and Communications in October 2004 as a Senior Advisor to the Director, OSPC. Before coming to NIDA, he spent a year working for the U.S. Senate Committee on Health, Education, Labor and Pensions, Subcommittee on Substance Abuse and Mental Health Services. At NIDA, Geoff will focus on a variety of intergovernmental issues and projects. Mr. Laredo has significant federal experience in the substance abuse field. Prior to his staff role in the Senate, he was the Director of the Office of Policy and Public Liaison at the National Institute on Alcohol Abuse and Alcoholism of the National Institutes of Health. Before being named Director, he was a senior analyst and public liaison officer in that office, focusing on collaborative activities with national groups, associations, and scientific societies across the alcohol research, prevention, and treatment field. Prior to joining NIAAA in 1996, Mr. Laredo was a senior analyst in the Office of the Administrator at the Substance Abuse and Mental Health Services Administration (SAMHSA), and was responsible for the planning and policy analysis of prevention and treatment activities of SAMHSA, with particular emphasis on alcohol and other drug policy. His work also emphasized the interface and linkages between alcohol and drug abuse and criminal justice communities. Geoff began his federal career as a program specialist with the National Institute of Justice, U.S. Department of Justice. During his tenure with NIJ, he worked in a number of program areas, including drugs and crime issues.

Genevieve deAlmeida-Morris joined the Science Policy Branch in the Office of Science Policy and Communications in November 2004. She will be taking the lead working on many of the performance measurement and evaluation activities for the Institute, including serving as the lead in responding to Government Performance Results Act (GPRA) requests. Ms. deAlmeida-Morris had been serving as a Program Analyst, and most recently the Acting Chief, Office of Science Policy at the National Institute on Nursing Research (NINR). She has an M.S. in Program Planning and Evaluation from the University of Michigan, and an M.A. in Economics from

Georgetown. She is currently pursuing her doctoral degree.

Jeng-Jong Pan (a.k.a. JJ) has just joined the CCTN. He will serve as the CTN Information Technology Specialist and Data Manager. For the past ten years, JJ has worked on data management to support scientific research projects, including health care database design and analysis. His professional experience includes software quality assurance, IT architecture, contracts, evaluation of data mining tools and data mining techniques, data management (integrity, consistency, accessibility, security and privacy), and evaluation of system performance, software development, and system integration. He also taught graduate and undergraduate courses in digital signal processing and data analysis. JJ has a PhD in Geophysics from the University of Connecticut. He comes to NIDA from the Center for Medicare and Medicaid Services (CMS) where he served for about 5 years. He has been with the federal government since 1995 (National Oceanic and Atmospheric Administration, Social Security Administration and CMS). He has received numerous performance awards throughout his career.

Jagjitsingh Khalsa, Ph.D., was named Chief, Medical Consequences Branch, Division of Pharmacotherapies and Medical Consequences of Drug Abuse, in October 2004. In this position he will be responsible for research on the medical consequences of drug abuse and co-occurring infections.

Margaret Ann Montgomery, R.N., M.S., Clinical Trials Specialist-Nurse, Clinical Medical Branch, Division of Pharmacotherapies and Medical Consequences of Drug Abuse retired on November 1, 2004 after 24 years of service.

Director's Report to the National Advisory Council on Drug Abuse - February, 2005

Grantee Honors

The 2004 Purdue Pharma Prize For Pain Research was awarded to NIDA Merit grantee, **Professor Gerald Gebhart**, University of Iowa. This prestigious award is given for excellence in pain research and for outstanding contributions being made to the pain field.

Dr. Antonello Bonci received the Jacob P. Waletzky Memorial Award for Innovative Research in Drug Addiction and Alcoholism at the Society for Neuroscience annual meeting in October, 2004. This prize is awarded each year to a scientist who has received an advanced degree of either PhD or MD within the past 15 years, and who has done notable research in the area of substance abuse and the brain and nervous system.

Mary Ann Pentz, Ph.D. of the University of Southern California Institute for Prevention Research has been asked to participate in a research study on the careers of Top NIH grantees.

The 2005 Edition of Who's Who in America lists **Dr. Phyllis L. Ellickson** as a political scientist who has made contributions to professional journals, holds membership on various advisory boards (e.g., The BEST Foundation, Monitoring the Future, Partnership for a Drug Free America, etc.) and has served on expert scientific panels (e.g., Dept of Education).

Drs. Sheppard Kellam, C. Hendricks Brown and **John Reid** were inducted as Fellows into the Academy of Experimental Criminology at the Academy's annual meeting in October 2004.

Jane Dimmitt Champion became Co-Director of the Community Outreach Core, at the University of Texas Health Sciences Center-San Antonio's National Center of Excellence in Women's Health. That Center is one of the National Centers supported by the Department of Health and Human Services.

JoAnne Keatley, MSW, University of California, San Francisco Center for AIDS Prevention Studies received a Certificate of Special Congressional Recognition (in recognition of outstanding and invaluable service to the community) from Congresswoman Nancy Pelosi, U.S. House of Representatives and a Certificate of Special Congressional Recognition (in honor of work for the LGBT immigrant community) from Congresswoman Barbara Lee, U.S. House of Representatives.

NIDA grantee **Samuel Friedman, Ph.D.,** was selected by the faculty in the Department of Epidemiology at the University of Michigan to deliver the 42nd Annual Don W. Gudakunst Memorial Lecture during the current academic year. This lecture series was established to honor Dr. Gudakunst, who directed the National Foundation for Infantile Paralysis until his untimely death in 1946. It also serves to single out a distinguished contributor to the study of infectious disease. Previous Gudakunst lecturers have included Albert Sabin, Jonas Salk, Thomas Francis, Alexander Langmuir, William Foege, and Richard Kaslow.

NIDA grantee, **Edward H. Kaplan,** the William N. and Marie A. Beach Professor of Management Sciences at the Yale School of Management, and Professor of Public Health at the Yale School of Medicine, has been elected to the Institute of Medicine of the National Academies, one of the highest honors in the fields of medicine and health (October 18, 2004). Professor Kaplan is one of 65 new members and five foreign associates announced by the Institute of Medicine (IOM). Kaplan, who is only the second professor from the Yale School of Management to be elected to the Institute of

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Medicine, is an operations research and statistics expert who studies problems in public policy and management. In addition to the Institute of Medicine, Kaplan is an elected (2003) member of another arm of the National Academies, the National Academy of Engineering. He is one of only 27 people to be an elected member of both and the principal basis for his election to the two academies has been his NIDA-supported research using advanced mathematics to model the AIDS and drug abuse epidemics and assess the public health impact and cost effectiveness of interventions in those epidemics.

Marc Galanter, M.D., (Co-PI New York Node) has been named the recipient of the 2004 Founders' Award from the American Academy of Addiction Psychiatry. This award is presented annually in recognition of a physician's major contribution to addiction treatment, training, and research.

Three CTN Community Treatment Providers (CTPs) have been awarded grants from the Robert Wood Johnson Paths to Recovery Program: **Signal** and **Island Grove Regional Treatment Center** (Rocky Mountain Node); and **Connecticut Renaissance** (New England Node).

Staff Highlights

Grantee Honors

In Memoriam

Director's Report to the National Advisory Council on Drug Abuse - February, 2005

In Memoriam

Jacqueline (Jackie) Porter, Office of Extramural Affairs, died at her home on October 20, 2004 after a courageous battle against cancer. Jackie had been the Special Assistant to the Director, Office of Extramural Affairs (OEA) for many years, and, in that role, she served NIDA in many pivotal ways, including preparing RFAs and PAs for publication in the NIH Guide, preparing Certificates of Confidentiality and serving as the NIDA expert on the Privacy Act. Withing OEA her role was also pivotal, with a range of responsibilities that included managing the budget, personnel, Council travel and expense vouchers and special NIH and NIDA announcements such as the PECASE award and the review of B/START and CEBRA applications.

Jackie began her career as a secretary at NIDA when NIDA was a small program within NIMH. Jackie's intelligence, organizational skills and work ethic were quickly recognized and she was promoted a number of times and received many awards, including the NIDA Director's Award, for her service to NIDA and NIH.

Jackie was devoted to her faith and her family. She spent many hours volunteering at St. Catherine's Catholic school and shared her many interests with her son, her parents and her 11 siblings. She especially loved to garden and her office "family" was always delighted to find fresh vegetables from her garden awaiting them and often Jackie would bring in delicious breads and cakes that she had baked.

She was generous, direct, tenacious, honest and dedicated to the mission of NIDA and NIH. She was also an incredibly brave and optimistic friend and colleague. Jackie is greatly missed by all in the scientific community, NIH, NIDA and OEA who benefited from her assistance, appreciated her efficiency, respected her knowledge and candor, and enjoyed her humor and energy.

Rodney (Jake) Marley died on December 6, 2004. Jake was born in Glasgow, Montana. He received his B.S in Biology from the University of Hawaii in 1983. He was a member of the School of Pharmacy and the IBG Training Program from 1983-1987. During that time he held an NSF Predoctoral Fellowship from 1983-1986 and an IBG NICHD Predoctoral Traineeship from 1986-1987. He received his Ph.D. in Pharmaceutical Sciences from the University of Colorado School of Pharmacy in 1987 under the mentorship of Dr. Jeanne Wehner.

Following his graduate program, Jake spent two years as a Postdoctoral Research Associate in the Department of Psychiatry at Yale University in the laboratory of Dorothy W. Gallager. This was followed by Staff and Senior Staff Fellow positions from 1989-1994 at the NIDA Addiction Research Center in Baltimore, MD. Jake left NIDA for the position of Visiting Assistant Professor in the Department of Psychology at SUNY, Albany, NY. He returned briefly to Colorado and IBG from 1999-2001 as a Research Associate in Dr. Allan Collin's laboratory before relocating permanently to Preston Hollow, NY.

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