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

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

Research Findings - Basic Neurosciences Research

Addiction, Plasticity and the Rate of Cocaine Administration

Moving from periodic to compulsive drug use (with a propensity to relapse) characterizes addiction. Much research has focused on how biological differences (such as genetics), rather than drug characteristics, themselves, may affect the transition to addiction. Although rapid drug entry into the brain appears to be associated with addiction potential, there has been almost no research on how the rate of drug delivery alters the neurobiological impact of drugs. For this reason, Dr. A.N. Samaha and colleagues at the University of Michigan undertook a study examining how the rate of intravenous cocaine administration in rats affects three outcomes: (1) psychomotor sensitization, (2) induction of the immediate early genes, c-fos and arc, and (3) the rate of dopamine uptake. Their results indicated that a single infusion of cocaine (2mg/kg) led to behavioral sensitization only when it was delivered rapidly (5 second duration). In their gene expression studies, they also found that rapidly administered cocaine preferentially engaged components of the mesocorticolimbic system. Additionally, they observed that rapid infusion is necessary to engage enkephalin (Enk +) neurons in the striatum, a finding they say is "...reminiscent of previous studies showing that when cocaine is administered under conditions that promote behavioral sensitization (i.e., a novel environment), this also facilitates its ability to engage Enk+ cells in the striatum." Finally, the authors used in vivo voltammetry to study the effect of intravenous cocaine delivery on dopamine uptake in the nucleus accumbens core. At all the rates they tested, they found increases in the half-life of electrically evoked dopamine. The greatest increase occurred and lasted longer when cocaine was rapidly delivered. For example, at 2mg/kg the half-life peaked within 60-100 sec after an injection over 5-25 seconds. (They observed a half-life for endogenously released dopamine in the range of 50-300msec.) Interestingly, the investigators found that cocaine induced greater immediate early gene expression when it was injected over 25 seconds, rather than 100 seconds, but that differences in dopamine reuptake inhibition lasted for only approximately three minutes. From this observation, they suggest that non-dopaminergic mechanisms also may contribute to the effects of infusion rate on gene expression. The authors postulate that rapid drug delivery may bring about adaptive neurobehavioral changes that relate to compulsive drug use. Samaha, A.N., Mallet, N., Ferguson, S.M., Gonon, F. and Robinson T.E. The Rate of Cocaine Administration Alters Gene Regulation and Behavioral Plasticity: Implications for Addiction. Journal of Neuroscience, 24(28), pp. 6362-6370, 2004.

New Study May Explain How Nicotine Cigarettes Help Smokers Concentrate

Dopamine is essential for attention and learning. The results of a new study indicate that how nicotine affects dopamine (DA) release from ventral tegmental area (VTA) neurons depends on the (baseline) firing pattern of the dopaminergic neurons. There are ordinarily 2 firing patterns of the VTA DA neurons, a low-frequency *tonic* mode (0.5-8 Hz) interrupted by bursts of *phasic* activity (about 15-50 Hz) that are matched to salient stimuli in learning and memory experiments. These researchers found that nicotine, at levels experienced by smokers (~300 nM), shifts the firing pattern of dopaminergic neurons from tonic firing to high-frequency burst firing. They used carbon-fiber microelectrodes and fast cyclic voltammetry to measure released DA at sub-second resolution in acutely prepared mouse brain slices. While nicotine curbed DA release at low firing frequencies, it allowed a rapid rise in DA at the higher firing frequencies that are associated with behavioral cues. Such contrast enhancement may underlie nicotine's ability to increase sensory gating and attention, and may help explain the appeal of nicotine use in healthy individuals, nicotine's ability to enhance

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cognition in disorders such as Alzheimer's and attention disorder, and the very high prevalence of smoking in schizophrenic patients, a disease in which sensory gating is impaired. Smoking is often suggested to be a form of self-medication in schizophrenia. Zhang, H. and Sulzer, D. Frequency-dependent Modulation of Dopamine Release by Nicotine. Nature Neuroscience, 7, pp. 581-582, 2004.

Presynaptic Actions of Dopamine

By recording the activity of individual presynaptic neuron terminals in the striatum, researchers found that dopamine (DA) released by either electrical stimulation of the striatum or by amphetamine inhibited the activity of about 85% of the neuronal inputs from the cortex to the striatum (i.e., the corticostriatal terminals). They accomplished these direct recordings by combining optical monitoring of motor area corticostriatal afferents using the fluorescent vesicle marker FM1-43 with electrochemical recordings of striatal DA release. Further, they found that this presynaptic inhibitory effect of DA is mediated by DA D2 receptors. This inhibition resembles DA input associated with either salient behavioral stimuli or psychostimulant drugs, and suggests how DA modifies striatal activity. They found that the most active terminals were selectively resistant to DA inhibition, while the remaining terminals were inhibited. Thus, DA release associated with salience during motor learning may reinforce specific corticostriatal connections by filtering out less effective inputs. The selective filtering of corticostriatal transmission by amphetamine may indicate how drugs of abuse reinforce drug-taking behavior, leading to the development of addiction. Bamford, N.S., Zhang, H., Schmitz, Y., Wu, N-P., Cepeda, C., Levine, M.S., Schmauss, C., Zakharenko, S.S., Zablow, L. and Sulzer, D. Heterosynaptic Dopamine Neurotransmission Selects Sets of Corticostriatal Terminals. Neuron 42, pp. 653-663, 2004.

Activator of G Protein Signaling 3: A Gatekeeper of Cocaine Sensitization and Drug Seeking

It is known that chronic cocaine administration reduces G (guanine nucleotide binding) protein signaling efficacy. It is now reported that expression of the G protein binding protein AGS3 (activator of G protein signaling 3), which complexes the Gi_ subunit and thus diminishes signaling through Gi_-mediated signal cascades, is upregulated in the prefrontal cortex (PFC) during late withdrawal (as late as 2 months after the end of treatment) from repeated cocaine administration. These researchers then employed a method to mimic elevated levels of AGS3 in the PFC of drug-naive rats by microinjecting a peptide containing the Gi_ binding domain of AGS3 fused to the cell permeability domain of HIV-Tat. Infusion of this peptide mimicked the phenotype of chronic cocaine-treated rats by manifesting (1) sensitized locomotor behavior to cocaine, (2) enhanced drug-seeking behavior when primed with a single injection of cocaine, and (3) increased glutamate transmission in nucleus accumbens. Then, by preventing cocaine withdrawal-induced AGS3 expression with antisense oligonucleotides, signaling through Gi_ was normalized, and both cocaine-induced relapse to drug seeking and locomotor sensitization were prevented. When antisense oligonucleotide infusion was discontinued, drug seeking and sensitization were restored. The involvement of AGS3 in drug reinstatement appears to be selective to cocaine-related reward, as infusion of the antisense into rats resuming lever pressing for food had no effect. Thus, it is proposed that AGS3 gates the expression of cocaine-induced plasticity by regulating G protein signaling in the PFC. Bowers, M.S., McFarland, K., Lake, R.W., Peterson, Y.K., Lapish, C.C., Gregory, M.L., Lanier, S.M. and Kalivas, P.W. Activator of G Protein Signaling 3: A Gatekeeper of Cocaine Sensitization and Drug Seeking. Neuron, 42, pp. 269-281, 2004.

Cocaine, Benzoylecgonine, Amphetamine, and N-Acetylamphetamine Binding to Melanin Subtypes in Hair

The two major melanin types in hair are the black eumelanins and the reddish-brown pheomelanins. The purpose of this study was to assess the binding of cocaine, benzoylecgonine (BE), amphetamine, and N-acetylamphetamine (N-AcAp) to these individual melanin types. These drugs were chosen because cocaine exhibits a known hair color bias whereas its chemical congener BE, has not been shown to exhibit this bias. Similarly, although amphetamine exhibits a hair color bias, its non-basic analog N-AcAp does not exhibit a hair color bias. Experiments were performed to document the in vitro binding of all above drugs to synthetic melanin subtypes. The melanins included in this study were two black eumelanin subtypes and a reddish brown pheomelanin and two mixed melanin copolymers. Results indicated that cocaine and amphetamine bind to eumelanins and mixed eu-/pheomelanins to varying degrees, but not to pure pheomelanin. BE and N-AcAp, net neutral molecules, do not bind to any type of melanin. Overall these findings show that basic drugs, such as cocaine

and amphetamine, have a greater affinity for melanin than their net neutral analogues. These data further reveal that melanin types differ when it comes to drug binding, and begin to elucidate what properties of melanin are important for drug binding, and why hair color drug-binding biases exist. Borges, C.R., Roberts, J.C., Wilkins, D.G. and Rollins, D.E. Cocaine, Benzoylecgonine, Amphetamine, and N-acetylamphetamine Binding to Melanin Subtypes. Journal of Analytical Toxicology, 27, pp. 125-134. 2003.

Kappa-Delta Receptor Association

Previous experiments have suggested the existence of a physical association between the delta (DOR) and kappa (KOR) opioid receptors. The so-called heterodimer of DOR and KOR shows some degree of difference in its trafficking, signaling in neurons and ligand binding, as compared to the properties of separate delta or kappa receptors. For instance, the heterodimer internalizes from the neuron's surface into the cell to a lesser extent than the delta receptor alone, when exposed to the opiate agonist etorphine. The potency of a kappa agonist (U69,593) or a delta agonist (DPDPE) is substantially reduced when interacting with the heterodimer receptor compared to the potency toward the individual receptors. There is also a synergy shown in binding of these compounds to the hetrodimer receptor. That is, there is low affinity for kappa agonists, by the heterodimer receptor, but high affinity for this compound in the presence of the delta agonist. Finally, the heterodimer receptor showed a greater affinity for what are known as partial agonists such as etorphine, as compared to the full agonists U69593 or DPDPE. Recently, Dr. Philip Portoghese has investigated the properties of several bivalent ligands, which contain one pharmacophoric group resembling GNTI (kappa sensitive) separated by a chain of atoms (a "spacer"), linked to a second pharmacophore group (a delta sensitive naltrindole). In particular, one of these bivalent ligands lacked agonist activity, but showed both significant kappa and delta antagonist properties when administered intrathecally to mice. In HEK cells co-expressing kappa and delta receptors, Ki values (displacement of tritiated diprenorphine) were optimal for a "spacer" of twenty-one atoms needed to allow interaction of the bivalent ligand with both receptors. It was also shown that administration of this ligand into the rodent brain antagonized only the delta receptor (DPDPE), but not the kappa (U50488), so that the rodent brain may not possess the same heterodimer organization as observed in the spinal cord. Bhushan, R.G., Sharma, S.K., Xie, Z., Daniels, D.J. and Portoghese, P.S. A Bivalent Ligand (KDN-21) Reveals Spinal δ and κ Opioid Receptors Are Organized as Heterodimers That Give Rise to δ_1 and κ_2 Phenotypes. Selective Targeting of δ-κ . Journal of Medicinal Chemistry, 47, pp. 2969-2972, 2004.

Antinociceptive Structure-Activity Studies with Enkephalin-Based Opioid Glycopeptides

To develop effective opioid peptides as therapeutic agents pharmacokinetic issues including stability and blood-brain barrier (BBB) permeability need to be considered. The chemical technique of glycosylation of opioid peptides can increase peptide stability and BBB penetration. To further refine and optimize pain-reducing antinociceptive potency, Dr. Hruby and his colleagues were able to synthesize a series of enkephalin-based glycopeptides using a solid phase method. Binding and functional smooth muscle bioassays indicated that these glycopeptides did not significantly affect the opioid receptor affinity or agonist activity. All of the glycopeptides tested produced potent antinociception in mice. Selected compounds were administered to mice to further test for antinociception, assess serum stability and blood brain barrier penetration. All compounds tested produced full antinociceptive effects with calculated A50 values ranging from 2.2-46.4 µmol/kg. These results provide additional support for the utility of glycosylation to increase CNS bioavailability of small peptides and complement ongoing stability and blood-brain barrier penetration studies. Elmagbari, N.O., Egleton, R.D., Palian, M., Lowery, J.J., Schmid, W.R., Davis, P., Navratilova, E., Yamamura, H.I., Porreca, F., Hruby, V.J., Dhanasekaran, M., Keyari, C.M., Polt, R. and Bilsky, E. Antinociceptive Structure-Activity Studies with Enkephalin-Based Opioid Glycopeptides. Journal of Pharmacology and Experimental Therapeutics, DOI:10.1124/jpet.104.069393, July 7, 2004.

A Single *in-vivo* Exposure to _9THC Disrupted Functional Plasticity Mediated by Endocannabinoid in the Hippocampus

Individuals who smoke marijuana often show impairments in learning, cognitive abilities, the perception of reward and in emotional well-being. Endogenous cannabinoids and their receptors in the hippocampus and the ventral tegmental area may be important in "tuning" neural activity such as the synaptic activity and plasticity of neurons. Dr. Castillo and his team have shown that the dynamic status of

neuronal excitement and the firing pattern of neurons, factors that control the pattern of neurotransmitter release, is tuned by DSI (depolarization suppression of inhibition), a retrograde feedback disinhibition of the inhibitory GABAergic inputs that occurs as a result of the activity of endogenous cannabinoids. These compounds have already been shown to underlie long-lasting synaptic plasticity such as LTP and LTD at excitatory synapses, and the current work shows that endogenous cannabinoids generate LTD at inhibitory synapses in GABAergic neurons within the hippocampus. Both DSI and LTD inhibit GABA neurons, resulting in enhanced activity in stimulated neurons, but they work on different time scales. Activity evoked by DSI lasts less than a minute while the LTD can persist for hours, even days. Coding of neuronal activities and their plasticity depends upon the balance between excitatory and inhibitory inputs in the neuronal network. As GABAergic transmission plays a critical role in the regulation of brain excitability, reduction in the level of inhibition will cause a long-lasting sensitization of the brain to stimulatory inputs and reinforcement of evoked responses, phenomena that could underlie the role of endocannabinoids in learning and memory. Disruption of the endogenous cannabinoids by a single exposure to _9THC, the exogenous cannabis derivative, was enough to produce a long lasting (3 days), reversible occlusion of LTD generation in hippocampus and N. Accumbens. It suggests that the functional disruption may be a use-dependent phenomenon. Chevaleyre, V. and Castillo, P.E. Heterosynaptic LTD of Hippocampal GABAergic Synapses: A Novel Role of Endocannabinoids in Regulating Excitability. Neuron. 38(3), pp. 461-472, 2003. Mato, S., Chevaleyre, V., Robbe, D., Pazos, A., Castillo, P.E. and Manzoni, O.J. A Single *in-vivo* Exposure to _9THC Blocks Endocannabinoid-Mediated Synaptic Plasticity. Nature Neuroscience 7, pp. 585-586, 2004.

Prenatal Cocaine Exposure and Behavioral Tolerance

Repeated exposure to cocaine during sensitive periods of forebrain development produces specific, long-lasting changes in the structure and function of maturing neural circuits. Similar regimens of drug exposure in adult animals with mature, homeostatically regulated nervous systems produce neuroadaptations that appear to be quite different in nature and magnitude. In a recent paper, Dr. Pat Levitt and his associate, Dr. Gregg Stanwood, Vanderbilt University School of Medicine, report that specific adaptive changes in neural signaling and/or circuitry that occur in response to repeated exposure to psychostimulants are highly dependent upon the maturational state of the brain. Their studies were designed to investigate the ability of cocaine to induce behavioral sensitization and/or tolerance following repeated administration of cocaine to pregnant rabbits during the period of peak differentiation within the rabbit cerebral cortex (embryonic day 16-25). Offspring and the mothers were later tested following acute administration of amphetamine challenge. The offspring, having received cocaine during the prenatal sensitive period, showed profound behavioral tolerance to the amphetamine challenge. In contrast, the mothers of these offspring, who received cocaine at the same dose and duration, and experienced the same period of withdrawal, exhibited robust behavioral sensitization. Stanwood, G.D. and Levitt, P. Repeated I.V. Cocaine Exposure Produces Long-lasting Behavioral Sensitization in Pregnant Adults, But Behavioral Tolerance in their Offspring. Neuroscience 122, pp. 579-583, 2003.

Vesicular Glutamate Transporters 1 and 2 Target to Functionally Distinct Synaptic Release Sites

Glutamate is the major excitatory neurotransmitter in the brain and in a number of studies has been shown to be important in mediating drug seeking behavior. Like many other neurotransmitters glutamate is stored in synaptic vesicles and is used to communicate with other neurons. Central to the process of synaptic transmission is the means by which neurons concentrate and transport neurotransmitters like glutamate in synaptic vesicles in the nerve terminal. In the April 29, 2004 issue of Science, Dr. Robert Edwards and his colleagues describe two glutamate transporters on nerve terminal (VGLUT1 and VGLUT2) that are targeted to two distinct synaptic release sites. Expression of VGLUT1 is observed in the hippocampus, cerebral cortex, and cerebellar cortex while VGLUT2 is expressed in thalamus, brain stem nuclei, and deep cerebellar nuclei. Synapses expressing VGLUT1 show a lower probably of transmitter release while synapses expressing VGLUT2 exhibit a greater probability of transmitter release when a nerve impulse invades the synaptic terminal. To test directly the role that VGLUT1 plays in synaptic transmission, Dr. Robert Edwards and his colleagues created a mouse lacking the VGLUT1 transporter. The mice lacking the VGLUT1 transporter appear normal for the first two weeks, but then began to show progressive neurological defects resulting in incoordination, blindness, and enhanced startle response. This phenotype is associated with VGLUT1 independent synaptic transmission in the cerebellar cortex and hippocampus that precipitously declines to

nothing during the first two months after birth. Analysis, using in situ hybridization, suggests that VGLUT2 is co-expressed with VGLUT1 in the hippocampus and cerebellum during the first two weeks followed by rapid decline of VGLUT2 expression. The overlapping pattern of expression is different from the non-overlapping patterns of expression. So this raises the question of whether the VGLUT1 and VGLUT2 have unique functions within the same neuron. Both electrophysiological analysis and immunohistochemistry shows that VGLUT1 and VGLUT2 are targeted to distinct synaptic release sites instead of being localized to the same synaptic vesicle or different synaptic vesicles at the same release site. Dr. Edwards and his colleagues suggest that differences in vesicles recycling may explain the differences in the probability of release at synapses where VGLUT1 and VGLUT2 are expressed. Synapses that show lower probability of release such as in the hippocampus and cerebellum are more likely to show plasticity. Thus, analysis of the roles that glutamate transporter play may help understand the mechanisms underlying synaptic plasticity. The next key question is whether VGLUT1 and VGLUT2 contribute to differences in the probability of release or are simply a marker for this difference. Fremeau, R.T. Jr., Kam, K., Qureshi, T., Johnson, J., Copenhagen, D.R., Storm-Mathisen, J., Chaudhry, F.A., Nicoll, R.A. and Edwards, R.H. Vesicular Glutamate Transporters 1 and 2 Target to Functionally Distinct Synaptic Release Sites. Science, 304(5678), pp. 1815-1819, 2004.

MuLK: A Novel Eukaryotic Multi-substrate Lipid Kinase

One of the fundamental questions in biology is how components of cells communicate within a cell and between cells. One class of molecules that act as cellular messengers is lipids or fatty molecules. The addition of phosphates to these lipid messengers by protein kinases or removal of phosphate molecules by protein phosphatases from the lipid molecules such as mono- and diacylglycerols, sphingosine and ceramides produces signaling molecules that can regulate their function and in turn alter cellular processes such as the secretion of a neurotransmitter from the nerve terminal. A calcium dependent ceramide kinase has previously been found to be associated with synaptic vesicles that store neurotransmitter. In an attempt to identify this ceramide kinase Dr. Bajjalieh and her colleagues searched the human genome database for sequences that resembled the sequence for sphingosine kinase 2, a kinase they hypothesized to share some sequence similarity with the ceramide kinase they sought. As a result of their search Dr. Bajjalieh and her colleagues discovered a unique lipid kinase that phosphorylates not only ceramides, but also other lipids. Typically, the kinases that phosphorylate different lipid types, such as diacylglycerols, ceramides and sphingosine belong to different molecular families that are selective for a specific lipid type. Because of its ability to phosphorylate multiple substrates, they have named the new kinase MuLK for multi-substrate lipid kinase. Based on its sequence, one would conclude that MuLK is expressed in the cytosol or in the nucleus of cells, but localization studies performed in fibroblast cells suggest that MuLK is associated with intracellular membranes. The sequence also suggests that MuLK itself may be a kinase substrate, although the researchers did not conduct those experiments as part of this study. While phosphorylation and dephosphorylation through kinase and phosphatase activities are ways to regulate the activity of molecules in a cell, the kinase activities are also affected by the conditions of the cell. In this case, they found that MuLK is stimulated by calcium when magnesium concentrations are low and inhibited by calcium when magnesium concentrations are high. While the significance of this mode of regulation has not been elucidated, calcium is a regulator of several cellular processes including the secretion of neurotransmitter. One of the other things the researchers observed was low-level activity of MuLK toward the phosphorylation of 2AG, a lipid and endocannabinoid, the endogenous ligand for the cannabinoid receptor. Since phosphorylation often affects molecular interactions, it is likely that phosphorylation of 2AG and other lipid molecules by MuLK results in modification of those molecules with other molecules in the cell. Modification of the molecular interactions often results in changes in cellular activity. What started as a database query to look for ceramide kinases, has led to the beginning of an understanding of the regulation of the first identified multiple substrate lipid kinase. The characterization of this multi substrate lipid kinase and similar molecules may help to elucidate fundamental cellular processes as well as shedding light on how the biochemical pathway involved in processing endogenous cannabinoids is regulated. Waggoner, D.W., Johnson, L.B., Mann, P.C., Morris, V., Guastella, J., and Bajjalieh, S.M. MuLK: A Novel Eukaryotic Multi-substrate Lipid Kinase. Journal of Biological Chemistry, Jul 13 [Epub ahead of print], 2004.

MPDZ Is a Quantitative Trait Gene for Drug Withdrawal Seizures

About 50-60% of drug dependence is genetically determined and its effects include

influence on physiological dependence and associated withdrawal from sedative hypnotics, including alcohol, benzodiazepines, inhalants and barbiturates. Buck and colleagues used robust behavioral models of drug physiological dependence in mice and identified an addiction-relevant quantitative trait gene, called the multiple PDZ domain gene (*Mpdz*), among five candidate genes. PDZ domains are modular protein interaction domains that bind in a sequence-specific manner to short C-terminal peptides or internal peptides. They are typically involved in the assembly of supramolecular complexes that perform localized signaling functions at particular subcellular locations. The *Mpdz* gene was the only one of the five candidates to show genotype-dependent differences in coding sequence. *Mpdz* expression was significantly associated with severities of withdrawal from alcohol and pentobarbital, such that lower expression of *Mpdz* was genetically correlated with greater withdrawal seizure susceptibility. They speculate that *Mpdz* protein expression and/or structure both affect drug dependence and withdrawal by altering the rate and/or fidelity of signal transduction mediated by one or more of its interaction partners. One mechanism may be that the *Mpdz* protein interacts with GABAB receptors, which regulate glutamate and GABA release. Findings like these may help to identify new targets for pharmacotherapies for withdrawal. Shirley, R.L., Walter, N.A.R., Reilly, M.T., Fehr, C. and Buck, K.J. *MPDZ* Is a Quantitative Trait Gene for Drug Withdrawal Seizures. Nature Neuroscience, 7, pp. 699-700, 2004.

Dopamine Transporter Inhibitors Decrease Cocaine Self-Administration in Rhesus Monkeys

The dopamine transporter (DAT) is thought to play a critical role in mediating the reinforcing efficacy and subjective effects of cocaine. It has been known for many years that the affinity of drugs for the DAT is positively correlated with their capacities to maintaining self-administration behavior in animals. There has been an interest in DAT inhibitors as medications to treat cocaine dependence. Dr. Leonard Howell and his associates at Yerkes National Regional Primate Research Center investigated a series of DAT inhibitors with varying affinities for other monoamine transporters for their ability to block cocaine self-administration in rhesus monkeys. In addition, the behavioral effects of the drugs were compared to their DAT occupancy using PET imaging, both in awake animals and in animals under isoflurane anesthesia. Doses of GBR 12909 and RTI-177 that reduced cocaine self-administration by 50% were associated with DAT occupancies of approximately 67 and 73%, respectively. Both of these compounds were also self-administered by the animals at doses that produced DAT occupancies of 57 and 92%, respectively. RTI-112 is a mixed action monoamine transporter inhibitor that is about equally potent at the DAT and the serotonin transporter (SERT). This compound also inhibits cocaine self-administration in monkeys at a dose that does not produce detectable changes in DAT occupancy. It does, however, occupy approximately 90% of SERT, suggesting that RTI-112's contributions were due to its serotonergic properties and not its dopaminergic ones. Additionally, RTI-112 was not self-administered by monkeys and therefore not likely to have any abuse liability. Lindsey, K.P., Wilcox, K.M., Votaw, J.R, Goodman, M.M., Plisson, C., Carroll, F.I., Rice, K.C. and Howell, L.L. Effects of Dopamine Transporter Inhibitors on Cocaine Self-Administration in Rhesus Monkeys: Relationship to Transporter Occupancy Determined by Positron Emission Tomography Neuroimaging. Journal of Pharmacology and Experimental Therapeutics, 309(3), pp. 959-969, 2004.

Menthol Pharmacology and its Potential Impact on Cigarette Smoking

Mentholated cigarettes are disproportionately smoked by African American smokers which, as a group, are the least likely "ever smokers" to quit smoking. However, since cigarette smoke consists of over 4000 substances, it has been difficult to study the effects due to the menthol additive. This article reviews the research to date on menthol, cigarettes, and smoking behavior. Menthol has cooling and local anesthetic effects, which may be mediated by action on agonist action on a thermally responsive receptor. In addition to thermal effects, menthol has been found to augment nicotine's reinforcing effects, possibly due to a decrease in nicotine and cotinine (a nicotine metabolite) metabolism, increased lung exposure to tobacco smoke constituents, and/or stimulant and depressant effects on the central nervous system. Menthol may also possess reinforcing effects independent of nicotine. There may also be differences in some of menthol's effects across racial and ethnic groups, as illustrated by African American smokers showing typically higher levels of cotinine as compared to Mexican American and Caucasian smokers. Future research directions are also discussed. Ahijevych, K. and Gerrett, B.E. Menthol Pharmacology and its Potential Impact on Cigarette Smoking Behavior. Nicotine Tobacco Research, 6 (supple 1), S17-S28, 2004.

Cannabinoids Activate Sensory Pain Fibers

Delta^{9}-tetrahydrocannabinol (THC), the psychoactive component of marijuana, is known to activate cannabinoid receptors in the brain and periphery to produce many of its effects. However, research supported by NIDA has demonstrated that in sensory nerve fibers, THC also opens the ANKTM1 channel, a calcium channel that has recently been implicated in the detection of noxious cold stimuli. Likewise, mustard oil (allyl isothiocyanate), which produces pain with topical application, also was found to activate the ANKTM1 channel. The activation of the ANKTM1 channel by either THC or mustard oil was blocked by ruthenium red, a ANKTM1 channel blocker. These findings demonstrate a novel site of action of cannabinoids, where activation of this site appears to be pro-nociceptive (pain inducing). Jordt, S-E., Bautisa, D., Chaung, H., McKemy, D.D., Zygmunt, P.M., Hogestatt, E.D., Meng, I.D. and Julius, D. Mustard Oils and Cannabinoids Excite Sensory Nerve Fibers through the TRP Channel ANKTM1. Nature, 427, pp. 260-265, 2004.

Dopaminergic Supersensitivity in G Protein-Coupled Receptor Kinase 6-Deficient Mice

Brain dopaminergic transmission is a critical component in numerous vital functions, and its dysfunction is involved in several disorders, including addiction and Parkinson's disease. Responses to dopamine are mediated via G protein-coupled dopamine receptors (D1-D5). Desensitization of G protein-coupled receptors is mediated via phosphorylation by members of the family of G protein-coupled receptor kinases (GRK1-GRK7). Dr. Richard Premont of the Department of Medicine, Duke University Medical Center and his colleagues show that GRK6-deficient mice are supersensitive to the locomotor-stimulating effect of psychostimulants, including cocaine and amphetamine. In addition, these mice demonstrate an enhanced coupling of striatal D2-like dopamine receptors to G proteins and augmented locomotor response to direct dopamine agonists both in intact and in dopamine-depleted animals. The present study indicates that postsynaptic D2-like dopamine receptors are physiological targets for GRK6 and suggests that this regulatory mechanism contributes to central dopaminergic supersensitivity. Gainetdinov, R.R., Bohn, L.M., Sotnikova, T.D., Cyr, M., Laakso, A., Macrae, A.D., Torres, G.E., Kim, K.M., Lefkowitz, R.J., Caron, M.G. and Premont, R.T. Dopaminergic Supersensitivity in G Protein-coupled Receptor Kinase 6-deficient Mice. Neuron, 38(2), pp. 291-303, 2003.

Cyclin-Dependent Kinase 5 Phosphorylates the N-terminal Domain of the Postsynaptic Density Protein PSD-95 in Neurons

PSD-95 (postsynaptic density 95) is a scaffolding protein that links NMDA receptors to the cytoskeleton and to its signaling molecules. The N-terminal domain of PSD-95 is involved in the synaptic targeting and clustering of PSD-95 and in the clustering of NMDA receptors at synapses. There are consensus phosphorylation sites in the N-terminal for cyclin-dependent kinase 5 (cdk5), a serine-threonine kinase that is necessary for brain development. This kinase is also implicated in synaptic plasticity, dopamine signaling, cocaine addiction, and neurodegenerative disorders. Dr. Maria Morabito of Harvard Medical School and her research team report that PSD-95 is phosphorylated in the N-terminal domain by cdk5 both in vitro and in vivo. Furthermore, this phosphorylation is not detectable in brain lysates of mice that lack cdk5 (cdk5-/- mice). The phosphorylated product was found in postsynaptic densities together with cdk5 and its activator, p35, suggesting that phosphorylated PSD-95 may have an important action at synapses. In heterologous cells, coexpression of active cdk5 with PSD-95 reduces the ability of PSD-95 to multimerize and to cluster neuronal ion channels. When cdk5 was omitted from the cultures, there were larger clusters of PSD-95/NMDA receptors. In cortical neurons from mice that did not express cdk5 (-/-) cortical neurons, there were more PSD-95 immunostained clusters than were observed in wild-type neurons. In hippocampal neurons, expression of the inactive form on cdk5 (DNcdk5) or of full-length PSD-95 with the triple alanine mutant (T19A, S25A, S35A), the size of the PSD-95 cluster was increased. These results are important because they identify cdk5-dependent phosphorylation of the N-terminal domain of PSD-95 as a novel mechanism for regulating the clustering of PSD-95/NMDA receptors and support the possibility that cdk5-dependent phosphorylation of PSD-95 dynamically regulates the clustering of PSD-95/NMDA receptors at synapses. Such an activity would provide a possible mechanism for rapid changes in density and/or number of receptors at synapses. Morabito, M.A., Sheng, M. and Tsai, L.H. Cyclin-dependent Kinase 5 Phosphorylates the N-terminal Domain of the Postsynaptic Density Protein PSD-95 in Neurons. Journal of Neuroscience, 24(4), pp. 865-876, 2004.

Morphine-induced Alterations of Immune Status are Blocked by the Dopamine D2-like Receptor Agonist

In is known that morphine administration produces profound effects on the immune system, including reductions in natural killer cell activity, mitogen-induced lymphocyte proliferation, and cytokine production. Although it has been established that the activation of central nervous system (CNS) mu-opioid receptors by morphine induces immunomodulation, little is known about the neural mechanisms underlying such processes. Interestingly, it has been shown that the dopamine (DA) D-2-like receptor agonist (7-OH-DPAT) blocks the effect of morphine on a number of behaviors that are mediated by central dopamine pathways. The present study examined whether dopamine is involved in the immunomodulatory effects of morphine. In separate experiments, 7-OH-DPAT was administered either systemically or in the brain prior to morphine treatment in male Lewis rats. The results demonstrate that both systemic and central administration of 7-OH-DPAT attenuate the suppressive effect of morphine on several measures of immune status. Overall, these findings provide the first evidence that brain dopaminergic mechanisms are directly involved in morphine-induced immunomodulation. Saurer, T.B., Carrigan, K.A., Ijames, S.G. and Lysle, D.T. Morphine-induced Alterations of Immune Status are Blocked by the Dopamine D2-like Receptor Agonist 7-OH-DPAT. Journal of Neuroimmunology, 148, pp. 54-62, 2004.

Proinflammatory Chemokines Can Affect Opioid Receptors

Pain is one of the hallmarks of inflammation. Opioid receptors mediate anti-pain responses in both the peripheral nervous system and the brain. The present study showed that pretreatment of the CCR1and mu-opioid receptor combination in a HEK293 cell preparation with the chemokine CCL3 (MIP-1alpha) induced internalization of mu-opioid receptors and severely impaired the mu-opioid receptor-mediated inhibition of cAMP accumulation. Further analysis using immunohistochemical staining showed that CCR1 and mu-opioid receptors were co-expressed on small to medium diameter neurons in rat dorsal root ganglion, and that both types of receptors were functioning. Pretreatment of neurons with CCL3 impaired the mu-opioid receptors. Other chemokines, such as CCL2, CCL5, and CCL8, exhibited similar inhibitory effects. These data indicate that proinflammatory chemokines are capable of desensitizing mu-opioid receptors on peripheral sensory neurons, providing a novel potential mechanism for peripheral inflammation-induced hyperalgesia. Zhang, N., Rogers, T.J., Caterina, M. and Oppenheim, J.J. Proinflammatory Chemokines, Such as C-C Chemokine Ligand 3, Desensitize Mu-opioid Receptors on Dorsal Root Ganglia Neurons. Journal of Immunology, 173, pp. 594-599, 2004.

Neuromolecular Activation in cAMP Response Element-binding Protein (pCREB) is Important in Stress-induced Relapse

Relapse to drug addiction is often precipitated by exposure to stress. Using animal models, relapse can be precipitated by administering the drug itself (i.e., drug-induced relapse), by exposure to a stressor (i.e., stress-induced relapse), or through exposure to the environment where drug taking previously took place (i.e., cue-induced relapse). To investigate the neurobiological changes associated with stress-induced relapse, Drs. Kreibich and Blendy from the University of Pennsylvania, exposed mice to a forced swim stressor (FS), which has been successfully used to test the efficacy of putative anti-depressants in animal models. In this experiment, exposure to FS induced relapse to cocaine preference in mice. Importantly, relapse was accompanied by an increase in the phosphorylated cAMP response element-binding protein (pCREB) in discrete brain regions that were distinct from the pattern observed after cocaine-induced relapse. Activation of pCREB mediates several aspects of addiction, depending on the specific region of the brain involved. For example, morphine-induced activation of CREB in the a region of the brain known as the locus coeruleus (LC) can lead to some of the symptoms underlying physical opiate dependence and withdrawal. Furthermore, chronic exposure to opiates, cocaine, and alcohol also activates pCREB in the nucleus accumbens (NA), a brain region associated with drug reward. Increased activation of CREB in this brain region is associated with a decrease in the rewarding effects of drugs of abuse such as cocaine. CREB may also affect the release of stress hormones such as corticotrophin-releasing factor, which can increase the likelihood of relapse. In this study, researchers further demonstrated that the alterations seen in CREB are a necessary molecular change for stress-induced relapse because the researchers showed that genetically altered mutant mice that lack CREB were not as susceptible to stress-induced relapse as wild-type mice. In contrast, however, these mutant mice lacking CREB were still susceptible to cocaine-induced relapse. Overall these results suggest that CREB's

involvement and its pattern of activity in drug- and stress-induced relapse is different. Developing pharmacotherapies that regulate CREB may be useful for reducing and treating stress-induced relapse. Kreibich, A.S. and Blendy, J.A. cAMP Response Element-binding Protein is Required for Stress but not Cocaine-induced Reinstatement. Journal of Neuroscience, 24(30), pp. 6686-6692, 2004.

Homer Proteins Regulate Sensitivity to Cocaine

The consequences of addiction to cocaine include changes in brain chemistry and behavior. One consequence is reduced Homer protein. Szumlinski et al. demonstrate that reducing Homer1 or Homer2, but not Homer3, in drug-naive mice causes increased sensitivity to the locomotor activating effects of cocaine and PCP, but not heroin or caffeine. Furthermore, reduction of these two genes also enhanced glutamate output in the nucleus accumbens, an outcome usually observed upon withdrawal of cocaine. Restoration of the genes via adeno-associated virally mediated gene transfers reversed the cocaine-induced phenotype, which reulted in a decreased sensitivity to cocaine reward and motor activation, as well as less excitatory drive in the nucleus accumbens. The parallel between animals addicted to cocaine and reduced Homer suggests that Homer may regulate the development of addiction. Szumlinski, K.K., Dehoff, M.H., Kang, S.H., Frys, K.A., Lominac, K.D., Klugmann, M., Rohrer, J., Griffin, W., III, Toda, S., Champtiaux, N.P., Berry, T., Tu, J.C., Shealy, S.E., During, M.J., Middaugh, L.D., Worley, P.F. and Kalivas, P.W. Homer Proteins Regulate Sensitivity to Cocaine. Neuron, 43(3), pp. 401-413, 2004.

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

Research Findings - Behavioral Research

Environmental Enrichment During Rearing Selectively Affects Dopamine Transport in the Prefrontal Cortex

In preclinical studies, early environmental enrichment (EC) affects subsequent behavioral responsivity to drugs of abuse such as amphetamine. For example, EC rats show an attenuated amphetamine-induced sensitization and a decrease in self-administration of this drug. EC also induces structural changes in neurons of the cortex and striatum. These structural changes may affect synaptic transmission in brain dopamine systems that give rise to behavioral effects of psychostimulants. Recently, NIDA-funded investigators at the University of Kentucky performed a kinetic analysis of dopamine transporter (DAT) function in the medial prefrontal cortex (mPFC), striatum and nucleus accumbens (NAS) of rats reared in EC conditions or in isolation (IC). Initially the investigators administered the selective DAT inhibitor, GBR 12935, to assess behavioral effects on the locomotor activity of EC and IC groups. Although EC animals had a lower basal level of behavioral activity, GBR increased activity to a greater extent in this group than in the IC group, when given acutely (dose range: 1.0-10.0 mg/kg). Surprisingly, when 3.0 or 5.6 mg/kg was given repeatedly, only the EC group developed a behavioral sensitization to the locomotor activating effects of GBR. The authors note that this contrasts with previous observations from repeated amphetamine administration, but behavioral differences may be accounted for by different neurochemical mechanisms of action in central dopamine neurons. Subsequent DAT analysis revealed no differences in Ki values of [^{3}H]dopamine uptake between groups for any brain area. However, EC significantly decreased (36%) Vmax in the mPFC, in comparison to the IC condition. This difference was evident for the mPFC only, with no between group differences for subcortical areas. HPLC measures of the DA metabolite DOPAC also revealed a significant difference between groups for the mPFC only. The observation that EC selectively decreases DAT function and DA metabolism in the mPFC suggests that the environment can modulate the activity of central DA systems that participate in chronic neuroadaptations that give rise to psychostimulant craving and relapse. 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.

Glutamate Group II mGluR2/3 Receptor Activation Attenuates Relapse Triggered by Drug-related Stimuli

Alterations of central glutamatergic neurotransmission are involved in the neuroadaptive changes that give rise to psychostimulant-induced behavioral sensitization. The metabatropic Glu2/3 agonist LY379268 attenuates amphetamine's acute behavioral activating effects and the locomotor sensitization produced with repeated cocaine treatment. A recent study conducted by Dr. Friedbert Weiss and colleagues at The Scripps Research Institute sought to determine if this glutamatergic receptor is also involved in relapse to drug-seeking behavior. These investigators employed a preclinical reinstatement paradigm that mimics the ability of drug-associated environmental cues that can trigger relapse in humans. Rats were taught to self-administer cocaine, and drug delivery was paired with a discrete stimulus cue. Other animals were taught to make a response for a non-drug reward — sweetened condensed milk. Milk delivery was also paired with a discrete cue. After animals were trained to respond to receive milk or self-administer cocaine, they underwent extinction procedures during which responses no longer had consequences (i.e., no

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drug and no milk delivery, and no cue presentation). After animals extinguished responding, reward-paired cues were reintroduced and the reinstatement of responding for milk or cocaine was measured. Results show that cocaine-paired cues prompted a return of drug-seeking behavior and that LY dose-dependently (0.0, 0.3, 1.0, 3.0 mg/kg) decreased reinstatement. Exposure to the milk-paired cue also triggered reinstatement, and LY also attenuated the relapse to operant responding for this non-drug reward, but only at the highest dose tested. When the investigators examined LY effects on primary reinforcement, they found the LY compound decreased the number of cocaine-reinforced responses, but only with the highest dose of this mGlu agonist, whereas responding for milk was not altered at any dose of LY. These findings show that a mGlu 2/3 agonist is more potent in reversing reinstatement induced by environmental stimuli paired with cocaine than in blocking cue-induced behavior *per se*. These data further suggest that group II metabotropic glutamate receptors may be a target for pharmacotherapeutic interventions in relapse prevention. Baptista, M.A.S., Martin-Fardon, R. and Weiss, F. Preferential Effects of the Metabotropic Glutamate 2/3 Receptor Agonist LY379268 on Conditioned Reinstatement Versus Primary Reinforcement: Comparison Between Cocaine and a Potent Conventional Reinforcer. Journal of Neuroscience, 24, pp. 4723-4727, 2004.

Relapse to Cocaine-seeking Behavior for Up To One Year After a Single Drug Exposure

Environmental stimuli associated with the reinforcing properties of drugs of abuse are able to trigger relapse during abstinence. However, it is not known whether these learned associations between the environment and early drug experiences contribute to the development of compulsive drug taking and addiction. Dr. Friedbert Weiss and colleagues trained rats to lever respond for food and then replaced food with cocaine for one training session. These drug deliveries were paired with a discrete cue. This cocaine self-administration session was followed by another conditioning session, where responding on a different lever produced saline infusions and a new cue. After this session, animals experienced daily extinction sessions wherein responses were without consequence (no i.v. infusions and no cue presentation), until animals reached a low level of responding during the session. Then animals were returned to their home cages and removed at three-month intervals to test for cue-induced relapse. In this model of relapse, animals were placed back in the test chamber where cues previously paired with drug or saline delivery were reintroduced. When the cues previously paired with a single cocaine self-administration were presented 3, 6 and 9 months later the cues induced drug seeking behavior, but not when the cues were introduced 12 months later. Presentation of the cue previously paired with saline did not reinstate responding. For comparison, a separate group of rats underwent a similar sequence of training and test procedures, but with a non-drug reward — sweetened condensed milk. While these animals did respond to receive milk, reinstatement was not seen following extinction when a milk-paired cue was reintroduced; nor was reinstatement seen 3 months later. The present findings indicate that environmental cues paired with a drug of abuse exert a potent and persistent effect on drug-motivated behavior. Environmental cues paired with a non-drug reward such as milk, do not exert as powerful a response. Moreover, these drug-paired cues can exert a long-lasting effect on behavior after only a single drug self-administration session, which suggest environmental cues may contribute to the transition from initial drug use to addiction. Ciccocioppo, R., Martin-Fardon, R. and Weiss, F. Stimuli Associated with a Single Cocaine Experience Elicit Long-lasting Cocaine-seeking. Nature Neuroscience, 7, pp. 495-496, 2004.

Chronic Cocaine Exposure Produces Learning Deficits on a Cognitive Task that Involves the Orbitofrontal Cortex

Studies in both humans and animals have shown that addictive drugs cause long-lasting neural changes in prefrontal cortex. The orbital frontal prefrontal cortex (OFC) is of particular interest because it appears to be involved in the integration of motivational information with environmental cues that signal reward, and in guiding goal-directed behavior. To test the hypothesis that OFC-mediated behaviors are altered by drug exposure, Dr. Geoffrey Schoenbaum and his colleagues examined the effects of cocaine exposure on performance in an odor discrimination task that involves the OFC. In this task, rats are trained to respond to odor cues to obtain reward and avoid punishment, and to modify these responses when the rules (i.e., cue-outcome associations) are reversed. Rats given injections of cocaine (30 mg/kg/d, i.p.) or for 14 days and then trained on this discrimination after a 2-week withdrawal from cocaine, failed to show normal changes in response latency during discrimination learning, and they were slower than control animals that did not receive cocaine to learn the reversal rules. These behavioral impairments seen in

cocaine-exposed rats were identical to the effects seen in rats with OFC lesions. These data indicate that cocaine exposure can cause long-lasting effects on OFC-dependent functions. The experimenters also tested the rats for the development of behavioral sensitization to the locomotor activating effects of cocaine. They found no correlation between the degree of locomotor sensitization and the magnitude of the learning deficits, suggesting that the brain changes underlying the behavioral effects needed for the discrimination task are different from those mediating psychomotor sensitization. The results of this study, together with other studies of OFC function, indicate that cocaine exposure produces an impaired ability to use motivational value for guiding responding, which may help explain why addicts continue to take drugs, or to relapse, despite the adverse outcomes of drug taking. Dr. Schoenbaum is testing this idea in ongoing experiments in which rewards are systematically devalued. Schoenbaum, G., Saddoris, M.P., Ramus, S.J., Shaham, Y. and Setlow, B. Cocaine-experienced Rats Exhibit Learning Deficits in a Task Sensitive to Orbitofrontal Cortex Lesions. European Journal of Neuroscience, 19, pp. 1997-2002, 2004.

Role of Dose and Delay in Drug Choice

Drug abuse is often considered a problem related to impulse-control disorders, but little is known about the factors that determine the choice to self-administer a drug in a self-control/impulsivity paradigm. Animal models provide excellent procedures for studying choice behavior and its control. The present study was designed to evaluate choice between a low dose of cocaine administered after a relatively short delay (impulsive option) and a high dose of cocaine following a relatively longer delay (self-control option). Rhesus monkeys self-administered intravenous cocaine in a discrete trials choice procedure. First, choice was between different 3:1 doses (0.3/0.1 and 0.1/0.03 mg/kg per injection) following equal 30-s delays to infusion. Second, choice was between equal doses (0.1 mg/kg per injection) following 3:1 delays (30 s/10 s, 90 s/30 s, 270 s/90 s, 810 s/270 s). Third, choice was between 0.1 or 0.03 mg/kg per injection after the same 3:1 delays with the larger dose following the longer delay and the smaller dose following the shorter delay. Fourth, the same 3:1 delays were used to study choice between 0.3 and 0.1 mg/kg per injection. The results showed that with equal delays, the larger dose of cocaine was chosen almost exclusively, and with equal doses, the shorter delay was chosen almost exclusively. When both dose and delay were manipulated, mean large-dose (0.1 mg/kg per injection) choices for three of four subjects was 98% when the delays were the shortest (30 s/10 s), but this preference reversed as the delays increased, so that 74% of choices were for the smaller dose (0.03 mg/kg per injection) at the longest delays (810 s/270 s). This systematic decrease in large-dose choices as the absolute, but not relative, values of the delays were increased, was also observed with the higher dose combination. Delay discounting was supported by the present findings in that the value of a large reinforcer (higher cocaine dose) was decreased as its delay to presentation was increased. The importance of not only relative, but also absolute, values of delays to drug reinforcement in determining drug choice was also demonstrated. Thus, a self-control/impulsivity paradigm can be extended to conditions with non-human subjects and drug reinforcers. Anderson, K.G. and Woolverton, W.L. Effects of Dose and Infusion Delay on Cocaine Self-administration Choice in Rhesus Monkeys. Psychopharmacology, 167(4), pp. 424-430, 2003.

Nicotine Sensitizes Responding For Conditioned Reinforcers

It has been known for many years that stimuli associated with an addictive drug can acquire conditioned reinforcing properties. That is, environmental stimuli present at the time of drug use can themselves reinforce responding (e.g., drug seeking and drug taking). Moreover, clinical observations indicate that smoking depends strongly upon conditioned reinforcement (i.e., cues support smoking behavior), but little is known about the effects of repeated nicotine exposure on these processes. The purpose of this study was to investigate the consequences of prior repeated nicotine exposure on responding with conditioned reinforcement and on the potentiation of conditioned reinforcement by intra-nucleus accumbens (NAc) amphetamine infusion. Rats received repeated saline or nicotine injections (0.35 mg/kg; 15 days) and were, following 3 days of withdrawal, trained to associate a tone + light stimulus with water reinforcement for 10 days. Animals were subsequently tested on acquisition of a new instrumental response with conditioned reinforcement (i.e., 14 days after the final nicotine injection). In additional experiments, animals received an infusion of amphetamine (20 microg in NAc) prior to the conditioned reinforcement test. The results indicated that prior repeated nicotine exposure produced a behaviorally specific enhancement of responding with conditioned reinforcement. Furthermore, repeated nicotine pretreatment also augmented the potentiation of conditioned reinforcement by intra-NAc amphetamine. These findings demonstrate that prior

repeated nicotine exposure augments the control over behavior by a conditioned reinforcer. Such long-lasting alterations in incentive motivational processes produced by repeated nicotine exposure may depend on drug-induced neuroadaptations in dopamine-regulated signaling within limbic-striatal brain regions that could underlie persistent and compulsive aspects of addiction. Olausson, P., Jentsch, J.D. and Taylor, J.R. Repeated Nicotine Exposure Enhances Responding with Conditioned Reinforcement. Psychopharmacology, 173, pp. 98-104, 2004.

Morphine-elicited Morphine Withdrawal

Recent evidence indicates that associative learning processes are important for regulating basic aspects of drug addiction. In particular, Pavlovian conditioning mechanisms have been hypothesized by NIDA grantee Shepard Siegel to mediate drug tolerance and withdrawal. According to this analysis, cues present at the time of drug administration function as conditioned stimuli (CSs). The direct effect of the drug constitutes the unconditioned stimulus (UCS), which prior to any learning elicits unconditioned responses (UCRs) that compensate for drug-induced disturbances. After paired presentations of the CS and UCS, drug compensatory responses are elicited by predrug cues (i.e., CSs). These conditioned compensatory responses (CCRs) are hypothesized to mediate the development of tolerance and the elicitation of withdrawal in drug-associated contexts. Although many drug associated CSs are exteroceptive (i.e., in the environment) , another source of drug associated CSs can be found in the early, drug-onset cues (DOCs) or sensations that precede and signal the later, larger drug effect. The present experiment evaluated the contribution of DOCs to morphine withdrawal in rats. It was hypothesized that DOCs would elicit CCRs in the form of hypoalgesia and other withdrawal signs. In these experiments, rats were given a 50mg/kg injection of morphine on 10 consecutive days and tested on a separate day with a 5mg/kg dose. The rationale was that the small test dose would simulate the DOCs associated with the 50mg/kg dose. The results indicated that the 5mg/kg dose elicited behavioral and thermic withdrawal symptoms and that these symptoms were not a sensitized response to the opiate. That is, a small dose of a drug can serve as a cue for a larger dose of that drug and can function as a CS to elicit withdrawal CCRs in the absence of the high dose. What makes this report especially intriguing is that Siegel supports the associative hypothesis by demonstrating that morphine withdrawal can be elicited by *morphine* itself. Previously, it was believed that withdrawal symptoms are uniquely associated with drug absence. The inclusion of such DOCSs during extinction- based treatment might better reproduce the CSs responsible for craving and relapse. McDonald, R.V. and Siegel, S. Intra-Administration Associations and Withdrawal Symptoms: Morphine-Elicited Morphine Withdrawal. Experimental and Clinical Psychopharmacology, 12(1), pp. 3-11, 2004.

The Ventral Pallidum Dynamically Encodes Information About Reward and Reward-Related Cues During Learning

The ventral pallidum (VP) is a critical integration, output and feedback pathway of the mesocorticolimbic reward circuit in the brain. Behavioral studies have shown that VP mediates both the hedonic value of, and an animal's response to, drug and natural rewards, and electrical or pharmacological stimulation of this nucleus elicits appetitive and reward-related behaviors. However, little is known about how information is processed in VP. Dr. Wayne Aldridge and his colleagues have now recorded the activity of individual VP neurons while rats learned a Pavlovian reward association. Rats learned to distinguish a tone that predicted sucrose pellets (CS+) from a different tone with no predictive value (CS-). As training proceeded, many VP neurons became responsive to CS+, but few of them responded to CS-. Neurons also responded to a second CS+ (the click of the feeder), but after extensive training, responses to the tone were much more prevalent than to the second predictor. Many VP units were also activated when the sucrose reward was received, and unlike neurons in other parts of the reward system, they did not stop responding to reward as they became responsive to the CS+. Thus, after training, cells that responded to both CS+ and sucrose reward were common. The authors characterized the neural representation of information about reward and reward learning as a population code. That is, the population of neurons that responded to CS+ increased with learning, whereas the population that responded to the primary reward did not change. Neurons also encoded information in their relative firing rates, in that neurons that responded to multiple stimuli did so with different levels of firing. These differences in firing rate to the various stimuli were acquired early in training and remained stable as training went on, whereas population codes and behavioral conditioned responses continued to develop during subsequent training. Thus, the VP makes use of dynamic population and rate codes to conditioned stimuli to encode Pavlovian reward cues in

reward learning and uses stable population and firing codes to encode sucrose reward itself. Dr. Aldridge is currently carrying out experiments to determine how motivational information (reward value) is encoded in VP. These studies will help us understand how compulsive drug seeking arises in the brain. Tindell, A.J., Berridge, K.C. and Aldridge J.W. Ventral Pallidal Representation of Pavlovian Cues and Reward: Population and Rate Codes. Journal of Neuroscience, 24, pp. 1058-1069, 2004.

Amphetamine Self-administration Produces Specific Effects on Dendritic Morphology in Medial and Orbital Prefrontal Cortex that May Underlie Long-lasting Behavioral Consequences of Drug Exposure

Changes in dendritic branching and spine density of neurons are thought to reflect changes in the synaptic connectivity and operation of a brain area, and consequently its role in behavior. The laboratories of Dr. Terry Robinson and Dr. Brian Kolb are investigating long-term changes in the anatomical structure of neurons produced by drugs of abuse. In many of their previous studies, drugs were administered by the experimenters. In the current study, headed by Dr. Hans Crombag, they have used a drug self-administration paradigm and focused on additional brain areas involved in learning. Specifically, they measured the effects of amphetamine self-administration on dendritic spine density in nucleus accumbens (NAc), medial (MPC) and orbital prefrontal cortex (OFC), and the hippocampus (areas CA1 and the dentate gyrus). In a separate group of animals, they examined these same brain regions after training animals to respond for a sucrose reward. By comparing sucrose reward training versus drug self-administration, they were able to determine whether changes were produced by drug exposure, operant learning, or both. Rats were trained under a continuous schedule of reinforcement to nose-poke for infusions of amphetamine (0.125 mg/kg/inf) or to receive sucrose pellets during 2 h daily test sessions for 14-20 days. One month after the last training session, the brains were collected and processed for Golgi-Cox staining, which reveals the fine details of neuronal anatomy. Amphetamine self-administration experience selectively increased spine density on medium spiny neurons in the NAc and pyramidal neurons in the MPC, whereas sucrose reward training had no effect in these areas. In contrast, in OFC, spine density was decreased by amphetamine self-administration, but *increased* by sucrose-reward training. Both amphetamine self-administration and sucrose reward experience increased the number of spines in hippocampal CA1, and produced no effect in the dentate gyrus. These results demonstrate that amphetamine self-administration experience produces long-lasting and regionally-selective morphological alterations in the rat forebrain. To the extent that the current study is comparable to previous ones from this group, both self-administered and experimenter administered amphetamine produce similar effects in the NAc and MPC, which may underlie long lasting increases in sensitivity to the motor effects of psychostimulants and to drug-associated stimuli after chronic drug exposure. The increase in spine density in NAc and MPC, and the decrease in OFC, were specific for the animals' experience with amphetamine, as these effects were different from those observed after training for sucrose reward. This observation contrasts with morphological changes typically observed for the hippocampus, where learning about drug and natural rewards *both* increase spine density in CA1. Moreover, these specific results for the OFC are consistent with findings of OFC abnormalities and cognitive deficits in human stimulant users. Both human and animal studies suggest that the OFC is part of a circuit for attaching motivational information with cues that signal rewards. Overall, the alterations in NAc, MPC, and OFC may underlie some of the persistent psychomotor, cognitive and motivational consequences of chronic drug exposure. Crombag, H.S., Gorny, G., Li, Y., Kolb, B. and Robinson, T.E. Opposite Effects of Amphetamine Self-administration Experience on Dendritic Spines in the Medial and Orbital Prefrontal Cortex. Cerebral Cortex Advance Access, DOI:10.1093/cercor/bhh136, published July 21, 2004.

The Effects of Prenatal Cocaine Exposure on Reversal Learning Using a Simple Visual Discrimination Task in Rhesus Monkeys

Dr. John Chelonis and colleagues at the University of Arkansas and the National Center for Toxicological Research report behavioral effects of prenatal exposure to cocaine in adult rhesus monkeys. At ages 1.5 and 3.0 the monkeys had undergone extensive behavioral testing involving a large battery of tasks that correlate with IQ in humans and had failed to exhibit any behavioral deficits. When tested as adults, however, data suggest possible deficits in behavioral adaptation to changing contingencies. At age 7, after the monkeys had been performing an operant conditional discrimination task based on color and response position for six years, the discrimination rules for reinforcement were reversed. This reversal in the reinforcement rules led to impairment in performance compared to monkeys that had

not been prenatally exposed to cocaine. In some cases, the impairment was still evident two and a half years after the reversal when the observations were terminated, thus suggesting that the deficit may be permanent. When these animals learned the initial discrimination six years prior, they did not exhibit any impairment in acquiring the discrimination. The reversal task, of course, is more demanding because it involves extinction of the old behavior and acquisition of new behavior incompatible with the old. This work could have implications for research on prenatal cocaine exposure in humans. Based on the authors prior age-related work with these same monkeys showing that adults are 10-30 times more sensitive to dopaminergic challenges than are young monkeys, the authors suggest that some effects of prenatal cocaine may not be manifest until certain neurotransmitter systems are fully functional. Alternatively, the authors raise the possibility that had the reversal procedure been implemented at an earlier age, the same deficit may have occurred. Chelonis, J.J., Gillam, M.P. and Paule, M.G. The Effects of Prenatal Cocaine Exposure on Reversal Learning Using a Simple Visual Discrimination Task in Rhesus Monkeys. Neurotoxicology and Teratology, 25, pp. 437-447, 2003.

Alcohol Outcome Expectancies, Risk For Alcohol Use Problems, and Menstrual Cycle Effects in Women with and Without a Family History of Alcoholism

Drs. Allison Dorlen and Suzette Evans at the New York State Psychiatric Institute studied the role of alcohol outcome expectancies in the risk for alcoholism in women with either a family-history-positive (FHP) or family-history-negative (FHN) background for alcoholism. They prospectively tracked 85 women, ranging in age from 18-35, with regard to mood, alcohol use, and daily positive and negative consequences of alcohol used across one menstrual cycle. Results indicate that (a) at screening, expectancy scores on the Alcohol Expectancy Questionnaire (AEQ) were significantly higher in FHP than FHN women, regardless of drinking level, on four of the six AEQ subscales and on the composite score, (b) AEQ scores correlated with drinking behavior among FHN women, but among FHP women, AEQ scores were elevated independently of their level of drinking, (c) following prospective tracking of their drinking behavior and its consequences, AEQ scores decreased among FHP, but not FHN, women, and (d) independently of family history status, in moderate drinkers alcohol use was significantly greater during menses than during the follicular and luteal phases of the menstrual cycle, but this increased use during menses was not associated with significant increases in negative mood or physical discomfort. These data suggest that alcohol expectancies prospectively predict drinking behavior and may be associated with further risk for the development of alcohol use problems among high-risk women. Pastor, A.D. and Evans, S.M. Alcohol Outcome Expectancies and Risk for Alcohol Use Problems in Women With and Without a Family History of Alcoholism. Drug and Alcohol Dependence, 70, pp. 201-214, 2003.

Pharmacogenetic Analysis of Sex Differences in Opioid Antinociception in Rats

Animal research has shown that males are, in general, more sensitive to painkillers than females. This sex difference in the antinociceptive properties of opiates has been described in mice, rats and monkeys. There are some inconsistencies, however, in the outcomes of these experiments, inconsistencies that Dr. Jolan Terner from University of North Carolina at Chapel Hill hypothesized may be due in part to different genetic backgrounds of experimental animals and to the relative efficacy of the tested opioids. To assess this hypothesis, Dr. Terner and her colleagues used 12 rat strains and a warm-water tail-withdrawal procedure to test the antinociceptive properties of four different opioids (butorphanol, nalbuphine, morphine and buprenorphine). Males were more sensitive to the opiates than females in all 12 strains and for all four opiates. Among the opiates, the largest sex differences in the potency of the opioids were found with the low-efficacy opioids, butorphanol and nalbuphine, which were on average 14 times more potent in males than females, while the smallest differences were found with the high efficacy opiates, morphine and buprenorphine, which were on average 2.4 times more potent in males than females. Among the 12 strains, the largest sex differences were found in the F344 and F344-Sasco strains and the smallest differences were found in the Long Evans - Blue Spruce, Long Evans, Brown Norway, and Holtzman strains. This work suggests that studying strain variation response to low-efficacy opioids might be useful for understanding the mechanisms underlying sex differences in opioid antinociception. Terner, J.M., Lomas, L.M., Smith, E.S., Barrett, A.C., and Picker, M.J. Pharmacogenetic Analysis of Sex Differences in Opioid Antinociception in Rats. Pain, 106, pp. 381-391, 2003.

Sex Differences in the Conditioned Rewarding Effects of Cocaine

Studies have shown the importance of the hypothalamic-pituitary-adrenal axis in the

acquisition of cocaine self-administration in rats. When corticosterone levels, for example, are decreased by either surgical or pharmacological adrenalectomy, cocaine self-administration is abolished. In the present study, Drs. Scott Russo and Vanya Quinones-Jenab and colleagues at Hunter College investigated the effects of surgical adrenalectomy on conditioned place preference (CPP) induced by cocaine in male and female rats. In the CPP design, rats receive cocaine or saline in separate, distinctive experimental chambers for 4 or 8 days followed by a test day in which preference for the cocaine-paired chamber is assessed. In the present experiment, intact female rats developed CPP for cocaine at lower doses and with fewer trials than intact males. Adrenal-ectomy, however, did not affect the acquisition of cocaine CPP in either males or females. The authors interpret these results as indicating that females are more sensitive to the rewarding effects of cocaine and that this higher sensitivity is not dependent on the HPA axis. Russo, S.J., Jenab, S., Fabian, S.J., Festa, E.D., Kemen, L.M. and Quinones-Jenab, V. Sex Differences in the Conditioned Rewarding Effects of Cocaine. Brain Research, 970, pp. 214-220, 2003.

Sex and Estrogen Influence Drug Abuse

In this review article, Dr. Marilyn Carroll and colleagues from the University of Minnesota describe animal and clinical research showing sex differences in all the phases of drug abuse: acquisition, maintenance, escalation, dependence, withdrawal, relapse and treatment. Animal models, for example, have shown that females are more sensitive than males to the rewarding effects of a variety of drugs, they often acquire self-administration faster and at lower doses than males, and they self-administer more drugs than males during the maintenance and escalation phases. Similar to the results obtained with animals, clinical studies, for example, show that women progress from drug use to abuse/dependence faster than men. Some of these sex differences are related to estrogen levels and to the role estrogen plays in reward. The research findings reviewed in this article serve to highlight the importance of sex and sex hormones in both animal models of drug abuse and in clinical research on drug abuse. Carroll, M.E., Lynch, W.J., Roth, M.E., Morgan, A.D. and Cosgrove, K.P. Sex and Estrogen Influence Drug Abuse. Trends in Pharmacological Sciences, 25, pp. 273-279, 2004.

Sex Differences in the Behavioral Effects of 24-h/day Access to Cocaine under a Discrete Trial Procedure

Clinical studies have shown a variety of sex differences in drug abuse. Women, for example, have an accelerated transition from casual use of cocaine to compulsive use when compared to men. Women also report higher levels of cocaine cravings than men suggesting greater motivation to use cocaine. These differences, which could be due to either sociocultural factors and/or to biological factors, were recently examined by Dr. Wendy Lynch and colleagues at Yale University using animal models of cocaine self-administration that permit study of the transition from use/abuse to addiction and that permit assessment of motivation for cocaine following that transition. The transition from use/abuse to addiction was studied by providing rats with a high-access to a cocaine regimen in which they could self-administer during four 10-min trials per hour, 24-hr per day, for seven days. This procedure has previously been shown to result in an escalation of cocaine self-administration and a binge-abstinence pattern of intake. Dr. Lynch and her colleagues found that under this procedure, compared to males, females self-administered more cocaine, self-administered for longer periods of time, showed greater disruption in the diurnal control over cocaine intake, and exhibited more cocaine toxicity as evidenced by rapid weight loss and death. In order to study the effect of the 7-day binge period on subsequent motivation to use cocaine, following a 10-day forced abstinence period, rats responded for cocaine under a progressive ratio (PR) schedule in which the number of responses required to receive a cocaine infusion was increased over successive infusions. Females exhibited an increase in PR responding compared to their own baseline of PR responding prior to the binge period. Males, however, did not exhibit an increase in PR responding following the binge period. The authors interpret their data as an indication that females have greater biological vulnerability to cocaine addiction than males and that following addiction females have greater motivation or compulsion for cocaine than males. Lynch, W.J. and Taylor, J.R. Sex Differences in the Behavioral Effects of 24-h/day Access to Cocaine Under a Discrete Trial Procedure. Neuropsychopharmacology, 29, pp. 943-951, 2004.

Sex Differences in the Acquisition of IV Methamphetamine Self-administration and Subsequent Maintenance under a Progressive Ratio Schedule in Rats

Studies have shown that female rats are more vulnerable than male rats to the

acquisition of i.v. cocaine self-administration as evidenced by a faster rate of acquisition and by a greater percentage of females than males meeting the acquisition criterion. Additionally, female rats exhibit greater motivation for cocaine as evidenced by performance on a progressive ratio schedule wherein the number of responses required to obtain a cocaine infusion increases over successive infusion deliveries. Responding for cocaine under this schedule is greater by females than males. The present study by Drs. Megan Roth, Marilyn Carroll, and colleagues at the University of Minnesota extends those findings to another psychostimulant drug, methamphetamine (METH). In order to meet criterion for METH acquisition, rats had to self-administer a mean total of 500 infusions over a 5-day period. This criterion was met by over 50% (five out of nine) of the females, but only by 11 % of the males (one out of nine). Not only did more females than males meet the acquisition criterion, they did so faster. The female rats met criterion in an average of 9.4 days, whereas the single male that met criterion did so in 20 days. Sex differences were also observed during the maintenance phase of study in which under a progressive ratio schedule, females self-administered significantly more METH than males at each of four doses of cocaine (0.01, 0.02, 0.04 and 0.08 mg/kg) tested. The authors conclude that these data suggest that female rats are more vulnerable than males to the acquisition of METH self-administration and that they exhibit more motivation for METH. Roth, M.E. and Carroll, M.E. Sex Differences in the Acquisition of IV Methamphetamine Self-administration and Subsequent Maintenance Under a Progressive Ratio Schedule in Rats. Psychopharmacology, 172, pp. 443-449, 2004.

Emotion Regulation and Behavior During a Separation Procedure in 18-month-old cocaine-and-other-drug-exposed Children

Dr. Linda Mayes and colleagues at Yale University report that among toddlers prenatally exposed to cocaine, both maternal and child impairment was observed during a maternal-child separation procedure. The researchers observed 78 18-month old toddlers and their mothers before, during and after a play period during which a stranger entered the playroom and subsequently the mother left for approximately 3-minutes. Three groups of mother-child dyads from an ongoing longitudinal study were studied: those prenatally exposed to cocaine and other drugs (n= 26), those exposed to other drugs including alcohol, tobacco, and/or marijuana but not cocaine (n= 26), and those not exposed to any drugs prenatally (n= 26). All three groups are a very high-risk sample characterized by extreme poverty, adversity, and environmental instability. Upon separation from the mothers, the toddlers from the cocaine group did not show heightened reactivity, but rather showed the least level of reactivity. This effect was unrelated to various measures of maternal psychological functioning, other drug use, or by demographic or perinatal differences. During the mother-child reunion following the separation, the mothers in the cocaine group exhibited significantly less emotional engagement than the non-drug using mothers, an effect related to alcohol use among mothers in the cocaine group. The cocaine-exposed toddlers upon reunion exhibited less positive emotional engagement with their mothers compared to toddlers from the non-drug-using group. This effect was mediated by the mother's low level of emotional engagement and by a lower birth weight status in the cocaine group. Molitor, A., Mayes, L.C. and Ward, A. Emotion Regulation and Behavior During a Separation Procedure in 18-month-old cocaine-and-other-drug-exposed Children. Development and Psychopathology, 15, pp. 39-54, 2003.

Developmental Trajectories of Cocaine-and-other-drug Exposed and Non-cocaine-exposed Children

Dr. Linda Mayes and colleagues at Yale University report data on the effects of prenatal cocaine exposure on the developmental trajectory of mental and motor performance, as measured by the Bayley Scales of Infant Development-II, in children assessed bi-yearly from age 3 months to age 36 months. Three groups of children in an ongoing longitudinal study were studied: those prenatally exposed to cocaine and other drugs (n= 265), those exposed to other drugs including alcohol, tobacco, and/or marijuana but not cocaine (n= 66), and those not exposed to any drugs prenatally (n= 129). All three groups are a very high-risk sample characterized by extreme poverty, adversity, and environmental instability. Dr. Mayes and her colleagues found that the Bayley motor index indicated a decline in motor performance across time in all three groups. The decline was greater in the cocaine-exposed group, though not statistically significant. The Bayley mental index also indicated a decline across age, but only to 24 months. Although the rate of mental performance decline, i.e., the trajectory, did not differ among the groups, the cocaine-exposed children had lower mental performance scores than those in the other two groups at each age level. These data indicate that impoverished cocaine- and non-cocaine-exposed children develop along the same trajectories in the mental

and motor domains, but that cocaine-exposed children exhibit delays in mental development relative to the non-cocaine-exposed children. Mayes, L.C., Cicchetti, D., Acharyya, S. and Zhang, H. Developmental Trajectories of Cocaine-and-other-drug exposed and Non-cocaine-exposed Children. Journal of Developmental and Behavioral Pediatrics, 24, pp. 1-13, 2003.

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

Research Findings - Human Development and Clinical Neuroscience Research

Impact of Cannabis Use on Brain Function in Adolescents

Dr. Leslie Jacobsen and colleagues reported on a pilot study to determine the potential effect of cannabis exposure in adolescents. Seven adolescent marijuana users that also used tobacco, seven tobacco users with a minimal history of cannabis use, and seven non-smokers with no history of cannabis use were compared. Participants were tested on a number of assessments of attention and working memory while fMRI was used to assess hippocampal activation patterns, since both preclinical and clinical evidence suggests that cannabis modulates hippocampal function. Cannabis users were found to have significantly more errors on a continuous performance task, which tests sustained attention, than participants that did not use tobacco and had not used cannabis. Cannabis users also had more errors than tobacco users, although the difference did not reach statistical significance. The performance of cannabis users on the most difficult working memory task used (the 2-back task) was found to differ significantly from both the tobacco-using group and those individuals that used neither tobacco nor cannabis. Analysis across all tasks showed that, overall, cannabis users performed worse than the individuals in the other two groups and also differed in their hippocampal activation pattern from non-using adolescents. Although a pilot study with relatively few participants, the data from this investigation do suggest that adolescent use of cannabis may affect memory and attention and that these effects are reflected in neurobiological alterations. Jacobsen, L.K., Mencl, E.W., Westerveld, M. and Pugh, K.R., Annals of the New York Academy of Sciences. 1021, pp. 384-390, 2004.

Mapping Changes in the Human Cortex Throughout the Span of Life

Dr. Elizabeth Sowell and her colleagues recently published an article in which they described their findings on changes in the morphology of the human cerebral cortex as a function of age, using sophisticated, quantitative analyses of MRI images, and compared them with data from previous imaging and postmortem studies. Dr. Sowell's research group has developed a method of anatomical analysis that incorporates pattern matching, which provides an advance over other currently used morphometric techniques in that it can more reliably take into account individual differences in cortical anatomy. Their findings using these techniques demonstrate quantitatively the variation in patterns of development, maturation and aging in the many areas that make up the human cerebral cortex. These data can serve as the basis for defining relationships between brain morphology and cognitive changes over the human lifespan. Sowell, E.R., Thompson, P.M., and Toga, A.W., The Neuroscientist.10(4), pp. 372-392, 2004.

Acute No-Effect Dose for in Ova Exposure to C3F7 Tagged 5-Hydroxytryptophan, a Novel Probe for Investigating Neural Development

Many of the neurotransmitters that are known to be affected by exposure to abused drugs are present in the brain in quantities too small to be detected with magnetic resonance imaging methods. In an effort to increase the detectability of these transmitters, Dr. Sherry Dingman and colleagues have developed isomers of 5-hydroxytryptophan (5-HTP) tagged with multiple fluorine atoms that have the potential to be used in studies of the effects of drugs of abuse during development. Previous work by this group has demonstrated that the tagged molecules accumulate in the expected areas of the brain during chick development. In this most recent publication, this research team has demonstrated that the injection of up to 5

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micrograms of the labeled compound, which results in the accumulation of 0.5 to 1.0 micrograms in the developing brain, does not cause any detectable deleterious effects. This lack of neurotoxicity for the modified transmitter precursor provides additional evidence supporting its potential utility in studies of the neurodevelopmental effects of abused drugs. Dingman, S., Hurlburt, R., and Branch, C. Molecular Imaging and Biology 6(1), pp. 12-16, 2004.

Assessing the Sensitivity of fMRI Group Maps

A significant problem in conducting functional magnetic resonance imaging studies is the variability in the strength of activation in any specific brain region among individuals. Typically, when group comparisons are made, the mean activation of one group is compared with that of the other. Dr. McNamee and colleagues have compared a number of statistical analysis methods to determine how much the activation pattern of any individual in a group affects the mean and, therefore, the conclusions from such studies. They have demonstrated that methods used for combining fMRI data for the performance of group comparisons involve compromises between sensitivity to changes in activation and the chance that individual differences in activation pattern will be detected. McNamee, R.L. and Lazar, N.A., NeuroImage. 22, pp. 920-931, 2004.

Relationship of Ethnicity, Gender, and Ambulatory Blood Pressure to Pain Sensitivity: Effects of Individualized Pain Rating Scales

There have been many reports that the sensation of pain is modulated by blood pressure, but no systematic studies had been performed to determine whether this phenomenon is consistent across genders and ethnicities. Dr. Susan Girdler and her colleagues have investigated this issue in a study of 135 African American and white men and women. Their findings confirm the inverse relationship between blood pressure and the perception of pain. They also found that, when using a standardized scale for pain assessment, both African American men and women reported higher levels of pain intensity than white men and women. However, they also found that this difference was not present when using a scale in which each participant ranked the descriptors, rather than using a standardized scale. Beyond confirming previous findings relating blood pressure to the perception of pain, the results of this investigation emphasize that demographic differences may need to be taken into account in clinical pain assessment and management. Campbell, T.S., Hughes, J.W, Girdler S.S., Maixner, W., and Sherwood, A. The Journal of Pain. 5(3), pp. 183-191, 2004.

Prenatal Marijuana Exposure and Academic Achievement at Age 10 Years

University of Pittsburgh researchers have reported their latest findings from a longitudinal cohort study of children exposed to marijuana in utero. In this study, women were interviewed about their substance use at the end of each trimester of pregnancy, and at multiple times during the child's development. The children were assessed on physical, emotional, and cognitive development at 8 and 18 months, and at 3, 6, 10, 14, and 16 years postpartum. This report provides findings on academic achievement at age 10 (606 children were assessed), using the Wide Range Achievement Test-Revised (WRAT-R), the reading comprehension subtext of the Peabody Individual Achievement Test-Revise (PIAT-R), and teacher reports of child performance in school. As a group, the women were of lower socioeconomic status, high-school-educated, light-to-moderate users of marijuana and alcohol, and equally distributed in terms of race/ethnicity (Caucasian and African-American). Exposure to one or more marijuana joints per day during the first trimester predicted deficits in WRAT-R reading and spelling scores, and a lower rating on the teachers' evaluations of the children's performance. These associations existed when home environment, race/ethnicity, socioeconomic status, and other prenatal substance exposure were controlled. However, these associations were mediated by effects of first-trimester marijuana exposure on the children's symptoms of depression and anxiety. Second-trimester marijuana use was associated with reading comprehension and underachievement. Exposure to alcohol during the first and second trimesters predicted poorer teacher ratings of overall school performance, whereas second-trimester binge drinking predicted lower reading scores. There was no interaction between prenatal marijuana and alcohol exposure. Each was an independent predictor of aspects of academic performance. The investigators compared their findings to those of the other cohort study of prenatal marijuana exposure reported in the literature, and they discussed possible reasons for differences in findings on school performance between the two studies. The investigators also discuss the limitations of the analyses and of the generalizability of the findings. Goldschmidt, L., Richardson, G.A., Cornelius, M.D., and Day, N.L. Prenatal Marijuana and Alcohol Exposure and

Academic Achievement at Age 10. Neurotoxicology and Teratology, 26, pp. 521-532, 2004.

Cognitive Outcomes of Preschool Children with Prenatal Cocaine Exposure

Researchers at Case Western Reserve University report that 4-year-old children who were exposed to cocaine in utero scored significantly lower on some specific measures of intelligence than did children who were not exposed to the drug in utero. The two groups did not differ on overall, verbal, and performance IQ scores, although exposed children were less likely to have above-average overall IQ. The study results also suggest that mentally stimulating home environments may positively affect brain development and lessen prenatal effects of cocaine. At 4 years of age, 190 cocaine-exposed and 186 nonexposed children were assessed using the Wechsler Preschool and Primary Scales of Intelligence-Revised. This test revealed that exposed children had lower scores than nonexposed children in the specific areas of information, arithmetic, and object assembly (reflecting visual-spatial skills). In arithmetic skills, cocaine-exposed boys had lower scores than girls and nonexposed boys. The researchers also compared two groups within the cocaine-exposed children, i.e., 148 cocaine-exposed children living with their biological mothers or other relatives, and 42 cocaine-exposed children living in adoptive or foster care. They found that 25 percent of cocaine-exposed children living with their mothers or relatives had overall IQ scores lower than 70, compared with only 10 percent of cocaine-exposed children in adoptive or foster care. The researchers report that caregivers in the adoptive and foster homes were better educated, and had better vocabulary and intelligence test scores than the caregivers who were family members. Additional findings indicated that adoptive or foster care was associated with a lower rate of mental retardation in the cocaine-exposed children, despite the fact that these children had been exposed to twice as much cocaine while in utero, and that the cocaine-exposed children in the more stimulating environments had IQ scores that were similar to those of nonexposed children. The findings of this study are consistent with and expand on other preschool cocaine-exposure studies that show specific (but not global) IQ deficits. The results also emphasize how important it is to examine childrearing environments when assessing developmental progress of drug-exposed children, and they also provide optimism that interventions may be effective for children who are affected by prenatal cocaine exposure. Singer, L.T., Minnes, S., Short, E., et al. Cognitive Outcomes of Preschool Children with Prenatal Cocaine Exposure. JAMA, 291(20), pp. 2248-2456, 2004.

Developmental Outcomes of 2-Year Old Cocaine-Exposed Children Relative to their Childrearing Environments

Researchers conducting a longitudinal study in Atlanta with children exposed to cocaine in utero have reported on analyses that examine the role of caregiving environments for these children. The investigators note that the few previous studies examining whether type of care affects the development of exposed children have been inconsistent in their findings. The current analyses focused on cognitive and social-emotional outcomes of 2-year-old cocaine-exposed toddlers. Forty-nine of 83 cocaine-exposed children were reared in parental care, and 34 were reared in non-parental care (resulting from voluntary and involuntary relinquishment of care. Findings indicated that, in general in this sample, nonparental caregivers had more economic resources, experienced less psychological distress, and provided more stimulating and responsive home environments than did birth parents who continued to care for their cocaine-exposed children. The children in nonparental care performed better in several developmental domains. Also reported was the fact that within the group of nonparental caregivers, nonkin caregiving was different from kin caregiving, and was associated with different child outcomes. The investigators discuss the challenges and methodological limitations of doing these kinds of analyses (e.g., defining who is a primary caregiver in families where children are cared for by numerous adults in the course of a day or week is very difficult). They also point out that findings from these kinds of analyses, which are being reported in the literature with increasing frequency, underscore the importance of considering the specifics of the caregiving context when evaluating the potential developmental impact of prenatal cocaine exposure. Such analyses also should provide guidance for interventions to prevent or ameliorate negative developmental outcomes. Brown, J.V., Bakeman, R., Coles, C.D., Platzman, K.A., and Lynch, M.E. Prenatal Cocaine Exposure: A Comparison of 2-Year-Old Children in Parental and Nonparental Care. Child Development, 75(4), pp. 1282-1295, 2004.

Maternal Substance Use Patterns During Pregnancy and Infant Growth Parameters at Birth

Maternal cocaine use during pregnancy has been associated with decreased growth parameters in multiple previous studies. Women who use cocaine often use other substances as well (e.g., alcohol and tobacco, both of which have been shown to have effects on birth weight). A recent publication from the Maternal Lifestyle Study (MLS) reported on how patterns of cocaine, alcohol, tobacco, and marijuana use during pregnancy were related to infant birth weight, length, and head circumference in a sample of 651 mothers and their infants. Because cocaine use has been associated with preterm delivery, only term pregnancies were evaluated for this report. The MLS is a multisite longitudinal study of in utero drug exposure that is jointly funded by NICHD and NIDA. It is the largest study of its type. Histories of substance use were obtained for the 3-month period before pregnancy and the three trimesters of pregnancy. Patterns of use were categorized for each substance as consistently high, moderate, or low/none, and increasing or decreasing. The effects on growth parameters were analyzed in multivariate linear regression analyses, with adjustment for clinical site, maternal age, prepregnancy weight, multidrug use, and socioeconomic status. Detailed results of use patterns and growth parameters are reported in the publication. Overall, with adjustments made for confounders, including multi-drug use, patterns of tobacco use during pregnancy were associated with deficits in birth weight, length, and head circumference, whereas cocaine use was linked to deficits in birth weight and head size. In addition, birth weight, length, and head circumference were significantly greater among infants born to women who used no drugs compared to women with any cocaine, opiate, alcohol, tobacco, or marijuana use during pregnancy. The investigators emphasize that a clinical implication of the study is the importance of curtailing use during pregnancy of illicit drugs as well as alcohol and tobacco. Shankaran, S., Das, A., Bauer, C.R., et al. Association between Patterns of Maternal Substance Use and Infant Birth Weight, Length, and Head Circumference. Pediatrics, 114(2), pp. e226-e234, 2004.

Immune System Parameters and Clinical Morbidity in Infants Exposed to Drugs and HIV in Utero

Recently published data from the Women and Infants Transmission Study (WITS) reported on associations between maternal drug use during pregnancy and lymphocyte subsets and clinical morbidity in uninfected infants born to HIV-infected mothers. 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. The outcomes of HIV-exposed but uninfected infants is a major focus within WITS. The current report presents findings for infants through 2 years of age. The definition of drug use during pregnancy included use of cocaine, methadone, heroin, and other opiates. History of illness and clinical findings were recorded using standardized collection instruments for medical history and medical chart abstraction. Measurement of immune system parameters (CD4, CD8, CD19, NK cell lymphocyte percentage and absolute numbers) utilized standard laboratory procedures. A total of 401 of the 1436 uninfected infants were born to drug-using mothers. Infants born to drug-using mothers had lower gestational age and birth weight, and lower CD4 lymphocyte percentage over the first 4 months of life after adjusting for covariates and higher natural killer lymphocyte percentage. The clinical significance of the lower CD4 percentage and higher NK cell level remain unclear. The investigators suggest that future studies evaluating immunologic parameters in HIV-exposed but uninfected infants should control for the effect of drug exposure. They also indicate that additional research that includes functional assays of lymphocyte cell populations is needed in order to evaluate effects of drug exposure on immune function in addition to phenotype, whether such effects are transient or persist over time, and whether there is any clinical significance of such findings. Neu, N., Leighty, R., Adeniyi-Jones, S., et al. Immune Parameters and Morbidity in Hard Drug and Human Immunodeficiency Virus-Exposed but Uninfected Infants. Pediatrics, 113(5), pp. 1260-1266, 2004.

Nicotine Effects on Brain Function and Functional Connectivity in Schizophrenia

Dr. Leslie Jacobsen and colleagues at Yale School of Medicine used functional magnetic resonance imaging (fMRI) to determine whether nicotine had a differential effect on cognitive performance and regional brain activation in schizophrenic patients compared to smokers with no mental illness. Since nicotine in tobacco smoke can improve functioning in multiple cognitive domains, high rates of smoking among schizophrenic patients may reflect an effort to remediate cognitive dysfunction. Thirteen smokers with schizophrenia and 13 smokers with no mental illness were withdrawn from tobacco and underwent functional magnetic resonance imaging (fMRI) scanning after placement of a placebo patch and again after placement of a

nicotine patch. During scanning, subjects performed an n-back task with two levels of working memory load and of selective attention load. Nicotine improved performance of schizophrenic subjects and worsened performance of control subjects during the most difficult (dichotic 2-back) task condition. Nicotine also enhanced activation of a network of regions, including anterior cingulate cortex and bilateral thalamus, and modulated thalamocortical, functional connectivity to a greater degree in schizophrenic than in control subjects during dichotic 2-back task performance. This study demonstrates that in tasks that tax working memory and selective attention, nicotine may improve performance in schizophrenia patients by enhancing activation of and functional connectivity between brain regions that mediate task performance. Jacobsen, L.K., D'Souza, D.C., Mencl, W.E., Pugh, K.R., Skudlarski, P. and Krystal, J.H. Biological Psychiatry, 55(8), pp. 850-858, 2004.

Retrospective Study: Influence of Menstrual Cycle on Cue-Induced Cigarette Craving

Dr. Theresa Franklin and colleagues at the University of Pennsylvania investigated whether menstrual cycle phase contributes to some of the sex differences observed in smokers. Since smoking in females is posited to be influenced more by cues whereas male smoking is influenced predominantly by the direct pharmacological actions of nicotine in the brain, this study tested the hypothesis that females may report more intense craving to smoking cue exposure than males and, further, that female craving scores may be influenced by menstrual cycle phase. The study sample consisted of 69 male and 41 female treatment-seeking subjects who smoked more than 15 cigarettes per day for more than 10 years. Self-report measures were collected from subjects prior to and immediately following exposure to visual smoking stimuli. Females were grouped according to cycle phase. Of the female subjects, 17 were classified as follicular phase females (FFemales) and 24 were classified as luteal phase females (LFemales). Contrary to our hypothesis, overall, males and all females did not differ in their level of cue-induced craving. However, when females were separated into groups by cycle phase, FFemales reported significantly less craving than either males or LFemales ($p < .05$). The suppressed craving response in FFemales suggests an influence of cycle phase on cue-induced craving. These results suggest that menstrual cycle phase needs to be incorporated in the development of treatments for nicotine addiction. Franklin, T.R., Napier, K., Ehrman, R., Gariti, P., O'Brien, C.P. and Childress, A.R. Nicotine & Tobacco Research, 6(1), pp. 171-175, 2004.

Cocaine Dependence and D2 Receptor Availability in the Functional Subdivisions of the Striatum: Relationship with Cocaine-Seeking Behavior

Dr. Diana Martinez and colleagues at Columbia University used PET imaging to assess D2 receptor availability with [11C]raclopride in the subdivisions of the striatum in 17 recently detoxified chronic cocaine-dependent (CCD) subjects and 17 matched healthy control (HC) subjects. In addition, the relationship between regional D2 receptor availability and behavioral measures obtained in cocaine self-administration sessions was investigated in CCD subjects. [11C]Raclopride binding potential was significantly reduced equally in the limbic striatum, associative striatum, and sensorimotor striatum in CCD subjects compared to HC subjects. In CCD subjects, no relationship was detected between D2 availability in striatal regions and either the positive effects of smoked cocaine or the choice of cocaine over an alternative reinforcer (money) following a priming dose of cocaine (a laboratory model of relapse). This study confirms previous reports of a modest decrease in D2 receptor availability in CCD subjects, and establishes that this decrease is generalized throughout the striatum. However, this study failed to demonstrate a relationship between D2 receptor availability and cocaine-induced cocaine-seeking behavior. Martinez, M., Broft, A., Foltin, R.W., Slifstein, M., Hwang, D-H., Huang, Y., Perez, A., Frankel, W.G., Cooper, T., Kleber, H.D., Fischman, M.W. and Laruelle, M. Neuropsychopharmacology, 29, pp. 1190-1202, 2004.

The Neural Correlates of Cue-Induced Craving in Cocaine-Dependent Women

Dr. Clinton Kilts and colleagues at Emory University School of Medicine used [O-15]HO positron emission tomography (PET) imaging to determine if there are gender-related differences in the neural correlates of cocaine craving. Changes in regional cerebral blood flow to imagery depicting cocaine use and neutral imagery were examined in 8 cocaine-dependent women and a matched group of eight cocaine-dependent men. Compared with the results in cocaine-dependent men, conditioned cocaine craving in women was associated with less activation of the amygdala, insula, orbitofrontal cortex, and ventral cingulate cortex and greater activation of the central sulcus and widely distributed frontal cortical areas. These findings suggest the presence of sex differences in the functional anatomy of cue-induced cocaine craving

associated with drug dependence and may underlie apparent sex differences in the effects of cocaine abstinence and the expectations of treatment outcome. Some support for the need for sex-specific strategies for treatment of cocaine dependence is also furnished by the findings of this study. Kilts, C.D., Gross R.E., Ely T.D. and Drexler, K.P.G. American Journal of Psychiatry, 161(2), pp. 233-241, 2004.

Human Striatal Responses to Monetary Reward Depend on Saliency

Dr. Gregory Berns and colleagues at Emory University School of Medicine used functional Magnetic Resonance Imaging to determine how monetary rewards are processed in the striatum in normal human subjects. Skin Conductance responses to a monetary reward were maximal when its receipt depended on a correct response (active) and minimal when its receipt was completely independent of the task (passive). Significant caudate and nucleus accumbens activations occurred following the active compared to passive money delivery. Such activations were attributed to saliency (response-contingency) of the monetary reward rather than the motor requirement associated with the active money because striatal activations were not observed when the money was replaced by inconsequential, non-monetary visual stimuli. The present study provides evidence that the striatum's role in reward processing is dependent on the saliency associated with reward, rather than value or hedonic feelings per se. Zink, C.F., Pagnoni, G., Martin-Skurski, M., Chappelow, J.C. and Berns, G.S. Neuron, 42(3), pp. 509-517, 2004.

Functional Subdivisions within Anterior Cingulate Cortex and their Relationship to Autonomic Nervous System Function

Dr. Martin Paulus and colleagues at the University of California, San Diego used functional Magnetic Resonance Imaging to investigate the functions of subdivisions of the anterior cingulate cortex (ACC) in normal healthy subjects. Subjects performed a counting Stroop task with trial every 2.0 s in one run and every 1.5 s in the other. A cluster of activation related to response inhibition was observed in the left dorsal ACC, whereas a cluster of activation was observed in the left ventral ACC related to the interaction of speed with stimulus congruency. The activation in the ventral ACC correlated significantly with an index of parasympathetic modulation of heart rate. This study demonstrates functional subdivisions within the ACC and links the processes of cognitive interference and parasympathetic modulation with activation in specific subregions of the ACC, a structure that has been repeatedly implicated in substance abuse. Matthews, S.C., Paulus, M.P., Simmons, A.N., Nelesen R.A. and Dimsdale, J.E. Neuroimage, 22(3), pp. 1151-1156, 2004.

Effects of Integrated Simon and Spatial Stroop on Attentional Control

Using event-related fMRI, investigators from the University of Colorado examined the neural mechanisms of attentional control involved in the Simon task (interference people experience when there is a stimulus-response conflict) as compared to a spatial Stroop task (interference people experience when two attributes of the same stimulus conflict with each other). These tasks activated the dorsolateral prefrontal cortex and posterior regions that serve as a source of attentional control. There were also specific brain regions activated to a significantly greater degree by one task and/or only by a single task. The brain regions significantly more activated by the Simon task were those sensitive to detection of response conflict, response selection, and planning (Anterior Cingulate cortex, supplementary motor areas and precuneus), and visuospatial-motor association areas. In contrast, the regions significantly more activated by the Stroop task were those involved in biasing the processing toward the task-relevant attribute (inferior parietal cortex). These findings suggest that the interference effects of these two tasks are caused by different types of conflict but both invoke similar sources of top-down modulation. Liu, X., Banich, M.T., Jacobson, B.L. and Tanabe, J.L. Neuroimage, 22(3), pp. 1097-1106, July 2004.

Structural Abnormalities in the Brains of Human Subjects Who Use Methamphetamine

Using high-resolution magnetic resonance imaging (MRI) and new computational brain-mapping techniques, UCLA researchers were able to visualize, for the first time, the profile of structural deficits in the human brain associated with chronic methamphetamine (MA) abuse. ROI's included the cortex, hippocampus, white matter, and ventricles. MA abusers and age-matched controls were evaluated. Cortical maps revealed severe gray-matter deficits in the cingulate, limbic, and paralimbic cortices of MA abusers (averaging 11.3% below control). On average, MA abusers had 7.8% smaller hippocampal volumes than control subjects and significant white matter hypertrophy. Hippocampal deficits were mapped and correlated with

memory performance on a word-recall test. Findings suggested that chronic MA abuse causes a selective pattern of cerebral deterioration that contributes to impaired memory performance. MA may selectively damage the medial temporal lobe and, consistent with metabolic studies, the cingulate-limbic cortex thereby inducing neuroadaptation, neuropil reduction, or cell death. Thompson, P.M., Hayashi, K.M., Simon, S.L., Geaga, J.A., Hong, M.S., Sui, Y., Lee, J.Y., Toga, A.W., Ling, W. and London, E.D. Journal of Neuroscience, 30, pp. 6028-6036, 2004.

Smoking-Induced Ventral Striatum Dopamine Release

To test if dopamine (DA) release in the ventral striatum underlies the reinforcing properties of nicotine, UCLA researchers used [(11)C]raclopride bolus-plus-continuous-infusion positron emission tomography (PET) to determine smoking-induced ventral striatum DA release in humans. Dependent smokers underwent PET scan with bolus plus continuous infusions. During the session, subjects had a 10-minute break outside the PET apparatus during which half (n=10) smoked a cigarette and the other half did not. The group that smoked had greater reductions in [(11)C]raclopride binding potential in ventral striatum ROI than the group that did not smoke, particularly in the left ventral caudate/nucleus accumbens and left ventral putamen. Significant correlations were found between pre-post smoking break in craving ratings and change from pre-post in binding potential for these two regions. Nicotine-dependent subjects who smoked during a break in PET scanning had greater reductions in [(11)C]raclopride binding potential (an indirect measure of dopamine release) than nicotine-dependent subjects who did not smoke. The magnitude of binding potential changes was comparable to that found in studies that used similar methods to examine the effects of other addictive drugs. Brody, A.L., Olmstead, R.E., London, E.D., Farahi, J., Meyer, J.H., Grossman, P., Lee, G.S., Huang, J., Hahn, E.L. and Mandelkern, MA. American Journal of Psychiatry, 61(7), pp. 1211-1218, 2004.

Effects of Bupropion on Attenuation of Cue-Induced Cigarette Craving and Anterior Cingulate Cortex Activation

In untreated smokers, exposure to cigarette-related cues increases both the intensity of cigarette craving and relative glucose metabolism of the perigenual/ventral anterior cingulate cortex (ACC). Given that treatment with bupropion hydrochloride reduces overall craving in dependent smokers, Drs. Brody, London and colleagues at UCLA conducted a preliminary study to determine if treatment with bupropion hydrochloride attenuated cue-induced cigarette craving and associated brain metabolic activation. Healthy smokers (20 untreated and 17 who had received open-label treatment with bupropion hydrochloride) underwent two PET scanning sessions in randomized order--one when presented with neutral cues and the other when presented with cigarette-related cues. Bupropion-treated smokers had smaller cigarette cue-induced increases in craving scores and less activation of perigenual/ventral ACC metabolism from the neutral to the cigarette cue scan than untreated smokers. Thus, in addition to its known effects on spontaneous cigarette craving and withdrawal symptoms, bupropion hydrochloride diminishes cue-induced cigarette craving and appears to attenuate cigarette cue-induced ACC activation. These results are consistent with the known effects of bupropion hydrochloride, including its enhancement of catecholaminergic neurotransmission. Brody, A.L., Mandelkern, M.A., Lee, G., Smith, E., Sadeghi, M., Saxena, S., Jarvik, M.E. and London, E. Psychiatry Research: Neuroimaging, 130(3), pp. 269-281, 2004.

Partial Recovery of Brain Metabolism in Methamphetamine Abusers after Protracted Abstinence

Researchers at Brookhaven assessed whether brain metabolism recovers with protracted abstinence following methamphetamine (MA) abuse. Brain glucose metabolism was measured in five MA abusers with PET and [18F]fluorodeoxyglucose. They were evaluated after both a short (<6 months) and protracted (12-17 months) abstinence interval. Eight abusers were tested only after protracted abstinence, and their data was compared to 11 subjects who were not drug users. Significantly greater thalamic, but not striatal, metabolism was seen following protracted abstinence relative to metabolism assessed after a short abstinence interval, and this increase was associated with improved performance in motor and verbal memory tests. Relative to the comparison subjects, the MA abusers tested after protracted abstinence had lower metabolism in the striatum (most accentuated in the caudate and nucleus accumbens) but not in the thalamus. The researchers conclude that persistent decreases in striatal metabolism in MA abusers could reflect long-lasting changes in dopamine cell activity, and decreases in the nucleus accumbens could account for the persistence of amotivation and anhedonia in detoxified MA abusers. The recovery of thalamic metabolism could reflect adaptation responses to

compensate for the dopamine deficits, and the associated improvement in neuropsychological performance further indicates its functional significance. These results suggest that while protracted abstinence may reverse some of the drug-induced alterations in brain function, other deficits persist. Wang, G.J., Volkow, N.D., Chang, L., Miller, E., Sedler, M., Hitzemann, R., Zhu, W., Logan, J., Ma, Y. and Fowler, J.S. American Journal of Psychiatry, 161(2), pp. 42-48, 2004.

Antiretroviral Treatment Alters Relationship Between MCP-1 and Neurometabolites in HIV Patients

Prior studies found higher CSF MCP-1 levels in patients with HIV-associated dementia compared to those in neuroasymptomatic patients. Linda Chang and her colleagues hypothesized that CSF MCP-1 levels might correlate inversely to neuronal metabolites. The relationships between neurometabolites and macrophage chemoattractant protein (MCP-1) in serum and cerebrospinal fluid (CSF) were evaluated in HIV patients before and after antiretroviral treatment. Thirty-nine antiretroviral-naive HIV patients were evaluated prospectively with proton magnetic resonance spectroscopy (1H MRS), and serum and CSF MCP-1 measurements prior to highly active antiretroviral therapy (HAART); 31 of these patients completed follow-up studies after 3 months of HAART but only 24 had follow-up CSF studies. After HAART, brain metabolites and clinical signs showed no change despite improvements in systemic and CSF variables. CSF, but not serum, MCP-1 levels correlated inversely with the neuronal component (from PCA) prior to treatment. Conversely, after 3 months of HAART, the glial component (from PCA) correlated positively with CSF MCP-1 levels. These findings suggest that higher CSF MCP-1 levels are associated with neuronal dysfunction in untreated patients. Chang, L., Ernst, T., St. Hillaire, C. and Conant, K. Antiviral Therapy, 9(3), pp. 431-440, 2004.

Exposure to Appetitive Food Stimuli Markedly Activates the Human Brain

The increased incidence of obesity in our society demands more study, in general, and interactions between the environment and metabolism. Researchers at the Brookhaven National Laboratories assessed the response of the human brain to the presentation of appetitive food stimuli during food presentation using PET and FDG. Metabolic changes in response to food presentation were examined in 12 healthy normal body weight subjects who were food deprived before the study. Food presentation significantly increased metabolism in the whole brain, and these changes were largest in superior temporal, anterior insula, and orbitofrontal cortices. The increases in the right orbitofrontal cortex were the ones that correlated significantly with the increases in self-reports of hunger and desire for food. The marked increase in brain metabolism by the presentation of food provides evidence of the high sensitivity of the human brain to food stimuli. This high sensitivity coupled with the ubiquitousness of food stimuli in the environment is likely to contribute to the epidemic of obesity. In particular, the activation of the right orbitofrontal cortex, a brain region involved with drive, may underlie the motivation to procure food, which may be subjectively experienced as "desire for food" and "hunger" when exposed to food stimuli. Wang, G.J., Volkow, N.D., Telang, F., Jayne, M., Ma, J., Rao, M., Zhu, W., Wong, C.T., Pappas, N.R., Geliebter, A. and Fowler, J.S. Neuroimage, 21(4), pp. 790-797, 2004.

Cerebral Reserve Capacity: Implications for Alcohol and Drug Abuse

This review article discusses cerebral reserve capacity (or functional reserve), which refers to the brain's ability to maintain function when confronted by degenerative processes. There is accumulating evidence that the magnitude of reserve capacity is important in determining the onset and progression of the clinical manifestations of neurodegenerative brain diseases. The concept of cerebral functional reserve has important implications for alcohol and drug abuse morbidity. First, given the high genetic contribution to substance abuse, there is an increased likelihood that the parents of substance abusers were substance abusers themselves. Substance abuse during pregnancy can inhibit brain growth, resulting in reduced brain size and reduced reserve capacity (and therefore less ability to compensate for loss of function later in life). Second, substance abuse is often coupled with poverty, and both substance abuse and poverty are associated with some of the same conditions that reduce brain growth. The authors comment on the most important public health implications of the cerebral reserve capacity model for drug and alcohol addiction. Fein, G. and Di Sclafani, V. Alcohol, 32(1), pp. 63-67, 2004.

The Effects of Controlled Deep Breathing on Smoking Withdrawal Symptoms in Dependent Smokers

This study was designed to assess the effect of controlled deep breathing on smoking withdrawal symptoms. In two laboratory sessions, dependent smokers refrained from smoking for 4 h. During a deep breathing session, participants were instructed to take a series of deep breaths every 30 min. During a control session, participants sat quietly. Controlled deep breathing significantly reduced smoking withdrawal symptoms, including craving for cigarettes and negative affect (tense, irritable), while resulting in the maintenance of baseline arousal (wide awake, able to concentrate) levels. Furthermore, a history of heavy smoking was associated with greater increases in arousal during the deep breathing session. The results of this preliminary study suggest that controlled deep breathing may be useful for relieving symptoms of smoking withdrawal. McClernon, F.J., Westman, E.C. and Rose, J.E. Addictive Behaviors, 29(4), pp. 765-772, 2004.

A Mu-Opioid Polymorphism Conferred Substantial Attributable Risk to Heroin Addiction in a Homogeneous Population Sample

Dr. Kreek and associates studied a Swedish sample including a subsample in which participants identified themselves and both parents as Swedish descent and found presence of the G allele in the A118G polymorphism in exon 1 of the OPRM1 gene conferred an odds ration of 2.3 in the total sample and 2.7 in the only-Swedish sample. This was associated with an attributable risk (estimated proportion of cases in the population who are affected due to the given at-risk genotype) of 18.0. Since, this association has not been found previously in Caucasian populations, it is suggested that the reason may be the diversity of the allele frequencies across different samples within the "Caucasian" category. It was shown by this group that encoded receptors in those who have the A118G allele have increased affinity for the endogenous mu-opioid ligand, beta-endorphin, and increased activation of G protein-activated inwardly rectifying potassium channels following binding by beta-endorphin. Bart, G., Heilig, M., LaForge, K.S., Pollak, L., Leal, S.M., Ott, J. and Kreek, M.J., Molecular Psychiatry, advance online publication (23 March 2004); doi:10.1038/sj.mp.4001504.

Prevalence of Drug Use and Duration of Problematic Use is Greater in Men Than Women, but Severity and Age of Onset Seems to be Equal

Among the many analyses conducted by Dr. Iacono and colleagues among families of the Minnesota Twin-Family Study, an assessment of twins' parents revealed that despite the greater prevalence of drug use among men, dependence symptoms and drug-associated difficulties were not different from those of women. Two exceptions were hallucinogens where there was no difference in duration of use but there was an earlier onset in women, and amphetamines where women had more frequent use of them. The latter may be related to eating disorders since more women with amphetamine abuse were anorexic. Also, the differences and similarities observed could not be attributed to age differences in the cohorts, assertive mating (marrying with individuals with like profiles), or ability to report symptoms. These data provide insight into characteristics of drug use between men and women. Holdcraft, L.C. and Iacono, W.G. Drug and Alcohol Dependence, 74, pp. 147-158, 2004.

Suggestive Links on Chromosomes 9 and 11 for Increased Risk for Cigarette Smoking

Dr. Gelernter and colleagues at Yale University performed a genome-wide scan in affected individuals and their families identified through an anxiety clinic and defined on the basis of cigarettes smoked—more than a pack/day for one year or _ pack/day for 10 years. Linkage was observed near markers, D11S4046, D9S283 and D9S1677. The marker on chromosome 11 is in a region where linkage to alcohol dependence and linkage disequilibrium to substance dependence has been reported previously. The chromosome 9 region has been previously linked to panic disorder. There was also support for linkage on chromosomes 14, 16, and X. Confirmation with additional studies of finer mapping need to be done, but it is of interest that the chromosome 11 region contains potential candidate genes including brain-derived neurotrophic factor (BDNF), the DRD4 locus, the TPH locus and the tyrosine hydroxylase locus. Gelernter, J., Liu, X., Hesselbrock, V., Page, G.P., Goddard, A. and Zhang, H. American Journal of Medical Genetics Part B (Neuropsychiatric Genetics), 128B, pp. 94-101, 2004.

Homozygous DRD2-Taq A2/A2 Individuals in Bupropion Therapy Have Reduced Symptoms of Nicotine Withdrawal

Dr. David and colleagues at Brown University randomly assigned 30 smokers to bupropion hydrochloride or placebo. They were assessed before medication and 14 days afterward on a withdrawal scale. It was found that, as a group, those on

bupropion therapy had fewer symptoms of craving, irritability, and anxiety than those on placebo, but subsequent analysis showed that this result was due to those with the homozygous A2A2 allele. This suggests that bupropion attenuates specific symptoms of the nicotine withdrawal syndrome and that this effect may be modified by genotype for the dopamine D2 receptor. David, S.P., Niaura, R., Papandonatos, G.D., Shadel, W.G., Burkholder, G.J., Britt, D.M., Day, A., Stumpff, J., Hutchison, K., Murphy, M., Johnstone, E., Griffiths, D.E. and Walton, R.T. Nicotine and Tobacco Research, 5(6), pp. 935-942, 2003.

Additive Increase in Impulsivity in Bipolar Patients with Substance Abuse

Dr. Moeller and colleagues investigated whether impulsivity was linked to bipolar disorder and substance abuse thereby suggesting a reason for poor outcome in treatment. Trait questionnaire (Barratt Impulsiveness Scale) as well as laboratory performance measures (Immediate/Delayed Memory task) were administered to inpatients with bipolar disorder who were also interviewed for substance abuse. While trait impulsiveness was increased in patients with either substance abuse or bipolar disorder, there was an even greater increase in those with both disorders after correcting for age. Performance impulsivity was increased in those with substance abuse regardless of whether they had bipolar disorder. Among subjects with bipolar disorder, after correction for age, impulsivity scores were increased in those with substance abuse. Performance impulsivity was increased in bipolar patients without substance abuse during a manic episode or it was increased in bipolar patients with substance abuse between episodes. These results suggest that bipolar patients with a history of substance abuse may be more refractory to treatment because of a complicating underlying (additional) pathology. Swann, A.C., Doughtery, D.M., Pazzaglia, P.J., Pham, M., and Moeller, F.G. Bipolar Disorder, 6, pp. 204-212, 2004.

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

Research Findings - Epidemiology and Etiology Research

Prevalence of Marijuana Use Disorders in the United States: 1991-1992 and 2001-2002

Among illicit substance use disorders, marijuana use disorders are the most prevalent in the population. Yet, information about the prevalence of current DSM-IV marijuana use disorders and how prevalence has changed is lacking. To examine changes in the prevalence of marijuana use, abuse and dependence in the United States between 1991-1992 and 2001-2002, face-to-face interviews were conducted in two large national surveys conducted ten years apart: the 1991-1992 National Longitudinal Alcohol Epidemiologic Survey (NLAES: n=42,862), and the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC: n = 43,093). Among the adult U.S. population, the prevalence of marijuana use remained stable at about 4.0% over the past decade. In contrast, the prevalence of DSM-IV marijuana abuse or dependence significantly ($p < 0.05$) increased between 1991-1992 (1.2%) and 2001-2002 (1.5%), with the greatest increases observed among young Black men and women and young Hispanic men ($p < 0.01$). Further, marijuana use disorders among marijuana users significantly increased ($p < 0.01$) in the absence of increased frequency and quantity of marijuana use, suggesting that the concomitant increase in potency of $_{9}$-THC may have contributed to the rising rates. Despite the stability in the overall prevalence of marijuana use, more adults in the U.S. had a marijuana use disorder in 2001-2002 than in 1991-1992. Increases in the prevalence of marijuana use disorders were most notable among young Black men and women and young Hispanic men. Although rates of marijuana abuse and dependence did not increase among young white men and women, their rates have remained high. The results of this study underscore the need to develop and implement new prevention and intervention programs targeted at youth, particularly minority youth. Compton, W.M., Grant, B.F., Colliver, J.D., Glantz, M.D. and Stinson, F.S. Prevalence of Marijuana Use Disorders in the United States: 1991-1992 and 2001-2002. Journal of the American Medical Association, 291(17), pp. 2114-2121, 2004.

Impact of Childhood Treatment of Anxiety on Later Drug Abuse

This study evaluated outcomes in 86 individuals who had received cognitive behavioral treatment for anxiety disorders in childhood an average of 7.4 years earlier. Based on diagnostic interviews, the authors conclude that a good number of the participants maintained gains in terms of reduced anxiety several years later. They also found that those who responded more positively to the initial treatment had less drug involvement, and fewer drug-related problems, than those who responded less positively. However, this is not a randomized trial, and it is not clear whether the treatment itself was related to the differences in outcome, or whether other characteristics rendered some children at risk for poor outcomes in both arenas. Thus, while this study suggests that treatment of childhood psychiatric conditions holds potential for reducing later drug abuse, further work is needed to confirm this finding. Kendall, P.C., Safford, S., Flannery-Schroeder, E, and Webb, A. Child Anxiety Treatment: Outcomes in Adolescence and Impact on Substance Use and Depression at 7.4-Year Follow-Up. Journal of Consulting and Clinical Psychology, 72, pp. 276-287, 2004.

Cannabis and Other Drugs: Modeling Comorbidity

The authors sought to use a genetically informed approach to explain the comorbidity between cannabis and other drug use. Data from over 2000 same-sex twin pairs were used to test 13 models of comorbidity including versions of the gateway and common

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risk factor models. For drug use, the correlated liability (common risk factor) model was the best fit, although there may be a subgroup of high-risk cannabis users at increased risk for other drug use (the extreme multiformity of cannabis model). For abuse/dependence, the correlated liability model fit the data best for males; it was difficult to distinguish models for females, probably due to low prevalence of drug abuse. The authors discuss the implications of these findings for prevention: if indeed the use, abuse, and dependence on various drugs is related to common risk factors, then programs that seek to control a specific drug such as cannabis as a "gateway" will not be effective; rather, interventions that focus on common risk factors may be appropriate. Agrawal, A., Neale, M.C., Prescott, C.A., and Kendler, K.S. Cannabis and Other Illicit Drugs: Comorbid Use and Abuse/Dependence in Males and Females. Behavior Genetics, 34, pp. 217-228, 2004.

Personality and Drug Use, Abuse and Dependence

This study used data from a population-based twin registry to assess the genetic and environmental factors contributing to the associations between personality factors and illicit drug use, abuse, and dependence. Based on data from a large sample of same-sex adult twin pairs, the authors found that genetic factors explained much of the relationship between personality and drug abuse. Novelty-seeking related most strongly, particularly for males and particularly for cannabis use. Neuroticism showed the greatest genetic overlap with sedative use. The authors conclude that the findings on novelty-seeking and cannabis use in males may be useful for candidate gene studies. Agrawal, A., Jacobson, K.C., Prescott, C.A., and Kendler K.S. A Twin Study of Personality and Illicit Drug Use and Abuse/Dependence. Twin Research, 7, pp. 72-81, 2004.

Factors Associated with Cessation of Smoking in Young Adults

As part of a longitudinal study of psychopathology and smoking in a school-based sample, 242 daily smokers provided complete data on factors associated with successful smoking cessation. Factors positively associated with successful cessation included being married and having higher household income; those negatively associated included lifetime major depressive disorder, antisocial personality symptoms, family history of drug and alcohol use disorder, and nicotine dependence (for women). In a multivariate analysis, marital status, nicotine dependence (for women), and male gender were significant, and major depression approached significance. Of note, factors associated with successful cessation in young adulthood differed from those predicting smoking initiation and progression; while all Axis I psychiatric diagnoses were associated with uptake and progression, only depression and antisocial behavior had some association (negatively) with cessation in this age group. Thus, factors that predict onset of nicotine use and dependence should not be used to predict cessation, which has implications for intervention programs. Rohde, P., Kahler, C.W., Lewinsohn, P.M., and Brown, R.A. Psychiatric Disorders, Familial Factors, and Cigarette Smoking: III. Associations with Cessation by Young Adulthood Among Daily Smokers. Nicotine & Tobacco Research, 6, pp. 509-522, 2004.

Prevalence, Severity, and Unmet Need for Treatment of Mental Disorders in the World Health Organization World Mental Health Surveys

This study estimated the prevalence, severity, and treatment of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) mental disorders in 14 countries in the World Health Organization (WHO) World Mental Health (WMH) Survey Initiative. Face-to-face household surveys of 60,463 community residents were conducted from 2001-2003 using the WMH version of the WHO Composite International Diagnostic Interview (WMH-CIDI), a fully structured, lay-administered psychiatric diagnostic interview. Results indicate that prevalence of having any disorder in the prior year varied widely, from 4.3% in Shanghai to 26.4% in the United States. Between 33.1% (Colombia) and 80.9% (Nigeria) of 12-month cases were mild. Serious disorders were associated with substantial role disability. Although disorder severity was correlated with probability of treatment in almost all countries, 35.5% to 50.3% of serious cases in developed countries and 76.3% to 85.4% in less-developed countries received no treatment in the 12 months before the interview. Due to the high prevalence of mild and subthreshold cases, the number of those who received treatment far exceeds the number of untreated serious cases in every country. The authors suggest that reallocation of treatment resources could substantially decrease the problem of unmet need for treatment of mental disorders among serious cases, and that careful consideration needs to be given to the value of treating some mild cases, especially those at risk for progressing to more serious disorders. Demyttenaere, K., Bruffaerts, R., Posada-Villa, J., Gasquet, I., Kovess, V., Lepine, J.P., Angermeyer, M.C., Bernert, S., de Girolamo, G., Morosini, P., Polidori,

G., Kikkawa, T., Kawakami, N., Ono, Y., Takeshima, T., Uda, H., Karam, E.G., Fayyad, J.A., Karam, A.N., Mneimneh, Z.N., Medina-Mora, M.E., Borges, G., Lara, C., de Graaf, R., Ormel, J., Gureje, O., Shen, Y., Huang, Y., Zhang, M., Alonso, J., Haro, J.M., Vilagut, G., Bromet, E.J., Gluzman, S., Webb, C., Kessler, R.C., Merikangas, K.R., Anthony, J.C., Von Korff, M.R., Wang, P.S., Brugha, T.S., Aguilar-Gaxiola, S., Lee, S., Heeringa, S., Pennell, B.E., Zaslavsky, A.M., Ustun, T.B., Chatterji, S. WHO World Mental Health Survey Consortium. JAMA, 291, pp. 2581-2590, 2004.

Unequal Opportunity: Neighborhood Disadvantage and the Chance to Buy Illegal Drugs

This study investigates 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. Standardized survey data were collected using stratified, multistage area probability sampling of household residents age 12 or older (N=25,500) living in the United States of America in 1998. Results suggest that women are less likely to be approached by someone selling illegal drugs. The study also 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. These findings lend support to the inference that physical and social characteristics of a neighborhood can set the stage for opportunities to become involved with drugs. Storr, C.L., Chen, C.Y. and Anthony, J.C. Journal of Epidemiology and Community Health, 58(3), pp. 231-237, 2004.

Neighborhood Environment and Opportunity to Try Methamphetamine ("Ice") and Marijuana: Evidence from Guam in the Western Pacific Region of Micronesia

This study examines the occurrence of youthful drug involvement among youths living in village and metropolitan regions of Guam during 1998. A probability sample of 776 high school students living in Guam, Micronesia, completed a self-report anonymous survey, one that assessed their village and metropolitan neighborhood environments as well as drug involvement. Results indicate that higher levels of neighborhood disadvantage were associated with youths being more likely to have been offered a chance to try drugs. This study adds new evidence on the potential importance of environmental and psychosocial contexts of neighborhood environment that might help account for the nonrandom distribution of youthful drug involvement. Storr, C.L., Arria, A.M., Workman, Z.R. and Anthony, J.C. Substance Use and Misuse, 39(2), pp. 253-276, 2004.

Defining a Never-Smoker Phenotype

The U.S. Centers for Disease Control defines a never-smoker as someone who has smoked <100 cigarettes per lifetime. In an attempt to explore differences among nonsmokers and to validate this cutpoint, this study surveyed 69 nonsmokers who had smoked between 1 and 200 cigarettes in their lifetime on their experiences during the time they smoked. Of the 7 who classified themselves as ex-smokers, 2 met DSM-IV criteria for nicotine dependence, compared with none who classified themselves as never-smokers. No respondents provided data permitting the computation of a Fagerstrom Test for Nicotine Dependence (FTND) score. Withdrawal effects were minimal, but craving, tolerance, and subjective effects showed a pattern of significant differences that were most prominent between those who smoked only 1 cigarette and those who smoked at least a pack. The data indicate a graded effect but also suggest that 19 cigarettes per lifetime is a more conservative cutpoint than 99 for defining the never-smoker phenotype. Further investigation of the smoking trajectory and characteristics associated with development of signs of dependence in never- vs. ever-smokers may help refine this cutpoint and shed light on what protects some people who experiment with smoking from becoming chronic users. Pomerleau, C.S., Pomerleau, O.F., Snedecor, S.M. and Mehringer, A.M. Addictive Behaviors, 29(6), pp. 1149-1154, 2004.

Early Adolescent Through Young Adult Alcohol and Marijuana Use Trajectories

This study takes a developmental approach to subgrouping and examines the trajectories of substance use from early adolescence through young adulthood among a community sample of 481 individuals. The patterns of use were examined, subgroups were identified separately for men and women and for alcohol and marijuana, and psychosocial predictors and psychopathology outcomes that differentiated the groups were identified. The results revealed three substantially

overlapping subgroups for both alcohol and marijuana: early onset, late onset, and nonuser. Although the general patterns of which dependent variables were related to group were similar for alcohol and marijuana, a closer examination revealed important subgroup differences. For alcohol use, the early-onset group was more dysfunctional in terms of predictors and outcomes whereas the late-onset and nonuser groups were better adjusted. In contrast, for marijuana, the early- and late-onset groups were both more dysfunctional than the nonuser group. In a final analysis, the researchers examined the predictive utility of our developmental approach to subgrouping compared to a traditional, static approach. Flory, K., Lynam, D., Milich, R., Leukefeld, C., and Clayton, R. Early Adolescent through Young Adult Alcohol and Marijuana Use Trajectories: Early Predictors, Young Adult Outcomes, and Predictive Utility. Development and Psychopathology, 16(1), pp. 193-213, 2004.

Relationship Between Early Experiences with Tobacco and Early Experiences with Alcohol

Prior research indicates that smoking and alcohol use are highly comorbid, animal studies indicate cross-sensitivity, and genetic correlates of nicotine and alcohol dependence overlap. Given these background findings, this study examined the association between retrospectively-reported responses to tobacco and alcohol in current smokers (n=111) and never-smokers (n=86). Results indicated that early smoking experiences were correlated with comparable responses to alcohol in smokers, and to a lesser extent, in never-smokers. Both pleasurable early experiences with nicotine and pleasurable experiences with alcohol predicted current alcohol intake, and pleasurable early experiences with alcohol predicted alcohol dependence. Neither pleasurable nor displeasurable experiences with either substance predicted current amount smoked or degree of nicotine dependence. These preliminary findings may have implications for understanding the mechanisms underlying the smoking-alcohol link. Pomerleau, C.S., Marks, J.L., Pomerleau, O.F. and Snedecor, S.M. Addictive Behaviors, 29(6), pp. 1245-1251, 2004.

Early Childhood Misbehavior and the Estimated 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 (nearly 75% of the original sample). 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). These findings suggest that 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. American Journal of Epidemiology, 160(2), pp. 126-130, 2004.

Latent Classes of Tobacco Dependence Syndromes Observed in Recent-Onset Tobacco Smokers

This study examined tobacco dependence syndromes that may appear during the first 2 years of tobacco smoking, as such clinical features may provide insights into the transitions that lead from initial smoking toward tobacco dependence. 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 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). Seven clinical features were assessed for a measure of the tobacco dependence syndrome. 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). These findings suggest that 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 & Tobacco Research, 6(3), pp. 533-545, 2004.

MAOA Haplotypes and Risk for Substance Use Disorders

Monoamine oxidase A (MAOA) locus is an attractive candidate for exploring genetic contribution to the variation in the risk for substance use disorders (SUD) because of its important role in the metabolism of neurotransmitters, including dopamine and serotonin. Prior findings have suggested an association of the MAOA gene with the risk for early onset SUD. To extend this research, this study genotyped four MAOA markers (two VNTR polymorphisms and two SNPs) and built a cladogram reflecting the evolutionary history of MAOA haplotypes (Nguyen et al., under review). The cladogram served as the framework for nested ANOVA and logit analyses of association between MAOA and indices of liability to SUD (diagnosis, age of onset, and a dimensional index of substance use related problems) in a sample of adult males of European ancestry. Whereas no association was found for the categorical diagnosis, a significant relationship was detected between the dimensional liability indices and MAOA haplotypes. These results are consistent with the hypothesis that variants in MAOA account for a small portion of the variance of SUD risk, possibly mediated by liability to early onset behavioral problems. Vanyukov, M.M., Maher, B.S., Devlin, B., Tarter, R.E., Kirillova, G.P., Yu, L.M. and Ferrell, R.E. American Journal of Medical Genetics, 125B(1), pp. 120-125, 2004.

Family Attention and Tobacco Smoking Among Adolescents

This study examined the association between family attention and tobacco use among 5549 adolescent students in five Central American countries, Panama, and the Dominican Republic who participated in a survey of drug use in 1994. Drug use and other variables were assessed using an adapted version of the Drug Use Screening Inventory (DUSI) in Spanish. Students with the highest level of family attention had a lower occurrence of tobacco smoking than students with the lowest level of family attention. Country-specific analyses show similar associations. These findings underscore the need to understand tobacco use in Central America and neighboring countries and to test whether interventions aimed at enhancing parental—child attention, communication, and monitoring reduce the incidence of tobacco use among youths. Gosebruch, G., Sanchez, M., Delva, J., Wagner, F., and Anthony, J.C. Family Attention and Tobacco Smoking Among Adolescents in Central America, Panama, and the Dominican Republic. Substance Use Misuse 38(8), pp. 1037-1106, 2003.

Anxiety and Risk for Substance Use Disorders Among Late Adolescents/Young Adults

This study examined the relation between comorbid and pure (non-comorbid) anxiety disorders and both substance dependence and substance use problems in a community sample of 1,751 young adults ages 18-23. Results indicate that collectively anxiety disorders, both pure and comorbid with other psychiatric diagnoses are predictive of substance dependence. When temporal order was controlled, anxiety disorders generally preceded the onset of substance dependence. However, in analyses in which PTSD was excluded, anxiety disorders were no longer predictive of substance dependence, suggesting that the increased risk associated with anxiety disorders is largely if not wholly attributable to PTSD. Finally, comorbid and pure anxiety disorders were found to be predictive of the number of alcohol and drug use problems. Lopez, B., Turner, R.J., and Saavedra, L.M. Anxiety and Risk for Substance Use Disorders Among Late Adolescents/Young Adults. Journal of Anxiety Disorders. Corrected proof available online 10 May 2004.

Transitions to Drug Use

This study examines whether patterns in the transition from alcohol and tobacco in the Mexican State of Morelos, Mexico are similar to those observed in other countries. The data were from a representative sample of youth age 11-21 (n=13,105), who participated in a paper-and-pencil survey in middle schools, high schools, and colleges in the State of Morelos, Mexico. Drug use was assessed via the standardized instrument most used in Mexican student surveys. Cox's models for discrete-time survival analyses, stratified by school and age group were used to estimate the risk of drug use in relation to early or non early alcohol and tobacco use initiation by gender, while accommodating the complex survey design. The study findings suggest that about five percent of the students were estimated to have used drugs in their life. Male early users of alcohol or tobacco were more likely to use other drugs, compared

to students who did not have an early alcohol or tobacco onset. Recommendations for future studies includes an exploration of the role of social mechanisms and their relationship to patterns of drug involvement, even in the context of important differences in rates of drug use. Wagner, F.A., Velasco-Mondrag—n, H.E., Herrera-Vazquez, M., Borges, G. and Lazcano, E. Early Alcohol and Tobacco Use and Transition to Other Drug Use Among Students in the State of Morelos, Mexico. Drug and Alcohol Dependence. Corrected proof available online 24 August 2004.

Relationship of Tobacco Smoking with Depressive Symptomatology

This study aims to estimate the association of depressive symptomatology with tobacco smoking, nicotine dependence, cigarettes smoked daily, and smoking cessation in a representative sample of the Mexican population. A probability sample of 1,935 adults answered a version of the Third National Mexican Addictions Survey that included the CES-D depression scale and specific questions on tobacco use. Analyses addressed the survey's complex design. Active smokers had higher odds of depression than ex-smokers, who had higher odds than non-smokers. Higher levels of tobacco use were more strongly associated with depression as was nicotine dependence in women. Those who ceased smoking recently had lower odds of depression than active smokers. Study findings suggest that smoking cessation interventions should be coupled with attention to depressive symptomatology. Benjet, C., Wagner, F.A., Borges, G., and Medina-Mora M.E. The Relationship of Tobacco Smoking with Depressive Symptomatology in the Third Mexican National Addictions Survey. Psychological Medicine. Published online 18 March 2004.

Correlates of Aggression in African American and Puerto Rican Children

This cross-sectional study examines the interrelationship of psychosocial domains as they relate to aggression in a sample of African American and English-speaking Puerto Rican children living in New York City. The sample included 80 biological children of African American and Puerto Rican young adults who have participated in the authors ongoing longitudinal study and 77 mothers or mother substitutes (rearing mothers) of those children. Hierarchical multiple regression analysis was performed, with childhood aggression as the dependent variable and the following domains as independent variables: child and maternal personality attributes; mother-child relationship; ethnic identification and discrimination; and the partner/marital relationship. The results indicated that: (a) the child's personality and maternal attributes were significantly related to the child's aggression, despite control on all the other domains; (b) the ethnic identification and discrimination domain was no longer related to the child's aggression with control on the mother-child relationship domain or the child's personality domain. The findings have implications for clinical practice and public policy, and provide significant insights into childhood risk factors that need to be altered to reduce physical aggression. Brook, J.S., Rosenberg, G., Brook, D.W., Balka, E.B. and Meade, M. Correlates of Aggression in African American and Puerto Rican Children. Journal of Genetic Psychology, 165(2), pp. 185-202, 2004.

Illicit Drug Use and Risky Sexual Behavior Among African American and Puerto Rican Urban Adolescents: The Longitudinal Links

This study assessed whether (a) early illicit drug use predicts later risky sexual activity; (b) early risky sex predicts later illicit drug use; and (c) common factors affect both risky sex and illicit drug use. African American and Puerto Rican youth completed questionnaires in their classrooms at Time 1 (T1) and face-to-face interviews five years later at Time 2 (T2). Logistic regression analyses showed the association between T1 illicit drug use and T2 risky sexual activity and between T1 risky sexual behavior and T2 illicit drug use. With few exceptions, T1 illicit drug use was associated with all of the T2 risky sexual behaviors. After controlling for demographic factors, multiple sex partners at T1 was not related to illicit drug use at T2. Condom use at T1 was related to illicit drug use at T2, whereas sexually transmitted diseases and early pregnancy were not. The findings indicated that assessments of and treatments for substance use should focus on the risky sexual behaviors that seem to accompany illicit drug use. Brook, J.S., Adams, R.E., Balka, E.B., Whiteman, M., Zhang, C. and Sugerman, R. Illicit Drug Use and Risky Sexual Behavior Among African American and Puerto Rican Urban Adolescents: The Longitudinal Links. Journal of Genetic Psychology, 165(2), pp. 203-220, 2004.

Risk-Taking Behaviors Among African American Adolescents

This study explores the relationship between peer status, peer groups' social influence and risk-taking behavior in an urban sample of 647 African American seventh grade students. Highest rates of problem behaviors were seen in those youth who were both

highly liked and highly disliked by other youth. Findings also revealed contrasting patterns of peer group leadership. The more controversial the youth the more likely the involvement in deviant peer groups. Results highlight the importance of controversial status students as key influence agents during early adolescence, and implications for prevention interventions to reduce adolescent problem behaviors. Miller-Johnson, S., Costanzo, P.R., Cole, J.D., Rose, M.R., Browne, D.C., and Johnson, C. Peer Social Structure and Risk-Taking Behaviors Among African American Early Adolescents. Journal of Youth and Adolescence, 32(5), pp. 375-384, 2003.

Drug Use Among American Indian Adolescents

This study examines the trends in drug use among American Indian adolescents attending school on or near the Indian reservations in the United States. The study provides comparisons between American Indian and non-Indian youth to assess their drug use and issues of prevention. Reliable and valid school administered surveys have been given every year for 25 years (1975 — 2000) to representative samples of American Indian youth living on reservations, providing a continuous record of drug use. Comparisons are made with non-Indian youth with data from the Monitoring the Future project. 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 that by non-Indian youth. Indian youth who use drugs can be divided into two groups, moderate category and high levels of use. The number of youth in the moderate category vary overtime, whereas the number in the high level category are relatively constant. There is a clear need for intensive efforts to reduce the levels of drug use among Indian youth, however future 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. Journal of Adolescent Health, 34, pp. 493-500, 2004.

Sources of Information about MDMA/Ecstasy

Researchers conducted a cross-sectional study to assess the perceived accuracy and importance of various sources of information about MDMA/ecstasy among young adult users. They used a respondent driven sampling plan to recruit and then interview recent ecstasy users (n = 304), aged 18-30, in Ohio. Information collected included the most common venue of ecstasy use; the total number of occasions ecstasy had been used; behavioral intentions to use ecstasy again; and the perceived accuracy as well as the importance of 16 sources of information about ecstasy, including the Internet. Friends, drug abuse treatment programs, and physicians were identified as the most accurate sources of information about ecstasy by 45.7%, 37.2%, and 30.3% of the sample, respectively. Friends were considered the most important source of information about ecstasy (40.2%), followed by web sites like DanceSafe (16.2%), and MTV/VH1 television specials (6.9%). More than half the sample used the Internet to obtain information about ecstasy, with younger and more educated participants significantly more likely to do so. Educated users were also significantly more likely to consider the Internet to be an important source of information, and visited sites like DanceSafe as many as 4 times more often than government-sponsored web sites. These findings support the development of peer-oriented, network strategies to reach ecstasy users with prevention messages. In particular, efforts should be made to make prevention information web sites more attractive and useful. Falck, R.S., Carlson, R.G., Wang, J. and Siegal, H.A. Sources of Information about MDMA/Ecstasy: Perceived Accuracy, Importance, and Implications for Prevention Among Young Adult Users. Drug and Alcohol Depend, 74, pp. 45-54, 2004.

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

Research Findings - Prevention Research

Revised Project ALERT Modifies Risk Factors in Adolescents

The revised Project ALERT curriculum is designed to help young people resist pro-drug pressures and contains additional lessons on smoking cessation, and alcohol misuse, and a series of new home-learning activities that encourage parental involvement. To test the impact of the revised curriculum, fifty-five middle schools from South Dakota were randomly assigned to the revised ALERT or control condition. Treatment group students received 11 lessons in Grade 7 and 3 more in Grade 8. Effects for 4,276 eighth graders were assessed 18 months after baseline. Results indicated that the revised ALERT had statistically significant effects on all targeted risk factors associated with cigarette and marijuana use and more modest gains with pro-alcohol risk factors. The program showed beneficial changes in adolescents at all risk levels (i.e., low, moderate and high) for future use, with the effect sizes typically stronger for the low and moderate risk groups. Gosh-Dastidar, B., Longshore, D., Ellickson, P. and McCaffrey, D. Modifying Pro-Drug Risk Factors in Adolescents: Results from Project ALERT. Health Education & Behavior, 31(3), pp. 318-334, 2004.

Classroom Environment Influences On Aggression, Peer Relations and Academic Focus

Peers provide models of behavior, and consequently classrooms containing high numbers of students with poor academic skills or behavioral problems are likely to promote bad behavior in individual students. This study examined the extent to which variations in social and academic classroom composition as well as the larger school context affected behavior in a normative sample of children over a 2-year period. Teachers provided ratings of individual students, which were then aggregated to form teacher-based measures of classroom environment. Concurrent and longitudinal effects of classroom and school environments on individual behaviors were examined for students in 65 classrooms in 17 schools. Poorer classroom environments were associated with higher levels of student aggression, poor peer relations, and lack of academic focus. Changes in student behavior over time can be explained by the classroom environment. Barth, J.M., Dunlap, S.I., Dane, H., Lochman, J.E. and Wells, K.C. Journal of School Psychology, 42(2), pp. 115-133, 2004.

Advocacy Interventions Reduce Smoking among Teenagers

The purpose of this study was to determine whether high school students' participation in advocacy activities related to the advertising, availability and use of tobacco in communities would prevent or reduce their own use. Eleventh and 12th grade students in 10 continuation high schools were randomly assigned to advocacy activities (treatment in 5 schools) or to learning about drug and alcohol abuse prevention during a semester-long program (5 control schools). Based on self-reports, students were classified as nonsmokers, light smokers (those who smoked less than a pack per week) or regular smokers (those that smoked one or more packs per week. Three additional measures were assessed: perceived self-efficacy, perceived incentive value, and outcome expectances. There was a significant net change from baseline to the end of the semester (after the intervention) between treatment and control schools for students who were regular smokers but not for students who were nonsmokers or light smokers. Regular smoking decreased 3.8% in treatment schools and increased 1.5% in control schools (P<.001). Regular smoking continued to decrease at 6-months post-intervention in treatment schools, with a total change in prevalence from 25.1% to 20.3%. Measures of community-advocacy involvement and the three social constructs also showed significant net changes

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between control and treatment schools. Winkelby, M.A., Feighery, E., Dunn, M., Kole, S., Ahn, D. and Killen, J.D. Effects of an Advocacy Intervention to Reduce Smoking Among Teenagers. Archives of Pediatric and Adolescent Medicine 158, pp. 269-275, 2004.

Brief Family Intervention Effects 6 Years Past Baseline

This study examines the effects of two brief family-focused interventions on the trajectories of substance initiation over a period of 6 years following a baseline assessment. The interventions, designed for general population families of adolescents, were the 7-session Iowa Strengthening Families Program (ISFP) and the 5-session Preparing for the Drug Free Years Program (PDFY). Thirty-three rural public schools were randomly assigned to the ISFP, the PDFY, or a minimal contact control condition. These interventions have been previously proven to reduce alcohol use at 2.5 years and 4 years past baseline. The curvilinear growth observed in school-level outcome measures of drug initiation was evaluated using a logistic growth curve analysis. Alcohol and tobacco composite use indices—as well as lifetime use of alcohol, cigarettes, and marijuana—and lifetime drunkenness, were examined in the current analysis, in which study participants are an average of 18.2 years old. Significant intervention-control differences were observed, indicating favorable delays in growth rates of initiation of alcohol use without parental permission, drunkenness, and cigarette use initiation in the intervention groups. Spoth, R.L., Redmond, C., Shin, C. and Azevedo, K. Brief Family Intervention Effects on Adolescent Substance Initiation: School-level Growth Curve Analyses 6 Years Following Baseline. Journal of Consulting and Clinical Psychology, 72(3), pp. 535-542, 2004.

The Role of Parental Risk in the Moderation of Child Intervention Outcomes

Four years of longitudinal data from 373 families participating in a randomized intervention trial were used to examine whether intervention effects on adolescent alcohol and tobacco use trajectories were moderated by family risk, as defined by parental social emotional adjustment. A single parental social emotional maladjustment score was calculated by summing average scores from subscales tapping anxiety, depression, and hostility based on parent report. Consistent with previous studies based on a different analytic technique, the current analyses confirmed that both the Preparing for the Drug Free Years program and the Iowa Strengthening Families Program favorably influenced youth alcohol use index trajectories across the time frame of the study while only the latter program evidenced positive effects on a tobacco use index. With regard to the role of parental risk in moderating these program outcomes, analyses provided no support for family risk moderation of any intervention effect. Guyll, M., Spoth, R.L., Chao, W., Wickrama, K.A.S. and Russell, D. Family-focused Preventive Interventions: Evaluating Parental Risk Moderation of Substance Use Trajectories. Journal of Family Psychology, 18(2), pp. 293-301, 2004.

Violence Prevention among African American Adolescent Males

This study tests whether the efficacious, multi-year Aban Aya intervention has significant effects on the proposed mediating variables and whether the significant preventive effects in reducing violence found in previous analyses are mediated by changes in proposed mediators. Five hundred seventy-one African American adolescent males participated in this randomized trial. Multi-level modeling techniques were used to ascertain both intervention and mediated effects. The intervention significantly reduced the rate of growth of violence and five social and psychological factors in the treatment group relative to the control group. Four of these social and psychological factors, behavioral intentions, attitudes toward violence, estimates of peers' behaviors, and estimates of best friends' behaviors, were found to be complete mediators between the intervention and its preventive effects. Ngwe, J.E., Liu, L.C., Flay, B.R., Segawa, E. and the Aban Aya coinvestigators. Violence Prevention among African American Adolescent Males. American Journal of Health Behavior, 28(Suppl 1), pp. S24-S37, 2004.

Social Assertiveness, Internalizing, and Gender Moderation Effects Of A Preventive Intervention

The current study investigated gender moderation of the longitudinal pathways from internalizing to both social competency and the initiation of substance use as well as the effects of a preventive intervention on that process. Rural Midwestern adolescents who were participating in a school-based preventive intervention study were an average of 12.3 years old at the pretest assessment. A latent growth curve comparison analysis found that internalizing was inversely related to initial levels of

social assertiveness skill among girls. Internalizing was positively related to substance use initiation growth trajectories among girls. Girls who participated in the preventive intervention demonstrated a slower increase over time in substance use initiation and a faster increase in social assertiveness. Lillehoj, C.J., Trudeau, L., Spoth, R.and Wickrama, K.A.S. Internalizing, Social Competence, and Substance Initiation: Influence of Gender Moderation and a Preventive Intervention. Substance Use and Misuse, 39(6), pp. 963-991, 2004.

Educational Resilience among Youth at Risk

Educational experts and others recognize the importance of early school experiences on later educational outcomes. Following a sample of youth based on 692 files from low-income, single parent families from one urban school district from 1898-90 to 1996-97, the authors apply event history analytic techniques to examine the relationship between first grade retention and high school completion. The findings indicate that being retained in first grade increases the risk of dropping out of high school years later. However, there is a link between retention, extracurricular activity participation and high school completion such that those students who were retained but were involved in extracurricular activities had drop out rates that were lower than the retained uninvolved students. Thus educational trajectories can be redirected such that positive educational outcomes can occur. Randoph, K.A., Fraser, M.W. and Orthner, D.K. Educational Resilience among Youth at Risk: Substance Use and Misuse 39, pp. 747-767, 2004.

D.A.R.E Plus Is More Effective in Preventing Violence Among Boys Than Girls

Twenty-four middle schools were randomly assigned to: 1) DARE curriculum; 2) DARE Plus multi-component curriculum; or 3) control condition. Outcomes of the three conditions on violence-related behaviors were compared, and mediational analyses were conducted to examine how interventions reduced physical and verbal violence. Generally, boys demonstrated higher rates of violence and victimization than girls. Boys in the DARE Plus condition had a marginally significant lower number of verbally violent acts than boys in the control condition. Boys in the DARE Plus condition had a marginally lower number of physically violent acts than boys in the DARE condition. There were no significant differences between the DARE only and control groups. There were no significant differences between the three groups in victimization. The small behavioral effect that DARE Plus demonstrated on physical and verbal violence among boys was mediated by a decrease of norms that support violence, an increase in outcome expectancies about being violence-free, and an increase in parental consequences for fighting. DARE Plus was not as effective in preventing violence among girls, however, girls in the DARE Plus condition had significantly lower scores on the Victimization Scale than girls in the DARE only condition. Komro, K.A., Perry, C.L., Veblen-Mortenson, S., Stigler, M.H., Bosma, L.M., Munson, K.A. and Farbakhsh, K. Violence-related Outcomes of the DARE Plus Project. Health Education & Behavior, 31(3), pp. 335-354, 2004. Perceptions of Rural Parents Regarding Family-Focused Programs Data collected in the Promoting School-Community-University Partnership to Enhance Resilience (PROSPER) project during telephone interviews with 1,156 parents of sixth graders from 36 rural schools were used in multilevel structural equation modeling. Results of analyses show that: 1) parents considered their children to be at low risk for substance use; 2) parents perceived themselves to be effective in helping their children avoid maladaptive behaviors; 3) mothers perceived themselves to be more efficacious than did fathers; 4) parental efficacy perceptions inversely affected perceptions of child susceptibility; 5) parents' perceptions of child susceptibility positively affected perceived program benefits; and 6) higher perceived program benefits and higher perceived child susceptibility were associated with mothers, male children, single parents, lower household income, and lower parent education. Redmond, C., Spoth, R, Shin, C. and Hill, G. Engaging Rural Parents in Family-Focused Programs to Prevent Youth Substance Abuse. Journal of Primary Prevention, 24(3), Spring, 2004.

Alcohol and Marijuana Use in Early and Late Adolescence

This study examined alcohol and marijuana use over a 9-year period between ages 11-12 and ages 19-21 using a community based dataset collected prospectively as part of the evaluation of Project DARE. Because the DARE intervention was found to have no effects on any program targets, this dataset provides an appropriate community sample for investigating developmental changes in drug use over time. 481 participants (50.17% male, 79.2% Caucasian) were interviewed once a year in the sixth through tenth grades and again at age 20. A growth mixture model approach was used to analyze interview data from 6 time points in an attempt to empirically identify subgroups of alcohol and marijuana users over time. Three

subgroups were identified for both alcohol use and marijuana use: a group that initiated substance use in early adolescence (age 11-12), a group that initiated use in late adolescence/early adulthood (age 15-16), and an abstainer group. Several variables measured in early adolescence including school and church involvement, self-esteem, peer pressure resistance, sensation seeking, expectancies, and conduct problems significantly differentiated the alcohol and marijuana subgroups. The subgroups also differed significantly on young adult outcomes, including alcohol and marijuana dependence, antisocial personality disorder symptoms, and number of arrests. For alcohol use, the early-onset group was more dysfunctional in terms of early psychosocial risk factors and later deleterious outcomes whereas the late-onset and nonuser groups were better adjusted. In contrast, for marijuana, the early- and late-onset groups were both more dysfunctional than the nonuser group. Flory, K., Lynam, D., Milich, R., Leukefeld, C. and Clayton, R. Early Adolescent through Young Adult Alcohol and Marijuana Use Trajectories: Early Predictors, Young Adult Outcomes, and Predictive Utility. Development and Psychopathology, 16, pp. 93-213, 2004.

Children's Intuitive Theories of Drug Action

In an effort to develop a method for characterizing children's intuitive theories of drug action, 217 children (53.7% girls) in grades 1 through 6 were interviewed about how alcohol and cocaine cause behavioral changes in users. Using Piagetian and intuitive theories perspectives children's responses to interview questions were classified in terms of both structure and content. With respect to structure, responses were coded for their complexity of causal reasoning, coherence, and level of construction of a casual explanatory framework with nodes, links, and causal mechanisms. In terms of content, responses were coded for relevant biological ontology, mastery of propositions in a scientifically correct theory of drug action, and reliance on alternative theoretical models. Scores on all measures of structure and content increased with age, especially between first and second grade and third and fourth grade. Growth between third/fourth and fifth/sixth grades was more evident for cocaine than for alcohol. Overall, elementary school age children appear capable of framing causal explanations of drug action and they possess relevant biological knowledge, particularly about the central role of the brain in mediating the effects of drugs on behavior. Davies, E.P., Sigelman, C.K., Bridges, L.J., Rinehart, C.S. and Sorongon, A.G. A Characterization of Children's Intuitive Theories of Drug Action. Applied Developmental Science, 8, pp. 58-74, 2004.

Psychosocial Factors Related to Drinking Among Rural Adolescents

This study examined the relationship of psychosocial factors to alcohol use for adolescent boys and girls residing in rural Iowa. Seventh graders (n=1673) self-reported alcohol use, peer drinking norms, adult drinking norms, drug refusal assertiveness, drug refusal techniques, life skills, pro-drinking attitudes, risk-taking tendency, and perceived family management practices. Multiple regressions indicated that peers' drinking norms, drug refusal assertiveness, drug refusal techniques, life skills, pro-drinking attitudes, and risk taking tendency were related to drinking measures. Perceived family management skills and drug refusal techniques were associated with drinking for girls but not boys. Risk-taking tendency was related to drinking for boys but not girls. Epstein, J.A., Botvin, G.J. and Spoth, R. Which Psychosocial Factors are Related to Drinking Among Rural Adolescents? Journal of Child and Adolescent Substance Abuse, 13(1), pp. 19-35, 2003.

Spirituality and "Health-As-A-Value" Are Protective Against Teen Substance Use

This study investigated the influence of two potentially protective factors, Health-as-a-Value (HAV) and spirituality, on monthly alcohol, cigarette, and marijuana use in two multiethnic groups of adolescents varying in risk. Survey respondents included 382 students from continuation/alternative high school, a population considered at risk for drug use, and 260 students drawn from a medical magnet high school, and considered to be at lower risk. The data indicated that spirituality was protective against monthly alcohol use and marijuana use in the lower risk sample. In the higher risk sample, spirituality was protective against all monthly use. HAV was protective against monthly alcohol use in the low risk sample, and protective against all monthly use in the higher risk sample. When both constructs were entered into the same model, spirituality and HAV were independently protective of all monthly use for the higher risk sample and of monthly alcohol use in the lower risk sample, supporting the earlier finding that both are independently protective values. Thus, HAV and spirituality may be protective in various environments, independent of the level of use in the environment. Ritt-Olson, A., Milam, J., Unger, J.B., Trinidad, D., Teran, L.,

Dent, C.W., and Sussman, S. The Protective Influence Of Spirituality And "Health-As-A-Value" Against Monthly Substance Use Among Adolescents Varying In Risk. Journal Of Adolescent Health, 34 (3), pp. 192-199, 2004.

Gender Identity, Ethnicity, Acculturation and Drug Use

This article presents the findings of a survey completed by 1351 predominantly Mexican American middle school students residing in a large urban center in the U.S. Southwest. The study explores possible associations between drug use attitudes and behaviors and biological sex, gender identity, ethnicity, and acculturation status. Based on the concepts of "machismo" and "marianismo" that have been used to describe Mexican populations, four dimensions of gender identity were measured: aggressive masculinity, assertive masculinity, affective femininity, and submissive femininity. In explaining a variety of indicators of drug use behaviors and anti-drug norms, gender alone had limited explanatory power, while gender identity—often regardless of gender—was a better predictor. Aggressive masculinity was generally associated with higher risk of drug use, while the other three gender identity measures had selected protective effects. The impact of gender identity was strongly mediated by acculturation: less acculturated Mexican American students reported lower aggressive masculinity scores than non-Latinos; less acculturated Mexican American girls reported both the lowest aggressive masculinity scores and the highest submissive femininity scores; more acculturated Mexican American students, along with the less acculturated Mexican American boys, did not appear to be polarized by gender identity. The findings suggest that some aspects of culturally prescribed gender roles can have a protective effect against drug use behaviors and attitudes, possibly for both girls and boys. Kulis, S., Marsiglia, F.F. and Hurdle, D. Gender Identity, Ethnicity, Acculturation, and Drug Use: Exploring Differences Among Adolescents in the Southwest. Journal of Community Psychology, 31(2), pp.167-188, 2003.

Promoting Academic Success among Latino Youths

The Oregon Latino Youth Survey samples included a total of 564 Latino and non-Latino middle school and high school students and their parents. Analyses showed that Latino students reported a high frequency of discriminatory experiences and institutional barriers at school and that both Latino students and their parents were more likely to experience institutional barriers compared to non-Latinos. Further, Latino students and parents reported that they and/or their youngsters were more likely to drop out of school compared to non-Latinos. Path models showed that lower acculturation and more institutional barriers were related to less academic success for Latino students. More parent academic encouragement and staff extracurricular encouragement were associated with better academic outcomes for Latino students. Finally family socioeconomic disadvantage had an indirect effect on Latino youngster academic success through effects on parent monitoring and school involvement. Martinez, C.R., DeGarmo, D.S. and Eddy, J.M. Promoting Academic Success among Latino Youths. Hispanic Journal of Behavioral Sciences, 26(2), pp. 128-151, 2004.

Measuring Historical Trauma among American Indians

The developmental process and measurement characteristics observed in The American Indian Historical Loss Scale and the Historical Loss Associated Symptoms Scale are described. Measurement characteristics including frequencies, internal reliability, and confirmatory factor analysis were calculated based on responses from 143 American Indian adult parents of children aged 10-12 years who are a part of an ongoing longitudinal study of American Indian families in the Upper Midwest. Results indicate both scales have high internal reliability. Frequencies indicate that the current generation of American Indian adults have frequent thoughts pertaining to historical losses and that they associate these losses with negative feelings. Two factors of the Historical Loss Associated Symptoms Scale indicate one anxiety/depression component and one anger/avoidance component. The results are discussed in terms of future research and theory pertaining to historical trauma among American Indian people. Whitbeck, L.B., Adams, G.W., Hoyt, D.R. and Chen, Xiaojin. Conceptualizing and Measuring Historical Trauma Among American Indian People. American Journal of Community Psychology, 33(3/4), pp. 119-130, 2004.

Resolving Tensions Between Fidelity & Fit in Adapting Prevention Interventions

Debate over the need for strict fidelity of implementation versus the need for prevention that is responsive to the needs of specific populations from a community-based participatory research approach is the subject of this article. This approach to

program adaptation emphasizes motivating community participation to enhance program outcomes. Both fidelity and adaptation are essential elements of prevention intervention program design and are best addressed through a planned, organized, and systematic approach. Castro, F.G., Barrera, M. and Martinez, C.R. The Cultural Adaptation of Prevention Interventions: Resolving Tensions between Fidelity and Fit. Prevention Science, 5(1), pp. 41-45, March 2004.

Agreement of Program Provider and Observer Ratings of School-Based Preventive Intervention Implementation & Relation to Youth Outcomes

Few prevention studies have examined the degree to which different measures of program implementation adherence predict youth outcomes. The current study was conducted with rural middle school youth participating in a longitudinal school-based preventive intervention program. Study participants' average age at the pretest assessment was 12.3 years. The association between program implementation ratings supplied by provider self-reports and trained independent observer reports were evaluated. In addition, the relationship between measures of implementation and youth outcomes were examined. Results indicated that although program providers tended to report higher implementation than independent observers, most ratings were correlated significantly across raters. Moreover, observer-reported implementation ratings significantly predicted several youth substance-related outcomes, while provider reported self-ratings did not. Findings suggest that there might be a social desirability bias in provider self-reported ratings of implementation and that caution must be used when interpreting self-reported ratings of implementation. Lillehoj, C.J., Griffin, K.W. and Spoth, R. Program Provider and Observer Ratings of School-based Preventive Intervention Implementation: Agreement and Relation to Youth Outcomes. Health Education and Behavior, 31(2), pp. 242-257, 2004.

Piecewise Growth Curve Modeling of Prevention Study Data

Longitudinal data from the Midwestern Prevention Project (MPP) was used as an example to illustrate an alternative growth curve model with multiple profiles to incorporate multiple developmental stages. The data contained a total of 50 junior high schools (23 control and 27 program schools) observed at 7 time points beginning at the seventh grade and crossing junior high school and high school stages. Baseline data were obtained in the fall of 1987 and 6 follow-ups were conducted, with the first being 6 months after baseline, and then 1 year apart for the other five follow-ups. The percentage of students reporting any cigarette use in the last 30 days in each school was used as the outcome measure. Several two-piece growth curve models were developed to examine longitudinal prevention effects. Each piecewise model included growth profiles at two separate developmental stages: the junior high school years and the high school years. Comparisons revealed that the piecewise growth curve models incorporating multiple stages demonstrated significant improvement of model fitting compared to the single-piece growth curve model. Results showed marginal prevention effects in the junior high school stage but not in the high school stage. Piecewise growth curve models offer both more substantively and analytically appropriate model specification and greater flexibility in incorporating transitional periods when studying changes across time. Chou, C.P., Yang, D., Pentz, M.A. and Hser, Y.I. Piecewise Growth Curve Modeling Approach for Longitudinal Prevention Study. Computational Statistics and Data Analysis, 46, pp. 213-225, 2004.

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

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

Adherence to Treatment of Depression in Active Injection Drug Users

Investigators at Brown University School of Medicine recruited injection drug users for a randomized study of combined psychotherapy and pharmacotherapy for the treatment of depression. Among the 53 SCID diagnosed depressed subjects assigned to the combined treatment group, 43.4% were "fully adherent" to treatment (75% or greater attendance at cognitive-behavioral therapy sessions or 75% or greater adherence to the pharmacotherapy regimen). The correlation between cognitive-behavioral therapy attendance and pharmacotherapy use was high (r(s)=.74). Persons with major depression and dysthmia were most likely to be fully adherent (p=.01); frequency of heroin use was inversely associated with adherence. The impact of depression on drug users is extensive, serving as a trigger for high-risk injection practices and continued drug use. Stein, M.D., Herman, D.S., Solomon, D.A., Anthony, J.L., Anderson, B.J., Ramsey, S.E., and Miller, I.W. Journal of Substance Abuse Treatment, 26(2), pp. 87-93, 2004.

Network Therapy Decreased Secondary Opioid Use During Buprenorphine Maintenance Treatment

Network therapy utilizes family members and/or friends to support compliance with an addiction treatment carried out in office practice. Investigators at New York University conducted a study to examine whether Network Therapy is a useful psychosocial adjunct, relative to a control treatment, for achieving diminished illicit heroin use for patients on buprenorphine maintenance. Patients agreeing to randomization to either Network Therapy (N=33) or Medication Management (N=33) were inducted onto short-term buprenorphine maintenance and then tapered to zero dose at the end of the 18-week study. Network Therapy resulted in significantly more urine toxicologies negative for opioids than Medication Management (65% vs. 45%), and more Network Therapy than Medication Management patients (50% vs. 23%) experienced a positive outcome relative to secondary heroin use by the end of treatment. The use of Network Therapy in office practice may improve the effectiveness of eliminating secondary heroin use during buprenorphine maintenance. Galanter, M., Dermatis, H., Glickman, L., Maslansky, R., Sellers, M., Neumann, E., and Rahman-Dujarric, C. Journal of Substance Abuse Treatment, 26(4), pp. 313-318, June 2004.

Choosing a Behavioral Therapy Platform for Pharmacotherapy of Substance Users: A Review of Empirically Supported Manual Guided Behavioral Therapies

Behavioral therapy platforms have become requirements in pharmacotherapy trials due to their utility in reducing noise variability, preventing differential medication adherence and protocol attrition, enhancing statistical power and addressing ethical issues in placebo-controlled trials. Selecting an appropriate behavioral platform for a particular trial requires study-specific tailoring, taking into account both the stage of development of the medication being evaluated, as well as the specific strengths and weaknesses of a broad array of available empirically supported behavioral therapies and the range of their possible targets (e.g., enhancing medication adherence, preventing attrition, addressing co-morbid problems, fostering abstinence, and targeting specific weaknesses of the pharmacologic agent). Choosing a suitable behavioral platform also requires consideration of the characteristics of the population to be treated, stage of scientific knowledge regarding the medication's effects,

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appropriate balance of internal and external validity, and consideration of potential ceiling effects. In this paper researchers at Yale University reviewed the available manualized behavioral treatments, noting the strengths and limitations of these empirically supported treatments for use as behavioral therapy platforms for pharmacotherapy trials. Carroll, K.M., Kosten, T.R., and Rounsaville, B.J. Drug and Alcohol Dependence, 75, pp. 123-134, 2004.

Funding Contingency Management Programs Via Community Donations

Researchers at Friends Research Institute have shown that direct mail solicitations can be used to finance donations to a community store through which contingent reinforcement opportunities may be provided for drug abusers who maintain abstinence. Over a two month period in Toronto over $8,000 worth of goods and services were donated. In Los Angeles over a 34 month period over $160,000 worth of goods and services were donated. Contributions were received from 19% and 26% of those contacted respectively. Cost is believed to be one of the main barriers to implementing contingency management programs for drug abuse. This method of financing a contingency management program may eliminate this barrier to providing efficacious treatment. Amass, L. and Kamien, J. Experimental and Clinical Psychopharmacology, 12(2), pp. 147-155, 2004.

Method to Improve Work Performance in Cocaine Abusers Attending Therapeutic Workplace

Researchers at Johns Hopkins University have shown a therapeutic workplace business in which drug abusers work as paid data entry operators contingent on abstinence can be an efficacious intervention for drug abuse. However, many data entry operators in the business failed to work the maximal amount they could work and earn maximal pay even though they were abstinent and eligible to work. In focus groups many participants reported that strict work schedules posed difficulties for adherence. Thus, participants often skipped work even when abstinent from drugs. Using an ABA reversal design researchers implemented a contingency in which participants who completed a full shift of work earned the opportunity to arrive to work at a flexible start time. Preliminary results show that overall attendance at the therapeutic workplace including number of full day shifts participants worked increase when the contingency is in place. This modification may be important for improving adherence to this behavioral intervention and ultimately may improve its efficacy. Wong, C.J., Dillon, E.M, Sylvest, C. and Silverman, K. Drug and Alcohol Dependence, 74(3), pp. 319-323, 2004.

Scales Used to Judge Therapist Adherence and Competence Effectively Differentiate Behavioral Treatments in Cocaine Collaborative Study

The NIDA Cocaine Collaborative Treatment Study was the first large scale clinical trial of behavioral treatments for addiction to measure therapist competence using scales administered by expert raters with experience in psychotherapy. Investigators at the University of Pennsylvania demonstrated that the scales used were reliable and internally consistent. Additionally, findings show that therapists administered the four therapies tested, Cognitive Therapy, Supportive Expressive Therapy, Individual Drug Counseling, and Individual and Group Drug Counseling combined, according to the manual instructions and training guidelines. Results showed that most of the time therapists administered the prescribed elements of the treatment to which the client was assigned rather than the elements of an intervention to which the client was not assigned. These results suggest that distinct therapies were administered each of which had an impact on drug abuse. Thus this study provides further support for the efficacy of the study treatments when administered with strict adherence to the treatment manual. Barber, J.P., Foltz, C., Crits-Christoph, P. and Chittams, J. Journal of Clinical Psychology, 60(1), pp. 29-41, 2004.

How to Word Effective Messages About Smoking and Oral Health: Emphasize the Benefits of Quitting

Investigators at Yale examined whether smokers differentially responded to messages about oral health that emphasized either the benefits of quitting smoking (gain-framed) or the risks of continued smoking (loss-framed). These messages were embedded in recruitment brochures for smoking cessation trials, which were placed in 20 dental office waiting rooms for a six-month period. The number of brochures taken from the waiting rooms was tracked, as well as calls to inquire about smoking cessation studies. As hypothesized, dental patients were more likely to acquire gain-framed brochures. Out of 271 brochures taken from the dental office waiting rooms, significantly more brochures contained gain-framed messages compared to loss-

framed messages (59% vs. 41%, p<.05). There were an equal number of calls to inquire about smoking cessation studies for each message type. This study found that smokers are more receptive to information that emphasizes the benefits of quitting. McKee, S.A., O'Malley, S., Steward, W.T., Neveu, S., Land, M. and Salovey, P.J. Dent. Educ., 68(5), pp. 569-573, 2004.

Bupropion SR in Adolescents with Comorbid ADHD and Nicotine Dependence: A Pilot Study

Investigators at the Medical University of South Carolina conducted an open-label pilot study designed to examine the feasibility and preliminary tolerability of bupropion SR in adolescents with nicotine dependence. Sixteen adolescents were enrolled in the study. Eleven of the 16 participants also had comorbid ADHD. Two brief smoking cessation counseling sessions were also delivered. Over the course of treatment, a significant decrease in the average number of cigarettes smoked and carbon monoxide levels was found. There was no significant change in ADHD symptoms during the study. The investigators conclude that bupropion SR along with brief counseling may be safe and potentially efficacious for adolescents with nicotine dependence with and without ADHD. Smoking cessation trials in adolescents need to focus on strategies to increase retention for optimal effects. Upadhyaya, H.P., Brady, K.T. and Wang, W. J. Am. Acad. Child Adolesc. Psychiatry, 43(2), pp.199-205, 2004.

Training Support Persons to Help Smokers Quit: A Pilot Study

Mayo Clinic investigators evaluated the feasibility, acceptability, and potential efficacy of a skills-training intervention for adults interested in helping someone to stop smoking (i.e., support persons). Sixty adult support persons (77% female) were directly recruited from the community and randomly assigned to this intervention (manual plus five weekly group-based sessions) or a control condition (one-page leaflet). All intervention and outcome assessments occurred through the support persons. Assessments occurred at weeks 0 (baseline), 6 (end of treatment), 12, and 24. Outcomes were ratings of treatment acceptability, recruitment and retention rates, supportive behaviors provided to the smoker, and smoking behavior change in the smoker as reported by the support person. Support persons in skills training showed significant increases in their supportive behavior scores compared with control subjects at weeks 6 and 12. Although not statistically significant, the skills-training intervention was associated with more quit attempts, greater improvement in stage of change, and higher 7-day point prevalence abstinence rates in the smokers than the control condition. A skills training intervention for support persons is feasible and acceptable. Further studies are needed to test the efficacy of this approach for smoking cessation. Patten, C.A., Offord, K.P., Hurt, R.D., Sanderson Cox, L., Thomas, J.L. Quigg, S. M., Croghan, I.T., Wolter, T.D. and Decker, P.A. Am J Prev Med., 26(5), pp. 386-390, 2004.

An Experimental Test of the Influence of Prior Cigarette Smoking Abstinence on Future Abstinence

The present study was conducted to examine experimentally whether prior smoking abstinence histories can directly facilitate later abstinence, using a contingency management procedure to manipulate prior abstinence. A total of 40 adult cigarette smokers who were not trying to quit were randomly assigned to one of two conditions: Contingent ALL (C-ALL), who earned monetary incentives contingent on smoking abstinence during three 5 day experimental periods; or Contingent LAST (C-LAST), who earned incentives independent of abstinence during the first two periods (i.e., noncontingent payments) and contingent on abstinence during the final period. The contingency management procedure was effective in establishing different abstinence histories in the two conditions during the first two periods. Comparison of abstinence levels between the C-ALL and C-LAST conditions during the third period showed significantly greater abstinence in the C-ALL condition, although nicotine withdrawal and other subject ratings generally did not differ significantly between the two conditions. These results provide experimental evidence that prior abstinence histories can directly influence subsequent efforts to abstain from smoking. Heil, S.H., Alessi, S.M., Plebani Lussier, J., Badger, G.J., and Higgins, S.T. Nicotine & Tobacco Research, 3(3), pp. 471-479, 2004.

Do Changes in Mood and Concerns About Weight Relate to Smoking Relapse in the Postpartum Period?

The majority of women who quit smoking during pregnancy will resume smoking during the postpartum period. Little is known about the predictors of postpartum relapses to smoking. Changes in mood and increases in concerns about weight are

common during the postpartum period, and these factors may affect women's postpartum smoking behavior. Investigators at the University of Pittsburgh reviewed the literature on postpartum relapse prevention trials and present evidence of a connection between changes in mood and weight concerns to postpartum relapse. Directions for future research on the prevention of smoking relapses during the postpartum period, and the roles of mood and weight concerns in smoking relapse are presented. Levine, M.D. and Marcus, M.D. Archives of Women's Mental Health, 7(3), pp. 155-166, 2004.

Aggressive Juvenile Offenders Transitioning into Emerging Adulthood: Factors Discriminating Persistors and Desistors

As part of a randomized clinical trial comparing Multisystemic Therapy to usual community services, researchers tracked juvenile offenders through early adulthood to assess psychosocial factors that were associated with success in treatment. Of the 115 adolescents participating in the original study, 80 completed multiple assessments in young adulthood, about 5 years later. Of these 80 participants, 55 were classified as "persistors", having engaged in crimes related to property or aggression in young adulthood based on self-reports and official law enforcement records; 25 were classified as "desistors", having no such self-reported or officially reported criminal behavior. In adolescence, those who became desistors in young adulthood showed less aggressive behavior than persistors, and behaved more positively toward peers. At young adulthood, desistors reported better psychosocial adjustment overall, including more emotional support, higher job satisfaction, closer peer relationships, and fewer psychiatric problems. Differences between desistors and persistors at young adulthood remained significant even after controlling for initial differences during adolescence. These results identify several targets for prevention and treatment interventions that could impact the long-term functioning of juvenile offenders as they transition to adulthood. Clingempeel, W.G. and Henggeler, S.W. American Journal of Orthopsychiatry, 73, pp. 310-323, 2003.

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

Research Findings - Research on Pharmacotherapies for Drug Abuse

Benzodiazepine Attenuates the Behavioral Effects of d-Amphetamine in Humans

The results of preclinical studies suggest that gamma-aminobutyric acidA (GABAA) receptor agonists attenuate the behavioral effects of stimulants. In this study, the investigators from College of Medicine, University of Kentucky trained 6 humans to discriminate 15-mg oral d-amphetamine. After acquiring the discrimination, the effects of d-amphetamine (0, 2.5, 5, 10, and 15 mg), alone and following pretreatment with alprazolam (0 and 0.5 mg), were assessed. d-Amphetamine alone produced stimulant-like self-reported drug effects in a dose-dependent fashion. Alprazolam alone did not occasion d-amphetamine-like discriminative effects, nor did it increase ratings of sedation or impair performance, but Alprazolam pretreatment significantly attenuated the discriminative stimulus effects of d-amphetamine and some of the self-reported drug effects. This study conforms that GABA-A agonists reduce some subjective effects of psychostimulants in humans. Rush, C.R., Stoops, W.W., Wagner, F.P., Hays, L.R. and Glaser, P.E. Alprazolam Attenuates the Behavioral Effects of d-Amphetamine in Humans. Journal of Clinical Psychopharmacology, 24(4), pp. 410-420, 2004.

GABA Agonist Decreases Subjective Effects of Cocaine

Animal research indicates that GABA agonists decrease cocaine self-administration, but their effectiveness to do so in humans has not been investigated in the laboratory. The investigators from the College of Physicians and Surgeons of Columbia University evaluated the effects of gabapentin, a GABA agonist, on cocaine-related behaviors in humans under laboratory conditions. During a 48-day double-blind, crossover design study, the effects of gabapentin maintenance on response to cocaine were investigated in seven cocaine abusers. Cocaine significantly increased choice to self-administer cocaine, subjective-effect ratings, blood pressure and heart rate. Gabapentin did not reduce cocaine choice or cardiovascular measures, but it decreased some subjective effects of cocaine (e.g., "Good Drug Effect" and "Anxious"). The data suggest a potential of gabapentin in treating cocaine dependence. 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 and Alcohol Dependence, 73(3), pp. 279-287, 2004.

Intranasal Cocaine Produces Acute Tolerance in Humans

Although recent research has focused on "crack" cocaine, the majority of the cocaine users in the United States snort cocaine rather than smoke it. Acute tolerance to smoked or intravenous cocaine is known to develop, but it was not known whether this is also the case with cocaine snorting. The investigators from the Department of Psychiatry, College of Physicians and Surgeons of Columbia University examined the dose-dependent effects of repeated intranasal cocaine in humans. Ten male cocaine users were admitted to the hospital on two separate occasions for four days each, with a minimal two-week interval between admissions. During each admission, an intranasal cocaine dose-response curve was determined during four laboratory sessions: Two administrations of the same cocaine dose occurred each session at 40-min intervals. Intranasal cocaine produced dose-related increases in ratings of "positive" drug effects, heart rate, and blood pressure. Plasma cocaine levels peaked following the second cocaine snorting of each session, while metabolite levels

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increased during each session. Although the plasma cocaine level approximately doubled following the second cocaine administration, the ratings of positive drug effects, heart rate, and blood pressure did not increase. The data demonstrate that, as observed with smoked and intravenous cocaine, acute tolerance develops also during repeated intranasal cocaine administration. Foltin, R.W. and Haney, M. Intranasal Cocaine in Humans: Acute Tolerance, Cardiovascular and Subjective Effects. Pharmacology Biochemistry and Behavior, 78(1), pp. 93-101, 2004.

Lack of a Relationship Between D2 Receptor Availability and Cocaine-Taking Behavior

Some brain imaging and animal studies suggested that low availability of striate dopamine D2 receptors may promote cocaine addiction. The investigators from the Department of Psychiatry, College of Physicians and Surgeons of Columbia University assessed D2 receptor availability with positron emission tomography (PET) and [11C]raclopride in the limbic, associative, and sensory-motor subdivisions of the striatum in 17 recently detoxified chronic cocaine-dependent (CCD) subjects and 17 matched healthy control (HC) subjects. The relationship between D2 receptor availability and behavioral measures obtained during cocaine self-administration sessions was also examined in CCD subjects. [11C]Raclopride binding potential was significantly reduced by 15.2% in the limbic striatum, 15.0% in the associative striatum, and 17.1% in the sensori-motor striatum in CCD subjects compared to HC subjects, but no relationship was found between D2 availability and either the positive effects of smoked cocaine or the choice of cocaine over an alternative reinforcer (money) following a priming dose of cocaine. This study confirmed a decrease in striatal D2 receptor availability in CCD subjects, but failed to demonstrate a relationship between D2 receptor availability and cocaine-induced cocaine-taking behavior. Martinez, D., Broft, A., Foltin, R,W., Slifstein, M., Hwang, D.R., Huang, Y., Perez, A., Frankel, W.G., Cooper, T., Kleber, H.D., Fischman, M.W. and Laruelle, M. Cocaine Dependence and D2 Receptor Availability in the Functional Subdivisions of the Striatum: Relationship with Cocaine-Seeking Behavior. Neuropsychopharmacology, 29(6), pp. 1190-1202, 2004.

Predictors of Treatment Contact Among Individuals with Cannabis Dependence

Epidemiological studies have repeatedly shown that cannabis is the most commonly used illegal drug in the United States. Furthermore, individuals with cannabis dependence have high rates of comorbid substance use disorders and depression. A significant proportion of individuals with addictive disorders develop withdrawal symptoms, cannot control their drug use despite substantial adverse psychosocial consequences, and frequently have a coexisting psychiatric disorder. Nevertheless, only a minority of persons with cannabis dependence ever seek treatment. The main findings of this study were that persons with cannabis dependence were more likely to contact a professional during the past year if they previously sought treatment and had alcohol dependence with major depression. Agosti, V. and Levin, F.R. Predictors of Treatment Contact Among Individuals with Cannabis Dependence. Am. J. Drug Alcohol Abuse, 30, pp. 121-127, 2004.

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

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

preliminary, may have clinical implications for postmenopausal women who attempt to quit smoking while on HRT, particularly since depressed mood following abstinence is associated with a relapse to smoking. Allen, S.S., Hatsukami, D.K. and Christianson, D. Nicotine Withdrawal and Depressive Symptomatology During Short-term Smoking Abstinence: A Comparison of Postmenopausal Women Using and Not Using Hormone Replacement Therapy. Nicotine. Tob. Res., 5, pp. 49-59, 2003.

The Evidence-based Pharmacological Treatment of Social Anxiety Disorder

Social anxiety disorder (SAD) is a highly prevalent and often disabling disorder. This paper reviews the pharmacological treatment of SAD based on published placebo-controlled studies and published meta-analyses. It addresses three specific questions: What is the first-line treatment of SAD? How long should treatment last? What should be the management of treatment-resistant cases? Based on their efficacy for SAD and common comorbid disorders, tolerability, and safety, SSRIs should be considered as the first-line treatment for most patients. Less information is available regarding the optimal length of treatment, although individuals who discontinue treatment after 12-20 wk appear more likely to relapse than those who continue on medication. Even less empirical evidence is available to support strategies for treatment-resistant cases. Clinical experience suggests that SSRI non-responders may benefit from augmentation with benzodiazepines or gabapentin, or from switching to MAOIs, RIMAs, benzodiazepines or gabapentin. Cognitive-behavioral therapy may also be a helpful adjunct or alternative. Blanco, C., Raza, M.S., Schneier, F.R. and Liebowitz, M.R. The Evidence-based Pharmacological Treatment of Social Anxiety Disorder. Int. J. Neuropsychopharmacol., 6, p. 427-442, 2003.

Pharmacological Treatment of Social Anxiety Disorder: A Meta-Analysis

Placebo-controlled trials have evaluated the efficacy of several medications in the treatment of social anxiety disorder but information regarding their relative efficacy is lacking. We compared the efficacy of medications systematically studied for the treatment of social anxiety disorder using meta-analytic techniques. The methodology included a database search of articles published between January 1980 and June 2001 and manual searches of bibliographies in published manuscripts. Trials were included if they reported outcome data on the Liebowitz Social Anxiety Scale (LSAS) or a categorical measure of responder status. Data were extracted independently by two authors. The Q statistic was used to assess homogeneity across trials. All analyses were conducted using intent-to-treat data. There was substantial heterogeneity across trials. The medications with largest effect sizes were phenelzine [effect size, 1.02; 95% Confidence Interval (CI), 0.52-1.52], clonazepam (effect size, 0.97; 95% CI, 0.49-1.45), gabapentin (effect size, 0.78; 95% CI, 0.29-1.27), brofaromine (effect size, 0.66; 95% CI, 0.38-0.94), and the selective serotonin reuptake inhibitors (SSRIs; effect size, 0.65; 95% CI, 0.50-0.81). There were no statistically significant differences between medications or medication groups. However, formal methods of interim monitoring adapted for meta-analyses suggested strongest evidence of efficacy for SSRIs and brofaromine. Several medications are efficacious for the treatment of social anxiety disorder. The stability of the SSRI effect size estimate in conjunction with other evidence for safety and tolerability and their ability to treat comorbid conditions supports the use of SSRIs as the first-line treatment. Direct comparisons of SSRIs vs. other promising medications deserve consideration. Blanco, C., Schneier, F.R., Schmidt, A., Blanco-Jerez, C.R., Marshall, R.D., Sanchez-Lacay, A. et al. Pharmacological Treatment of Social Anxiety Disorder: A Meta-Analysis. Depress. Anxiety,18, pp. 29-40, 2003.

Tobacco Specific Nitrosamines and Potential Reduced Exposure Products for Smokers: A Preliminary Evaluation of Advance(TM)

The purpose of this study was to develop a method for evaluating the carcinogen delivery of potential reduced exposure products (PREPs) like Advance(TM), a PREP marketed to reduce smokers' exposure to one tobacco specific nitrosamine (TSN), NNK, a potent lung carcinogen. Design, setting, and participants: Latin square ordered, three condition, outpatient, crossover design with 12 smokers of light or ultra-light cigarettes (15 or more cigarettes/day). In each five-day condition, participants either smoked own brand, Advance(TM), or no cigarettes. Also, on the first and last day of each condition, participants smoked one cigarette in the laboratory. Past experience with PREPs that failed to reduce smoking's harm demonstrates the need for clinical methods in PREP evaluation. This study shows how assessing PREP induced changes in withdrawal and exposure to carbon monoxide, nicotine, and carcinogens may help predict PREP harm reduction potential. Adequate withdrawal suppression, slightly lower concentrations of carbon monoxide, and reduction of one TSN biomarker were observed for Advance(TM). In the future,

clinical methods like those described here may be valuable for evaluating PREPs before they are marketed publicly. Breland, A.B., Acosta, M.C. and Eissenberg, T. Tobacco Specific Nitrosamines and Potential Reduced Exposure Products for Smokers: A Preliminary Evaluation of Advance(TM). Tob. Control, 12, pp. 317-321, 2003.

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

Modafinil is a novel compound that is approved for the treatment of narcolepsy. It is now being studied as a potential treatment for cocaine dependence. Cocaine withdrawal symptoms are associated with poor clinical outcome and are likely to be reversed by modafinil. In addition, the neurotransmitter actions of modafinil are opposite to cocaine-induced neuroadaptations affecting dopamine and glutamate reward circuits. Since cocaine-dependent subjects might use cocaine during a clinical trial with modafinil, this study tested the safety of intravenous cocaine (30 mg) in combination with modafinil. Each of seven subjects received a baseline (open-label) cocaine infusion. Three subsequent cocaine infusions were administered after subjects received 4 days of low dose modafinil (200 mg/day), high dose modafinil (400 mg/day), or placebo in randomized double-blind sequences. One subject received placebo prior to all infusions. Our results indicate that co-administering modafinil and a single dose of intravenous cocaine is not associated with medical risk in terms of blood pressure, pulse, temperature, or electrocardiogram measures. Furthermore, pretreatment with modafinil did not intensify cocaine euphoria or cocaine-induced craving. In fact, cocaine euphoria was significantly blunted (P=0.02) in one of our subjective measures. Dackis, C.A., Lynch, K.G., Yu, E., Samaha, F.F., Kampman, K.M., Cornish, J.W. et al. Modafinil and Cocaine: A Double-blind, Placebo-controlled Drug Interaction Study. Drug Alcohol Depend., 70, pp. 29-37, 2003.

Response to Alcohol in Females with a Paternal History of Alcoholism

Several studies have demonstrated that males with a family history of alcoholism (FHP) show less of a response to alcohol (e.g. lower ratings of intoxication) than males without a family history of alcoholism (FHN). The purpose of this pilot study was to determine if FHP females also showed a reduced sensitivity to alcohol compared to FHN females. The effects of placebo and alcohol (0.25, 0.50, 0.75 g/kg, based on total body water) were evaluated using a double-blind, placebo-controlled outpatient design. Drug effects were assessed using performance tasks, observer ratings of drug effect and subjective ratings of drug effect. There were no differences in breath alcohol levels between FHN and FHP women. FHP women were less impaired by alcohol than FHN women, as shown by DSST scores and observer-ratings. However, FHP women were more impaired on the Digit Recall task after alcohol than FHN women and they tended to have higher ratings of "Good Drug Effect," "Drug Liking" and "Willingness to Take Again." Of note, FHP women reported more dysphoric mood than FHN women in the absence of alcohol administration. The results of the study suggest that FHP women may have a reduced response to alcohol on some measures, but FHP women report greater positive effects on other measures. Overall, the differences between FHP and FHN women are subtle compared to the previous studies demonstrating a reduced response to alcohol in FHP men. Evans, S.M. and Levin, F.R. Response to Alcohol in Females with a Paternal History of Alcoholism. Psychopharmacology (Berl), 169, pp. 10-20, 2003.

Differential Response to Alcohol in Light and Moderate Female Social Drinkers

Individuals who are moderate drinkers are at increased risk to abuse alcohol. Moreover, women are more vulnerable than men to the adverse consequences of alcohol consumption and recent data indicate that the drinking pattern in women is becoming more similar to that of men. However, few studies have determined whether female moderate drinkers (MD) show a differential response to the subjective and performance effects of alcohol, compared to female light drinkers (LD). Fifteen female MD who consumed an average of 34.7 drinks/month were compared to 15 female LD who consumed an average of 6.7 drinks/month. None of the participants had a first-degree family history of alcoholism or substance abuse. The acute effects of alcohol (0, 0.25, 0.50, 0.75 mg/kg) were evaluated using a double-blind, placebo-controlled outpatient design. Drug effects were assessed using a full range of performance measures, subjective-effects questionnaires and observer ratings. Alcohol impaired performance in a dose-related manner on all performance tasks for both groups of females. However, MD was less impaired than LD on balance and Digit Symbol Substitution Test (DSST). This reduced response was also evident from the observer ratings, with MD being viewed as less impaired by alcohol than LD. While ratings of Drug Liking increased in both groups of women on the ascending limb of

the breath alcohol curve, alcohol was disliked by LD on the descending limb and LD reported increased ratings of Bad Drug Effects following the high dose of alcohol. The reduced performance impairment, coupled with the positive subjective effects and relative absence of adverse subjective effects, suggestive of behavioral tolerance, could result in a progression towards increased alcohol consumption among moderate female social drinkers. Evans, S.M. and Levin, F.R. Differential Response to Alcohol in Light and Moderate Female Social Drinkers. Behav. Pharmacol., 15, pp. 167-181, 2004.

The Problem of the Placebo Response in Clinical Trials for Psychiatric Disorders: Culprits, Possible Remedies, and a Novel Study Design Approach

The placebo response is a major issue in clinical trials for psychiatric disorders. Possible contributing factors to this problem include diagnostic misclassification, issues concerning inclusion/exclusion criteria, outcome measures' lack of sensitivity to change, measurement errors, poor quality of data entry and verification, waxing and waning of the natural course of illness, regression toward the mean phenomenon, patient and clinician expectations about the trial, study design issues, non-specific therapeutic effects, and high attrition. Over the past few decades, researchers have attempted to reduce the placebo effect in a variety of ways. Unfortunately, approaches with very little or no benefit have included restricting enrollment to selected populations, rater training, requirement of same rater, and placebo lead-in phases. Some benefits, although often marginal, have been derived from standardizing diagnostic procedures, managing clinicians' overestimation of change, simplification of study visits and assessments, minimizing non-specific, therapeutic effects, extending trial duration, reducing number of sites, increasing the sensitivity of outcome measures, and reducing the number of treatment arms. Thus far, there has been no attempt to develop new study designs aimed at reducing the placebo effect. We are proposing a novel study design, called 'Sequential Parallel Comparison Design', suitable for double-blind, placebo-controlled trials in psychiatric disorders. This design is aimed at reducing both the overall placebo response rate and the sample size required for such trials. Its usefulness in clinical research needs to be tested empirically. If this study design were to be found to meet its stated goals, this could markedly facilitate the process of clinical development of new compounds for the treatment of psychiatric disorders. Fava, M., Evins, A.E., Dorer, D.J. and Schoenfeld, D.A. The Problem of the Placebo Response in Clinical Trials for Psychiatric Disorders: Culprits, Possible Remedies, and a Novel Study Design Approach. Psychother. Psychosom., 72, pp. 115-127, 2003.

Selection of a Substance Use Disorder Diagnostic Instrument by the National Drug Abuse Treatment Clinical Trials Network

Several instruments for diagnosing substance use disorders (SUD) have been developed, but to date none has emerged as the standard for community-based clinical studies. To select the most suitable SUD diagnostic instrument for its clinical trials, the National Drug Abuse Treatment Clinical Trials Network (CTN) implemented a procedure in which 36 university-based addiction researchers and 62 community-based addiction treatment providers evaluated and ranked five widely recognized diagnostic instruments: (1) the SUD section of the Structured Clinical Interview for DSM-IV (SCID); (2) the SUD section of the Composite International Diagnostic Interview, 2nd ed. (CIDI-2); (3) the SUD section of the Diagnostic Interview Schedule for DSM-IV Diagnosis (DIS-IV); (4) the Diagnostic Statistical Manual-IV Checklist (DSM-IV Checklist); and (5) the Substance Dependence Severity Scale (SDSS). To assist the evaluation and ranking process, key characteristics of each instrument were presented in tabular and narrative formats. Participants ranked each instrument from 1 (most preferred) to 5 (least preferred). The SCID received the best overall mean score (2.24) followed by the CIDI-2 (2.59), DIS (2.94), DSM Checklist (3.40) and the SDSS (3.83). After discussing the pragmatic and scientific advantages and disadvantages of each instrument, the CTN Steering Committee selected the CIDI-2. The selection of the CIDI-2 standardizes the collection of diagnostic data and provides a common diagnostic tool for practitioners and clinical researchers in the CTN. Implications for practice/research collaboration and initiatives are explored. Forman, R.F., Svikis, D., Montoya, I.D. and Blaine, J. Selection of a Substance Use Disorder Diagnostic Instrument by the National Drug Abuse Treatment Clinical Trials Network. J. Subst. Abuse Treat., 27, pp. 1-8, 2004.

Comorbid Major Depressive Disorder as a Prognostic Factor in Cocaine-Abusing Buprenorphine-Maintained Patients Treated with Desipramine and Contingency Management

Depression is common among patients who abuse both opiates and cocaine, and its

treatment has had mixed success. This study compares buprenorphine-maintained patients with lifetime major depressive disorder (MDD, N = 53) with those never depressed (ND, N = 96) on cocaine and opiate-free urines during a 12-week outpatient double-blind, placebo-controlled, randomized clinical trial. The 149 subjects were assigned to four groups: 1) desipramine (DMI) + contingency management (CM); 2) DMI + noncontingency management (NCM); 3) placebo + CM; and 4) placebo + NCM. Depression assessments included Hamilton Depression Rating Scale, Center for Epidemiological Studies Depression Inventory, and Structured Clinical Interview for DSM-IV interview for diagnosis of lifetime MDD. Urine toxicologies were performed thrice weekly and the CES-D was performed monthly. The MDD group had a larger proportion of females (45% vs. 21%, P = 0.02) and was more likely to be married (13.2% vs. 7.3%, P = 0.02) than the ND group. Treatment retention did not vary by depression status. Hierarchical Linear Modeling found that depressive symptoms decreased comparably across the four treatment groups. Although participation in CM improved drug-free urines more for patients with MDD than for the ND group (Z = 2.44, P = 0.01), treatment with DMI was significantly more efficacious for the ND group than for the MDD group (Z = -2.89, P = 0.003). These results suggest that patients with MDD may respond better to behavioral treatments such as CM than to desipramine plus buprenorphine. The ND cocaine-abusing, opiate-dependent patients may be more responsive to the anti-craving effects of DMI. Gonzalez, G., Feingold, A., Oliveto, A., Gonsai, K. and Kosten, T.R. Comorbid Major Depressive Disorder as a Prognostic Factor in Cocaine-abusing Buprenorphine-maintained Patients Treated with Desipramine and Contingency Management. Am. J. Drug Alcohol Abuse, 29, pp. 497-514, 2003.

Tiagabine Increases Cocaine-free Urines in Cocaine-dependent Methadone-treated Patients: Results of a Randomized Pilot Study

The investigators sought to evaluate the safety and efficacy of the GABAergic agent tiagabine in reducing cocaine use among methadone-treated patients. The participants were 45 cocaine-dependent methadone-treated patients who were predominately Caucasian (75.6%), male (77.8%) and never married (53%) with an average age of 38 years (SD = 6.5). Comparison groups received tiagabine 12 mg/day (n = 15), tiagabine 24 mg/day (n = 15) or placebo (n = 15). Treatment retention was over 80% for all treatment groups. The sample mean (+/- SE) of cocaine-free urines for the first week after study entry and before tiagabine was started was 1.16 (0.19) urines/week. During weeks 9 and 10 cocaine-free urines increased significantly from baseline by 33% with high-dose tiagabine (24 mg/day), by 14% with low-dose tiagabine (12 mg/day) and decreased by 10% with placebo (hierarchical linear model, Z= 2.03; P < 0.05). Self-reported cocaine use also decreased significantly more with active medications than with placebo. Tiagabine at 24 mg/day was well tolerated among these methadone-treated patients with only one reporting headache. Tiagabine appears to be a promising GABAergic medication that moderately improves cocaine-free urines. Gonzalez, G., Sevarino, K., Sofuoglu, M., Poling, J., Oliveto, A., Gonsai, K. et al. Tiagabine Increases Cocaine-free Urines in Cocaine-dependent Methadone-treated Patients: Results of a Randomized Pilot Study. Addiction, 98, pp. 1625-1632, 2003.

Paroxetine Treatment of Pathological Gambling: A Multi-center Randomized Controlled Trial

Previous studies have suggested the efficacy of serotonergic agents in the treatment of pathological gambling. The aim of the present study was to determine whether treatment with paroxetine in a large sample of subjects with pathological gambling would effectively diminish the severity of gambling symptoms. A 16-week, double-blind, placebo-controlled trial was conducted at five outpatient academic research centers in two countries (USA and Spain). Seventy-six outpatients (mean age 45.4+/-10.6 years; 30 women, 46 men) with pathological gambling were randomized to acute treatment with paroxetine in flexible daily dosages of 10-60 mg/day (n=36) or placebo (n=40). The primary outcome measure was the Clinical Global Impressions scale. Both the paroxetine- and the placebo-treated groups demonstrated comparable improvement at 16 weeks (59% response rate in the paroxetine group, 49% rate in the placebo group; chi squared=0.737; d.f.=1; P=0.390). Paroxetine consistently resulted in a greater percentage of responders at each study visit compared to placebo but failed to demonstrate statistical superiority to placebo on scores on the Clinical Global Impressions scale, the Yale-Brown Obsessive-Compulsive Scale Modified for Pathological Gambling, or the Gambling Symptom Assessment Scale. High rates of symptom improvement were observed in pathological gamblers receiving either paroxetine or placebo after 16 weeks. Paroxetine consistently demonstrated an advantage over placebo on the Clinical Global Impressions scale;

however, a larger sample size may have registered significant differences. Grant, J.E., Kim, S.W., Potenza, M.N., Blanco, C., Ibanez, A., Stevens, L. et al. Paroxetine Treatment of Pathological Gambling: A Multi-center Randomized Controlled Trial. Int. Clin. Psychopharmacol., 18, pp. 243-249, 2003.

Effects of Buprenorphine Maintenance Dose on Mu-opioid Receptor Availability, Plasma Concentrations, and Antagonist Blockade in Heroin-dependent Volunteers

The clinical effectiveness of opioid maintenance for heroin dependence is believed to result from a medication's ability to decrease mu-opioid receptor (muOR) availability thereby replacing agonist effects, alleviating withdrawal symptoms and attenuating heroin effects. Authors empirically tested this hypothesis in five heroin-dependent volunteers who were successively maintained on 32, 16, 2, and 0 mg daily buprenorphine (BUP) tablet doses. Authors predicted and confirmed that higher BUP doses would decrease in vivo muOR availability (measured with PET and [(11)C]carfentanil), increase plasma levels of BUP and its metabolite nor-BUP, and decrease withdrawal symptoms and hydromorphone (HYD) responses. Relative to placebo, BUP significantly decreased mean (+/-SEM) whole-brain muOR availability 41+/-8, 80+/-2, and 84+/-2% at 2, 16, and 32 mg, respectively. Regions of interest (ROIs) (prefrontal cortex, anterior cingulate, thalamus, amygdala, nucleus accumbens, caudate) showed similar dose-dependent effects. Changes in muOR availability varied across ROIs (prefrontal cortex, 47% vs. amygdala, 27%) at BUP 2 mg, but were more homogeneous across ROIs at BUP 32 mg (94-98%; except thalamus, 88%). Relative to placebo (0 ng/ml), peak plasma levels of BUP and nor-BUP were comparable and dose-dependent (0.5-1, 5-6, and 13-14 ng/ml at 2, 16, and 32 mg, respectively). muOR availability decreases were negatively correlated with BUP plasma level and positively correlated with questionnaire-based opioid withdrawal symptoms and attenuation of HYD symptoms. These findings suggest that high-dose BUP maintenance produces near-maximal muOR occupation, muOR availability correlates well with plasma levels, and BUP-related opioid symptoms and antagonist blockade exhibit concentration-effect relationships. Greenwald, M.K., Johanson, C.E., Moody, D.E., Woods, J.H., Kilbourn, M.R., Koeppe, R.A. et al. Effects of Buprenorphine Maintenance Dose on Mu-opioid Receptor Availability, Plasma Concentrations, and Antagonist Blockade in Heroin-dependent Volunteers. Neuropsychopharmacology, 28, pp. 2000-2009, 2003.

Transferring Methadone-maintained Outpatients to the Buprenorphine Sublingual Tablet: A Preliminary Study

There is no accepted algorithm to transfer opioid-dependent patients from methadone (METH) to its new alternative, buprenorphine (BUP). Five outpatients transferred (double blind, double dummy) from METH 60 mg/day (with one day at 45 mg) to BUP 8 mg s.l. tablet. Relative to METH maintenance, BUP decreased opioid agonist symptoms (transfer day 1) and increased withdrawal symptoms (days 1 and 2) and blood pressure (day 2). Self-reported heroin use did not increase from METH maintenance levels. It may be feasible to transfer outpatients on METH 60 mg/day to BUP 8 mg/day s.l. tablet, although this pilot protocol needs refinements to improve tolerability and clinical efficacy. Greenwald, M.K., Schuh, K.J. and Stine, S.M. Transferring Methadone-maintained Outpatients to the Buprenorphine Sublingual Tablet: A Preliminary Study. Am. J. Addict., 12, pp. 365-374, 2003.

Treatment of Adolescent Smokers with the Nicotine Patch

This study examined the effects of the nicotine patch on craving and withdrawal symptoms, safety, and compliance among adolescents. The secondary goal was to conduct a preliminary investigation of the effectiveness of the nicotine patch in helping adolescents quit smoking. The study design was a double-blind, placebo-controlled, randomized trial of the nicotine patch. The intervention also provided intensive cognitive-behavioral therapy and a contingency-management procedure. Participants (n=100) attended 10 treatment visits over 13 weeks. Compared with the placebo patch group, the active nicotine patch group experienced a significantly lower craving score and overall withdrawal symptom score ($p=.011$ and $p=.025$, respectively), as well as a time trend toward lower scores ($p<.001$) in craving only. Moreover, the nicotine patch appeared safe for adolescents to use. No differences by treatment group were found in experiencing adverse events, except that the participants in the placebo patch group reported more headaches than those in the active nicotine patch group. As another measure of safety, the overall mean salivary cotinine levels were significantly lower at 1, 6, 8, and 10 weeks post quit (all $p<.05$) compared with baseline levels, although these results were confounded by dropouts. Additionally, a significant number of participants were compliant with using the

nicotine patch daily. Finally, point prevalence (7-day and 30-day abstinence rates) and survival analysis of participant abstinence indicated no significant differences between treatment groups. The results of this study suggest that the nicotine patch is a promising medication and a larger clinical trial of the nicotine patch among adolescents is warranted. Hanson, K., Allen, S., Jensen, S. and Hatsukami, D. Treatment of Adolescent Smokers with the Nicotine Patch. Nicotine. Tob. Res., 5, pp. 515-526, 2003.

Genetics of Pathological Gambling

Pathological gambling (PG) is an impulse control disorder and a model 'behavioral' addiction. Familial factors have been observed in clinical studies of pathological gamblers, and twin studies have demonstrated a genetic influence contributing to the development of PG. Serotonergic, noradrenergic, and dopaminergic dysfunction have been reported as biological factors contributing to the pathophysiology of PG. Molecular genetic techniques have been used to investigate the role of genetic factors in PG. Molecular genetic research has identified specific allele variants of candidate genes corresponding to these neurotransmitter systems to be associated with PG. Associations have been reported between pathological gamblers and allele variants of polymorphisms at dopamine receptor genes, the serotonin transporter gene, and the monoamine-oxidase A gene. Although preliminary data suggest that some of these differences are gender-specific, more research needs to be performed to substantiate gender-specific genetic contributions to the development of pathological gambling. The review of the current findings on genetics of PG suggests that liability to PG is in part mediated by genetic factors. Additional studies are needed to replicate and extend these findings, as well as to better understand the influence of specific allelic variants to differences in biological and behavioral functioning. Ibanez, A., Blanco, C., de Castro, I.P., Fernandez-Piqueras, J. and Saiz-Ruiz, J. Genetics of Pathological Gambling. J. Gambl. Stud., 19, pp. 11-22, 2003.

Gender Differences in Pathological Gambling

Sixty-nine consecutive individuals with DSM-IV pathological gambling (47 men and 22 women) applying to a specialized outpatient treatment program were evaluated with structured interviews, self-report questionnaires, and psychological scales. Sixty-seven percent of men (N = 26) versus 25% of women (N = 5) had been exposed to gambling in adolescence. Women had a later age at first bet and a faster evolution of the disorder. Female pathological gamblers were more likely to play bingo, whereas men tended to prefer slot machines. Male and female pathological gamblers had similar gambling severity and overall rates of psychiatric comorbidity. However, male pathological gamblers had higher rates of alcohol abuse/dependence and antisocial personality disorder, whereas women had higher rates of affective disorders and history of physical abuse. There are substantial gender differences in the clinical presentation and comorbidity of pathological gambling. These gender differences should be incorporated in the selection and planning of treatment for pathological gamblers. Ibanez, A., Blanco, C., Moreryra, P. and Saiz-Ruiz, J. Gender Differences in Pathological Gambling. J. Clin. Psychiatry, 64, pp. 295-301, 2003.

Desipramine and Contingency Management for Cocaine and Opiate Dependence in Buprenorphine Maintained Patients

Co-dependence on opiates and cocaine occurs in about 60% of patients entering methadone treatment and has a poor prognosis. However, authors recently found that desipramine (DMI) could be combined with buprenorphine to significantly reduce combined opiate and cocaine use among these dually dependent patients. Furthermore, contingency management (CM) has been quite potent in reducing cocaine abuse during methadone maintenance. To test the efficacy of combining CM with these medications authors designed a 12-week, randomized, double blind, four cell trial evaluating DMI (150 mg/day) or placebo plus CM or a non-contingent voucher control in 160 cocaine abusers maintained on buprenorphine (median 16 mg daily). Cocaine-free and combined opiate and cocaine-free urines increased more rapidly over time in those treated with either DMI or CM, and those receiving both interventions had more drug-free urines (50%) than the other three treatment groups (25-29%). Self-reported opiate and cocaine use and depressive and opioid withdrawal symptoms showed no differences among the groups and symptom levels did not correlate with urine toxicology results. Lower DMI plasma levels (average 125 ng/ml) were associated with greater cocaine-free urines. DMI and CM had independent and additive effects in facilitating cocaine-free urines in buprenorphine maintained patients. The antidepressant appeared to enhance responsiveness to CM reinforcement. Kosten, T., Oliveto, A., Feingold, A., Poling, J., Sevarino, K., McCance-Katz, E. et al. Desipramine and Contingency Management for Cocaine and Opiate

Dependence in Buprenorphine Maintained Patients. Drug Alcohol Depend., 70, pp. 315-325, 2003.

Pharmacotherapy for Marijuana Dependence: A Double-blind, Placebo-con trolled 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. We 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. et al. Pharmacotherapy for Marijuana Dependence: A Double-blind, Placebo-controlled Pilot Study of Divalproex Sodium. Am. J. Addict., 13, pp. 21-32, 2004.

Gender and Smoking Status-based Analysis of Views Regarding Water Pipe and Cigarette Smoking in Aleppo, Syria

Narghile (water pipe) smoking is increasing across the Eastern Mediterranean region (EMR), though little is known about the social attitudes and perceptions related to this method of tobacco use, and how those attitudes and perceptions are influenced by gender. Data from two cross-sectional surveys conducted in 2003 in Aleppo, Syria, were used to examine these issues. Overall, 855 participants were included (439 men, 416 women; mean age, 24.4+/-7.1 years; response rate, 97%). The current analysis focuses on responses to four similar nine-item questions tapping perceptions related to narghile smoking by women or men, and cigarette smoking by women or men. Scores on the nine items were summed to yield a total score to gauge participants' perceptions about narghile and cigarette. Generally, participants were less positive about women smoking relative to men smoking, and cigarette smoking relative to narghile smoking. Cigarette smoking by women was the behavior least associated with positive perceptions. Individuals who resided in the city, were economically better off, and were Christian, had higher perception scores (i.e., more positive attitudes) toward all forms of smoking, whereas older and married participants had higher perception scores for narghile only. Smoking status of participants, especially narghile smoking, was also associated with more positive perceptions toward smoking in general. We conclude that preliminary analysis shows that views on different forms of smoking in Syria differ by gender and smoking status. Maziak, W., Rastam, S., Eissenberg, T., Asfar, T., Hammal, F., Bachir, M.E. et al. Gender and Smoking Status-based Analysis of Views Regarding Water Pipe and Cigarette Smoking in Aleppo, Syria. Prev. Med., 38, pp. 479-484, 2004.

Randomized Trial of Buprenorphine for Treatment of Concurrent Opiate and Cocaine Dependence

This study evaluated buprenorphine for the treatment of concomitant cocaine and opiate dependence. Two hundred outpatients currently dependent on both cocaine and opiates were randomly assigned to double-blind groups receiving a sublingual solution of buprenorphine (2, 8, or 16 mg daily, or 16 mg on alternate days, or placebo), plus weekly individual drug abuse counseling, for 13 weeks. The chief outcome measures were urine concentrations of opiate and cocaine metabolites (quantitative) and proportion of urine samples positive for opiates or cocaine (qualitative). Group differences were assessed by use of mixed regression modeling. The target dose of buprenorphine was achieved in 179 subjects. Subjects receiving 8 or 16 mg buprenorphine daily showed statistically significant decreases in urine morphine levels ($P = .0135$ for 8 mg and $P < .001$ for 16 mg) or benzoylecgonine concentrations ($P = .0277$ for 8 mg and $P = .006$ for 16 mg) during the maintenance phase of the study. For the 16-mg group, mean benzoylecgonine concentrations fell from 3715 ng/mL during baseline to 186 ng/mL during the withdrawal phase; mean morphine concentrations fell from 3311 ng/mL during baseline to 263 ng/mL during withdrawal. For the 8-mg group, mean benzoylecgonine concentrations fell from 6761 ng/mL during baseline to 676 ng/mL during withdrawal; mean morphine concentrations fell from 3890 ng/mL during baseline to 661 ng/mL during withdrawal.

Qualitative urinalysis showed a similar pattern of results. Subjects receiving the highest dose showed concomitant decreases in both urine morphine and benzoylecgonine concentrations. There were no significant group differences in treatment retention or adverse events. The results suggest that a sublingual buprenorphine solution at 16 mg daily is well tolerated and effective in reducing concomitant opiate and cocaine use. The therapeutic effect on cocaine use appears independent of that on opiate use. Montoya, I.D., Gorelick, D.A., Preston, K.L., Schroeder, J.R., Umbricht, A., Cheskin, L.J. et al. Randomized Trial of Buprenorphine for Treatment of Concurrent Opiate and Cocaine Dependence. Clin. Pharmacol. Ther., 75, pp. 34-48, 2004.

Treatment of Depression in Patients with Alcohol or Other Drug Dependence: A Meta-Analysis

Depression and substance abuse are common and costly disorders that frequently co-occur, but controversy about effective treatment for patients with both disorders persists. The purpose of this study was to conduct a systematic review and meta-analysis to quantify the efficacy of antidepressant medications for treatment of combined depression and substance use disorders. Data was obtained from PubMed, MEDLINE, and Cochrane database search (1970-2003), using the keywords antidepressant treatment or treatment depressed in conjunction with each of the following alcohol dependence, benzodiazepine dependence, opiate dependence, cocaine dependence, marijuana dependence, and methadone; a search of bibliographies; and consultation with experts in the field. Among inclusion criteria used for study selection were prospective, parallel group, double-blind, controlled clinical trials with random assignment to an antidepressant medication or placebo for which trial patients met standard diagnostic criteria for current alcohol or other drug use and a current unipolar depressive disorder. Of the more than 300 citations extracted, 44 were placebo-controlled clinical trials, 14 of which were selected for this analysis and included 848 patients: 5 studies of tricyclic antidepressants, 7 of selective serotonin re-uptake inhibitors, and 2 from other classes. The investigators independently screened the titles and abstracts of each citation, identified placebo-controlled trials of patients with both substance dependence and depression, applied the inclusion criteria, and reached consensus. Data on study methods, sample characteristics, and depression and substance use outcomes were extracted. The principal measure of effect size was the standardized difference between means on the Hamilton Depression Scale (HDS). For the HDS score, the pooled effect size from the random-effects model was 0.38 (95% confidence interval, 0.18-0.58). Heterogeneity of effect on HDS across studies was significant ($P < .02$), and studies with low placebo response showed larger effects. Moderator analysis suggested that diagnostic methods and concurrent psychosocial interventions influenced outcome. Studies with larger depression effect sizes (>0.5) demonstrated favorable effects of medication on measures of quantity of substance use, but rates of sustained abstinence were low. The results suggest that antidepressant medication exerts a modest beneficial effect for patients with combined depressive- and substance-use disorders. It is not a stand-alone treatment, and concurrent therapy directly targeting the addiction is also indicated. More research is needed to understand variations in the strength of the effect, but the data suggest that care be exercised in the diagnosis of depression-either by observing depression to persist during at least a brief period of abstinence or through efforts by clinical history to screen out substance-related depressive symptoms. Nunes, E.V. and Levin, F.R. Treatment of Depression in Patients with Alcohol or Other Drug Dependence: A Meta-Analysis. JAMA, 291, pp. 1887-1896, 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. Results showed that 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. The results suggest that 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.

Prediction of Treatment Outcome by Baseline Urine Cocaine Results and Self-reported Cocaine Use for Cocaine and Opioid Dependence

This study examined the usefulness of baseline cocaine urine toxicology results and self-reported days of cocaine use in predicting treatment response in cocaine- and opioid-dependent subjects. Ninety-nine male and 52 female subjects, maintained on buprenorphine, participated in a 24-week, randomized, double-blind, four-cell trial that evaluated desipramine (150 mg/d) or placebo plus contingency management or a non-contingent voucher control. Out of 151, 102 (67%) subjects had cocaine-positive and 49 (32%) cocaine-negative urines at the beginning of treatment. For the previous 30 days before study participation, 91 (60%) subjects reported using cocaine 15 or less days (low baseline cocaine use) and 60 (40%) subjects reported more than 15 days (high baseline cocaine use). By using the treatment effectiveness score (TES) as the outcome measure, a negative urine for cocaine at baseline predicted a better outcome during a 24-week trial for cocaine and opioid use. There also was a significant interaction between baseline cocaine urine results and desipramine response with the urine cocaine-negative group showing greater desipramine response than placebo for opioid and cocaine use. Self-reported cocaine use at baseline did not show significant predictive power for TES scores during the clinical trial. These results suggest that baseline cocaine urine results should be considered as stratifying variables in clinical trials for cocaine dependence. Sofuoglu, M., Gonzalez, G., Poling, J. and Kosten, T.R. Prediction of Treatment Outcome by Baseline Urine Cocaine Results and Self-reported Cocaine Use for Cocaine and Opioid Dependence. Am. J. Drug Alcohol Abuse, 29, pp. 713-727, 2003.

Serious Mental Illness and Tobacco Addiction: A Model Program to Address this Common but Neglected Issue

Tobacco addiction among persons with serious mental illness (SMI) has been largely ignored. About 75 to 85% of persons with schizophrenia, bipolar disorder, and other SMI use tobacco; most will either die and/or have reduced quality of life because of tobacco-caused medical diseases. Tobacco addiction is the most common co-occurring disorder for the SMI population. A dramatic reduction in tobacco use in the general population has occurred during the past 40 years; however, there has been almost no reduction for smokers with SMI. Clinical and research evidence supports motivation-based treatment, blending mental health and addiction treatment approaches, and integrating tobacco dependence treatment within mental health settings. The unique barriers and clinical issues for this population are described. Ziedonis, D., Williams, J.M. and Smelson, D. Serious Mental Illness and Tobacco Addiction: A Model Program to Address this Common but Neglected Issue. Am. J. Med. Sci., 326, pp. 223-230, 2003.

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

Research Findings - Research on Medical Consequences of Drug Abuse

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). This study examined 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 Puerto Rican 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 higher seroconversion rate found in PR indicates a need to enhance HIV prevention efforts, including increasing methadone treatment and access to sterile syringes. The findings also underscore the importance of interventions that target sexual risk behaviors in both locations. Efforts to reduce HIV transmission in the Caribbean should address the significant role of high-risk drug use in the epidemic in Puerto Rico. Deren, S., Kang, S.Y., 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(5), pp. 1067-1107, 2004.

Effects of Changes in Perceived Self-Efficacy on HIV Risk Behaviors Over Time

This study examined the impact of changes in self-efficacy over time on HIV-related injection and sex risk behaviors among Puerto Rican drug injectors and crack smokers. Baseline (T1) and 6-month follow-up (T2) data were collected between 1998 and 2000 in New York and Puerto Rico (follow-up rate=79%, 952/1199). Differences in scores on self-efficacy (for risk behaviors) between T1 and T2 were first computed and dichotomized (negative change vs. no/positive change). Those with negative change in self-efficacy were more likely than those with no/positive change to engage in HIV injection and sex risk behaviors at T2. The relationships were significant in multiple logistic regressions after controlling for the effects of potential confounding variables. The findings indicate that improving perceived self-efficacy for risk reduction can help reduce HIV transmission behaviors in high-risk drug users, and have implications for the development of effective HIV/AIDS prevention. Kang, S.Y., Deren, S., Andia, J., Colon, H.M. and Robles, R. Effects of Changes in Perceived Self-Efficacy on HIV Risk Behaviors Over Time. Addict Behav, 29(3), pp. 567-74, 2004.

Detection of Hepatitis C Virus in the Nasal Secretions of an Intranasal Drug User

Hepatitis C virus (HCV) is a major cause of liver-related morbidity and mortality worldwide, with an estimated global prevalence of 170 million chronic infections. HCV-induced liver disease is the most common indication for liver transplantation and it has emerged as a leading cause of death among hospitalized HIV-infected patients treated during the HAART era. Although much is known about the routes of HCV transmission, nearly 15% of infected individuals report no identifiable source of exposure. Unexplained cases are particularly high among drug-users who have no history of injection risk and no other identifiable risk factors. One hypothesis that

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might account for the high number of unexplained HCV infections among noninjection drug users is the sharing of contaminated implements, such as straws or spoons, to nasally inhale cocaine and other powdered drugs. An essential precondition for this mode of transmission is the presence of HCV in the nasal secretions of intranasal drug users. In this preliminary study, researchers recruited five patients from clinics in East Harlem, New York. All subjects were male between 46 to 56 years of age and HIV-1 seropositive, had previously tested HCV seropositive, and reported a history of intranasal drug use. Blood and nasal secretion samples were collected and tested for HCV RNA using RT-PCR. HCV was detected in each of the five blood samples and in the nasal secretions of the subject with the highest serum viral load. This finding does not confirm intranasal viral transmission, but it does lend virological support to previous indications that intranasal drug use poses a risk by confirming an important precondition for this route of infection. McMahon, J., Simm, M., Milano, D. and Clatts, M. Detection of Hepatitis C Virus in the Nasal Secretions of an Intranasal Drug User. Ann Clin Microbiol Antimicrob, 73(1), pp. 6-10, 2004.

HIV Risk, Seropositivity, and Predictors of Infection Among Homeless and Non-Homeless Women Sex Workers in Miami

Although homelessness has frequently been associated with substance abuse, and has been established as a predictor of HIV risk among substance abusers, little is known about the impact of homelessness on HIV risk among female sex workers. This analysis investigated the contribution of homelessness to sexual risk taking among a sample of 485 female sex workers recruited into an HIV prevention program in Miami, Florida, 41.6% of whom considered themselves to be currently homeless. In comparison to non-homeless sex workers, significantly more homeless sex workers were daily users of alcohol and crack, and their past month sex work reflected more frequent vaginal and oral sex acts, higher levels of unprotected vaginal sex and more numerous sexual activities while 'high' on drugs. At the same time, a significantly greater proportion of homeless sex workers encountered customers that refused to use condoms than did the non-homeless sex workers. There were no significant differences in HIV seropositivity between the homeless and non-homeless women (22.5 and 24.9%, respectively), primarily because the majority of the women in the study cycled in and out of homelessness. These findings show how urgent it is to break the continuing cycle of homelessness in the lives of these women. Such cost-effective approaches as specialized HIV/AIDS interventions, intensive outreach to the homeless sex worker community to increase willingness to participate and retention in intervention programs, improved referral linkages to substance abuse treatment facilities, and readier access to treatment and other community services, would have tremendous public health benefit both to the women and to society as a whole. Surratt, H. and Inciardi, J. HIV Risk, Seropositivity, and Predictors of Infection Among Homeless and Non-Homeless Women Sex Workers in Miami. AIDS Care, 16(5), pp. 594-604, 2004.

Prevalence and Incidence of HIV, Hepatitis B Virus, and Hepatitis C Virus Infections Among Males in Rhode Island Prisons

Concerns exist that jails and prisons could serve as reservoirs that could amplify transmission of infectious diseases in the wider community as inmates who become infected while behind bars are released. Such reservoirs would be formed by the high prevalence of infections such as HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) among inmates, particularly those with a history of injection drug use. In this study, researchers evaluated the prevalence and intraprison incidence of HIV, HBV, and HCV among male prison inmates by observing intake prevalence for 4269 sentenced inmates at the Rhode Island Adult Correctional Institute between 1998-2000 and incidence among 446 continuously incarcerated inmates (incarcerated for 12 months or more). They found that HIV, HBV, and HCV prevalences were 1.8%, 20.2%, and 23.1%, respectively, and that infections were significantly associated with injection drug use (odds ratio =10.1, 7.9, and 32.4). Incidence per 100 person-years was 0 for HIV, 2.7 for HBV, and 0.4 for HCV. These findings are a cause for continuing public health concern. Although HIV infection was relatively low, the infection rate was similar to what has been previously reported from Rhode Island. These data are indicative of significant HBV transmission. They underscore the importance of offering HBV vaccinations in prisons as a cost-effective public health priority, particularly given the impact of infected individuals on the incarcerated population and, beyond the prison walls, on the transmission of HIV, HBV, and HCV in the communities to which inmates return. Macalino, G., Vlahov, D., Sanford-Colby, S., Patel, S., Sabin, K., Salas, C. and Rich, J. Prevalence and Incidence of HIV, Hepatitis B Virus, and Hepatitis C Virus Infections Among Males in Rhode Island Prisons. Am J Public Health, 94, pp. 1218-1223, 2004.

Prevention Myths and HIV Risk Reduction by Active Drug Users

A survey was conducted among 526 drug injectors and crack smokers in South Florida to explore beliefs concerning the effectiveness of 14 HIV prevention strategies used in sexual situations, with a focus on the relationship between these beliefs and reported use of condoms. Each of 14 identified sexual risk reduction strategies was believed to be an effective method of HIV prevention by at least 25%, and condom use was endorsed as an effective HIV prevention strategy by 95%. Substantial numbers of sexually active drug users believed in alternative, ineffective strategies for preventing the spread of HIV, and those who subscribed to such "prevention myths" were also more likely to report inconsistent or non-use of condoms. However, HIV prevention strategies that would generally be considered "safe" or "safer," such as condom use, abstinence, and having sex with only one partner, were most likely to be endorsed as effective, indicating that drug users have general knowledge about the correct set of prevention strategies but that their prevention arsenals also include a variety of prevention myths. Given the public health importance of stemming the spread of HIV through reduction in risk behaviors, and the apparent prevalence of misconceptions regarding effective risk reduction strategies, interventions conducted among all risk groups should take into account the roles that risk reduction beliefs and perceived social norms play in shaping risk practices of drug users. Metsch, L.R., McCoy, C.B., Miles, C.C. and Wohler, B. Prevention Myths and HIV Risk Reduction by Active Drug Users. AIDS Educ and Prev, 16(2), pp. 150-159, 2004.

Efficacy of a Woman-Focused Intervention to Reduce HIV Risk and Increase Self-Sufficiency Among African American Crack Abusers

Researchers compared 3- and 6-month outcomes of a woman-focused HIV intervention for crack abusers, a revised NIDA standard intervention, and a control group. Outreach workers in the community were trained to refer out-of-drug-treatment African American women (n=620) who used crack to field sites for participation in a randomized field experiment. The results showed that all 3 groups significantly reduced crack use and high-risk sex at each follow-up, but only woman-focused intervention participants consistently improved on measures of employment and housing status. Compared with control subjects at 6 months, woman-focused intervention participants were least likely to engage in unprotected sex; revised standard intervention women reported greatest reductions in crack use. The results of this study are consistent with previous research that out-of-treatment African American women who use crack and are at high risk of HIV successfully reduce drug use and sex risk behaviors when they receive tailored educational and skill-building interventions. Moreover, the women who received the women-focused intervention also improved in measures of employment and housing status. These changes can provide greater stability to the daily lives of these women and thereby help to reduce the frequency of drug use and unprotected sex in the longer term. Wechsberg, W., Lam, W., Zule, W. and Bobashev, G. Efficacy of a Woman-Focused Intervention to Reduce HIV Risk and Increase Self-Sufficiency Among African American Crack Abusers. Am J Public Health, 94, pp. 1165—1173, 2004.

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

Researchers examined HIV risk behaviors among drug-using African American, Asian/Pacific Islander (API), and Latina male-to-female (MTF) transgender persons to identify factors that can be addressed in behavioral prevention interventions aimed at reducing HIV and other infections and transmissions. They conducted individual survey interviews with MTF transgender persons of color (n=332; 112 African Americans, 110 Latinas, and 110 APIs), and found that the prevalence and correlates of receptive anal sex and unprotected receptive anal sex (URAS) varied by type of partner (primary, casual, or commercial sex partners). In addition, 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. Of major public health concern was the finding that HIV-positive participants were 3.8 times more likely to have recently engaged in URAS with casual partners than HIV-negative participants. Findings on ethnic differences in HIV-related sexual risk behaviors under the influence of drugs and with commercial partners were consistent with previous findings. The extremely high-risk behaviors found among MTF transgender persons in this study demonstrate the important need for community outreach, drug treatment, and social service programs to target and reach MTF transgender persons to participate in 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. Am J Public Health, 94, pp. 1193—1199, 2004.

Intravenous Drug Users' HIV-Risk Behaviors with Primary/Other Partners

The objective of this study was to determine how injection drug users' (IDUs) HIV-risk behavior differs with primary and other sex partners. Interviews were conducted with IDUs from a needle exchange program (n = 243). The sample was composed of 79 women and 164 men; their ages ranged from 18 to 67 (M = 35.02, SD = 9.25). The ethnic make-up of the sample was 86% (209) Caucasian, 9% (22) African American, 3% (7) Hispanic, and 2% (5) Other. There were significant differences in age (w 2=34.58, df =4, p < 0.0001) and marital status (w 2 = 23.26, df =4, p = 0.0001) among those who reported no partners, those who reported one partner, and those who reported more than one partner in the past six months. Age was negatively related to the number of sexual partners (i.e., those with no partners were older than those with one partner, who, in turn, were older than those with more than one partner). Those with one sexual partner were more likely to report never using condoms with primary partners than were those with more than one partner (74% vs. 54%, p < 0.001). Those with more than one partner differed in their disclosure of HIV and IDU status, condom use, and drug use in combination with sex between their primary and other partners. These findings indicate that primary sexual partners of IDUs are placed at risk from IDUs' risk behavior with other sexual partners. Given that IDUs behave differently with primary partners than with other partners, HIV-risk reduction interventions for IDUs should address risk behavior with primary partners separately from behavior with other partners. In addition, when resources for risk-reduction prevention are scarce, a particular focus should be given to reducing HIV risk behaviors among those IDUs who report both primary and other partners. Rosenberg, C., Anderson, B. and Stein, M. Intravenous Drug Users' HIV-Risk Behaviors with Primary/Other Partners. Amer J Drug Alc Abuse, 30(2), pp. 225—236, 2004.

Medication Compliance and Satisfaction with Treatment for HIV Disease in a Sample of African-American Crack Cocaine Smokers

The development of treatment regimes for African-American HIV-infected crack cocaine users has often been based on assumptions about compliance with medication regimes rather than evidence. This study sought to obtain baseline information on the adherence to antiretroviral medications among 137 members of this important risk population in Houston, Texas. The median age of respondents was 40 years, with half (51%) aged 40 years and older; one-fourth (27%) were women. All participants in the sample were smoking crack or injecting drugs at the time they were interviewed. Most who reported smoking crack (82%) reported smoking daily. About one-fifth (18%) of injectors were injecting daily. Of those who were injecting, 18% had shared needles and 82% had shared paraphernalia used for preparing drug solution. Length of time since HIV diagnosis ranged among the respondents from less than 1 year to 18 years. It was found that for only 5 of a range of 16 antiviral medications was there a significant correlation between levels of compliance and beliefs as to how effective these medications are. Medication compliance was also found not to be associated with frequency of crack cocaine use in the month prior to interview. Irrespective of gender and reported extent of medication compliance, the respondents tended to report positive relationships with their treating physicians, with higher levels of satisfaction reported by women. These results suggest that the majority of African-American crack cocaine users are able to comply with HIV treatment regimes, with more than half (53%) claiming full compliance for one or more medications, and a further one third (31%) claiming compliance more than half the time. Medication compliance, which presumably reflects responsibility and desire to maximize both the quality and the length of one's life, seems to be at odds with reports of HIV-infected cocaine users engaging in irresponsible and high-risk behaviors, yet these findings suggest that they will continue to take antiretroviral medications even if they have doubts about the effectiveness of these medications. Crisp, B., Williams, M., Timpson, S. and Ross, M. Medication Compliance and Satisfaction with Treatment for HIV Disease in a Sample of African-American Crack Cocaine Smokers. AIDS and Behavior, 8(2), pp. 199-206, 2004.

Cocaine's Effect on HIV Expression Can Be Modulated by the Kappa Opioids

The HIV virus acts on chemokine receptors to enter macrophages, glia and lymphocytes. Opiates and other drugs have been shown to compete with these sites and modify the toxicity of the virus. Therefore, many laboratories are focusing on the nature of this interaction to clarify the role of drugs in HIV toxicity or in the development of (HIV)-1-associated dementia (HAD). Cocaine abuse, for example, has

been implicated as a cofactor in HAD. In this study, investigators tested the hypothesis that exposure of microglial cells, the resident macrophages of the brain, to cocaine would increase HIV-1 expression. Because kappa-opioid receptor (KOR) agonists have been shown to suppress neurochemical and neurobehavioral responses to cocaine and to inhibit HIV-1 expression in microglial cell cultures, the investigators hypothesized that KOR ligands would inhibit cocaine-induced HIV-1 expression. In this experiment, microglial cells were infected with HIV-and viral expression was quantified. Treating the microglia with the KOR inhibited viral expression. Consistent with the hypothesis, treatment of microglia with cocaine increased HIV-1 expression, and pretreatment of microglia with these KOR agonists as well as with the KOR-selective antagonist abolished cocaine-induced potentiation of HIV expression. Further analysis suggested that KOR ligands inhibit cocaine's stimulatory effect on viral expression by suppressing cocaine-induced activation of extracellular signal-regulated kinase1/2, reducing cocaine-enhanced up-regulation of the HIV-1 entry chemokine co-receptor CCR5. These findings suggest that in addition to its neurotoxic effects, cocaine could foster development of HAD by increasing viral expression in the brain and, importantly, this process is inhibited by KOR ligands. Gekker, G., Hu, S.X., Wentland, M.P., Bidlack, J.M., Lokensgard, J.R. and Peterson, P.K. Kappa-opioid Receptor Ligands Inhibit Cocaine-induced HIV-1 Expression in Microglial Cells. Journal of Pharmacology and Experimental Therapeutics,309, pp. 600-606, 2004.

Drug Interactions Between Opioids and Antiretroviral Medications: Interaction Between Methadone, LAAM, and Nelfinavir

Understanding drug interactions between antiretrovirals and opiate therapies may decrease toxicities and enhance adherence, with improved HIV outcomes in injection drug users. Dr. McCance-Katz and her colleagues report results of a clinical pharmacology study designed to examine the interaction of the protease inhibitor, nelfinavir, with methadone and LAAM (N = 48). Nelfinavir decreased methadone exposure, but no withdrawal was observed over the 5-day study period. LAAM and dinorLAAM concentrations were decreased, while norLAAM concentrations were increased, with minimal overall change in LAAM/metabolite exposure. Methadone and LAAM did not affect nelfinavir concentrations, but methadone decreased M8 metabolite exposure. The authors stated that while no toxicities were observed, clinicians should be aware of the potential for drug interactions when patients require treatment with nelfinavir and these opiate medications. McCance-Katz, E.F., Rainey, P.M., Smith, P., Morse, G., Friedland, G., Gourevitch, M. and Jatlow, P. Am. J. Addict., 13(2), pp. 163-180, 2004.

Abuse Experiences in a Community Sample of Young Adults: Relations with Psychiatric Disorders, Sexual Risk Behaviors, and Sexually Transmitted Diseases

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., and Wagner, E.F. Abuse Experiences in a Community Sample of Young Adults: Relations with Psychiatric Disorders, Sexual Risk Behaviors, and Sexually Transmitted Diseases. American Journal of Community Psychology. 34(1/2), pp. 147-162, September 2004.

Substance Use and Sexual Risk: A Participant- and Episode-level Analysis Among a Cohort of Men Who Have Sex with Men

Researchers determined whether substance use during sex was independently associated with sexual risk during recent sexual episodes, as reported by 4,295 HIV—negative men who have sex with men. Prior reports associating substance use with sexual risk behavior have generally used summary measures and have not adjusted for participants' background levels of substance use. In this 1999—2001 US study, the main outcome measure was serodiscordant unprotected anal sex (i.e., with an HIV-positive partner or a partner whose serostatus is unknown). The influence of participant-level characteristics was examined by using repeated-measures logistic

models, such that the influence of participant-level characteristics, including 6-month substance use, was removed by using conditional logistic regression (in effect making each participant his own control). Eleven percent of participants reported heavy alcohol use, 37% used poppers, 19% sniffed cocaine, and 13% used amphetamines. In the participant-level analysis, use of poppers, amphetamines, and sniffed cocaine as well as heavy alcohol use in the prior 6 months were independently associated with unprotected anal sex. In the conditional analysis, consumption of alcohol or use of poppers, amphetamines, or sniffed cocaine just before or during sex was independently associated with serodiscordant unprotected anal sex. These findings underscore the importance of HIV prevention interventions and the influence that substance use during sex can have on increased risk behavior. Colfax, G., Vittinghoff, E., Husnik, M., McKirnan, D., Buchbinder, S., Koblin, B., Celum, C., Chesney, M., Huang, Y., Mayer, K., Bozeman, S., Judson, F., Bryant, K., Coates, T., and the EXPLORE Study Team. Substance Use and Sexual Risk: A Participant- and Episode-level Analysis among a Cohort of Men Who Have Sex with Men. Amer J Epidemiol, 159(10), pp. 1002- 1012, 2004.

Mortality in a Long-term Open Cohort of Prostitute Women

In this study, the authors estimated overall and cause-specific mortality among prostitute women. They recorded information on prostitute women identified by police and health department surveillance in Colorado Springs, Colorado, from 1967 to 1999. The authors assessed cause-specific mortality in this open cohort of 1,969 women using the Social Security Death Index and the National Death Index, augmented by individual investigations. They identified 117 definite or probable deaths and had sufficient information on 100 to calculate a crude mortality rate (CMR) of 391 per 100,000 (95% confidence interval (CI): 314, 471). In comparison with the general population, the standardized mortality ratio (SMR), adjusted for age and race, was 1.9 (95% CI: 1.5, 2.3). For the period of presumed active prostitution only, the CMR was 459 per 100,000 (95% CI: 246, 695) and the SMR was 5.9 (95% CI: 3.2, 9.0). Violence and drug use were the predominant causes of death, both during periods of prostitution and during the whole observation period. The CMR for death by homicide among active prostitutes was 229 per 100,000 (95% CI: 79, 378), and the SMR was 17.7 (95% CI: 6.2, 29.3). Deaths from AIDS occurred exclusively among prostitutes who admitted to injecting drug use or were inferred to have a history of it. Potterat, J., Brewer, D., Muth, S., Rothenberg, R., Woodhouse, D., Muth, J., Stites, H. and Brody, S. Mortality in a Long-Term Open Cohort of Prostitute Women. Am J Epidemiol, 159(8), pp. 778-785, 2004.

Urging Others to be Healthy: "Intravention" by IDUs as a Community Prevention Goal

In this article, researchers present data on a culture of support for risk reduction and risk avoidance among IDUs in Bushwick, within New York City—a city in which an enormous HIV/AIDS epidemic killed tens of thousands of IDUs in the 1980s and 1990s, but also a city in which HIV prevalence among IDUs has declined from about 50% to about 10% to 15%, and HIV incidence among IDUs has declined from about 13% per person per year at risk to about 1% to 2%. They describe "intravention" activities that are conducted by and sustained through ongoing actions of members of communities-at-risk and present data from 120 IDUs to show how their supportive efforts may influence others to engage in one or more self-protective actions. These findings suggest that the common image of IDUs as sources of social and medical problems is inaccurate. They also have a number of implications for public health practice. First, they suggest that many IDUs are active participants in trying to reduce HIV transmission and other problems that afflict themselves and others. Second, they suggest that even in the context of strong stigmatization of drug users, there is at least a subset of IDUs who are involved in community agencies and activities in various ways. Although only a small proportion, they may nonetheless be important allies for public health prevention and drug treatment. Friedman, S., Maslow, C., Bolyard, M., Sandoval, M., Mateu, P. and Neaigus, A. Urging Others to be Healthy: "Intravention" by IDUs as a Community Prevention Goal. AIDS Educ and Prev, 16(3), pp. 250-263, 2004.

Long-Term Effects of Syringe Exchange on Risk Behavior and HIV Prevention

The purpose of this study was to assess stability of population-level injection risk behavior over time among participants in a syringe exchange program and compare factors affecting syringe sharing at two points in time. Participants of the Tacoma Syringe Exchange Program (SEP) were interviewed in 1997 and 2001 using audio computer assisted self-interviewing technology. In each wave of data collection, a random cross section of participants was recruited and interviewed, with no attempt

made to follow respondents over time. Rates of injection risk behavior remained stable across the 4-year period, despite increases in factors associated with syringe sharing. Homelessness, rates of depression symptoms, and injection of amphetamines all increased from 1997 to 2001. The central factors associated with syringe sharing in both 1997 and 2001 were depression symptoms and the interaction of younger age with amphetamine injection. The data indicate that the syringe exchange program has helped to stabilize risk among a high-risk population of drug injectors for a substantial period of time, and confirms previous findings about the significant role that SEPs play in the prevention of HIV in marginal and impoverished communities. Braine, N., Des Jarlais, D., Ahmad, S., Purchase, D. and Turner, C. Long-Term Effects of Syringe Exchange on Risk Behavior and HIV Prevention. AIDS Educ and Prev, 16(3), pp. 264-275, 2004.

Public Funding of US Syringe Exchange Programs

Although there has been no federal government funding of syringe exchange, there is substantial state and local government funding. This paper describes program characteristics associated with receiving state and local government funding. Annual telephone surveys were made of program directors of syringe exchange programs known to the North American Syringe Exchange Network. The number of syringe exchange programs (SEPs) known to this network has increased from 63 in 1994—1995 to 127 in 2000. Approximately 80% of programs participated in each of the surveys. The results indicate that approximately 50% of programs receive state and local government funding, which has remained constant from 1994 to 2000. Receiving state and local government funding was associated with larger numbers of syringes exchanged per year, which is a fundamental purpose of SEPs, and with providing more on-site services, including HIV counseling and testing so that clients can learn their serostatus and seek appropriate treatment and medical services. Among the programs that received state or local government funding, this funding accounted for a mean of 87% of the budget for syringe exchange services. In the absence of federal funding, state and local government support is associated with better syringe exchange performance. Des Jarlais, D., McKnight, C. and Milliken, J. Public Funding of US Syringe Exchange Programs. J Urban Health, 81(1), pp. 118-121, 2004.

Attachment Style, Childhood Adversity, and Behavioral Risk Among Young Men

In a study of young men who have sex with men (YMSM), researchers sought to examine relationships among childhood adversity, attachment style (core beliefs regarding the self and others), and homelessness, daily substance use, participation in sex work, involvement in the criminal justice system, and being out of school or work. They used a targeted sampling approach to recruit and then interview 569 YMSM aged 17-28 years in New York City. After controlling for demographic characteristics and childhood adversity, YMSM with a fearful attachment style were more likely to have been homeless (OR 2.93, 95% CI 1.65-5.18), to have participated in sex work (OR 2.35, 95% CI 1.44-3.85), to use substances daily (OR 2.79, 95% CI 1.29-6.03), to have been involved in the criminal justice system (OR 2.04, 95% CI 1.38-3.01), and to be out of school/work (OR 2.47, 95% CI 1.47-4.15). YMSM who identified as heterosexual, or bisexual, and/or transgender were especially vulnerable. These findings suggest that a fearful attachment style contributes to some YMSM remaining outside of the protective systems of family, school, and work, and is associated with risky contexts where they are less likely to encounter prosocial peers and adults. It is also associated with high-risk drug use and sexual behavior. Attachment theory has potential for guiding the development of more effective interventions by elucidating the links between an individual's experience of relationships and management of developmental transitions. Gwadz, M.V., Clatts, M.C., Leonard, N.R. and Goldsamt, L. Attachment Style, Childhood Adversity, and Behavioral Risk Among Young Men Who Have Sex With Men. J Adolesc Health, 34(5), pp. 402-413, 2004.

Psychosocial Factors Associated with Adherence to Antiretroviral Medication in a Sample of HIV-Positive African American Drug Users

Researchers sought to investigate factors affecting antiretroviral adherence among African American drug users to identify associations between self-reported adherence levels and psychosocial measures (from the Transactional Model of Stress and Coping). The study used data from 137 HIV-positive drug users who were receiving antiretroviral medications at the time they were interviewed. Multiple regression analysis showed only perceived self-efficacy of antiretrovirals and one measure of perceived barriers, simply forgetting to take medications, to be independently related to adherence. These findings suggest that theoretical approaches to understanding

antiretroviral adherence among HIV-positive African American drug users need to consider and address a range of variables including but not limited to behavioral practices, cognitive appraisals, affective responses, and social support. Harzke, A., Williams, M., Nilsson-schšnnesson, L., Ross, M., Timpson, S. and Keel, K. Psychosocial Factors Associated with Adherence to Antiretroviral Medication in a Sample of HIV-Positive African American Drug Users. AIDS Care, 16(4), pp. 470, 2004.

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

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

Bioavailabilities of Rectal and Oral Methadone in Healthy Subjects

Rectal administration of methadone may be an alternative to intravenous and oral dosing in cancer pain, but the bioavailability of the rectal route is not known. Dr. Kharash and his colleagues compared the absolute rectal bioavailability of methadone with its oral bioavailability in healthy humans. Seven healthy subjects (six males, one female, aged 20-39 years) received 10 mg d(5)-methadone-HCl rectally (5 ml in 20% glycofurol) together with either d(0)-methadone intravenously (5 mg) or orally (10 mg) on two separate occasions. Blood samples for the LC-MS analyses of methadone and it's metabolite EDDP were drawn for up to 96 h. Noninvasive infrared pupillometry was performed at the same time as blood sampling. Data showed that the mean absolute rectal bioavalability of methadone was 0.76 (0.7, 0.81), compared to 0.86 (0.75, 0.97) for oral administration (mean (95% CI)). Rectal absorption of methadone was more rapid than after oral dosing with Tmax values of 1.4 (0.9, 1.8) vs. 2.8 (1.6, 4.0) h. The extent of formation of the metabolite EDDP did not differ between routes of administration. Single doses of methadone had a duration of action of at least 10 h and were well tolerated. Rectal administration of methadone resulted in rapid absorption, a high bioavailability and long duration of action. No evidence of pre-systemic elimination was seen. Data suggested that rectal methadone has characteristics that make it a potential alternative to intravenous and oral administration, particularly in cancer pain and palliative care. Dale, O., Sheffels, P., Kharasch, E.D., Br. J. Clin. Pharmacol. 58(2), pp. 156-162, 2004.

Marijuana Withdrawal in Humans: Effects of Oral THC or Divalproex

Abstinence following daily marijuana use can produce a withdrawal syndrome characterized by negative mood (e.g. irritability, anxiety, misery), muscle pain, chills, and decreased food intake. Two placebo-controlled, within-subject studies investigated the effects of a cannabinoid agonist, delta-9-tetrahydrocannabinol (THC: Study 1), and a mood stabilizer, divalproex (Study 2), on symptoms of marijuana withdrawal. Participants (n=7/study), who were not seeking treatment for their marijuana use, reported smoking 6-10 marijuana cigarettes/day, 6-7 days/week. Study 1 was a 15-day in-patient, 5-day outpatient, 15-day in-patient design. During the in-patient phases, participants took oral THC capsules (0, 10 mg) five times/day, 1 h prior to smoking marijuana (0.00, 3.04% THC). Active and placebo marijuana were smoked on in-patient days 1-8, while only placebo marijuana was smoked on days 9-14, that is, marijuana abstinence. Placebo THC was administered each day, except during one of the abstinence phases (days 9-14), when active THC was given. Mood, psychomotor task performance, food intake, and sleep were measured. Oral THC administered during marijuana abstinence decreased ratings of 'anxious', 'miserable', 'trouble sleeping', 'chills', and marijuana craving, and reversed large decreases in food intake as compared to placebo, while producing no intoxication. Study 2 was a 58-day, outpatient/in-patient design. Participants were maintained on each divalproex dose (0, 1500 mg/day) for 29 days each. Each maintenance condition began with a 14-day outpatient phase for medication induction or clearance and continued with a 15-day in-patient phase. Divalproex decreased marijuana craving during abstinence, yet increased ratings of 'anxious', 'irritable', 'bad effect', and 'tired.' Divalproex worsened performance on psychomotor tasks, and increased food intake regardless of marijuana condition. Thus, oral THC decreased marijuana craving

and withdrawal symptoms at a dose that was subjectively indistinguishable from placebo. Divalproex worsened mood and cognitive performance during marijuana abstinence. These data suggest that oral THC, but not divalproex, may be useful in the treatment of marijuana dependence. Haney, M., Hart, C.L., Vosburg, S.K., Nasser, J., Bennett, A., Zubaran, C. and Foltin, R.W. Neuropsychopharmacology, 29(1), pp. 158-170, 2004.

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

Research Findings - Services Research

Buprenorphine-Naloxone is Practical and Safe for Use in Diverse Community Treatment Settings

In October 2002, the U.S. Food and Drug Administration approved buprenorphine-naloxone (Suboxone) sublingual tablets as an opioid dependence treatment available for use outside traditionally licensed opioid treatment programs. The NIDA Center for Clinical Trials Network (CTN) sponsored two clinical trials assessing buprenorphine-naloxone for short-term opioid detoxification. These trials provided an unprecedented field test of its use in twelve diverse community-based treatment programs. Opioid-dependent men and women were randomized to a thirteen-day buprenorphine-naloxone taper regimen for short-term opioid detoxification. The 234 buprenorphine-naloxone patients averaged 37 years old and used mostly intravenous heroin. Direct and rapid induction onto buprenorphine-naloxone was safe and well tolerated. Most patients (83%) received 8 mg buprenorphine-2 mg naloxone on the first day and 90% successfully completed induction and reached a target dose of 16 mg buprenorphine-4 mg naloxone in three days. Medication compliance and treatment engagement was high. An average of 81% of available doses was ingested, and 68% of patients completed the detoxification. Most (80.3%) patients received some ancillary medications with an average of 2.3 withdrawal symptoms treated. The safety profile of buprenorphine-naloxone was excellent. Of eighteen serious adverse events reported, only one was possibly related to buprenorphine-naloxone. All providers successfully integrated buprenorphine-naloxone into their existing treatment milieus. Overall, data from the CTN field experience suggest that buprenorphine-naloxone is practical and safe for use in diverse community treatment settings, including those with minimal experience providing opioid-based pharmacotherapy and/or medical detoxification for opioid dependence. Amass, L., Ling, W., Freese, T.E., Reiber, C., Annon, J.J., Cohen, A.J., McCarty, D., Reid, M.S., Brown, L.S., Clark, C., Ziedonis, D.M., Krejci, J., Stine, S., Winhusen, T., Brigham, G., Babcock, D., Muir, J.A., Buchan, B.J. and Horton, T. Buprenorphine-Naloxone is Practical and Safe for Use in Diverse Community Treatment Settings. Am J Addict, 13 (1), pp. S42-66, 2004.

Training Rural Practitioners to Use Buprenorphine: Using the Change Book to Facilitate Technology Transfer

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, S. and Knudsen, J. Training Rural Practitioners to Use Buprenorphine: Using The Change Book to Facilitate Technology Transfer. J Subst Abuse Treat, 26(3), pp. 203-208, 2004.

Cost Effectiveness of Disulfiram for Treating Cocaine in Methadone Patients

Index

The cost-effectiveness of providing disulfiram to methadone-maintained opioid addicts in a randomized clinical trial setting is studied. The economic evaluation is based on a double blind clinical trial in which 67 cocaine-dependent methadone-maintained opioid-dependent subjects were randomized to get the additional treatment of disulfiram or placebo in a 12-week trial. Outcome measures used are the number of days of cocaine use and grams of cocaine per week. Cost measures used are the cost of providing standard methadone treatment and the incremental cost of adding disulfiram to the standard treatment. Cost measures of standard and disulfiram-enhanced treatment were collected retrospectively from the provider. Results from this cost-effectiveness analysis imply that, even though disulfiram increases slightly the cost of methadone treatment, its increase in effectiveness may be important enough to warrant its addition for treating cocaine dependence in methadone-maintained opiate addicts. Jofre-Bonet, M., Sindelar, J.L., Petrakis, I.L., Nich, C., Frankforter, T., Rounsaville, B.J. and Carroll, K.M. Cost Effectiveness of Disulfiram: Treating Cocaine Use in Methadone-Maintained Patients. Substance Abuse Treat; 26(3), pp. 225-232, 2004.

Organizational Absorptive Capacity Affects the Pace of Innovation in Privately-Funded Substance Abuse Treatment Clinics

Few studies have identified the organizational characteristics that are associated with the transfer of research-based treatment techniques into practice. One potentially fruitful concept is absorptive capacity, referring to an organization's ability to seek and utilize information, which may be positively associated with the use of innovative treatment techniques. Data from a nationally representative sample of 322 privately funded substance abuse treatment centers indicate that treatment organizations use a greater number of innovations when they scored high on absorptive capacity, which is defined as engaging in more environmental scanning, surveying referral sources, and third party payers for satisfaction, and having more professionals in their workforce. Knudsen, H.K. and Roman, P.M. Organizational Absorptive Capacity Affects the Pace of Innovation in Privately Funded Substance Abuse Treatment Clinics. Journal of Substance Abuse Treatment, 26(1), pp. 353-361, 2004.

Many Adults Do Not Link with Primary Medical Care after Alcohol or Drug Detoxification

This prospective cohort study—conducted in the context of a randomized trial of a linkage intervention and an expansion of Medicaid benefits—identified patient characteristics and health care experiences associated with primary care linkage after alcohol or drug detoxification. Researchers collected primary interview data over two years from 400 adults without primary medical care, in an urban residential detoxification program. Linkage was defined as self-report of at least one visit with a primary care clinician during follow-up. Of 400 subjects, 63% linked with primary medical care. In a multivariable model adjusting for randomization assignment, predisposing, enabling and illness variables, women, those with no recent incarceration, those with support for abstinence by family or friends, and those who had visited a medical clinic or physician recently were significantly more likely to link with primary care. Those with health insurance during follow-up were also more likely to link. Recent mental health or addictions treatment utilization and health status were not associated with linkage. Researchers conclude that a substantial proportion of adults with addictions do not link with primary medical care. These data suggest that efforts could be focused on those least likely to link, that contacts with mental health and addictions treatment providers are underutilized opportunities for these efforts, and that health policy changes such as expanding health insurance benefits may improve entry of substance dependent patients into primary medical care. Saitz, R., Larson, M.J., Horton, N.J., Winter, M., and Samet, J.H. Linkage with Primary Medical Care in a Prospective Cohort of Adults with Addictions in Inpatient Detoxification: Room for Improvement. Health Services Research, 39(3), pp. 587-606, 2004.

Woman-Focused HIV Intervention with African American Crack Abusers Out-of-drug-treatment

African American women (n = 620) who use crack participated in a comparison randomized trial comparing a women-focused HIV intervention, a revised National Institute on Drug Abuse standard intervention, and a control group. Risk behavior, employment, and housing status were assessed with linear and logistic regression. All groups significantly reduced crack use and high-risk sex at each 3 and 6 month follow-up, but only woman-focused intervention participants consistently improved employment and housing status. Compared with control subjects at 6 months, woman-focused intervention participants were least likely to engage in unprotected

sex; revised standard intervention women reported greatest reductions in crack use. A woman-focused intervention can successfully reduce risk and facilitate employment and housing and may effectively reduce the frequency of unprotected sex in the longer term. Wechsberg, W.M., Lam, W.K., Zule, W.A. and Bobashev, G. Efficacy of a Woman-Focused Intervention to Reduce HIV Risk and Increase Self-Sufficiency Among African American Crack Abusers. Am J Public Health, 94(7), pp. 1165-1173, 2004.

Family-Based Therapy was Shown to be More Effective Than Peer-Group Therapy in Treating Urban Adolescent Substance Abuse

A randomized clinical trial evaluated a family-based therapy (Multidimensional Family Therapy, MDFT; Liddle 2002a) and a peer group therapy with 80 urban, low-income, and ethnically diverse young adolescents (11 to 15 years) referred for substance abuse and behavioral problems. Both treatments were outpatient, relatively brief, manual-guided, equal in intervention dose, and delivered by community drug treatment therapists. Results indicated that the family-based treatment (MDFT, an intervention that targets teen and parent functioning within and across multiple systems on a variety of risk and protective factors) was significantly more effective than peer group therapy in reducing risk and promoting protective processes in the individual, family, peer, and school domains, as well as in reducing substance use over the course of treatment. Liddle, H.A., Rowe, C.L., Dakof, G.A., Ungaro, R.A. and Henderson, C.E. Family-based Therapy was Shown to be More Effective than Peer-group Therapy in Treating Urban Adolescent Substance Abuse. Journal of Psychoactive Drugs, 36(1), pp. 49-63, 2004.

Are Rates of Psychiatric Disorders in the Homeless Population Changing?

The objective is to examine the prevalence of psychiatric illness among 3 homeless populations in St. Louis, MO, in approximately 1980, 1990, and 2000. Selected demographics and lifetime substance abuse and dependence and other mental illness among the 3 populations are compared. Among the homeless populations, the prevalence of mood and substance use disorders dramatically increased, and the number of minorities within these populations has increased. The prevalence of drug use disorder increased dramatically among both men and women over the past 2 decades, and among women, the increase was higher than the prevalence of alcohol use disorder. In 2000, 84% of men and 58% of women had an alcohol or other drug use disorder. Also in 2000, substance use disorders accounted for the vast majority of psychopathology (prevalence of any psychiatric disorder was 88% among men and 69% among women). In 1980, the abused drug of choice was cannabis, but it was surpassed over the next 2 decades by cocaine, which had not been found among homeless men or women in 1980. The popularity of amphetamine and sedative-hypnotic abuse decreased after 1980. Opioid abuse remained relatively unchanged over the 2 decades and was the third most prevalent abused drug of choice in 2000. The prevalence of psychiatric illness, including substance abuse and dependence, is not static in the homeless population. Service systems need to be aware of potential prevalence changes and the impact of these changes on service needs. North, C.S., Eyrich, K.M., Pollio, D.E., and Spitznagel, E.L Are Rates of Psychiatric Disorders in the Homeless Population Changing? Am J Public Health, 94, pp. 103-108, 2004.

Are Health Plans Adequately Identifying Adolescents With Substance Use Problems?

Three measures developed by the Washington Circle, a group focused on the development of substance abuse performance measures, have been adapted for the 2004 Health Plan Employer Data and Information Set. One measure—the identification rate—can be used to examine the extent to which private health plans are able to identify adolescent enrollees with substance use problems. The researchers calculated this rate for adolescents using MarketScan, a database of private health plan claims for selected employers maintained by the MEDSTAT Group. About a quarter million adolescents were covered in 1997. The number of adolescents with any primary or secondary substance abuse claims during the year was divided by the member-years for adolescents aged 12 to 18. For enrolled adolescents, the overall identification rate was .5 percent and .7 percent for males and .4 percent for females. The researchers compared these results to the 6.8 percent rate of alcohol dependence or drug dependence—or both—obtained from a special analysis of a subset of adolescents covered by commercial insurance who were included in the 1998 National Household Survey on Drug Abuse. No meaningful variation was observed across health plan type. The low rate points to the urgent need to close the gap between the number of adolescents who need treatment and those who receive it. Lee, T.M., Garnick, D.W., Miller, K., and Horgan, C.M. Are Health Plans Adequately

Identifying Adolescents With Substance Use Problems? Psychiatric Services, 55(2), pp. 116, 2004.

Family and Peers Influence Severity of Alcohol and Drug Problems in Adolescents

To examine how parental limit setting, family conflict, and perception of family experience influence severity of alcohol and drug problems, and important gender differences in these relationships, the researchers interviewed consecutive intakes, aged 12 to 18 years, at 4 chemical dependency programs of a large group-model nonprofit health maintenance organization (HMO) (n=419). The Family Conflict, Limit Setting, and Positive Family Experience scales correlated with substance dependence ($p<0.01$, $p<0.01$, $p<0.05$, respectively). Depression also correlated with family conflict ($p<0.01$), absence of limit setting ($p<0.01$), poor family experience ($p<0.01$) and dependence symptoms ($p<0.01$). Number of substance-using friends correlated with number of dependence symptoms ($p<0.01$). Gender differences included the following: (1) girls scoring higher in family conflict ($p=0.0002$), negative perceptions of family experience ($p<0.0017$), and lower in absence of limit setting ($p<0.0001$); (2) how family environment predicted problem severity: absence of limit setting was significant for boys and girls but family conflict for boys only; (3) girls had more dependence symptoms ($p=<0.0001$), psychiatric diagnoses (e.g., depression ($p<0.0003$), anxiety ($p<0.0002$), conduct disorder ($p=0.07$)), and substance-abusing family members (53 % versus 39%; $p=0.006$). To conclude, family and peers influence severity of alcohol and drug problems in adolescents. Wu, N., Lu, Y., Sterling, S., and Weisner, C. Family Environment Factors and Substance Abuse Severity in an HMO Adolescent Treatment Population. Clinical Pediatrics, 43(4), pp. 323-333, 2004.

Multidisciplinary Health Clinic to Evaluate Patients During Detoxification Can Link Patients to Primary Medical Care

Researchers evaluated the feasibility of establishing a multidisciplinary Health Evaluation and Linkage to Primary care (HELP) clinic at an urban residential detoxification unit. Patients received a clinical evaluation and facilitated linkage to primary medical care including personalized referral, reminders, and appointment rescheduling. Of 235 adults reporting alcohol, cocaine or heroin as first or second drug of choice and without a primary care physician, 178 (76%) received a full HELP clinic evaluation, 35 (15%) some clinic components, and 7 (3%) only a primary care appointment. Of those with a full evaluation, 28% received pneumococcal vaccination, and most received health behavior counseling. Over the subsequent 2 years, 131 (60%) of the 220 patients who had any contact with the HELP clinic had at least one primary care visit. A multidisciplinary health clinic to evaluate patients during detoxification is feasible and can link patients with substance dependence to primary medical care. Sweeney, L.P., Samet, J.H., Larson, M.J. and Saitz, R. Establishment of a Multidisciplinary Health Evaluation and Linkage to Primary Care (HELP) Clinic in a Detoxification Unit. Journal of Addictive Diseases, 23(3), pp. 33-45, 2004.

DSM-IV Criterion for Cannabis Tolerance is Limited as an 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 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, and recommend a 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 Clinical Psychopharmacol, 12(2), pp. 136-146, 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. The 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.R., Zeni, M.B., Chitwood, D., Liberti, T.M., Gates, G.J., Metsch, L.R., Maddox, L.M. and Kuper, T. Journal of Urban Health: Bulletin of the New York Academy of Medicine, 81(3), pp. 401-415, 2004.

Chronic Marijuana Use Associated With Dropping Out of School

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 complete 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. Chronic Marijuana Use Associated With Dropping Out of School. Economics of Education Review, 23, pp. 133—141, 2004.

Activity Based Costing of Probation With and Without Substance Abuse Treatment: A Case Study

Since many offenders have drug problems, investigators have proposed that drug testing and treatment should be an integral part of probation. In 1994, the Office of National Drug Control Policy (ONDCP) funded a demonstration project designed to integrate drug treatment with traditional supervision services. As part of this demonstration a new procedure called 'seamless' probation was set up in which treatment providers were co-located with probation officers and probation officers coordinated offenders' participation in treatment. This study examines the cost of providing substance abuse treatment coordination through probation agencies. Activity Based Costing (ABC) is used to examine the cost of probation with and without treatment coordination in one probation agency. The agency budget was analyzed and allocated to various programs. A questionnaire was developed to assess probation officers' activities. The cost of coordinating treatment for one offender was calculated by dividing the total cost of the program by units of various activities done by the probation officers. Preliminary test of reliability of the instrument showed that it accurately portrayed the probation officers' time allocation. Probation officers spent 6.9% of their time in seamless supervision and 83.3% time in traditional supervision (83.83%). The seamless probation officers had more group meetings and more phone contact with their offenders than traditional probation officers. The average cost per offender per day was 12 dollars for seamless probation and 7 dollars for traditional probation. Comparison of seamless and traditional supervision activities showed major differences in terms of the probation officers' activities and costs. There are significant costs associated with asking probation officers to coordinate treatment. Alemi, F., Taxman, F., Doyon, V., Thanner, M. and Baghi, H. Activity Based Costing of Probation with and without Substance Abuse Treatment: A Case Study. Journal of Mental Health Policy Econ, 7(2), pp. 51-57, 2004.

Self-Help Organizations for Alcohol and Drug Problems: Toward Evidence-Based Practice and Policy

This expert consensus statement reviews evidence on the effectiveness of drug and alcohol self-help groups and presents potential implications for clinicians, treatment program managers and policymakers. Because longitudinal studies associate self-help group involvement with reduced substance use, improved psychosocial functioning,

and lessened health care costs, there are humane and practical reasons to develop self-help group supportive policies. Policies described here that could be implemented by clinicians and program managers include making greater use of empirically-validated self-help group referral methods in both specialty and non-specialty treatment settings and developing a menu of locally available self-help group options that are responsive to clients' needs, preferences, and cultural background. The workgroup also offered possible self-help supportive policy options (e.g., supporting self-help clearinghouses) for state and federal decision makers. Implementing such policies could strengthen alcohol and drug self-help organizations, and thereby enhance the national response to the serious public health problem of substance abuse. Humphreys, K., Wing, S., McCarty, D., Chappel, J., Gallant, L., Haberle, B., Horvath, A.T., Kaskutas, L.A., Kirk, T., Kivlahan, D., Laudet, A., McCrady, B.S., McLellan, A.T., Morgenstern, J., Townsend, M. and Weiss, R. Self-Help Organizations for Alcohol and Drug Problems: Toward Evidence-Based Practice and Policy. J Subst Abuse Treat, 26(3), pp. 151-158; discussion pp. 159-165, 2004.

Medical Provider Referrals of Adolescents to Substance Abuse and Mental Health Treatment

This study examines the factors related to referrals of adolescents with substance use disorders to substance abuse or mental health treatment by their medical providers. Administrative and chart review data from the membership of a large private health maintenance organization (HMO) were collected from a probability sample of 400 adolescents, ages 13-18, who were diagnosed with a substance use disorder in 1999. Logistic regression analyses examined referral to substance abuse treatment and referral to mental health treatment in the aggregate and stratified by gender. Documented use of both alcohol and another illicit drug, and legal problems increased likelihood of referral to substance abuse and mental health treatment, whereas diagnoses of alcohol and marijuana use disorders decreased likelihood of referral to substance abuse treatment. Mental health diagnoses played a limited role in both types of referrals, although specific psychosocial problems were associated with increased likelihood of referrals. Treatment history and location of first mention of problem were significant predictors of referral. There were no gender differences in referral rates to either substance abuse or mental health treatment; however predictors of referral differed by gender. These findings extend our knowledge about factors that influence clinicians' treatment referrals of adolescents with substance abuse diagnoses and have implications for influencing clinician referral behavior within health plans. Scott, M., Parthasarathy, S., Kohn, C., Hinman, A., Sterling, S. and Weisner, C. Medical Provider Referrals of Adolescents to Substance Abuse and Mental Health Treatment. Ment Health Serv Res, 6(1), pp. 47-60, March 2004.

Depression and Hostility as Predictors of Long-term Outcomes Among Opiate Users

Researchers investigated associations that pre-treatment depression and hostility have with drug use and criminal behavior at 1-year and 5-year follow-up in patients with and without additional treatment involvement in the year prior to each follow-up. Using data from an analytic sample of 727 patients at 1-year follow-up and 432 patients at 5-year follow-up, from 18 programs included in the national Drug Abuse Treatment Outcome Studies (DATOS), the researchers followed a naturalistic, non-experimental evaluation design. Multiple logistic regression analyses revealed that greater depression predicted less drug use in the year preceding each follow-up, whereas greater hostility predicted increased drug use and more arrests at each follow-up. These predictive relationships appeared only among individuals not involved in additional treatment. Depression and hostility showed opposite associations with outcomes, underscoring the need to assess these psychological conditions separately and to tailor treatment plans appropriately. Rao, S.R., Broome, K.M., and Simpson, D.D. Depression and Hostility as Predictors of Long-Term Outcomes Among Opiate Users. Addiction, 99(5), pp. 579-589, 2004. Predicting Adolescent Drug Abuse Treatment Outcome with the Personal Experience Inventory This study examined the clinical utility of the Personal Experience Inventory (PEI) Psychosocial scales to predict adolescent drug abuse treatment outcome. The role of psychosocial risk factors in predicting treatment outcome also has theoretical interest given that such factors have been associated with the development of drug abuse. The sample consisted of 138 male and 105 female adolescents recruited at a hospital-based adolescent drug abuse treatment program. Clients were assessed at intake, discharge, and 6 and 12 months after discharge. Intake PEI Psychosocial scales were modestly predictive of outcome; the magnitude of the predictions was higher for boys than girls. Three PEI Psychosocial domains of deviance, family dysfunction, and peer drug use were predictive of boys' outcome; sibling and peer drug use were predictive

of girls' outcome. The strength of these predictive relationships was similar to those found in other treatment outcome prediction research. There was limited support for the predictive validity of the PEI. These PEI Psychosocial scales that show predictive associations with outcome may be helpful in treatment planning. Stinchfield, R.D. and Winters, K.C. Predicting Adolescent Drug Abuse Treatment Outcome with the Personal Experience Inventory (PEI). Journal of Child and Adolescent Substance Abuse, 13, pp. 103-120, 2003.

Elevated Post Treatment Relapse Rates Among Recovering Youth with ADHD

Researchers used a sample of 220 adolescent drug abusers in treatment to estimate the degree to which probable ADHD status increases the odds of post treatment alcohol, marijuana, and other drug relapse during the first 6 months following discharge. Drug abusing youth with probable ADHD status exhibited 2.5 times the risk of post treatment 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 comorbid 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, pp. 1-16, 2004.

Suicidal Behavior In Urban American Indian Adolescents

The majority of American Indians do not live on reservations, yet research on suicidal behavior in this population overwhelmingly focuses on reservation Indians. This exploratory study uses a sample of 144 urban and 170 reservation American Indian adolescents to compare rates and correlates of suicidal behavior. One-fifth of urban youth and one-third of reservation youth reported lifetime suicidal ideation, although similar numbers (14%-18%) reported an attempt. Urban youth had fewer psychosocial problems, and in multivariate analyses, the two groups shared no common correlate of attempted suicide. The results suggest that different prevention measures may be warranted for urban Indian youth. Freedenthal, S. and Stiffman, A.R. Suicidal Behavior in Urban American Indian Adolescents: A Comparison with Reservation Youth in a Southwestern State. Suicide and Life-threatening Behavior, 34, pp. 160-171, 2004.

Prevalence of Psychiatric and Substance Use Disorders in Opioid Abusers in a Community Syringe Exchange Program

The present study evaluates the prevalence of psychiatric and substance use disorders in male and female intravenous opioid abusers participating at a community needle exchange program (NEP). All participants (n = 422) were administered the Structured clinical Interview for the DSM-IV (SCID) for Axis I disorders and antisocial personality disorder (APD). Psychiatric and substance abuse comorbidity were highly prevalent. Major depression was the most common current and lifetime Axis I non-substance use disorder (6 and 21% of the sample, respectively); 37% were diagnosed with APD. Over 50% of the sample was diagnosed with at least one non-substance use Axis I disorder or APD. In addition to opioid dependence, cocaine dependence was the most prevalent current and lifetime substance use disorder (68 and 78% of the sample, respectively), followed by alcohol and cannabis dependence. Overall, participants reported a mean of over one current and over three lifetime substance use disorders in addition to opioid dependence. Women reported higher rates of post-traumatic stress disorder (PTSD), while men were more likely diagnosed with APD. Presence of a psychiatric disorder was associated with increased prevalence of substance use disorder for all drug classes. The high rates of comorbidity observed in this sample suggest that the harm reduction efforts of NEPs can be significantly enhanced through referral of participants to programs that treat substance use and/or other psychiatric disorders. Kidorf, M., Disney, E.R., King, V.L., Neufeld, K., Beilenson, P.L. and Brooner, R.K. Prevalence of Psychiatric and Substance Use Disorders in Opioid Abusers in a Community Syringe Exchange Program. Drug and Alcohol Dependence, 74, pp. 115—122, 2004.

Effects of Drug Treatment for Heroin Sniffers: A Factor Against Moving to Injection?

This article explores the relationship between contact with treatment and transition to

injection for heroin sniffers. The primary research question is: Does contact with treatment delay onset of injection for heroin sniffers? A stratified network-based sample was recruited from multiple communities in South Florida, which were known for high drug use. Three categories of respondents were recruited based on injection outcome: long-term injectors, short-term injectors, and sniffers (n = 900). The research question was answered in two steps. First, the prevalence of drug treatment for heroin sniffers and injectors was investigated using case-control methods. Second, the relationship was further examined by attempting to identify the causal factors that delay initial injection for a subgroup of current injectors using survival regression procedures. A positive relationship was found between contact with treatment and injection status outcome. Drug treatment significantly reduced the likelihood of heroin sniffers transitioning to injection. Delaying or preventing transition to injection could significantly decrease risk of HIV transmission by reducing or eliminating risky injecting behaviors. Reaching users, either sniffers or smokers, before they transition to injection is crucial, but continuing efforts to intervene early in an injection career is also crucial for reducing physical and social risks to injection drug users. Kelley, M.S. and Chitwood, D.D. Effects of Drug Treatment for Heroin Sniffers: A Factor Against Moving to Injection? Social Science and Medicine, 58, pp. 2083-2092, 2004.

Higher Methadone Dose, Free Treatment, and a Cooperative Orientation Are Associated With Higher Retention in Treatment

This study examined factors associated with methadone maintenance retention, defined as remaining in treatment for a minimum of 90 days, among street recruited injection drug users (IDUs). A total of 577 IDUs were randomly assigned to either a risk reduction intervention, focusing on safer injection and sex behaviors, or motivational interviewing, addressing more sweeping lifestyle changes including drug treatment. All subjects who wanted treatment were provided transportation, rapid intake and a waiver of the intake fee. In addition, 50% were randomly assigned a coupon for 90 days of free treatment. Overall, 33% entered treatment and of these, 60% remained for at least 90 days. Factors associated with retention included higher methadone dose, free treatment, greater contacts with the clinic and counselor rating of patient cooperation. Although desire for treatment, or motivation, was associated in univariate analyses with greater retention, there were no differences observed between the motivational interviewing and risk reduction interventions. Booth, R.E., Corsi, K.F. and Mikulich-Gilbertson, S.K. Higher Methadone Dose, Free Treatment, and a Cooperative Orientation are Associated with Higher Retention in Treatment. Drug Alcohol Depend, 74(2), pp. 177-185, May 2004.

Recent Injection Drug Use With a Shared Needle Predicted HIV Infection Among Drug Injectors in Ukraine, But Risky Sex Behavior Did Not, Has Needle Sharers Engaged in Sex Less

From June through August 2002, 100 IDUs from sites in IDUs from Kiev, Odessa, and Makeevka/Donetsk, Ukraine were recruited through street outreach, including 212 who had previously been tested for HIV and knew their sero status. Subjects were administered a standardized computer-assisted interview assessing HIV-related drug and sex risk behaviors and history of HIV testing. Twenty six percent of the 212 participants reported they were HIV-positive. Univariate followed by multiple logistic regression analyses identified factors associated with HIV infection. In the 30-day period before their interview, HIV-infected IDUs were significantly more likely to have injected with a needle previously used by another injector without disinfecting, frontloaded and/or back loaded, and shared the drug solution from a common container. In addition, they had higher prevalence rates for hepatitis B virus and hepatitis C virus than those not infected with HIV. On the other hand, they were more likely to have reported no sex partners and, if sexually active, more likely to have used a condom. Booth, R.E., Mikulich-Gilbertson, S.K., Brewster, J.T., Salomonsen-Sautel, S. and Semerik, O. Recent Injection Drug Use with a Shared Needle Predicted HIV Infection Among Drug Injectors in Ukraine, but Risky Sex Behavior Did Not, Has Needle Sharers Engaged in Sex Less. J Acquir Immune Defic Synd., 35(1), pp. 82-88, January 2004.

Integrated Care for Substance Abuse Patient With Severe Mental Illness is Becoming Less Common, Especially Among Publicly-Funded Providers

Survey data from a nationally representative sample of privately funded substance abuse treatment centers, were used to identify the proportion of centers that offered psychiatric programs in 1995-1996, 1997-1998, and 2000-2001. Centers reported whether they treated clients with severe mental illness on-site or referred them to external providers. Repeated-measures general linear models were used to test for significant changes over time and to assess mean differences in service availability by

profit status and hospital status. About 59 percent of private centers offered a psychiatric program, and this proportion did not significantly change over time. The proportion of centers that referred clients with severe mental illness to external providers increased significantly from 57 percent to 67 percent. For-profit centers and hospital-based centers were significantly more likely to offer psychiatric programs and were less likely to refer severe cases to other providers. Although the importance of integrated care for clients with dual diagnoses is widely accepted, data suggested that this pattern of service delivery is becoming less available. Knudsen, H.K., Roman, P.M. and Ducharme, L.J. Integrated Care for Substance Abuse Patient with Severe Mental Illness is Becoming Less Common, Especially Among Publicly-funded Providers. Psychiatric Services, 55(3), pp. 270-273, March 2004.

Psychological Distress Predicted Relapse Among Drug and Alcohol Abusers

Participants (n=180) completed a baseline interview within their first month of substance user treatment (conducted in 1995/1996) and follow-up interview 2 years following the baseline interview (conducted in 1997/1998). Structural equation modeling analyses were used to examine the relationship among client background characteristics and problem severity indicators, measured during treatment, in relation to alcohol and illicit drug use 2 years post treatment. Psychological distress directly predicted alcohol and illicit drug use during follow-up and appeared to mediate the relationship between client background characteristics (such as gender, race, and marital status) and substance use consequences on post treatment substance use. Income directly predicted alcohol use and age directly predicted illicit drug use, regardless of problem severity (including psychological distress and substance use consequences). Results support long-term clinical monitoring of psychological distress as a marker for return to drug or alcohol use. Flynn, H.A., Walton, M.A., Curran, G.M., Blow, F.C. and Knutzen, S. Psychological Distress Predicted Relapse Among Drug and Alcohol Abusers. Substance Use & Misuse. 39(6), pp. 885-910, May 2004.

Abstinence From Illicit Drugs is Related to Self-Efficacy and Self-Mastery for Oxford House Residents

The relationship between optimism, abstinence self-efficacy, and self-mastery was examined by investigating levels of these cognitive resources among two samples of recovering substance abusers: Oxford House residents who attended twelve-step groups and twelve-step members who had never lived in an Oxford House. Participants' levels of optimism were significantly and positively related to both abstinence self-efficacy and self-mastery scores, as abstinence self-efficacy was significantly and positively related to participants' number of days abstinent. Oxford House residents reported significantly higher levels of abstinence self-efficacy than twelve-step members. Overall, findings suggest that cognitive resources facilitate substance abusers' recovery and that the Oxford House model might provide high levels of support in their ongoing abstinence. Majer, J.M., Jason, L.A. and Olson, B.D. Abstinence from Illicit Drugs is Related to Self-Efficacy and Self-Mastery for Oxford House Residents. Assessment, 11(1), pp. 57-63, March 2004.

HCV Drug-Free and Methadone Maintenance Programs

Drug treatment programs are uniquely situated to screen patients for antibodies for hepatitis C virus (HCV). Almost all methadone and 2/3 of the drug-free programs in the national sample (N=256 programs) apparently offered screening for HCV, but only 60% pf the patients in these programs actually provided specimens for testing. Unfortunately, while some programs were planning to offer such testing that were not at the time of this study, many more were withdrawing this testing service due to lack of funds. This study points to the need for providing more testing resources and motivational efforts to actually use those resources provided. Strauss, S., Astone, J., Des Jarlais, D. and Hagan, H. A Comparison of HCV Antibody testing in Drug-Free and Methadone Maintenance Treatment Programs in the United States. Drug and Alcohol Dependence, 73, pp. 227-236, 2004.

The ASI Can Now be Administrated by Automated Telephone or the Internet

Two versions of the Addiction Severity Index underwent concurrent validation with the traditional clinical interview method. Eighty-eight subjects were administered all three forms yielding an average composite score inter-test correlation of .91 (range .81-.95). History items did not fare quite so well, yielding a mean kappa of .75 (.46-1.0) and mean inter-test correlation of .77 (.14-1.0). Administration times were similar for the clinical interview and internet versions, with the automated voice version taking 25% less time but also reflecting the lowest level of participant

satisfaction. Brodey, B.B., Rosen, C.S., Brodey, I.S., Sheetz, B.M., Steinfeld, R.R., and Gastfriend, D.R. Validation of the Addiction Severity Index (ASI) for Internet and Automated Telephone Self-Report Administration. Journal of Substance Abuse Treatment, 26, pp. 253-259, 2004.

Estimating Episode Lengths When Some Observations are Probably Censored

This paper analyzed a case in censored failure time data problems where some observations are potentially censored. The traditional models for failure time data implicitly assume that the censoring status for each observation is deterministic. Therefore, they cannot be applied directly to the potentially censored data. The researchers propose an estimator that uses resampling techniques to approximate censoring probabilities for individual observations. A Monte Carlo simulation study shows that the proposed estimator properly corrects biases that would otherwise be present had it been assumed that either all potentially censored observations are censored or that no censoring has occurred. Finally, the researchers apply the estimator to a health insurance claims database. The resulting estimates indicate that just as ignoring the censoring problem provides estimated medians that are too low, assuming all of the potentially censored observations are censored leads to medians that are too high. The method proposed to address the probable censoring can effectively correct the biases and provide appropriate estimates of medians. From a health-care system perspective, where episode length is related to utilization and costs, this finding is most important for planning and resource allocation as it helps predict individuals' experience in the system. Goodman, A.C., Peng, Y., Hankin, J.R., Kalist, D.E. and Spurr, S.J. Estimating Episode Lengths when Some Observations are Probably Censored. Statistics in Medicine, 23, pp. 2071—2087, 2004.

Burden of Medical Illness in Drug- and Alcohol-dependent Persons Without Primary Care

Little is known about the frequency, severity, and risk factors for disease in drug- and alcohol-dependent persons without primary medical care. The aim is to assess the burden of medical illness, identify patient and substance dependence characteristics associated with worse physical health, and compare measures of illness burden in this population. This was accomplished through a cross-sectional study among alcohol-, heroin- or cocaine-dependent persons without primary medical care who were admitted to an urban inpatient detoxification unit. The mean age of these patients was 35.7 (SD 7.8) years: 76% were male and 46% were Black. Forty-five percent reported being diagnosed with a chronic illness, and 80% had prior medical hospitalizations. The mean age-adjusted SF-36 Physical Component Summary (PCS) score was lower than the general U.S. population norm (44.1 vs 50.1; p<0.001). In multivariable analysis, female gender (adjusted mean change in PCS score: _3.71 points, p=.002), problem use of hallucinogens (_3.51, p=0.013), heroin (_2.94, p=0.008), other opiates (_3.20, p=.045), living alone (_3.15, p=.023), having medical insurance (_2.26, p=0.014) and older age (_.22 points per year, p=0.001) were associated with worse health. From these data, it seems that alcohol- and drug-dependent persons without primary medical care have a substantial burden of medical illness compared to age- and gender-matched U.S. population controls. While the optimal measure of medical illness burden in this population is unclear, a variety of health measures document this medical illness burden in addicted persons. De Alba, I., Samet, J.H. and Saitz, R. Burden of Medical Illness in Drug- and Alcohol-dependent Persons without Primary Care. Am J Addict, 13, pp. 33-45, 2004.

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

Research Findings - Intramural Research

Development and Plasticity Section, Cellular Neurobiology Research Branch

A Perspective on Transplantation Therapy and Stem Cells for Parkinson's Disease Although the functioning of the brain is overwhelmingly complex, Parkinson's disease is one disorder that seems to be simple, straightforward, and amenable to human intervention. Mostly, a restricted population of cells (dopaminergic neurons) is lost, and it seems that the loss of striatal dopamine can, in effect, be partially replaced by administration of a drug (L-DOPA). L-DOPA simply helps the brain to produce the substance (dopamine) the lost dopamine-producing cells normally produce. These cells send projections to only a few areas, and just two of these brain regions (the caudate and putamen) seem to be responsible for almost the entire syndrome of Parkinson's disease. Therefore, if we can just find a way to restore this one simple circuit, the disease might be cured. So it appeared in 1977, and still, it seems that it might just be that simple. Freed, W.J. Cell Transplantation, 13, pp. 319-327, 2004.

Properties of Pluripotent Human Embryonic Stem Cells BG01 and BG02 Human ES (hES) cell lines have only recently been generated, and differences between human and mouse ES cells have been identified. In this manuscript IRP investigators describe the properties of two human ES cell lines, BG01 and BG02. By immunocytochemistry and reverse transcription polymerase chain reaction, undifferentiated cells expressed markers that are characteristic of ES cells, including SSEA-3, SSEA-4, TRA-1-60, TRA-1-81, and OCT-3/4. Both cell lines were readily maintained in an undifferentiated state and could differentiate into cells of all three germ layers, as determined by expression of beta-tubulin III neuron-specific molecule (ectoderm), cardiac troponin I (cardiomyocytes, mesoderm), and alpha-fetoprotein (endoderm). A large-scale microarray (16,659 genes) analysis identified 373 genes that were expressed at three-fold or higher levels in undifferentiated BG01 and BG02 cells as compared with pooled human RNA. Ninety-two of these genes were also highly expressed in four other hES lines (TE05, GE01, GE09, and pooled samples derived from GE01, GE09, and GE07). Included in the list are genes involved in cell signaling and development, metabolism, transcription regulation, and many hypothetical proteins. Two focused arrays designed to examine transcripts associated with stem cells and with the transforming growth factor-beta superfamily were employed to examine differentially expressed genes. Several growth factors, receptors, and components of signaling pathways that regulate embryonic development, in particular the nodal signaling pathway, were detected in both BG01 and BG02. These data provide a detailed characterization and an initial gene expression profile for the BG01 and BG02 human ES cell lines. Zeng, X., Miura, T., Luo, Y., Bhattacharya, B., Condie, B., Chen, J., Ginis, I., Lyons, I., Mejido, J., Puri, R.K., Rao, M.S., and Freed, W.J. Stem Cells, 22, pp. 292-312, 2004.

Absence of DNA Polymerase Eta Reveals Targeting of C Mutations on the Non-Transcribed Strand in Immunoglobulin Switch Regions Activation-induced cytosine deaminase preferentially deaminates C in DNA on the nontranscribed strand in vitro, which theoretically should produce a large increase in mutations of C during hypermutation of immunoglobulin genes. However, a bias for C mutations has not been observed among the mutations in variable genes. Therefore, IRP scientists examined mutations in the micro and gamma switch regions, which can form stable secondary structures, to look for C mutations. To further simplify the pattern, mutations were studied in the absence of DNA polymerase (pol) eta, which may produce substitutions of nucleotides downstream of C. DNA from lymphocytes of patients with xeroderma pigmentosum variant (XP-V) disease, whose polymerase eta

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is defective, had the same frequency of switching to all four gamma isotypes and hypermutation in micro-gamma switch sites (0.5% mutations per basepair) as control subjects. There were fewer mutations of A and T bases in the XP-V clones, similar to variable gene mutations from these patients, which confirms that polymerase eta produces substitutions opposite A and T. Most importantly, the absence of polymerase eta revealed an increase in C mutations on the nontranscribed strand. This data shows for the first time that C is preferentially mutated in vivo and pol eta generates hypermutation in the micro and gamma switch regions. Zeng, X., Negrete, G., Kasmer, C., and Gearhart, P.J. Journal of Experimental Medicine, 199, pp. 917-924, 2004.

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

Sigma-1 Receptor Ligands: Potential in the Treatment of Neuropsychiatric Disorders The sigma receptors are non-opioid, non-phencyclidine brain ER proteins that exist in two subtypes: sigma-1 and sigma-2. Sigma-1 receptors have been cloned and are known to bind certain sex hormones (neurosteroids) in the brain. Sigma-1 receptors regulate glutamate NMDA receptor function and the release of neurotransmitters such as dopamine, and are implicated in learning and memory, and in certain neuropsychiatric disorders. In particular, as several antipsychotics can bind to sigma-1 receptors, sigma-1 receptor ligands have been proposed as being of potential use in the treatment of schizophrenia. In clinical trials, sigma-1 receptor ligands failed to improve acute psychotic symptoms of schizophrenia but, interestingly, were shown in a few studies to attenuate negative symptomatology in schizophrenic patients. Preclinical studies, on the other hand, indicate that selective sigma-1 receptor agonists affect higher-ordered brain functions including learning and memory, cognition, and mood. These results implicate therapeutic potentials of sigma-1 agonists in depression and senile dementia. Indeed, a sigma-1 receptor agonist, igmesine, has been shown to improve depression in a clinical trial. The most distinctive feature of the action of sigma-1 receptor ligands is their "modulatory" role. In behavioral studies of depression and memory, they exert beneficial effects only when brain functions are perturbed. Given the recently accumulated preclinical and clinical data, it is time to reconstruct the concept of sigma-1 receptors and the associated pathophysiological conditions that ligands of these receptors target. This would allow clinical trials to be performed more efficiently, and the results may confirm a long-speculated possibility that sigma-1 receptor ligands represent a new class of therapeutic agents for neuropsychiatric disorders. Hayashi, T. and Su, T.P. CNS Drugs, 18, pp. 269-284, 2004.

Involvement of the Sigma1 Receptor in the Modulation of Dopaminergic Transmission by Amantadine Pharmacological effects of amantadine on dopaminergic transmission are proposed to result from an uncompetitive antagonism at glutamate N-methyl-D-aspartate (NMDA) receptors. However, the authors previous studies examining amantadine-mediated dopamine receptor regulation in the rat striatum revealed a discrepancy from a direct interference with glutamate transmission. Preliminary in vitro binding data from the literature suggested the interaction of amantadine with the sigma1 receptor. Therefore, the authors have now further characterized the pharmacological properties of amantadine and memantine at this receptor and investigated its involvement in the modulation of striatal dopaminergic transmission. Their binding studies using [3H]-(+)SKF-10,047 indicated that amantadine and memantine behave as ligands of the sigma(1) receptor in rat forebrain homogenates (Ki values of 7.44 +/- 0.82 and 2.60 +/- 0.62 microm, respectively). In NG108-15 neuroblastoma cells, both drugs (amantadine (100 microm) and memantine (10 microm)) potentiated the bradykinin-induced mobilization of intracellular Ca2+, mimicking the effect of the sigma1 receptor agonist PRE-084 (1 microm). Finally, authors previously showed that in striatal membranes from amantadine-treated rats, the functional coupling of dopamine receptors with G-proteins was enhanced. Similarly, PRE-084 dose-dependently increased the [35S]GTPgammaS binding induced by dopamine (Emax 28 and 26% of basal, 0.3 and 1 mg/kg PRE-084, respectively). By contrast, BD1047, which is without effect on its own, antagonized the effects of amantadine and PRE-084. Together, these data demonstrate that aminoadamantanes behave as sigma1 receptor agonists, and confirm an involvement of this receptor in modulating dopamine receptors exerted by therapeutically relevant concentrations of amantadine. Peeters, M., Romieu, P., Maurice, T., Su, T.P., Maloteaux, J.M., and Hermans, E. European Journal of Neuroscience, 19, pp. 2212-2220, 2004.

Sigma-1 Receptors Potentiate Epidermal Growth Factor Signaling Towards Neuritogenesis in PC12 cells: Potential Relation to Lipid Raft Reconstitution

IRP investigators previously demonstrated that overexpression of sigma-1 receptors (sigma-1R) potentiated neurite sprouting caused by nerve growth factor in PC12 cells. In this study authors examined if sigma-1R may be involved in the action of epidermal growth factor (EGF). EGF is conventionally recognized as a mitogenic factor that stimulates only the proliferation of various types of cells, including PC12 cells. Authors found here that in sigma-1 receptor-overexpressing PC12 cells (sigma-1R OE cells), EGF markedly stimulates neuritogenesis without affecting cellular proliferation. EGF receptors (EGFR) are largely reduced in lipid rafts and are enriched in non-raft regions in sigma-1R OE cells. The enrichment of EGFR in the non-raft region is correlated with enhanced downstream signaling of EGFR including the phosphorylation of both EGFR and extracellular signal-regulated kinases (ERKs). Destruction of cholesterol-containing rafts by treating cells with methyl-beta-cyclodextrin also causes a reduction of EGFR in lipid rafts, a concomitant increase in the phosphorylation of both EGFR and ERK, and an increase in the EGF-induced neurite sprouting in wildtype cells. Furthermore, while overexpression of sigma-1R increases the level of lipid raft-associated cholesterol, the overexpression alters the levels of gangliosides in lipid rafts: GM1 and GM2 are decreased, whereas GD1a is increased. The authors conclude that sigma-1R cause the remodeling of lipid rafts, at least by increasing the level of lipid raft-associated cholesterol and by altering the levels of certain critical lipid raft-forming gangliosides. Sigma-1R may thus play an important role in directing EGF signaling towards neuritogenesis, perhaps by shifting EGFR from the lipid raft into non-raft regions. Takebayashi, M., Hayashi, T., and Su, T.P. Synapse, 53, pp. 90-103, 2004.

Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Glial Cell Line-Derived Neurotrophic Factor is Essential for Neuronal Survival in the Locus Coeruleus-Hippocampal Noradrenergic Pathway It has been shown that the noradrenergic (NE) locus coeruleus (LC)-hippocampal pathway plays an important role in learning and memory processing, and that the development of this transmitter pathway is influenced by neurotrophic factors. Although some of these factors have been discovered, the regulatory mechanisms for this developmental event have not been fully elucidated. Glial cell line-derived neurotrophic factor (GDNF) is a potent neurotrophic factor influencing LC-NE neurons. IRP scientists have utilized a GDNF knockout animal model to explore its function on the LC-NE transmitter system during development, particularly with respect to target innervation. By transplanting various combinations of brainstem (including LC) and hippocampal tissues from wildtype or GDNF knockout fetuses into the brains of adult wildtype mice, the authors demonstrate that normal postnatal development of brainstem LC-NE neurons is disrupted as a result of the GDNF null mutation. Tyrosine hydroxylase immunohistochemistry revealed that brainstem grafts had markedly reduced number and size of LC neurons in transplants from knockout fetuses. NE fiber innervation into the hippocampal co-transplant from an adjacent brainstem graft was also influenced by the presence of GDNF, with a significantly more robust innervation observed in transplants from wildtype fetuses. The most successful LC/hippocampal co-grafts were generated from fetuses expressing the wildtype GDNF background, whereas the most severely affected transplants were derived from double transplants from null-mutated fetuses. These data suggest that development of the NE LC-hippocampal pathway is dependent on the presence of GDNF, most likely through a target-derived neurotrophic function. Quintero, E.M., Willis, L.M., Zaman, V., Lee, J., Boger, H.A., Tomac, A., Hoffer, B.J., Stromberg, I., and Granholm, A.C. Neuroscience, 124, pp. 137-146, 2004.

Electrophysiology Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

The Solubilizing Detergents, Tween 80 and Triton X-100 Non-Competitively Inhibit Alpha(7)-Nicotinic Acetylcholine Receptor Function in Xenopus Oocytes Because many studies rely upon detergents to solubilize lipophilic agents such as cannabinoid drugs, IRP scientists examined the effect of commonly employed detergents on the function of the cloned alpha(7) subunit of the nicotinic ACh receptor. Homomeric alpha(7) receptors were expressed in Xenopus oocytes and the two-microelectrode voltage-clamp technique was used to assess their electrophysiological properties. The detergents Tween 80 and Triton X-100 reversibly inhibited ACh (100microM)-induced inward currents in a concentration-dependent manner, with IC(50) values of 610nM and 1.4microM, respectively. The effects of these detergents were independent of membrane potential, and they were not meditated by endogenous Ca(2+)-dependent Cl(-) channels, since they were unaffected by intracellularly injected BAPTA, and recorded in Ca(2+)-free bathing solution containing 2mM Ba(2+). Both detergents also decreased the maximal effect

of ACh, without significantly affecting its EC(50), indicating a non-competitive interaction with the nACh alpha(7) receptors. In contrast to the effects of these detergents, authors found that cholic acid (10microM), DMSO (10microM) and Tocrisol((R)) (0.01% v/v) did not cause a significant effect on nicotinic responses. In conclusion, authors demonstrate that the detergents Tween 80 and Triton X-100 are potent inhibitors of neuronal nACh alpha(7) receptors expressed in Xenopus oocytes, and suggest that studies utilizing these detergents to solubilize lipophilic drugs be scrutinized for such effects. Oz, M., Spivak, C.E. and Lupica, C.R. Journal of Neuroscience Methods, 137, pp. 167-173, 2004.

Kinetics of Beta-Funaltrexamine Binding to Wild-Type and Mutant Micro-Opioid Receptors Expressed in Chinese Hamster Ovary Cells The two-stage reaction whereby the antagonist beta-funaltrexamine (beta-FNA) binds covalently to micro opioid receptors makes it a highly discriminating probe into the tertiary structure of the receptor's recognition pocket. To obtain a quantitative measure of how well this pocket is preserved in a mutated form of the receptor, in which His-297 is substituted with glutamine, IRP investigators employed [3H]-beta-FNA to evaluate the kinetic rate constants for both the reversible as well as the irreversible stages of its binding to wild-type and mutant H297Q micro receptors stably expressed in Chinese hamster ovary cells. The expression levels of the wild-type and mutant H297Q receptors were matched by exploiting the variation in receptor density as a function of plating day and by raising the expression level by pretreatment with naloxone. Authors found that all of the kinetic rate constants for [3H]-beta-FNA were diminished by about one-half at the mutant H297Q micro receptors with respect to wild-type receptors. By comparison, the association rate constant of [3H]-naloxone likewise decreased by one-half; however, the dissociation rate constant increased 5-fold at the mutant H297Q receptor. The authors conclude that the mutation has had only minor influence on the recognition site and that the function of position 297 is more likely as a link in the transduction chain. Spivak, C.E. and Beglan, C.L. Synapse, 52, pp. 123-135, 2004.

Molecular Neuropsychiatry Section, Molecular Neuropsychiatry Research Branch

Nicotine Dependence Criteria of the DIS and DSM-III-R: A Factor Analysis This paper reports a factor analysis of the symptoms of nicotine dependence that were determined in an assessment of 821 current cigarette-smoking research volunteers, according to the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised (DSM-III-R) of the American Psychiatric Association as well as an analysis of a subset who unsuccessfully attempted to quit (n=636). In the total sample, two factors with eigenvalues greater than 1 accounted for 62.7% of the variance. When the factor analysis was repeated with the subset of research volunteers who unsuccessfully attempted to quit, only one DSM-III-R nicotine dependence symptom loaded on the second factor. This finding suggests that the two-factor structure found in this and a previous factor analysis study of the nicotine dependence segment of the DSM-III-R may be an artifact of the skipout pattern of the DSM-III-R, which assumes that smokers who have not attempted to quit have not experienced withdrawal symptoms or used tobacco to avoid these symptoms. Goodness-of-fit measures suggested that the two-factor structure is a better fit than the one-factor structure for both the total population and the subset who unsuccessfully attempted to quit or cut down. The present study's sample of current smokers who had not attempted to quit (n=185) was too small to permit factor analyses. Further work with other large samples from the general population of current smokers who have unsuccessfully attempted to quit as well as those who have not attempted to quit will enhance understanding of the factor structure of the nicotine dependence segment of the DSM-III-R and clarify the effect of the skipout pattern on its factor structure. Radzius, A., Gallo, J., Gorelick, D., Cadet, J.L., Uhl, G., Henningfield, J. and Moolchan, E. Nicotine and Tobacco Research, 6, pp. 303-308, 2004.

Sex-related Differences in a Gambling Task and Its Neurological Correlates IRP scientists investigated sex-related differences in task performance and brain activity in the orbitofrontal cortex (OFC) and dorsolateral prefrontal cortex (DLPFC) during performance of a decision-making task (the Iowa Gambling Task). When men and women were examined separately, men activated extensive regions of the right lateral OFC and right DLPFC, as well as the left lateral OFC. In contrast, women activated the left medial OFC. Examining sex differences directly, men showed better task performance and greater lateralized brain activity to the right hemisphere than women. This was exemplified by greater activation in a large area of the right lateral OFC of men during their performance of the Iowa Gambling Task. In contrast, women

had greater activation in the left DLPFC, left medial frontal gyrus and temporal lobe during this task. Thus, brain mechanisms engaged by men and women when solving the same decision-making task are different. These observations indicate that sex-related differences contribute to the heterogeneity observed in both normal and abnormal brain functioning. These results also provide further evidence of sexual dimorphism in neurocognitive performance and brain function. Bolla, K.I., Eldreth, D.A., Matochik, J.A. and Cadet, J.L. Cerebral Cortex, VOLUME, PAGES, 2004.

Histological Evidence Supporting a Role for the Striatal Neurokinin-1 Receptor in Methamphetamine-induced Neurotoxicity in the Mouse Brain Several studies have documented the effect of methamphetamine (METH) on the toxicity of the dopamine (DA) terminals of the striatum but only a few studies have assessed the damaging effects of METH on striatal neurons postsynaptic to the nigrostriatal DA terminals. In the present study, IRP investigators employed histological methods to study the effect of METH on DA terminals and striatal neurons. They also assessed the role of the striatal neurokinin-1 (NK-1) receptor on pre- and post-synaptic METH-induced damage. Male mice were treated with METH (10 mg/kg) four times at 2-h intervals and were sacrificed 3 days after the treatment. A number of animals received the non-peptide NK-1 receptor antagonist WIN-51,708 (10 mg/kg) 30 min before the first and fourth injections of METH. Immunocytochemical staining for tyrosine hydroxylase (TH) showed significant deficits throughout all aspects of the caudate-putamen in animals exposed to METH. Pretreatment with WIN-51,708 prevented the METH-induced loss of TH immunostaining. Sections from a separate set of mice were stained with Fluoro-Jade B (FJB), a fluorochrome that binds specifically to degenerating fibers and cell bodies of neurons. Treatment with METH shows Fluoro-Jade B positive cell bodies in the striatum and pretreatment with WIN-51,708 abolished Fluoro-Jade B staining. Moreover, double labeling with Fluoro-Jade B and glial fibrillary acidic protein (GFAP) shows reactive astrocytosis in the area adjacent to the Fluoro-Jade B-positive cells but no Fluoro-Jade B staining of the astrocytes. This observation suggests that the degenerating cells must be striatal neurons and not astrocytes. The data demonstrate that METH induces pre- and post-synaptic damage in the striatum and the damage can be prevented with pharmacological blockade of the NK-1 receptor. These findings represent a new direction in the study of the mechanism of toxicity to METH and could be useful in the treatment of some neurological disorders. Yu, J., Wang, J., Cadet, J.L. and Angulo, J.A. Brain Research, 1007, pp. 124-131, 2004.

Paroxetine Retards Disease Onset and Progression in Huntington Mutant Mice IRP scientists report that administration of paroxetine, a widely prescribed antidepressant drug that acts by inhibiting reuptake of the neurotransmitter serotonin, suppresses the neurodegenerative process and increases the survival of huntington mutant mice, an animal model of Huntington's disease (HD). Paroxetine attenuated motor dysfunction and body weight loss and improved glucose metabolism in the HD mice. Paroxetine was beneficial when treatment was initiated before or after the onset of motor dysfunction, suggesting a potential for such antidepressant drugs in the treatment of presymptomatic and symptomatic HD patients. Duan, W., Guo, Z., Jiang, H., Ladenheim, B., Xu, X., Cadet, J.L. and Mattson, M.P. Annals of Neurology, 55, pp. 590-594, 2004.

Neural Protection and Regeneration Section, Molecular Neuropsychiatry Research Branch

Neuroprotective Effects of Diadenosine Teraphosphate In Animal Models of Stroke and Parkinson's Disease Diadenosine tetraphosphate (AP4 A), an endogenous diadenosine polyphosphate, reduces ischemic injury in the heart. In this study, IRP investigators report the potent and protective effects of AP4A in rodent models of stroke and Parkinson's disease. AP4A, given intracerebroventricularly before middle cerebral artery (MCA) ligation, reduced cerebral infarction size and enhanced locomotor activity in adult rats. The intravenous administration of AP4A also induced protection when given early after MCA ligation. AP4A suppressed terminal deoxynucleotidyl transferase-mediated biotinylated UTP nick end labeling (TUNEL) induced by hypoxia/reperfusion in primary cortical cultures, and reduced both ischemia-induced translocation of mitochondrial cytochrome c and the increase in cytoplasmic caspase-3 activity in vivo. The purinergic P2/P4 antagonist di-inosine pentaphosphate or P1-receptor antagonist sulfonylphenyl theophylline, but not the P2-receptor antagonist suramin, antagonized the effect of AP4A, suggesting that the observed protection is mediated through an anti-apoptotic mechanism and the activation of P1- and P4-purinergic receptors. AP4A also afforded protection from toxicity induced by unilateral medial forebrain bundle injection of 6-hydroxydopamine (6-OHDA). One month after lesioning, vehicle-treated rats exhibited amphetamine-

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

Clinical Psychopharmacology Section, Medications Discovery Research Branch

Identification and Characterization of a Novel Allosteric Modulator (SoRI-6238) of the Serotonin Transporter In the present study, IRP scientists describe a novel agent, SoRI-6238 (ethyl 5-amino-3-(3,4-dichlorophenyl)-1,2-dihydropyrido[3,4-b]pyrazin-7-ylcarbamate) that partially inhibits 5-HT transporter (SERT) binding and allosterically modulates SERT function. Membranes were prepared from rat brain. SoRI-6238 partially inhibited SERT binding to brain membranes with a plateau at about 40% of control. SoRI-6238 fully inhibited NET and DAT binding with IC50 values of 12.1 µM and 5.8 µM, respectively. The apparent Kd of [125I]RTI-55 binding to SERT increased, and then reached a plateau with increasing concentrations of SoRI-6238. SoRI-6238 fully inhibited [3H]5-HT uptake, acting to decrease the Vmax (non-competitive inhibition). In kinetic experiments, SoRI-6238 slowed the dissociation of [125I]RTI-55 from SERT and slowed the initial association rate. The authors conclude that SoRI-6238 partially inhibits SERT binding and function, most likely via an allosteric mechanism. Nandi, A., Dersch, C.M., Kulshrestha, M., Ananthan, S. and Rothman, R.B. Synapse, 53, pp. 176-183, 2004.

3,4-Methylenedioxymethamphetamine (MDMA) Administration to Rats Decreases Brain Tissue Serotonin but Not Serotonin Transporter Protein and Glial Fibrillary Acidic Protein Previous experiments conducted in this laboratory showed that administration of high-dose D-fenfluramine (D-FEN) and p-chloroamphetamine (PCA) decreased 5-HT transporter (SERT) binding and tissue 5-HT by 30% to 60% in caudate and whole brain tissue 2-days and 2-weeks after drug administration. However, protein expression as determined by Western blot analysis, did not change in either tissue or time point, except for a 30% decrease in the caudate 2-days after PCA administration. In the present study, Authors examined the effect of MDMA and 5,7-dihydroxytryptamine (5,7-DHT) on tissue 5-HT levels and the protein expression level of SERT and glial fibrillary acidic protein (GFAP), a validated neurotoxicity marker. The authors hypothesized that MDMA administration would decrease SERT expression. Two weeks after MDMA administration (7.5 mg/kg i.p., q 2hr x 3 doses) or two weeks after i.c.v. administration of 5,7,-DHT (150 µg/rat), male Sprague-Dawley rats were sacrificed, and the caudate, cortex and hippocampal tissue collected. Western blots for SERT and GFAP were generated using published methods. Tissue 5-HT levels were determined by HPLC coupled to electrochemical detection. Results indicated that MDMA treatment decreased tissue 5-HT in cortex, hippocampus and caudate by about 50%. However, MDMA treatment had no significant effect on expression level of SERT and GFAP in any brain region. In contrast, 5,7-DHT reduced tissue 5-HT by more than 90%, decreased SERT protein expression by 20% to 35%, and increased GFAP by 30% to 39%. These data suggest the MDMA treatment regimen used here does not cause degeneration of 5-HT nerve terminals. Viewed collectively with previous results from this laboratory and other published data, these data indicate that MDMA-induced persistent 5-HT depletion may occur in the absence of axotomy. Wang, X., Baumann, M.H., Xu, H. and Rothman, R.B. Synapse, 53, pp. 240-248, 2004.

Medicinal Chemistry Section, Medications Discovery Research Branch

The Effect of 6-substituted-4',4''-Difluorobenztropines on Monoamine Transporters and the Muscarinic M1 Receptor A series of racemic 6-hydroxy and carboalkoxy substituted-4',4''-difluorobenztropines was synthesized and evaluated at the dopamine (DAT), serotonin (SERT) and norepinephrine (NET) transporters as well as the muscarinic M1 receptor. Each of the analogs displaced [^{3}H]WIN 35,428 from DAT with a range of affinities (K_i= 5.81 to 175 nM) and [^{3}H]pirenzepine from muscarinic M1 receptors, with a range of affinities (K_i = 27.0-8430 nM). Binding affinities at the SERT and NET were generally low. A comparison of M1 with DAT binding affinities suggests that within this series of compounds, binding at the two

sites is related, however, these hydroxy and carboalkoxy substitutions on the 6,7-bridgehead may be exploited to provide selective and potent DAT ligands. *In vivo* studies and the synthesis and pharmacological evaluation of enantiomerically pure derivatives is currently underway. Grundt, P., Kopajtic, T. A., Katz, J.L. and Newman, A.H. Bioorganic and Medicinal Chemistry Letters, 14, pp. 3295-3298, 2004.

Structure-Activity Relationships at Monoamine Transporters for a Series of N-Substituted-3a-(Bis[4-fluorophenyl]methoxy)tropanes: Comparative Molecular Field Analysis, Synthesis and Pharmacological Evaluation The development of structure-activity relationships (SAR) with divergent classes of monoamine transporter ligands and comparing their effects in animal models of cocaine abuse has provided insight into the complex relationship between structure, binding profiles and behavioral activity. Many 3_(diphenylmethoxy)tropane (benztropine) analogues are potent dopamine uptake inhibitors but exhibit behavioral profiles that differ from cocaine and other compounds in this class. One of the most potent and dopamine transporter (DAT)-selective N-substituted benztropine analogues (N-(4-phenyl-n-butyl)-3α-(bis[4-fluorophenyl]methoxy) tropane; 1c) is devoid of cocaine-like behaviors in rodent models but is also highly lipophilic (cLogD = 5.01), which compromises its water solubility and may adversely affect its pharmacokinetic properties. In order to further explore the SAR in this series, and ultimately design dopamine uptake inhibitors, with favorable lipophilicities for drug development, a Comparative Molecular Field Analysis (CoMFA) was performed on a set of benztropine analogs previously synthesized in this laboratory. The CoMFA field analysis on the statistically significant (r^2_{cv} = 0.632; r^2_{ncv} = 0.917) models provided valuable insight into the structural features required for optimal binding to the DAT, which was used to design a series of novel benztropine analogs with heteroatom substitutions at the tropane N-8. These compounds were evaluated for binding at DAT, serotonin (SERT) and norepinephrine (NET) transporters, and muscarinic M1 receptor, in rat brain. Inhibition of [^{3}H]DA uptake in synaptosomes was also evaluated. Most of the analogues showed high DAT affinity (12-50 nM), selectivity (10-120 fold), potent inhibition of dopamine uptake and lower lipophilicities as predicted by cLogD values than the parent drug. Selected compounds are currently being evaluated in animal models of cocaine abuse. Kulkarni, S.S., Grundt, P., Kopajtic, T., Katz, J. L. and Newman, A. H. Journal of Medicinal Chemistry, 47, pp. 3388-3398, 2004.

Neurobiology of Relapse Section, Behavioral Neuroscience Research Branch

The Anxiogenic Drug Yohimbine Reinstates Methamphetamine Seeking in a Rat Model of Drug Relapse Brain noradrenaline is involved in footshock stress-induced reinstatement of drug seeking in a rat relapse model. Here, IRP scientists studied whether yohimbine, an alpha-2 adrenoceptor antagonist that increases noradrenaline release and induces anxiety-like responses in human or non-human subjects, would reinstate methamphetamine seeking in rats. In Exp. 1, the effect of yohimbine (1.25-2.5 mg/kg) on reinstatement was compared to that of intermittent footshock (5 min; 0.2-0.6 mA) in rats that were trained to lever press for intravenous methamphetamine (9-11 days) and subsequently underwent 7 days of extinction training. In Exp. 2, the effect of yohimbine on reinstatement of drug seeking was determined during early (1 day) and late (21 or 51 days) withdrawal periods. On the test days, rats were first given 3-h extinction sessions and were then tested for reinstatement induced by yohimbine. In Exp. 1, both yohimbine and footshock stress reinstated methamphetamine seeking after extinction. In Exp. 2, extinction responding was higher after 21 or 51 withdrawal days than after 1 withdrawal day. In contrast, no significant time-dependent changes in yohimbine-induced reinstatement were observed. Results indicate that the anxiogenic drug yohimbine is a potent stimulus for reinstatement of methamphetamine seeking in a rat relapse model. Shepard, J.D., Bossert, J.M., Liu, S., Shaham, Y. Biological Psychiatry, 55, pp. 1082-1089, 2004.

Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch

On the Molecular Basis of the Receptor Mosaic Hypothesis of the Engram This paper revisits the so-called "receptor mosaic hypothesis" for memory trace formation in the light of recent findings in "functional (or interaction) proteomics." The receptor mosaic hypothesis maintains that receptors may form molecular aggregates at the plasma membrane level representing part of the computational molecular networks. Specific interactions between receptors occur as a consequence of the pattern of transmitter release from the source neurons, which release the chemical code impinging on the receptor mosaics of the target neuron. Thus, the decoding of the chemical message depends on the receptors forming the receptor mosaics and on the

type of interactions among receptors and other proteins in the molecular network with novel long-term mosaics formed by their stabilization via adapter proteins formed in target neurons through the incoming neurotransmitter code. The internalized receptor heteromeric complexes or parts of them may act as transcription factors for the formation of such adapter proteins. Receptor mosaics are formed both at the pre- and postsynaptic level of the plasma membranes and this phenomenon can play a role in the Hebbian behavior of some synaptic contacts. The appropriate "matching" of the pre- with the postsynaptic receptor mosaic can be thought of as the "clamping of the synapse to the external teaching signal." According to the present hypothesis the behavior of the molecular networks at plasma membrane level to which the receptor mosaics belong can be set in a "frozen" conformation (i.e. in a frozen functional state) and this may represent a mechanism to maintain constant the input to a neuron. Thus, authors are suggesting that molecular networks at plasma membrane level may display multiple "attractors" each of which stores the memory of a specific neurotransmitter code due to a unique firing pattern. Hence, this mechanism may play a role in learning processes where the input to a neuron is likely to remain constant for a while. Agnati, L.F., Ferre, S., Leo, G., Lluis, C., Canela, E.I., Franco, R. and Fuxe, K. Cellular and Molecular Neurobiology, 24, pp. 501-516, 2004.

Striatal Plasticity at the Network Level: Focus on Adenosine A2A and D2 Interactions in Models of Parkinson's Disease Behavioral and microdialysis studies have been performed on antagonistic A(2A)/D(2) interactions in animal models of Parkinson's Disease. The behavioral analysis involved studies on locomotor activity in reserpinized mice, haloperidol-induced catalepsy in rats and rotational behavior in rats with unilateral 6-OHDA lesions of the ascending DA pathways (Ungerstedt model). Dual probe microdialysis studies were indirectly performed on the striatopallidal GABA neurons by studying extracellular glutamate levels in the striatum and globus pallidus of the awake freely moving rat. The striatum was perfused with A(2A) and/or D(2) agonists via reverse microdialysis. The results show that the A(2A) antagonists SCH58261 and KF17837 can increase locomotor activity in reserpinized mice and produce contralateral rotational behavior only after administration of subthreshold doses of l-DOPA or the D(2) like agonist quinpirole. Furthermore, antagonizing the A(2A) receptor (R) reduced haloperidol induced catalepsy. The behavioral results underline the view that A(2A) antagonists act by blocking A(2A) R in A(2A)/D(2) heterodimers where A(2A) R inhibits the D(2) R transduction and D(2) inhibits the adenylate cyclase (AC) activated by A(2A) R. The microdialysis studies show that the A(2A) agonist CGS21680 striatally coperfused with the D(2) agonist quinpirole more potently counteract the D(2) agonist (quinpirole) induced reduction of pallidal glutamate levels in the DA denervated vs the control striatum indicating an enhancement of the inhibitory A(2A)/D(2) interaction. In the DA denervated but not in the control striatum the A(2A) agonist CGS21680 could strongly increase striatal glutamate levels, indicating an increased receptor signaling in the A(2A) R located on the striatal glutamate terminals, where also D(2) like R exist, here probably as D(4). Thus, the signaling of this A(2A) R may be set free by the loss of D(4) tone on the AC activated by A(2A) in this postulated A(2A)/D(4) heteromer on the glutamate terminals. Taken together, the results indicate that the antiparkinsonian actions of A(2A) antagonists probably are produced by blockade of A(2A) R in the A(2A)/D(2) heterodimers mainly located in the striatopallidal GABA neurons. Tanganelli, S., Sandager Nielsen, K., Ferraro, L., Antonelli, T., Kehr, J., Franco, R., Ferre, S., Agnati, L. F., Fuxe, K., and Scheel-Kruger, J. Parkinsonism and Related Disorders, 10, pp. 273-280, 2004.

Adenosine A2A-dopamine D2 Receptor-receptor Heteromers. Targets for Neuro-psychiatric Disorders Emerging evidence shows that G protein-coupled receptors can form homo- and heteromers. These include adenosine A(2A) receptor-dopamine D(2) receptor heteromers, which are most probably localized in the dendritic spines of the striatopallidal GABAergic neurons, where they are in a position to modulate glutamatergic neurotransmission. The discovery of A(2A) receptor-dopamine D(2) receptor heteromers gives a frame for the well-known antagonistic interaction between both receptors, which is the bases for a new therapeutic approach for neuro-psychiatric disorders, such as Parkinson's disease and schizoprenia. The present review deals mainly with the biochemical and molecular aspects of A(2A) receptor-dopamine D(2) receptor interactions. Recent results at the molecular level show that A(2A) receptor-dopamine D(2) receptor heteromers represent the first example of epitope-epitope electrostatic interaction underlying receptor heteromerization. Most probably A(2A) receptor-D(2) receptor heteromerization is not static, but subject to a dynamic regulation, related to the phosphorylation dependence of the A(2A) receptor epitope and to the ability of the D(2) receptor epitope to bind different partners. Finding out the mechanisms involved in this dynamic regulation can have important implications for the treatment of basal

ganglia disorders, schizophrenia and drug addiction. Ferre, S., Ciruela, F., Canals, M., Marcellino, D., Burgueno, J., Casado, V., Hillion, J., Torvinen, M., Fanelli, F., Benedetti, Pd. P., Goldberg, S.R., Bouvier, M., Fuxe, K., Agnati, L.F., Lluis, C., Franco, R. and Woods, A. Parkinsonism and Related Disorders, 10, pp. 265-271, 2004.

Neuropsychopharmacology Section, Behavioral Neuroscience Research Branch

Blockade of Mesolimbic Dopamine D3 Receptors Inhibits Stress-induced Reinstatement of Cocaine-seeking in Rats IRP scientists have previously reported that selective dopamine D3 receptor blockade by the novel D3 receptor antagonist SB-277011A inhibits cocaine's reinforcing action and cocaine-triggered reinstatement (relapse) of cocaine-seeking behavior. In the present study, these researchers further demonstrated that systemic injections of SB-277011A also dose-dependently inhibits stress-induced reinstatement of cocaine-seeking behavior in animals completely extinguished from their drug-taking habits. To determine the locus of action in the brain, SB-277011A was locally microinjected into the bilaterally nucleus accumbens and the dorsal striatum. SB-277011A, when administered into the nucleus accumbens, but not into the dorsal striatum, significantly blocked stress-induced reinstatement. These findings suggest that the mesolimic dopamine D3 receptor plays an important role in mediating stress-induced reinstatement, and that DA D3 receptor antagonists are worthy of further investigation as potential anti-addiction medications. Xi, Z.X., Gilbert, J., Campos, A.C., Kline, N., Ashby, C.R. Jr., Hagan, J.J., Heidbreder, C.A. and Gardner, E.L. Psychopharmacology, 2004 Apr 9 [Epub ahead of print].

The Basolateral Complex of the Amygdala Mediates the Modulation of Intracranial Self-stimulation Threshold by Drug-associated Cues
Environmental cues (sights, smells, sounds) that have been previously associated with drug-taking are powerful triggers that provoke relapse to drug-seeking and drug-taking behavior. IRP scientists have previously reported that the ability of such environmental cues to trigger relapse depends upon the intact functioning of the basolateral amygdaloid nucleus in the brain. IRP scientists have also previously shown that such environmental cues alter brain-stimulation reward, and that electrical stimulation of the amygdaloid nucleus in the brain alters brain-reward functions. Now, these researchers have discovered that the ability of drug-associated environmental cues to alter brain-reward functions depends upon the intact functioning of the basolateral amygdaloid nucleus in the brain. Thus, the basolateral amygdala is necessary for cues associated with previous drug exposure to modulate reward functions within the classically-described reward circuitry of the brain. These findings have implications for understanding the brain substrates that underlie the motivation to engage in drug-taking behavior, and may help to elucidate the brain mechanisms underlying drug craving. Hayes, R.J. and Gardner, E.L. European Journal of Neuroscience, 20, pp. 273-280, 2004.

Opiate Tolerance by Heroin Self-administration: An fMRI Study in Rat
Functional magnetic resonance imaging (fMRI) was employed to determine whether repeated heroin self-administration produces tolerance or sensitization in the rat brain. Twelve rats were evenly divided into saline and heroin self-administration groups. There was a progressive increase in daily heroin intake during the 8-9 days of heroin self-administration training. Within 24 hr after the last session of daily heroin self-administration, acute heroin administration induced regional blood oxygen level-dependent (BOLD) signals in the brains of both groups of rats. The positive BOLD signals appeared mainly in the cortical regions, including the prefrontal cortex, cingulate, and olfactory cortex, while the negative BOLD signals were predominantly located in subcortical regions such as caudate and putamen, nucleus accumbens, thalamus, and hypothalamus. However, the number of activated voxels was significantly fewer, and the BOLD-signal intensity was significantly less in heroin self-administration rats in regions of prefrontal cortex, nucleus accumbens, and thalamus. Application of gamma-vinyl GABA, an irreversible GABA-transaminase inhibitor, which blocks heroin-induced increase in BOLD signal in na•ve rats, failed to block opiate actions in the heroin self-administration rats. Together, these data suggest that repeated heroin self-administration produces tolerance or desensitization of opiate actions in the rat brain, which may in turn potentiate drug self-administration behavior and drug intake. Xi, Z.X., Wu, G., Stein, E.A. and Li, S.J. Magnetic Resonance in Medicine, 52, pp. 108-114, 2004.

Attenuation of fMRI Brain Response to Heroin Correlates with Reinstatement of Heroin-seeking in Rats IRP scientists further investigated the possible correlation between heroin-induced brain BOLD signal responses and heroin-triggered reinstatement (relapse) of drug-seeking behavior. Rats that had been previously

heroin self-administering displayed robust reinstatement of drug-seeking behavior triggered by an acute heroin priming, whereas saline control rats did not show such a behavioral response. Regional positive or negative blood oxygen level-dependent (BOLD) signals, induced by heroin priming injection, were observed in both groups of rats during fMRI scanning. However, heroin-induced positive BOLD signals in the prefrontal cortex and parietal cortex were significantly attenuated in heroin self-administering rats. Similarly, heroin-induced negative BOLD signals in subcortical regions, such as the nucleus accumbens and hippocampus, were also significantly attenuated in both signal intensity and number of activated brain voxels in heroin self-administration rats. These data demonstrate that heroin-induced reinstatement of drug-seeking behavior coincides with a significant reduction in opiate-induced brain activity in heroin self-administration rats, suggesting a possible role of opiate tolerance in mediating reinstatement of drug-seeking behavior. Luo, F., Xi, Z.X., Wu, G., Liu, C., Gardner, E.L. and Li, S.J. Neuroimage, 22, pp. 1328-1335, 2004.

The Metabotropic Glutamate Receptor 5 Antagonist MPEP Blocks Reinstatement of Drug-seeking Triggered by Cocaine But Not By Stress or Cues Repeated exposure to cocaine has been shown to alter glutamate transmission in rat brain. Recent studies have demonstrated that mutation of the mGluR5 gene or selective mGluR5 blockade by 2-methyl-6-(phenylethynyl)pyridine (MPEP) significantly inhibits cocaine self-administration and cocaine-induced conditioned place preference. In the present study, IRP researchers investigated whether MPEP attenuates reinstatement (relapse) of cocaine-seeking behavior triggered by cocaine, stress or cocaine-associated environmental cues. Rats were allowed to self-administer cocaine until stable daily self-administration was reached. This was then followed by a once-daily extinction session until extinction criteria were met. After extinction, re-exposure to cocaine, stress or cocaine-associated environmental cues in separate groups of animals robustly reinstated the extinguished cocaine-seeking behavior. MPEP dose-dependently attenuated cocaine-induced reinstatement (maximally by 50%), but not reinstatement produced by stress or cues previously associated with cocaine self-administration. In addition, MPEP also produced a maximal 50% reduction of the 'break-point' (maximal work load to receive a cocaine infusion) under a progressive-ratio reinforcement schedule. These data suggest that mGluR5 receptors are involved in cocaine-induced reinstatement and reinforcement, and that mGluR5 antagonists may represent a promising new class of medication for the prevention of relapse to drug use. Xi, Z.X., Gilbert, J., Campos, A.C., Ashby, C.R. Jr. and Gardner, E.L. College on Problems of Drug Dependence, 66th Annual Scientific Meeting, San Juan, Puerto Rico, June 12-17, 2004.

The Dopamine D3 Receptor Antagonist SB-277011A Antagonizes THC-enhanced Brain-Stimulation Reward in Rats Marijuana is a widely used botanical with significant abuse liability, and there is no widely effective medication available to assist marijuana users in breaking the habit. Delta-9-tetrahydrocannabinol (THC), the active constituent in marijuana, stimulates the brain mesolimbic dopamine (DA) system and enhances brain stimulation reward, like other drugs with abuse potential. The mesolimbic DA system is highly enriched with DA D3 receptors, which have extraordinarily high affinity for endogenous DA. IRP researchers have previously shown that blockade of brain DA D3 receptors by SB-277011A attenuates cocaine-enhanced brain reward and cocaine-induced reinstatement of drug-seeking behavior. SB-277011A has also been previously shown to attenuate nicotine-triggered relapse to nicotine-seeking behavior in the reinstatement model. In the present study, IRP researchers further demonstrated that SB-277011A similarly inhibited THC-induced electrical brain stimulation reward, suggesting that DA D3 receptors also play an important role in mediating marijuana-enhanced brain stimulation reward, and that the D3 receptor antagonist SB-277011A may be promising in the treatment of marijuana dependence. Gilbert, J., Campos, A.C., Ashby, C.R. Jr., Heidbreder, C.A. and Gardner, E.L. International Cannabinoid Research Society, 14th Annual Meeting, Paestum, Italy, June 22 — 27, 2004.

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

Program Activities

New NIDA PAs and RFAs

On June 16, 2004, NIDA issued a Program Announcement entitled **Prescription Drug Abuse (PA-04-110)**. This PA supersedes PA-01-048 issued in the NIH Guide on February 12, 2001. In revising and reissuing this PA, NIDA continues to encourage research aimed at understanding and reducing prescription drug abuse while supporting appropriate medical use of therapeutic agents with abuse liability. Research is needed to understand the factors contributing to prescription drug abuse, to characterize the adverse medical, behavioral and social consequences associated with this abuse, and to develop effective prevention and service delivery approaches and behavioral and pharmacological treatments.

On August 26, 2004, NIDA issued a Program Announcment entitled **MDMA: Research Areas Needing More Emphasis (PA-04-152)**. The purpose of this PA is to provide an optimally comprehensive, strategic, and balanced MDMA research program, given the upsurge in MDMA use worldwide, including its abuse outside the rave scene. Although researchers have made great strides in characterizing MDMA's neural mechanisms and neurotoxicity, it is necessary now to focus on specific areas of MDMA research, across all research disciplines urgently needing our attention.

On July 7, 2004, NIDA released the RFA entitled **The National Drug Abuse Treatment Clinical Trials Network (RFA-DA-05-001)** for the fourth solicitation for the CTN. This RFA invites cooperative agreement applications from established clinical investigators to participate in the CTN. Applications from geographic areas not currently well represented in the CTN are particularly encouraged. This RFA includes both new applications (new Nodes) and competing continuations. The applications are due October 14, 2004, with an anticipated award date of July 2005.

PAs/RFAs Issued With Other NIH Components/Agencies

On June 8, 2004, NIDA, in conjunction with numerous other NIH components, issued a Program Announcement entitled **Midcareer Investigator Award in Patient-Oriented Research (K24) (PA-04-107)**. The purpose of this PA is to provide support for clinician investigators to allow them protected time to devote to patient-oriented reseach (POR) and to act as research mentors primarily for clinical residents, clinical fellows and/or junior clinical faculty. This award is primarily intended for clinician investigators who are at the Associate Professor level or are functioning at that rank in an academic setting or equivalent non-academic setting, and who have an established record of independent, peer-reviewed Federal or private research grant funding in POR.

On June 9, 2004, NIDA and the National Cancer Institute jointly issed a Program Announcement entitled **Cross-Disciplinary Translational Research at NIH (PA-04-109)**. The purpose of this PA is to foster research that will have a practical impact on the treatment and prevention of drug abuse through the development of new research technologies that are based on existing basic and/or clinical research knowledge, and technology transfer knowledge.

On June 18, 2004, NIDA, in conjunction with the National Institute of Child Health and Human Development (NICHD), issued a Program Announcement entitled **The Science and Ecology of Early Development (SEED) (PA-04-113)**. This PA invites research grant applications that seek to develop a comprehensive program of research focused on the mechanisms through which social, economic, cultural, and community-level factors, and their interactions, impact the early cognitive,

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neurobiological, socio-emotional, and physical development of children.

On June 22, 2004, NIDA, in conjunction with numerous other NIH components, issued a Program Announcement entitled **Understanding and Promoting Health Literacy (RO1) (PA-04-116)**. The goal of this PA is to increase scientific understanding of the nature of health literacy and its relationship to healthy behaviors, illness prevention and treatment, chronic disease management, health disparities, risk assessment of environmental factors and health outcomes including mental and oral health.

On June 22, 2004, NIDA, in conjunction with numerous other NIH components, issued a Program Announcement entitled **Understanding and Promoting Health Literacy (RO3) (PA-04-117)**. The goal of this PA is to increase scientific understanding of the nature of health literacy and its relationship to healthy behaviors, illness prevention and treatment, chronic disease management, health disparities, risk assessment of environmental factors and health outcomes including mental and oral health.

On July 6, 2004, NIDA, in conjunction with a number of other NIH components, issued a Program Announcement entitled **Understanding Mechanisms of Health Risk Behavior Change in Children and Adolescents (PA-04-121)**. Through this PA, participating NIH components invite research grant applications that will enhance our understanding of the factors and mechanisms that determine changes in health risk behaviors during childhood and adolescence. The concept of health risk behavior change is used in this PA to encompass the evolution of specific health impairing behaviors. Of particular interest are factors and processes that influence the initiation, continuation, and/or cessation of one or more of the following health risk behaviors: (1) substance abuse (2) inadequate exercise and poor dietary practices as they relate to being overweight or obese, and (3) intentional and unintentional injuries.

On July 8, 2004, NIDA, in collaboration with numerous other NIH Institutes, released a Program Announcement entitled **Novel Approaches to Enhance Animal Stem Cell Research (PA-04-125)**. The purpose of this PA is to encourage the submission of applications for research to enhance animal stem cells and model biological systems. Innovative approaches to isolate, characterize and identify totipotent and multipotent stem cells from from nonhuman biomedical research animal models, as well as to generate reagents and techniques to characterize and separate those stem cells from other cell types is encouraged.

On July 9, 2004, NIDA, in conjunction with numerous other NIH components issued a Program Announcement entitled **Supplements to Promote Reentry Into Biomedical and Behavioral Research Careers (PA-04-126)**. The aim of these supplements is to encourage individuals with a high potential to reenter an active research career after taking time off to care for children or attend to other family responsibilities to reenter research careers within the missions of all of the program areas of NIH. This program will provide administrative supplements to existing NIH research grants for the purpose of supporting full-time or part-time research by these individuals in a program geared to bring their existing research skills and knowledge up to date.

On August 18, 2004, NIDA, in collaboration with the Substance Abuse and Mental Health Services Administration (SAMHSA) released an RFA entitled **Enhancing State Capacity to Foster Adoption of Science-Based Practices (RFA-DA-05-002)**. This initiative is designed to strengthen State Agencies' capacity to support and engage in research that will foster statewide adoption of meritorious science-based policies and practices. Letter of Intent Receipt Date for this RFA is July 17, 2004; Application Receipt Date is August 17, 2004.

On July 28, 2004, NIDA in collaboration with several other NIH components and the Office of Global Health United States Agency for International Development (USAID), issued an RFA entitled **Phase II Comprehensive ICOHRTA AIDS/TB (RFA-TW-04-002)**. The training supported under this RFA will help to produce a cadre of experts who will facilitate integrated clinical, operational and health services research for the benefit of developed and developing country populations. These experts will comprise a resource that will facilitate additional training and research in the region. Letter of Intent Receipt Date for this RFA is November 19, 2004; Application Receipt Date is December 20, 2004.

On August 5, 2004, NIDA, in collaboration with the National Insitutue of Allergy and Infectious Diseases (NIAID) and the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) issued an RFA entitled **Hepatitis C Cooperative Research Centers (RFA-AI-04-028)**. The purpose of this RFA is to foster and stimulate high-quality, multi-disiplinary collaborative research that is focused on developing tools to

prevent and cure hepatitis C virus (HCV) infection and disease. The goal is to generate research findings that will be directly applicable, particularly to the development of vaccines and (immune) therapeutics. Letter of Intent Receipt Date for this RFA is October 22, 2004; Application Receipt Date is November 22, 2004.

On August 6, 2004, NIDA, several NIH Institutes and the DHHS Office of Research Integrity issued an RFA entitled **Research on Research Integrity (RFA-NS-05-003)**. The purpose of this grant program is to foster empirical research on societal, organizational, group, and individual factors that affect, both positively and negatively, integrity in research. Proposals must have clear relevance to biomedical, behavioral health sciences, and health services research. Letter of Intent Receipt Date for this RFA is October 22, 2004; Application Receipt Date is November 22, 2004.

Other Program Activities

CTN Update

Eight protocols have enrolled patients within the CTN Network, and several additional studies are in the planning stages. Five CTN studies have completed enrollment and follow-up phases. A total of 6,323 patients have been screened with 3,105 of those currently enrolled in trials. 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. Highlights of the active program include:

- Protocol CTN 0003 (Bup/Nx: Comparison of Two Taper Schedules) began enrollment June 30, 2003. The study involves 11 sites across 8 nodes, with a targeted enrollment of 480 participants. Participation is at 41% 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 November 2004.
- 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.
- 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 0014 (Brief Strategic Family Therapy for Adolescent Drug Abusers) is in the final stages of provider training and will involve three phases of implementation. The first wave of sites has finished protocol training. BSFT will be implemented at 14 sites across 10 nodes plus Puerto Rico. This intervention is the first CTN study to target adolescents and their families. Enrollment is expected to begin in the third quarter of 2004.
- Protocol CTN 0015 (Women's Treatment for Trauma and Substance Use Disorder: A Randomized Clinical Trial) began in March 2004. This study is being carried out at 8 sites across 7 Nodes and targeted enrollment is 480. The enrollment is at 24% of the target enrollment.
- CTN 0018 (Reducing HIV/STD Risk Behaviors: A Research Study for Men in Drug Abuse Treatment), and CTN 0019 (Reducing HIV/STD Risk Behaviors: A Research Study for Women in Drug Abuse Treatment) began enrollment in April 2004. The targeted enrollment is 480 patients for each study.
- 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.

New Collaborative Study: Starting Treatment with Agonist Replacement Therapies (START)

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 throughout the country. It is anticipated that 1,000 patients will be entered.

Guidelines for Substance Abuse Research Involving Children and Adolescents
Following discussions with bioethics experts and investigators who conduct research involving minors, the Bioethics Task Force of the National Advisory Council on Drug Abuse (NACDA), with assistance from OSPC, has drafted Guidelines for Substance Abuse Research Involving Children and Adolescents. These guidelines are intended to highlight and assist researchers and Institutional Review Boards (IRBs) in their consideration of some of the specific issues that are pertinent to substance abuse research in minors. They are not intended to replace or augment the regulations that already exist regarding the ethical conduct of research in minors. These draft guidelines are currently being circulated among investigators in the intramural and extramural community, IRB representatives, advocacy organizations, Office of Human Research Protections and NIDA staff for comments. Once these comments have been addressed, the Bioethics Taskforce will present the Guidelines to NACDA for endorsement, after which they will be posted on the NIDA website.

NIDA Summer Research Program
Flair Lindsey, Program Analyst, Special Populations Office, coordinated the eighth annual Summer Research with NIDA program. The program allowed high school and undergraduate students to engage in drug abuse research with NIDA grantees for 8-10 weeks during the summer. In 2004, 70 students and 27 grantees participated in the program.

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

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

Alterman, Arthur I. -- University of Pennsylvania
Does Psychological Wellness Predict Treatment Response?

Altice, Frederick L. -- Yale University
Direct/Observed Therapy/Community-Released HIV+ Prisoners

Amass, Leslie -- Friends Research Institute, Inc.
Voucher-Based Incentives In A Prevention Setting

Babor, Thomas F. -- University of Connecticut School of Medicine and Dentistry
Brief Intervention For Drug Abuse Using the WHO Assist

Babor, Thomas F. -- University of Connecticut School of Medicine and Dentistry
Brief Interventions for Nicotine and Cannabis Use

Baer, John S. -- University of Washington
Development and Evaluation of Context Tailored Training

Baker, David A. -- Marquette University
Cystine-Glutamate Antiporters and Cocaine Reinstatement

Barker, Eric L. -- Purdue University West Lafayette
Vr1 Receptor-Induced Synthesis of Anandamide in Caveolae

Bertram, Richard -- Florida State University
Crcns:Comput./Exp.Study:Hypothal.-Pituitary Interaction

Bevins, Rick A. -- University of Nebraska Lincoln
Acquired Appetitive Properties of Nicotine

Blow, Frederic C. -- University of Michigan at Ann Arbor
Services Interventions for Injured ED Substance Abusers

Bolton Oetzel, Keri -- University of New Mexico Albuquerque
Family Attachment As An Indicator of Treatment Outcome

Bonci, Antonello -- Ernest Gallo Clinic and Research Center
CRF Modulation of NMDA Currents & Behavior in the VTA

Brown, Gregory K. -- University of Pennsylvania
Drug Abuse, Psychological Variables and Suicide Attempts

Brown, Larry K. -- Rhode Island Hospital, Providence, RI

An Affect Management Intervention For Juvenile Offenders

Buck, Kari J. -- Oregon Health & Science University
Genetic Vulnerability of Drugs of Abuse

Cacciola, John -- Deltametrics
Computer Based Training for Drug Abuse Offenders

Cadoret, Remi J. -- University of Iowa
Gene-Environment Interaction in Etiology of Drug Abuse

Carelli, Regina M. -- University of North Carolina Chapel Hill
Combined Voltammetry/Electrophysiology In Behaving Rats

Carise, Deni -- Treatment Research Institute, Inc. (TRI)
Linking Services To Patient Needs For Improved Outcomes

Carroll, Frank I. -- Research Triangle Institute
Selective Opioid Antagonist as Medication for Drug Abuse

Catalano, Richard F. -- University of Washington
Long Term Follow-Up of Focus on Families

Chavkin, Charles -- University of Washington
Regulation of Opioid Signaling By Tyr-Phosphorylation

Chen, Jiang-Fan -- Boston University Medical Campus
Bioinformatics /Molecular Ident. /CIS Elements /Dopamine

Chermack, Stephen T. -- University of Michigan at Ann Arbor
Developing Violence Therapy for Substance Abusers

Cicchetti, Dante -- University of Rochester
Chronic Stress of Maltreatment: Drug Use Vulnerability

Cinciripini, Paul M. -- University of Texas MD Anderson Cancer Center
Pharmacogenetics, Emotional Reactivity & Smoking

Collins, Allan C. -- University of Colorado at Boulder
Genetics of Nicotine Tolerance: Role of Receptors

Cowan, Ronald L. -- Vanderbilt University
MR Analysis of Persistent CNS Damage In Human MDMA Users

Cravatt, Benjamin F. -- Scripps Research Institute
FAAH: Structure, Function, and In Vivo Inhibition

Dackis, Charles -- University of Pennsylvania
Modafinil Treatment for Cocaine Dependence

Davis, Betsy -- Oregon Research Institute
HIV Prevention: Strengthening Aboriginal Youth

De Wit, Harriet -- University of Chicago
Determinants of Drug Preference in Humans

Deren, Sherry -- National Development & Research Institutes
An Intervention For Migrant Puerto Rican Drug Users

Des Jarlais, Don C. -- Beth Israel Medical Center, New York
Risk Factors for AIDS Among Intravenous Drug Users

Dickson-Gomez, Julia B. -- Institute for Community Research
Housing Status/Stability and HIV Risk Among Drug Users

Edlin, Brian R. -- Weill Medical College of Cornell University
Acute HCV Infection in Injection Drug Users

El-Bassel, Nabila -- Columbia University New York Morningside
HIV/STI Prevention for Drug-Involved Couples

Ellinwood, Everett H. -- Duke University
Cocaine Withdrawal: A Window of Treatment Opportunity

Elman, Igor -- Mc Lean Hospital, Belmont, MA
PTSD and Drug Dependence: Neuroimaging of Reward Circuit

Elmer, Gregory I. -- University of Maryland Baltimore Professional School
Microarray Analysis of Morphine's Behavioral Effects

Farrens, David L. -- Oregon Health & Science University
Purification & Structural Analysis/Cannabinoid Receptor

Festinger, David S. -- Treatment Research Institute, Inc. (TRI)
Ethics of Participant Payment In Drug Abuse Research

Festinger, David S. -- Treatment Research Institute, Inc. (TRI)
Improving the Ethics of Consent In Drug Abuse Research

Friedman, Samuel R. -- National Development & Research Institutes
Community Vulnerability and Responses To IDU-Related HIV

Garcia, Victor Q. -- Indiana University of Pennsylvania
Drug Use Among Migrant Mexican Farmworkers

Garvey, Arthur J. -- Harvard University Medical School
Front-Loaded Counseling to Treat Tobacco Addiction

George, Susan R. -- University of Toronto
Receptors Mediating Drug Dependence

George, Tony P. -- Yale University
Selegiline for Smoking Cessation

Gilbert, David G. -- Southern Illinois University Carbondale
Attentional Bias & Affect In Stress-Vulnerable Smokers

Glick, Stanley D. -- Albany Medical College of Union University
Diencephalic Mechanisms of Drug Abuse

Godley, Susan H. -- Chestnut Health Systems
Adolescent Outpatient & Continuing Care Study (AOCCS)

Gonzalez-Haddad, Gerardo -- Yale University
Tiagabine for Cocaine Dependence In Methadone Treatment

Hagan, Holly -- National Development & Research Institutes
Synthesis: HCV Epidemiology and Prevention In Drug Users

Hamamoto, Darryl T. -- University of Minnesota Twin Cities
Chronic Cannabinoids, Tumor Growth and Hyperalgesia

Hammond, Donna L. -- University of Iowa
Spinal GABA Receptors In Neuropathic Pain

Hampson, Robert E. -- Wake Forest University Health Sciences
Cannabinoid Effects On Sensory Processing In Brain

Henggeler, Scott W. -- Medical University of South Carolina
Substance Abusing Delinquents: 5-Year Outcomes of RCT

Hirshfield, Sabina -- Medical and Health Research Associates
Behavioral Risk In Men Recruited Online

Honda, Christopher N. -- University of Minnesota Twin Cities
Peripheral Opioid Receptors and Analgesia

Honeycutt, Nancy A. -- Johns Hopkins University
Structural Brain Correlates of MDMA Use

Hook, Vivian Y. -- University of California San Diego
Biosynthesis of Enkephalin Opioid Peptides

Hops, Hyman -- Oregon Research Institute
Preventing HIV/AIDS In Treatment-Resistant Drug-Abusing Youth

Hu, Xiaoping P. -- Emory University
Developmental Effects of Prenatal Cocaine Exposure

Hughes, John R. -- University of Vermont & State Agricultural College
Gradual Vs Abrupt Cessation Treatment for Smoking

Hunt, Geoffrey P. -- Scientific Analysis Corporation

Club Drugs, Dance Events, and Asian-American Youth

Ialongo, Nicholas S. -- Johns Hopkins University
Development & Malleability From Childhood To Adulthood

Inturrisi, Charles E. -- Weill Medical College of Cornell University
Glutamatergic Systems In Pain and Opioid Action

Jayanthi, Lankupalle D. -- Medical University of South Carolina
Cocaine Regulation of Norepinephrine Transporter

Johnson, Mark E. -- University of Alaska Anchorage
HIV Risk Behaviors and Depression Among Drug Users

Jones, Hendree E. -- Johns Hopkins University
Tobacco Use In Opioid Agonist Treated Pregnant Women

Kantak, Kathleen M. -- Boston University Charles River Campus
Cognitive Aspects of Addiction-Related Behavior

Katz, Elizabeth C. -- Friends Research Institute, Inc.
Engaging Detoxification Clients Into Long-Term Treatment

Kelemen, William L. -- California State University Long Beach
Nicotine and Expectancy In Smokers' Cognitive Processes

Kern, Steven E. -- University of Utah
Impact of Gender Differences In Morphine Metabolites

Knight, John R. -- Children's Hospital, Boston MA
Medical Office Intervention for Adolescent Drug Use

Koob, George F. -- Scripps Research Institute
Central Mechanisms of Opiate Reinforcement /Dependence

Kosofsky, Barry -- Massachusetts General Hospital
Structural MR Analyses of Drug Exposed Brains

Kraemer, Kevin L. -- University of Pittsburgh at Pittsburgh
Societal & Patient Utilities for Drug Problems

Larkin, Heather -- Catholic University of America
Systems Integration and Substance Abuse Service Delivery

Law, Ping-Yee -- University of Minnesota Twin Cities
G Proteins and Opioid Receptor Functions

Lester, Henry A. -- California Institute of Technology
Alpha4 Nicotinic Receptor In Addiction: Mouse Models

Li, Ming D. -- University of Texas Health Sciences Center, San Antonio
Deciphering Genes and Pathways In Nicotine Dependence

Lichtman, Aron H. -- Virginia Commonwealth University
Endocannabinoid Modulation of Memory

Lindberg, Iris -- Louisiana State University Health Sciences Center, New Orleans
Opioid Peptide Synthesizing Enzymes

Little, Karley Y. -- University of Michigan at Ann Arbor
Brain Dopamine Alterations In Human Cocaine Users

Lombroso, Paul J. -- Yale University
The PTP, Step, Regulates Amphetamine Actions

Luciana, Monica -- University of Minnesota Twin Cities
Adolescent Brain Development and Effects of Drug Abuse

Lutfy, Kabirullah -- Western University of Health Sciences
The Ofq/N/Orl-1 Receptor System & Cocaine Sensitization

Marcus, Marianne T. -- University of Texas Health Sciences Center, Houston
Stress Reduction In Therapeutic Community Treatment

Matell, Matthew S. -- Villanova University
Neural Activity of the Frontal Cortex In Interval Timing

Mcauliffe, William E. -- North Charles, Inc.
Drug Abuse Treatment Access, Service Mix, and Need

Mccabe, Sean E. -- University of Michigan at Ann Arbor
Prescription Drug Abuse Among College Students

Mclaughlin, Jay P. -- Northeastern University
Endogenous Opioid Mechanisms Modulating Stress

Mcquiston, Adam R. -- Virginia Commonwealth University
Mop Receptor Effects on The Hippocampal Ca1 Network

Meltzer, Peter C. -- Organix, Inc.
Discovery of Novel Pharmacotherapies: Cocaine Dependence

Miczek, Klaus A. -- Tufts University Medford
Psychomotor Stimulants and Aggression In Animals

Mierke, Dale F. -- Brown University
Drug Design: Glutamate Receptor Signaling

Miller, Kathleen E. -- State University of New York at Buffalo
College Sports, Gender and Substance Use

Mintz, Isabelle -- Northwestern University
DAT Reversal In Isolated Dopaminergic Neurons

Morabito, Maria A. -- University of Massachusetts Medical School, Worcester
Regulation of Synapses By Cdk5-Dependent Phosphorylation

Morral, Andrew R. -- Rand Corporation
Adolescent Treatment Services: Young Adult Outcomes

Moss, Howard B. -- University of Pennsylvania
5-Ht1b Receptors, Impulsivity and Cocaine Dependence

Muraven, Mark B. -- State University of New York at Albany
Practicing Self-Control Lowers the Risk of Smoking Lapse

Neal-Beevers, A.R. -- Emma Pendleton Bradley Hospital
Joint Attention Predicts Cognitive Outcome In Mls Sample

Nuttbrock, Larry A. -- National Development & Research Institutes
HIV/STD Infection in an Urban High Risk Population

Otto, Michael W. -- Massachusetts General Hospital
Stress, Distress Intolerance, and Drug Dependence

Owens, S. Michael -- University of Arkansas Medical Sciences, Little Rock
Antibody-Based Therapy for Methamphetamine Abuse

Pacula, Rosalie L. -- Rand Corporation
Are There Economic Costs of Marijuana Use?

Paronis, Carol -- Mc Lean Hospital, Belmont, MA
Opioids: Relative Reinforcing Strength and Dependence

Paulus, Martin P. -- University of California San Diego
Neurobiology of Transition To Stimulant Dependence

Pearson, Frank S. -- National Development & Research Institutes
Evidence-Based Principles of Treatment

Perry, David C. -- George Washington University
Chronic Nicotine Effects on Receptor Subtypes

Peterson, Bradley S. -- New York State Psychiatric Institute
MRI of Infants Exposed Prenatally To Drugs of Abuse

Philibert, Robert A. -- University of Iowa
Genetic Studies of Substance Abuse in Iowa Adoptees

Piomelli, Daniele -- University of California Irvine
Characterization of Anandamide Transport in Brain

Polich, John M. -- Scripps Research Institute

Neuroelectric Assessment of Ecstasy Use In Young Adults

Polsky, Daniel E. -- University of Pennsylvania
Cea In Ctn: Bup/Nal Treatment for Opioid Addicted Youth

Potter, Steve M. -- Georgia Institute of Technology
Chemical Reward Systems For Embodied Cultured Networks

Premont, Richard T. -- Duke University
Dopamine Receptor Regulation By Grks In Drug Abuse

Raffa, Robert B. -- Temple University
Joint Action Analysis of Poly-Drug Withdrawal

Rao, Uma -- University of Texas SW Medical Center, Dallas
Neuronal Risk Markers for Nicotine Dependence In Youth

Rao, Uma -- University of Texas SW Medical Center, Dallas
Stress and Risk For Substance Abuse In Adolescents

Roehrs, Timothy A. -- Case Western Reserve University-Henry Ford Health Science Center
Abuse Liability Associated With Chronic Hypnotic Use

Roffman, Roger A. -- University of Washington
Reaching and Motivating Change In Teen Marijuana Smokers

Roll, John M. -- Friends Research Institute, Inc.
Contingency Management: Duration Effects

Rosen, Marc I. -- Yale University
Payees, Disability Payments and Dual Diagnosis

Rosen, Marc I. -- Yale University
Abstinence Linked Money Management

Rowland, Melisa D. -- Medical University of South Carolina
CRA for Substance Abusing Caregivers of Delinquent Youth

Rowlett, James K. -- Harvard University Medical School
Anxiolytic Effects and Abuse of Benzodiazepine Receptor Ligands

Rowlett, James K. -- Harvard University Medical School
Primate Model of the Transition To Cocaine Addiction

Safren, Steven A. -- Massachusetts General Hospital
CBT For Depression & Adherence In HIV Methadone Patients

Scheier, Lawrence M. -- Behavioral Health Research Center-Southwest
Validity of Ethnic Identity and Adolescent Drug Use

Schumacher, Joseph E. -- University of Alabama at Birmingham
Transporting Behavioral Treatment For IDU's In Ukraine

Schwartz, Robert P. -- Friends Research Institute, Inc.
Entry and Engagement In Methadone Maintenance Treatment

Setlow, Barry -- Texas A&M University System
Lasting Effects of Cocaine on Cognition and Motivation

Siggins, George R. -- Scripps Research Institute
Morphine Like Brain Peptides-Cellular Neurobiology

Slater, Michael D. -- Colorado State University-Fort Collins
In-School and Community Media Prevention

Spealman, Roger D. -- Harvard University Medical School
Mglur5 Mechanisms In Primate Models of Cocaine Abuse

Sprague, Jon E. -- Ohio Northern University
Ecstasy's Neurotoxicity: Role of Hyperthermia

Stevens, Craig W. -- OSU Center of Health Sciences
Functional Evolution of Opioid Receptors

Stout, Robert L. -- Pacific Institute for Research and Evaluation

O*rganizational Factors In Drug Abuse Treatment Outcomes*

Strauss, Shiela M. -- National Development & Research Institutes
Increasing HCV Knowledge & Service Use In Drug Treatment Programs

Suchman, Nancy E. -- Yale University
Fostering Mothers' Emotionally-Responsive Parenting

Sullivan, Tami P. -- Yale University
Violence, PTSD Symptoms and Substance Use

Swan, Gary E. -- SRI International
Impact of Smoking Cessation on Sleep

Teicher, Martin H. -- Mc Lean Hospital, Belmont, MA
Early Stress, PTSD, and the Neurobiology of Addiction

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

Thomas, David L. -- Johns Hopkins University
Hepatitis C Pathogenesis & the Human Genome

Tsao, Jennie C. -- University of California Los Angeles
Pain and Drug Abuse In HIV: Impact on Health Services

Victor, Ronald G. -- University of Texas SW Medical Center, Dallas
Cocaine and Sympathetic Nerve Activity In Humans

Vlahov, David H. -- New York Academy of Medicine
Club Drug Use and HIV Risks Among Minorities In NYC

Volsky, David J. -- St. Luke's-Roosevelt Institute for Health Sciences
Mouse Model of HIV-1 Infection and Drug Addiction

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

Walsh, Sharon L. -- Johns Hopkins University
Licit & Illicit Opioids: Comparative Studies In Humans

Wang, Guangdi -- Xavier University of Louisiana
Recepter Binding Properties of Cannabinoid Metabolites

Weisner, Constance M. -- University of California San Francisco
Long-Term Impact of Drug Treatment on Outcome & Cost

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

Weiss, Friedbert -- Scripps Research Institute
Dysregulation of Brain Stress Systems and of Relapse

Weitzman, Elissa R. -- Harvard University School of Public Health
Environment Alcohol Abuse Prevention--Drug Abuse Effect

Wilcox, George L. -- University of Minnesota Twin Cities
Mechanisms of Opioid Receptor Interactions

Winzer-Serhan, Ursula H. -- Texas A&M University Health Science Center
Nicotinic Modulation of Hippocampal Development

Wong, Conrad J. -- Johns Hopkins University
Integration of the Therapeutic Workplace In Drug Court

Yonkers, Kimberly A. -- Yale University
Psychosocial Research To Improve Drug Treatment In Pregnancy

Zubieta, Jon-Kar -- University of Michigan at Ann Arbor
Neurochemical Endophenotype Responses To Pain-Stress

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

Extramural Policies and Review

Receipt, Referral, and Review

NIDA received 1239 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 1085 applications.

OEA arranged and managed 28 review meetings in which 602 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 10 contract proposal reviews, 2 Phase II SBIR contract review meetings, 11 concept reviews and reviews for Loan Repayment Program applications.

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 24 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)
- 11 Special Emphasis Panels that reviewed RFA submissions

OEA managed the following RFA reviews:

- DA04-005: Novel approaches to phenotyping drug abuse
- DA04-006: Screening and intervention for youth in primary care settings
- DA04-008: Group therapy for individuals in drug abuse or alcoholism treatment
- DA04-009: Behavioral and cognitive processes related to adolescent drug abuse
- DA04-010: Targeted integrative research in drug abuse and HIV/AIDS in pregnancy
- DA04-011: Animal models of adolescent drug abuse: integrative studies of brain and behavioral development
- DA04-012: HIV/AIDS, drug use, and highly vulnerable youth: targeting research gaps
- DA04-013: Prevention research for the transition to adulthood
- DA04-014: Medications development for cannabis-related disorder
- DA04-015: HIV/AIDS and other infections among drug users in the criminal justice system

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- DA04-016: Consequences of marijuana use on the developing brain

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

- NO1DA-4-8845: Medications Development for Stimulant Dependence II
- NO1DA-4-9906: Taipei MDMA Usage Study
- NO1DA-4-9908: Washington University MDMA Study
- NO1DA-4-7747: High-resolution Genome Scan for Drug Abuse Loci
- NO1DA-4-8848: Medications Discovery for Addiction Treatment/Rat Relapse Models
- NO1DA-4-7739: Development of Novel Approaches in Human Neuroscience
- NO1DA-4-7746: Production, Analysis, & Distribution of Cannabis & Marijuana Cigarettes and Related Compounds
- N44DA-4-1112: Development of Science Education Materials Related to the Use of Animals
- N44DA-4-7738: Technologies for Proteomic Analysis in the Nervous System
- NO1DA-4-1119: Educational Marketing
- NO1DA-4-9905: Neuroimaging Branch Support Services
- NO1DA-4-2206: Clinical Laboratory Services

Concept Reviews

- NO1DA-5-2207: Data and Statistics Center
- NO1DA-5-2208: Clinical Coordinating Center
- N43DA-5-7750: High Throughput Cell Base Assays to Identify Therapeutic Targets for Substance Abuse & Addiction
- N43DA-5-7749: Development of New Chemical Probes and Discovery of Alternate Drug Dosage Forms for Drug Abuse Studies
- N43DA-5-1120: Develop Research Training Modules for International Application
- N43DA-5-8852: Regulatory Affairs Support
- N43DA-5-1121: Development of Science Education Materials or Programs
- N43DA-5-7751: Real-time Data Collection Paired with Ecological Momentary Assessment
- N43DA-5-5530: Internet-based Application of Existing Proven Therapies
- N43DA-5-5531: Prevention Training
- N43DA-5-5529: Develop New Technologies for Screening & Assessing Drug Abuse & Matching Patients with Appropriate Treatment Services

Staff Training and Development

The CTN Data and Safety Monitoring Board met July 15-16, 2004, in Bethesda, Maryland. The group reviewed several planned and ongoing protocols, focusing on their data and safety monitoring plans, progress to date, and feasibility. The DSMB recommended that study LIs attend future meetings to report on trial enrollment status and targets.

The OEA Symposium Series, a forum for staff training and sharing of ideas and information, continued through the spring and summer. Topics addressed have included extramural policy updates; implementation of the new Division of Extramural Activity Support (DEAS); Contracts and Consortium Agreements; the new R56 mechanism; modifications of the "standard" review criteria to accommodate clinical research grant applications; and uses of RFAs, PASs and other mechanisms for program development. The symposium series is organized and hosted by Dr. Mark Swieter.

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

Congressional Affairs (Prepared August 19, 2004)

FY 2005 Appropriations

On July 14, 2004, the House Committee on Appropriations reported the FY 2005 Labor, HHS, and Education Appropriation bill, which includes funding for NIH, making no change to the Subcommittee reported levels of funding for NIH. The Subcommittee on Labor, HHS, and Education (Representative Ralph Regula [R-OH], Chairman) marked up the measure on July 8, 2004. The Chairman's mark for the House Labor, HHS, and Education Appropriations Subcommittee is $142.526 billion, +$202 million over the request of $142.324 billion and 2% growth from the fiscal year 2004 level of $139.424 billion. It provides $28,526,871,000 for NIH, $726,823,000 more than FY 2004. The Subcommittee mark is identical to the FY 2005 President's Budget request.

For NIDA, the FY 2005 budget request is $1.02 billion, an increase of $28.27 million over the FY 2004 conference level of $990.79 million comparable for transfers proposed in the President's request for an increase of 2.9 percent. The revised President's budget reflects a recent budget amendment to provide $14.5 million to fund a new HIV Vaccine Research and Development Center as part of the Global HIV Vaccine Enterprise, announced by President Bush during the June 2004, G-8 Summit in Sea Island, Georgia. Funding is provided by reallocating $6.3 million in budget authority from NIDA and $8.2 million from NLM, to be restored through use of program evaluation funds.

The House will take up the fiscal 2005 Labor-HHS measure after Congress returns in early September from its summer recess. The Senate has not detailed how or when it intends to move its version of the bill. Budget constraints have made writing the legislation difficult in recent years. One problem for appropriators this year is that the discretionary funding increase — $3.1 billion, or 2.2 percent, more than for fiscal 2004 — is absorbed by increases in four major programs: Title I aid for low-income school districts, state grants for educating disabled children, Pell grants for poor college students and money for NIH. Those four programs alone, would receive $3.6 billion more than in 2004 under the House legislation and President Bush's budget request. That would exceed the total increase in the bill and translate into cuts for some programs and the elimination of others.

In his 2003 State of the Union address, President Bush asked Congress for $200 million annually for drug treatment vouchers that addicts could use at religious-affiliated clinics. Last year, Congress appropriated just $99 million. While applauding the President's efforts to increase treatment options, Chairman Regula's panel noted that the grants have not yet gone to states. The committee decided to keep funding just above the current level. The House bill would allocate $105 million, and the money shaved from the President's request was redirected to the appropriators' top priorities.

Bills of Interest

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

H.R. 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 bill would crack down on so-called steroid precursors, which are usually converted into testosterone by the body. Unlike anabolic steroids, which are classified as controlled substances, currently these supplements can legally be sold and used. Under current law (P.L. 101-647), 27

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types of anabolic steroids are classified as controlled substances. The bill passed by the House would expand that list to include any substance "chemically and pharmacologically related to testosterone," including products made with any of more than 50 specific substances. The legislation would ensure that the only way people could legally procure dozens of types of performance-enhancing supplements would be with a doctor's prescription.

The legislation is being propelled by concern about widespread misuse of the supplements by sports stars — and a fear that children and amateur athletes are mimicking them. The measure now heads to the Senate, where a similar bill (S. 2195) is pending before the Judiciary Committee.

The measure has attracted broad, bipartisan support in Congress but recently the bill became the subject of a dispute over whether the legislation should also take aim at the supplement dehydroepiandrosterone. The substance, known as DHEA, is naturally produced in the body, where it is converted into scores of other hormones and can mimic the effects of testosterone. Because DHEA can be converted into estrogen by the body, some women use the supplement to combat side effects of menopause. The House bill and its Senate counterpart specifically exempt DHEA.

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

S. 2195 - On March 11, 2004, Senator Joseph Biden (D-DE) introduced S. 2195, the "Anabolic Steroid Control Act of 2004," a companion bill to H.R. 3866. It closely resembles H.R. 3866, but would authorize $15 million in grants annually from fiscal 2005 through 2010 to bolster programs in elementary and secondary schools educating children on harmful effects of anabolic steroids. Related measures, H.R. 3866 and S. 1780.

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

H.R. 4883 - On July 21, 2004, Representative Sam Graves (R-MO) introduced H.R. 4883, "the Terrorism Against Animal-Use Entities Prohibition Improvement Act of 2004." Provisions would amend 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 includes a wiretapping provision. The bill was introduced with no co-sponsors and has been referred to the House Committee on the Judiciary.

H.R. 4888/S. 2718 - On July 21, 2004, Representative Lucille Roybal-Allard (D-CA) introduced H.R. 4888, "the Sober Truth on Preventing Underage Drinking Act." On July 22, 2004, Senator Mike DeWine (R-OH) 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, which has four cosponsors, was referred to the House Committee on Energy and Commerce. S. 2718, which has one cosponsor, was referred to the Senate Committee on Health, Education, Labor and Pensions.

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 introduced without cosponsors and referred to the Senate Committee on Health, Education, Labor and Pensions.

Congressional Briefings and Visits (Members and Staff)

July 14, 2004 - At the invitation of a group of constituent organizations known as "The Friends of NIDA," Dr. Nora Volkow, Director, NIDA, spoke at a Congressional

Briefing on the topic of latest advances in drug abuse prevention and treatment research.

August 13, 2004 - At the request of Jon Eskelsen, staff to Senator Richard Lugar (R-IN), Dr. Timothy P. Condon, NIDA Deputy Director, provided a briefing on the health effects and trends in use of methamphetamine and marijuana. Mary Mayhew, OSPC, accompanied Dr. Condon.

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International Activities

NIDA International Forum

The 2004 NIDA International Forum, *Progress Through Collaboration*, was held in conjunction with the College on the Problems of Drug Dependence (CPDD) Annual Meeting from June 11—14, 2004 in San Juan, Puerto Rico. Speakers included Puerto Rican Secretary of Health, Dr. John Rullán; Dr. Vladimir Poznyak, World Health Organization; Dr. Juana Tomas-Rossello, United Nations Office on Drugs and Crime; and Dr. Astrid Eberhart, Canadian Institutes of Health Research. The Forum is an integral component in NIDA's efforts to assist scientists from around the world in exchanging information and establishing collaborative drug abuse research projects. The meeting featured a day-long symposium; International Program networking, poster, and planning sessions included in the overall CPDD agenda; and pre-conference workshops. More than 200 scientists from 49 countries participated in the symposium, which focused on the status of HIV/HCV infection among drug users in Iberoamerica, research and funding activities conducted by other international drug abuse research organizations, and the international research priorities set by NIDA's divisions. The Forum was chaired by Dr. Steven W. Gust, International Program (IP), and featured remarks by NIDA Deputy Director, Dr. Timothy P. Condon, Dr. M. Patricia Needle, IP; Dr. Steven Goldberg, Intramural Research Program (IRP); Dr. David Shurtleff, Division of Basic Neurosciences and Behavioral Research (DBNBR); Dr. Jack Stein, Division of Epidemiology, Services & Prevention Research (DESPR); and Dr. Francis Vocci, Division of Pharmacotherapies and Medical Consequences of Drug Abuse (DPMCDA).

Research Training and Exchange Programs

Distinguished International Scientist Collaboration Awards (DISCA)

NIDA has selected three researchers as 2004 Distinguished International Scientists: Dr. Helena Barros, Fundacao Faculdade Federal Ciencias Medicas Porto Alegre, Brazil; Dr. Ivan Berlin, Groupe Haspitalier Universitaire Pitie-Salpetriere, France; and Dr. Kazutata Ikeda, Tokyo Institute of Psychiatry, Japan. The competitive DISCA awards provide support to senior scientists during research exchange visits of 1 to 3 months so that applicants and their partners can cooperate on new research methods and techniques; conduct data analysis; prepare joint research reports or proposals; or work together on basic, clinical, and applied research on drug abuse. The binational teams must propose an innovative approach, clearly define their expected product or outcome, and submit a final report to NIDA.

- Building on a relationship established at a NIDA-supported meeting in Brazil, Dr. Barros will spend two months in Boston working with NIDA grantee, Dr. Klaus Miczek, Tufts University. The team will conduct preliminary studies to address the importance of the GABA system regarding gender differences in cross-sensitization of social stress and cocaine use. The researchers anticipate using the results of the preliminary studies to plan and seek NIDA support for a three-year collaborative investigation of the interrelationships among gender differences, stress-induced sensitization, cocaine i.v. self-administration, depression, neurochemical changes in the GABA system, gene expression, and sex steroids.
- Dr. Berlin and Dr. Lirio S. Covey, New York State Psychiatric Institute, will use Dr. Berlin's two-month visit to expand their collaborative research on non-nicotinic drug treatments for smoking cessation for the high-risk group of smokers with higher levels of nicotine dependence,

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previous failed attempts to quit smoking, and a history of major depressive disorder (MDD). The researchers will design and conduct a randomized, controlled, double blind clinical trial of naltrexone vs. placebo for smokers with past MDD. Participants in that study who fail to stop smoking will be recruited into a second clinical trial assessing the efficacy of treatment with bupropion vs. a combination of naltrexone and bupropion.

- Continuing their research exchange visits, Dr. Ikeda will use his DISCA award to spend one month learning the procedures for conducting research with mice conditioned to self-administer drugs intravenously from Dr. Athina Markou, Scripps Research Institute, San Diego. Dr. Markou, whose research on rodent self-administration of cocaine, amphetamine, morphine, nicotine, and phencyclidine has primarily used rats, will learn about behavioral and molecular genetics investigations using mice from Dr. Ikeda. The two will use their new skills to collaborate on investigations to establish methamphetamine self-administration and the dose-response function for methamphetamine in mice. They anticipate that the preliminary investigations will lead to a NIDA grant application.

INVEST Drug Abuse Research Fellowship

Dr. Liliana M. Cancela, Universidad Nacional de Cordoba, Argentina, has been selected as a 2004-2005 NIDA INVEST Drug Abuse Research Fellow. She will spend her Fellowship year working with Dr. Peter W. Kalivas, Medical University of South Carolina, learning new techniques to investigate stress- and drug-induced neuroadaptations through molecular studies of pharmacological interventions or manipulation of genetic expression. This research could help scientists understand the role of common cellular networks in the influence of stress on addiction. A biochemist, Dr. Cancela is an associate professor at the Universidad Nacional de Cordoba, where she conducts research on stress-induced addiction to psychostimulants. Through the competitive INVEST Drug Abuse Research Fellowship, NIDA supports 12 months of postdoctoral training with a NIDA grantee at a U.S. institution and professional development activities to help Fellows establish personal relationships with NIDA grantees and staff.

Hubert H. Humphrey Drug Abuse Research Fellowships

NIDA, in conjunction with the U.S. Department of State and the Institute of International Education, has selected eight drug abuse professionals from seven nations as Hubert H. Humphrey Drug Abuse Research Fellows. The Fellows learn about NIDA-supported drug abuse research and the application of research to the development of government policy and prevention and treatment programs through 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. 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

Travel Support

In August, NIDA supported a preliminary visit to Kenya by researchers from Yale University to discuss the feasibility of initiating a clinical research protocol for treating heroin dependence and reducing HIV transmission and the burden of HIV in Kenya. During their visit, Drs. David Fiellin, Marek Chawarski, and Lynn Sullivan: 1) evaluated the patient characteristics, treatment needs and feasibility of recruitment at the Mathare Psychiatric Hospital, Nairobi, and Coast General Hospital, Mombassa; 2) identified potential project directors or Kenyan collaborators at each of the sites; 3) met with other healthcare personnel who might become involved in the project; 4) reviewed the sources of healthcare data that would be of potential importance to the project; 5) evaluated the technical capacity of the two sites to support research

activities; 6) provided initial training to physicians, psychologists, other health care providers, and policy makers about opioid agonist maintenance treatment, antagonist maintenance treatment, drug abuse counseling, HIV risk reduction counseling, and coordinating HIV and drug abuse treatment; and 7) met with staff from the UNODC Drug Control and Crime Prevention Programme for Eastern Africa, which is serving as the umbrella organization for projects developing drug abuse and HIV treatment services, outreach, and counseling for Kenyan heroin users under the U.S. President's Emergency Plan for AIDS Relief (PEPFAR).

If they conclude that the Kenya project is feasible, the Yale research team anticipates applying for a NIDA administrative supplement to Dr. Richard Schottenfeld's current studies in Malaysia and Iran (DA14718, "HIV Risk Reduction and Drug Abuse Treatment in Malaysia" and "HIV Risk Reduction and Drug Abuse Treatment in Iran") to develop a similar clinical research program at the two hospital-based outpatient clinics in Kenya. The studies in Malaysia and Iran compare the efficacy of buprenorphine and naltrexone maintenance treatment and are facilitating development of the drug abuse clinical research and treatment infrastructure in the two countries. This infrastructure will then develop and disseminate evidence-based behavioral treatments tailored to the specific circumstances of heroin addicts in each of the countries and train healthcare personnel to provide opioid agonist and antagonist maintenance treatment.

NIDA Director Dr. Nora Volkow traveled to the Menendez Pelayo International University, Santander, Spain, to make two presentations at the conference, *Advances in Drug Dependency Research*, hosted July 24-27, 2004 by the **Spanish National Plan on Drugs** (PNSD). NIDA and PNSD signed an Exchange of Letters in October 2003 to promote binational collaboration on biomedical and behavioral drug abuse research.

NIDA supported participation by grantees at the **International Cannabinoid Research Society** meeting, June 22-27, 2004, in Paestrum, Italy. Drs. Igor Grant and Drew Mattison, University of California at San Diego, participated in the workshop, Future Directions in Cannabinoid Therapeutics II: From the Bench to the Clinic. Several other U.S. researchers received support from NIDA: Dr. Daniele Piomelli, University of California, Irvine; Dr. Alexandros Makriyannis, University of Connecticut; Dr. Sumner H. Burstein, University of Massachusetts Medical School; Dr. Guy A Cabral, Medical College of Virginia; Dr. Benjamin F. Cravatt, The Scripps Research Institute, San Diego; Dr. J. Michael Walker, Brown University; and Dr. Patricia Reggio, Kennesaw State University, Georgia. NIDA also supported participation by the following international researchers: Dr. Guido Tettamanti, University of Milan; Prof. Emilio Clementi, San Raffaele Scientific Institute, Milan; Dr. Manuel Guzm´n, Complutense University, Madrid; Prof. Antonio Calignano, University of Naples; Dr. Vincenzo Di Marzo, Italian Istituto di Chimica Biomolecolare; and Dr. Raphael Mechoulam, Hebrew University, Jerusalem.

Three NIDA grantees participated in a conference, **Modeling Mental Processes and Disorders**, organized by the Royal Swedish Academy of Sciences AGORA for Biosystems and Turkey's Ege University Center for Brain Research, May 24-29, 2004, in Ku_adasõ, Turkey. Dr. Andrew B Norman, University of Cincinnati; Dr. Warren Bickel, University of Vermont; and Dr. Peter Killeen, Arizona State University, joined clinicians, basic scientists, mathematicians, computer scientists, physicists, and statisticians to discuss behavioral, statistical, and mathematical models of brain function.

The Singapore Institute of Mental Health and the Community Addictions Management Program (CAMP) sponsored the **First Asia Pacific Institute on Addiction**, (APIA) May 29-June 4, 2004, to exchange information about policies, research and addiction treatment programs in the region, and to provide clinical updates and training in prevention and treatment of addictive disorders and HIV/AIDS. NIDA supported the participation of three Chinese researchers: Dr. Guo Song, National Institute of Drug Dependence; Dr. Li Bing, Institute of Mental Health; and Dr. Cheng Hung, United Kingdom HIV/AIDS China Project. Faculty members included NIDA grantees Dr. Walter Ling, University of California, Los Angeles; Dr. Carlton Erickson, University of Texas; and Dr. Thomas Babor, University of Connecticut.

NIDA provided support to the 6th Annual Medical-Scientific Conference of the **International Society for Addiction Medicine** (ISAM 2004), June 2-5, 2004, in Helsinki, Finland. During the conference Dr. Steven Gust, IP, chaired a session on tobacco addiction treatment.

NIDA provided travel support for Dr. Stephen T. Higgins, University of Vermont, to

participate in the **28th International Congress of Psychology**, August 8-13, 2004, in Beijing, China.

International Visitors

Dale Weiss, IP, along with representatives of the Office of National Drug Control Policy and the Department of State, attended a roundtable discussion on July 14, 2004, sponsored by the Phelps Stokes Fund. The purpose of the roundtable was to discuss drug abuse research and policy issues with Mr. Abel Mart'nez Dur´n from the Dominican Republic. Mr. Mart'nez Dur´n is a legislator, Lower House of the National Congress of the Dominican Republic.

Dr. Frank Vocci, Director, DPMCDA, presented the plenary lecture on "Imaging the addicted Brain" at the 6th Annual International Society for Addiction Medicine (ISAM) in Helsinki, Finland. He attended the ISAM Meeting from May 31 — June 6, 2004. Dr. Vocci also co-chaired a symposium on addiction treatment where he spoke on pharmacological treatments for stimulant dependence.

Drs. Ahmed Elkashef and Ivan Montoya, DPMCDA, also attended at the ISAM Meeting from May 31 - June 6, 2004. Drs. Ahmed Elkashef and Ivan Montoya presented on "Marijuana: The Extent of the Problem and Treatment." Drs. Elkashef and Vocci also met with the members of the ISAM Board of Directors to discuss planning for the 2005 ISAM meeting.

Dr. Frank Vocci met with Simon McNabb, CDC, and two visitors from Poland, Krzysztof Przewozniak, M.A. and Witold Zatonski, M.D. on August 3, 2004.

Dr. Ivan Montoya presented at the ISAM meeting in Helsinki the NIDA initiative on medications development for cannabis related disorders and a research paper based on the results of the NIDA funded longitudinal study of adolescents in Colombia.

Dr. Ivan Montoya presented at the First Iberoamerican Congress of Addictions in Santiago de Compostela (Spain) a review of the scientific progress in the development of medications for cocaine dependence.

Wilson Compton, M.D., M.P.E. and Meyer Glantz, Ph.D., DESPR, represented the Institute at the July 2004 World Mental Health Consortium (WMH) Meeting in Portland, Maine. As NIDA's collaborating investigator in the National Comorbidity Study and as a member of the WMH Consortium and the Substance Use Data Analysis Workgroup, Dr. Glantz will be collaborating in the analysis and publication of national and international data on drug abuse and associated factors.

Dr. Yonette Thomas, DESPR, chaired a panel on "Adolescent Substance Abuse: Epidemiology and Predictors of Risk Factors" at the meeting of the International Society for Addiction Medicine in Helsinki, Finland on June 2, 2004.

On June 7, 2004, Dr. Yonette Thomas participated in the satellite symposium of the International Society for Addiction Medicine at the State Pavlov University in St. Petersburg, Russia.

Dr. Elizabeth Robertson, DESPR, presented two papers at the International Conference on Drug Abuse Prevention sponsored by the U.S. Embassy in Guatemala City, Guatemala, on August 2-6, 2004. The papers were entitled Fundamentals of Prevention Research and Practice and Research Advances in Interventions for Adolescents.

Dr. Elizabeth Robertson met with Drs. Marion Forgatch, Jerry Patterson and Ivar Holman of the Oregon Social Learning Center and Haktor Helland, Terje Ogden and other representative of the Norwegian research team collaborating on the Cross-national Dissemination trial of the Parent Management Training model in a day long meeting to discuss progress and future challenges of the study. The meeting took place May 29, 2004 in Quebec City, Canada.

Dr. Eve Reider, DESPR, collaborated with Dr. Steven Gust, International Office in organizing a symposium for the 12th Annual Meeting of the Society for Prevention Research, May 26, 2004, Quebec City, Canada. Dr. Reider chaired and Dr. Gust led the discussion for the symposium, "Forging International Research Collaborations: Adaptation and Testing of Drug Abuse Prevention Principles Across Cultures." Established, developing and emerging international collaborations were presented (respectively): 1) Terje Ogden, University of Oslo, Norway, and Marion Forgatch, Oregon Social Learning Center, 2) Lisa Wegner, University of the Western Cape, South Africa, and Edward Smith and Linda Caldwell, Pennsylvania State University, and 3) Amador Calador Far, Irefrea, Palma de Mallorca, Spain, and Jean Schensul,

Institute for Community Research, Hartford, CT.

Dr. Peter Hartsock, DESPR, served on the Organizing Committee of the Twelfth International Conference on AIDS, Cancer, and Related Problems that took place in St. Petersburg, Russia, May 24-29th, 2004. Dr. Hartsock also organized a symposium at the Conference titled "Multi-Disciplinary Research/Evaluation of the Public Health Impact and Cost Effectiveness of AIDS Interventions." Participants included NIDA grantees, scientists from across the former Soviet Union and representatives for the Center for Strategic and International Studies.

Dr. Peter Hartsock participated in the Center for Strategic and International Studies' Expert Working Group on the HIV/AIDS Epidemic in Russia's meeting on "Tuberculosis Control in the Russian Federation and the Tuberculosis/HIV Problem in Russia," July 7, 2004, Washington, D.C. Participants included representatives from the U.S. Departments of State, Defense, and Health and Human Services. Russian participants included representatives from the Russian Ministry of Health, the International Federation of Red Cross and Red Crescent Societies, and the Russian Medical Academy.

Drs. Aria Crump and Cecelia McNamara conducted a presentation for a Spanish Delegation on April 15th at NIDA Headquarters.

Dr. Steven Grant, Chief, Clinical Neuroscience Branch, DCNDBT, presented a talk entitled "Cognitive Approaches to Drug Addiction" and met with addiction researchers at three sites in Europe in June 2004. The sites included the Area d'Investigacio Farmacologica, Institut de Recerca, Hospital de la Santa Creu i Sant Pau., Barcelona, Spain on June 25, 2004, Addex Pharmaceuticals in Geneva, Switzerland on June 29, 2004 and Psychiatric University Hospital University of Zürich, Zurich Switzerland on June 28-29, 2004.

Dr. Steven Grant, presented a talk entitled "Evidence for Cognitive Dysfunction and Dependence in MDMA Users" at a symposium he co-chaired on "MDMA Neurotoxicity in Humans: Current Status and Future Prospects" at the 24th Congress of the Collegium Internationale Neuropsycho-pharmacologicum, June 20-24, 2004 in Paris France. The symposium focused on recent evidence related to cognitive dysfunction and alterations in brain activity associated with chronic MDMA abuse. The other speakers in the symposium were Dr. Katherine Bonson, Food and Drug Administration, Dr. Franz Vollenweider, Univ. Zurich, Dr. Euphrosyne Fouzoulis-Mayfrank, Medical Faculty of the University of Technology, Aachen, and Dr. John Halpern, McLean Hospital.

On May 26th & 27th, 2004, Drs. Joseph Frascella and Laurence Stanford, DCNDBT, attended the Annual Meeting of the Neurobehavioral Teratology Society in Vancouver, BC. Dr. Stanford served as the discussant for a symposium entitled Neuroimaging of Prenatal Drug Exposure.

Dr. Teri Levitin and Dr. Rita Liu of OEA participated in a Round Table on Writing Grants and Peer Review at the 10th Society of Chinese Bioscientists in America (SCBA) International Symposium in Beijing, China, July 18-14, 2004. Dr. Liu introduced NIH's organization and grants system. Dr. Levitin presented an in-depth description of the peer review policies and process. Dr. Levitin and Dr. Liu also met with Beijing high school students in a Q&A session to compare student life in US and China.

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Meetings and Conferences

On May 17-18 and June 22, 2004, NIDA convened a meeting of the **Medications Development Program Work Group** in Bethesda, Maryland. This meeting was coordinated by Dr. Denise Pintello, OSPC. The purpose of this Work Group was to evaluate NIDA's Medications Development program and advise the Institute on strategies to maximize the clinical development of new medications for the treatment of drug abuse and addiction. The Work Group members and Chair, Dr. Peter Kalivas, have prepared a report based on their findings and recommendations.

On July 26-27, 2004, NIDA convened the first meeting of the **Minority Health Disparities Work Group** in Washington D.C., which was coordinated by Dr. Denise Pintello, OSPC. The primary objective of this Work Group is 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 minority populations. The Work Group is chaired by Dr. Jose Szapocznik who is a member of the National Advisory Council on Drug Abuse.

NIDA, in collaboration with SAMHSA, hosted a pre-conference meeting for State Directors, **Strengthening Federal-State Partnerships to Enhance Adoption of Evidence-Based Practices**, at the annual NASADAD conference in Portland, Maine on June 5, 2004. The chief purpose of the meeting was to inform State Directors about the CTN and ATTC dissemination efforts and assist them in linking with CTN nodes and ATTCs. OSPC, DESPR, and CCTN staff from NIDA participated in the meeting.

NIDA held a **Tutorials Workshop** on June 12, 2004, prior to the 2004 College on Problems of Drug Dependence (CPDD) Conference in San Juan, Puerto Rico. The presentations this year included: (1) "Cultural sensitivity, human subject protection, community requirements, and data quality in addictions research" by Dr. Arlene Stiffman, (2) "Anti-craving medications: A potential target for medication development" by Dr. Charles O'Brien, (3) "Behavioral pharmacology (pre-clinical and clinical)" by Dr. Linda Dykstra, and (4) "Effects of drugs of abuse on the immune system, including HIV expression" by Dr. Jean Bidlack. Approximately 30 NIDA Director's Travel Awards were issued to current NIDA fellows and trainees. Dr. Suman Rao, OSPC, coordinated and chaired this annual workshop.

NIDA, along with seven T32 research training sites, hosted the **Training Mixer** on June 14, 2004, at the 2004 College on Problems of Drug Dependence (CPDD) Conference in San Juan, Puerto Rico. The Mixer, which was attended by over 100 current NIDA trainees and fellows, offered a casual forum for networking with T32 training directors as well as mingling with NIDA staff. Dr. Suman Rao, OSPC, organized this event.

NIDA held a **Grant Writing Workshop** on June 15, 2004, at the 2004 College on Problems of Drug Dependence (CPDD) Conference in San Juan, Puerto Rico. Approximately 50 early-career scientists participated in learning how to apply for grants and the grant process at NIDA. Drs. Cindy Miner, David Shurtleff, Mark Green from NIDA and Dr. Scott Lukas, McLean Hospital, Harvard Medical School, presented. Dr. Suman Rao, OSPC, chaired and coordinated this event.

On June 15, 2004, NIDA sponsored a symposium at the Annual Meeting of the College on Problems of Drug Dependence entitled **Aging and Substance Abuse: What Problems Lie Ahead?** The meeting was organized by Drs. Timothy P. Condon and Susan Weiss. Speakers included Drs. Thomas Patterson from the University of California, San Diego, Wilson Compton from NIDA, Frederic Blow from the University

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of Michigan, David Oslin from the University of Pennsylvania, and Timothy P. Condon from NIDA. Among the topics discussed were: prediction of treatment needs from existing databases; misuse and abuse of prescription drugs and alcohol in elderly populations; and challenges in assessment and treatment of elderly individuals. The purpose of this symposium was to increase awareness, begin discussion, encourage interest, and help generate a research agenda in this area.

The National Institute on Drug Abuse (NIDA) participated in a number of sessions at the **American Psychological Association (APA) Annual Meeting**, July 28-August 1, 2004 in Honolulu, Hawaii. Some of the topics in the program included: Treatment for Methamphetamine Abuse: Effectiveness and Prospects; Decision Making and Drug Abuse; Cross-Cutting - Substance Abuse, Mental Health, and HIV/AIDS; and Drug Abuse Treatment Issues in Adolescent Girls. NIDA also organized and collaborated with Divisions 28 and 50 of the APA to host a Young Investigators Poster Session that was very well received. In addition, NIDA produced and disseminated a brochure of all the NIDA activities at the APA meeting.

On September 8-9, 2004, NIDA sponsored a science meeting entitled **Cognitive & Affective Neuroscience and Behavioral Treatment Development: New Directions for Translational Research**. The meeting was co-chaired by Drs. Lisa Onken and Joseph Frascella, and organized with Dr. Mary Ann Stephens. Experts in neuroscience and behavioral treatment research were brought together to discuss how neuroscience might inform the development of new and improvement of existing behavioral treatments, and to aid in the development of a research agenda in this area. This meeting was part of NIDA's ongoing efforts to bridge the gap between basic and clinical science.

On September 20-21, 2004, NIDA sponsored a science meeting entitled **Integrating HIV Prevention Into Drug Abuse Treatment Research**. The meeting was co-chaired by Lisa Onken and Debra Grossman, and organized with Jacques Normand and Elizabeth Lambert. The purpose of this workshop was to bring together NIDA researchers and experts in HIV/AIDS, infectious disease prevention, and drug abuse treatment to discuss the need for the integration of infectious disease prevention in drug abuse treatment research. The workshop will focus on the current status of research efforts to integrate these activities, obstacles to getting research started, and recommendations to NIDA for its program of research that facilitates the integration of HIV prevention research into treatment research.

NIDA's Services Research Branch, Division of Epidemiology, Services & Prevention Research, in partnership with the National Institute of Mental Health (NIMH), the National Institute on Alcohol Abuse & Alcoholism (NIAAA), the Agency for Healthcare Research & Quality (AHRQ), the Health Resources & Services Administration (HRSA), and the Substance Abuse & Mental Health Services Administration (SAMHSA)—sponsored a research conference entitled **Complexities of Co-occurring Conditions: Harnessing Services Research to Improve Care for Mental, Substance Use, & Medical/Physical Disorders**, June 23-25, 2004, Washington, DC.

On June 13, 2004 a workshop entitled I**ntegration of Toxicology- and PK-related Testing into Early Medications Discovery: A Workshop for NIDA Medicinal Chemists**, was chaired by David McCann, Rik Kline, and Jane B. Acri, all of DPMCDA, at the College on Problems of Drug Dependence in San Juan, PR. The workshop included presentations by Arthur Brown (Chan Test), In Vitro Assays to Predict QT Prolongation, Arthur Weissman (NovaScreen Biosciences), In Vitro CYP Assays to Predict Drug-Drug Interactions, James Terrill (PMC, NIDA), In Vitro Assays for the Early Prediction of Mutagenic Potential, and Edwin Matthews (FDA), In Silico Prediction of Drug Toxicity. These assays have been incorporated into NIDA's preclinical medication Discovery Programs in PMC and are available to medicinal chemists who submit compounds for evaluation. The workshop covered methods and interpretations, as well as relevance for medication development.

Dr. Jag Khalsa, DPMCDA, organized a symposium on **The Role of Hormones and Nutrition in Drug Abuse and Co-occurring Infections: HIV and HCV**, August 9-10, 2004, Bethesda Marriott Suites Hotel, Bethesda, MD. Past symposia discussed various metabolic and endocrine disorders and interventions for these complications of drug abuse and HIV/AIDS. This meeting presented the state-of-the-art information on the role of hormones and nutrition in drug abuse and co-infections of HIV and hepatitis C. It is anticipated that the proceedings will be published as a supplement in *Clinical Infectious Diseases*.

Dr. Ming Shih and Dr. Jacques Normand in collaboration with CTN's HIV/AIDS Special

Interest Group organized a workshop entitled **Current Epidemiology and Intervention Approaches for HIV/AIDS among Drug Users** that was held in Bethesda, MD on August 12-13, 2004. The meeting presented current HIV epidemiology in the United States along with cutting edge approaches to structural and peer-driven intervention/prevention approaches among adult, adolescent, and minority drug using populations.

NIDA's Translationally Oriented Approaches, Devices, and Strategies workgroup sponsored a **Workshop on Deep Brain Stimulation** on Aug 3, 2004 at the Neuroscience Center in Rockville, MD. Several experts spoke to NIDA staff, and engaged in discussion on how this technology is being researched and used clinically. Discussion focused on issues in the potential application of this technology to drug abuse treatment. Mr. Hirsch Davis and Dr. David Thomas organized the meeting.

Drs. Robert Riddle, Jonathan Pollock and Jag Khalsa organized a meeting on **RNAi as A Therapeutic Intervention For Treatment of Hepatitis C and HIV** that was held on September 14-15th, 2004 at the Pooks Hill Marriott, Bethesda, MD.

Drs. Paul Schnur (NIDA/DBNBR), and Kay Wanke (NCI), co-chaired a NIDA/ NCI sponsored symposium entitled **Gene-Environment Interaction in Disorders of Addiction** on May 22, 2004 at the annual meeting of the American Psychological Society in Chicago, IL.

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

The inaugural **Hand-Off Meeting** to coordinate dissemination efforts of research results for the **CTN's Motivational Interviewing Protocol** (Dr. Kathleen Carroll, P.I.) took place on May 17-18, 2004, in Bethesda, Maryland. At this meeting, research results from the protocol were presented followed by discussion among NIDA researchers and ATTC members of potential dissemination product(s) that can help address the critical needs in the treatment field. Dr. Suman Rao, OSPC organized and Dr. Timothy P. Condon, Deputy Director, chaired this meeting which was designed to discuss dissemination strategies for a specific target audience.

The **Blending Team** for the **CTN Motivational Interviewing Protocol** met in Portland, Oregon on July 15-16, 2004. The objective of the meeting was to review, expand, and prioritize the brainstormed list of potential dissemination products identified at the Hand-Off meeting in May 2004. Three ATTC members and three NIDA researchers comprised the Blending Team. NIDA/OSPC and SAMSHA staff also participated in facilitating this Blending Team in determining dissemination packages from this first set of CTN results.

The **Hand-Off Meeting** for the **Buprenorphine Detox CTN protocol** (Dr. Walter Ling, P.I.) took place on July 19, 2004 in Los Angeles, California. The protocol team reported on the results of the Buprenorphine/Naloxone for opiate detoxification study in the NIDA Clinical Trials Network. Lessons learned from three different CTN sites that conducted the study were presented along with different models for training Buprenorphine detoxification. Dissemination product ideas were brainstormed by the NIDA researchers and ATTC members as well as NIDA and SAMHSA staff who all participated in this meeting. The Blending Team for this protocol is tentatively scheduled to meet in mid-November 2004. Dr. Suman Rao, OSPC, coordinated and organized this dissemination meeting and Dr. Timothy P. Condon, Deputy Director, NIDA chaired this meeting.

A second **CTN National Recruitment, Retention, and Return for Follow-Up Meeting** was held September 13-14, 2004 in Albuquerque, New Mexico. As in the past, the session included expert panels, breakout groups, review of current CTN protocols and problem solving cases. The workshops were open to all participants in the CTN and representatives from all 17 Nodes attended. The session focused on strategies for recruitment in drug abuse treatment clinical trials as well as plans for retention and follow-up of participants.

A CTN symposium chaired by Dr. Maxine Stitzer (Mid-Atlantic Node) and Dr. Betty Tai (NIDA CCTN Director) was held at the CPDD 2004 annual meeting in June in Puerto Rico. CTN Presenters included Betty Tai, Sam Ball, Walter Ling and Maxine Stitzer on the outcome results of Wave 1 protocols; Dr. Warren Bickel was the discussant.

The CTN presented an invited workshop: Collaborations in TRIP: Lessons from NIDA's Clinical Trials Network at the Agency for Healthcare Research and Quality (AHRQ) annual meeting on "Translating Research into Practice: Advancing Excellence from Discovery to Delivery" July 12 - 14, 2004, in Washington, DC. The panel discussed the development of the bi-directional practice and research collaboration using the Motivational Incentives protocol to illustrate its story. Maxine Stitzer (Mid-Atlantic Node) summarized the protocol and trial findings. Pat Stabile (HARBEL, Mid-Atlantic Node) shared the CTP perspective and the challenges associated with protocol participation. Scott Kellogg (New York Node) described his work facilitating the adoption of the motivational incentives intervention in treatment programs in New York City. Betty Tai (NIDA, CCTN) summarized the challenge of bridging the gap between research and practice. Other CTN participants in the conference included: Dennis McCarty (Oregon Node) moderated the panel. Jim Dahl (Long Island Node) was a co-presenter of a seminar, "Partnering to Improve Quality of Care in Substance Abuse Treatment," and Theresa Montini (CCTN) and Joe Guydish (California/Arizona Node) were co-presenters of "Gaps between Nicotine Dependence Research and Clinical Practice in Substance Abuse Treatment Programs."

The CTN was featured at a Symposium at the American Psychological Association Meeting held in Honolulu, HI, July 28 - August 1, 2004. Drs. Betty Tai (NIDA CCTN Director) and Kathleen M. Carroll (New England Node) chaired the session, entitled "National Institute on Drug Abuse Clinical Trials Network: Findings of the First Four Studies. Dr. Dennis McCarty (Oregon Node) described the participating treatment centers; Dr. Steve Shoptaw (Pacific Node) addressed buprenorphine detoxification in community treatment centers; Dr. Kathleen Carroll (New England Node), presented motivational interviewing (MI) to improve engagement and outcome in addiction treatment, and Dr. Maxine Stitzer (Mid-Atlantic Node) described the effects of motivational incentives on retention in treatment and drug use.

CTN National Steering Committee Meetings were held in Gaithersburg, Maryland May 10-14, 2004.

- The CTN Dissemination Subcommittee met face-to-face at the May Steering Committee Meeting. Plans for dissemination of the completed protocols and for "handing off' the protocols to other NIDA staff for external dissemination were discussed.
- The Genetics Special Interest Group of the CTN met and Dr. Joni Rutter, from NIDA's Genetics & Molecular Neurobiology Research Branch, described NIDA's Genetics Consortium. Dr. Betty Tai outlined mechanisms for using the CTN infrastructure for genetics studies, and led discussion of possible studies and future directions.
- The HIV/AIDS Special Interest Group and the Minority Special Interest Group met as well.

CTN National Steering Committee Meetings were held July 22-23, 2004 in Washington, DC.

- The SC discussed budget issues, the CTN implementation of future larger scale trials, and a plan to prioritize ongoing efforts.
- The CTP Caucus and the newly-formed PI Caucus met on July 22, 2004.
- The CTN Executive Committee met on July 22-23, 2004. The committee reviewed plans for prioritization of trials and protocols under development.

Dr. Timothy P. Condon, Deputy Director, NIDA, presented the NIDA Deputy Director's Report at the Clinical Trials Network Steering Committee meeting in Gaithersburg, Maryland on May 12, 2004.

Dr. Timothy P. Condon presented "Drug Abuse Research and the Criminal Justice System" at the National Association of Drug Court Professionals (NADCP) Training Conference in Milwaukee, Wisconsin on June 3, 2004.

Dr. Timothy P. Condon delivered the welcoming remarks at the NIDA pre-conference workshop at the National Association for Alcohol and Drug Abuse Directors (NASADAD) conference in Portland, Maine on June 5, 2004.

Drs. Timothy P. Condon and Susan Weiss co-chaired the NIDA Symposium, "Aging & Substance Abuse: What Problems Lie Ahead?" at the College on Problems of Drug Dependence (CPDD) conference in San Juan, Puerto Rico on June 15, 2004. Dr. Condon presented "Research Priorities for the Study of Substance Abuse in the

Elderly" as part of this session.

Dr. Timothy P. Condon delivered the welcoming remarks at the Advancing Research to Reduce Drug Abuse and HIV/AIDS Health Disparities Methodological Considerations meeting in Bethesda, Maryland on June 21, 2004.

Dr. Timothy P. Condon participated in the Motivational Interviewing Blending Team external meeting in Portland, Oregon on July 15, 2004.

Dr. Timothy P. Condon participated in the Buprenorphine Detox Hand-Off Meeting in Los Angeles, California on July 20, 2004.

Dr. Timothy P. Condon delivered the welcoming remarks and provided an update on NIDA dissemination activities at the Clinical Trials Network Steering Committee meeting in Washington, D.C. on July 22, 2004.

Dr. Timothy P. Condon gave the Charge to the Minority Health Disparities Work Group in Washington, D.C. on July 26, 2004.

Dr. Timothy P. Condon presented the keynote address, "Advances in Drug Abuse and Addiction Research: Implications for Prevention," at the Comprehensive Health Education Foundation (C.H.E.F.) conference in Seattle, Washington on July 29, 2004.

Dr. Timothy P. Condon presented, "Blending Practice and Research: What's New from the National Institute on Drug Abuse," at the Northwest Institute of Addiction Studies in Portland, Oregon on July 30, 2004.

Dr. Timothy P. Condon presented the keynote address, "Addiction Research: Implications for Blending Research and Practice," at the Summer Institute on Addiction and Prevention (CASAT) in Las Vegas, Nevada on August 4, 2004.

Dr. Cindy Miner, Deputy Director, OSPC, co-chaired a workshop with Dr. Dorothy Hatsukami, University of Minnesota, entitled "Transdisciplinary Research on Tobacco Addiction" at The 66th Annual College on Problems of Drug Dependence, June 15, 2004 in San Juan, Puerto Rico.

Dr. Cindy Miner, Deputy Director, OSPC, presented "The Brain, The Body, and Addiction" at the DC 2004 Summer Institute on July 19, 2004 in Washington, DC.

Dr. Cindy Miner, Deputy Director, OSPC, presented "Addiction as a Brain Disease: Blending Research and Practice" at the Nebraska Association of Behavioral Health Organizations' 4th Annual "Moving from Research to Practice in Behavioral Health" Conference on August 6, 2004 in Omaha, Nebraska.

Dr. Susan Weiss presented at the 25th Annual Long Island Conference on Chemical Dependency "Anabolic Steroids and Other Performance Enhancing Drugs: A Silent Epidemic" on May 21, 2004.

Dr. Khursheed Asghar, OEA, conducted a mock review panel meeting at a NIDA sponsored workshop entitled "NIDA Research Development Seminar Series: Minority Institutions Drug Abuse Research Development Program" on July 22, 2004.

Drs. Teri Levitin and Mark Green, OEA, were co-chairs of a workshop "Career Development: A Perspective from Junior and Senior Researchers" at the June meeting of CPDD.

Drs. Green and Levitin were co-chairs of a workshop "What's New at NIDA and NIH: How will it Affect You?" at the June meeting of CPDD.

Dr. Green made a presentation about peer review at the Grant Writing Workshop sponsored by NIDA at the June meeting of CPDD.

Drs. Rita Liu, OEA, David Shurtleff, DBNBR, and Cathrine Sasek, OSPC, served as guest editors for a special supplement issue to the Journal of Neuropharmacology, entitled "Frontiers of Addiction Research," to celebrate NIDA's 30th anniversary. More than 30 NIDA neuroscience grantees, have contributed to this special neuroscience issue.

Dr. Mark Green conducted a mock review on July 16, 2004 at a NIDA sponsored meeting for young investigators.

In May, Dr. Teri Levitin and Dr. Paul Schnur joined other NIH Institute representatives and NSF at the 16th annual convention of American Psychological Society in Chicago for a workshop for graduate students and new faculty on obtaining grant support.

In late June, Dr. Levitin organized a conversation hour at the annual meeting of the Society for the Psychological Study of Social Issues. The meeting was held in Washington D.C. and Dr. Levitin spoke about NIH extramural program and review policies and procedures.

In August 2004, Dr. Levitin joined Dr. Minda Lynch and Dr. David Shurtleff at the American Psychological Association's 112th Annual Convention for a workshop on "Funding Opportunities for New Researchers" that included representatives from several NIH Institutes.

Mr. Eric Zatman, OEA, attended the 6th Annual NIH SBIR/STTR Conference at the Natcher Conference Center on June 23 - 24, 2004.

Mr. Richard Harrison attended the Interagency Workgroup on American Indian and Alaska Native Education meeting in Washington D.C. on June 30, 2004.

Mr. Richard Harrison attended the African American Researchers and Scholars Meeting in Washington D. C. on July 12 — 13, 2004.

Dr. Lula Beatty, Chief, Special Populations Office, attended the NAPAFASA regional meeting on June 28, 2004 in Washington, DC.

Dr. Lula Beatty participated in a number of sessions at the American Psychological Convention, July 28 - August 1, 2004 in Honolulu, Hawaii including the following: panelist on a symposium entitled "Funding for Research on Women and Girls: Myths and Strategies," presentation entitled "Myths and Realities of Federal Funding About and To Women"; participant/Presenter on Funding Opportunities at NIH, Public Interest Suite Program; and panelist on conversation hour on NIH funding with colleagues from OD/NIH, NIAAA and NIMH, presentation entitled "Research Needs of the National Institute on Drug Abuse"

Dr. Lula Beatty participated in the following sessions at the convention of the Association of Black Psychologists, August 11-14, 2004 in Washington, DC: presenter/faculty in pre-convention workshop entitled "Mental Health Issues Influencing HIV Disease and Care among African Americans," presentation entitled "Prevention of HIV Infection: Risk Factors and Interventions"; presenter in professional development workshop entitled " Obtaining Federal Research Funds: Strategies, Grant Writing, and Opportunities," presentation on Health Disparities at NIDA/NIH; and developed session entitled "Meeting the Challenges of Service and Mentoring through Sponsored Research: Women Psychologists in Substance Abuse and HIV Research."

Ana Anders, Senior Advisor on Special Populations, gave the welcoming remarks for Dr. Nora Volkow at the Summer Training Institute of the National Hispanic Science Network on Drug Abuse on June 1, 2004 at the University of Texas in Houston, Texas.

Ana Anders participated in the NIDA International Forum on June 11, 2004 in San Juan, Puerto Rico.

Ana Anders participated in the Co-Occurring Conference on June 23, 2004 in Washington, D.C.

Ana Anders gave remarks at the NAPAFASA conference on June 28, 2004 in Washington, D.C.

Ana Anders participated on the CSAP Hispanic Initiative Expert Panel on August 4 and 5, 2004 in Las Vegas, Nevada.

Ana Anders presented at the CSAP RADAR Program Steering Committee held on August 10-11, 2004 in Miami, Florida.

Ana Anders moderated a panel at the Caribbean Basin ATTC on August 18-19, 2004 in San Juan, Puerto Rico.

Pamela Goodlow, Public Health Analyst, Special Populations Office, chaired 2-day Research Development Seminar workshops on April 13-14, 2004 and July 22-23, 2004 for new investigators interested in applying for NIDA funding. The technical assistance workshops focused on NIDA's Minority Institutions Drug Abuse Research Program (R-24 grant mechanism). Participants met with NIDA senior staff and funded investigators in small groups and one-on-one settings. They learned about NIDA's research priority areas, the NIH grants process and they received assistance in developing their research concepts into successful grant applications.

Pamela Goodlow presented an overview of NIDA research opportunities available to

minority researchers and students at the Association of Black Psychologists Annual Conference on August 12, 2004 in Washington, D.C.

Dr. Betty Tai, Director, CCTN, presented at the New Clinical Drug Education Unit (NCDEU) Meeting May 31-June 4, 2004 in Phoenix, Arizona. Dr. Tai participated in a panel focusing on developing networks for clinical research. Her presentation was entitled: "NIDA Clinical Trials Network Update: Challenges and Opportunities."

Dr. Janet Levy, Statistician, CCTN presented a talk on Interim Analysis and Sample Size Re-Estimation at the "face-to-face" meeting of the CTN Design and Analysis Workgroup on May 10, 2004.

Dr. Paul Wakim, Mathematical Statistician, CCTN, lead discussions on measurement burden, adaptive randomization, and interim analysis at the "face-to-face" meeting of the CTN Design and Analysis Workgroup in May 2004.

Carmen Rosa, M.S., CCTN liaison to the CTN Minority Special Interest Group, presented an overview of the Clinical Trials Network and its efforts in addressing addiction treatment in minorities to the NIDA African American Workgroup on July 12, 2004 in Washington, DC.

Carmen Rosa, M.S., CCTN liaison to the CTN Minority Special Interest Group, and Theresa Montini, Ph.D., Program Officer, CCTN attended the APA Minority Fellowship Program July 19, 2004 in Washington, DC. Ms. Rosa spoke about "Emerging Issues in Ethnic Minority Research," highlighting CTN activities that target racial and ethnic minorities. Dr. Montini spoke about training opportunities within NIDA and NIH, and provided detailed information about specific funding mechanisms.

Carmen Rosa, M.S., CCTN liaison to the CTN Minority Special Interest Group, presented an overview of the CCTN and details of several CTN protocols targeted to minority populations to the NIDA Minority Health Disparities Workgroup on July 26, 2004 in Washington, DC.

Dr. Steven Grant, DCNDBT, was a discussant in the session on "Design and Analysis Issues for Pediatric Development Studies" during the trans-NIH workshop on Pediatric Functional Neuroimaging held in Bethesda, MD on May 25-26, 2004.

On May 11-12, 2004, Dr. Laurence Stanford, DCNDBT, participated in the NIH MRI Study of Normal Human Brain Development Annual Workshop in Cincinnati, OH.

Dr. Harold Gordon, DCNDBT, was an invited "external advisor" to a discussion conference on "Resilience and Recovery: Refocusing Research and Services on the Restoration of Health" convened by the Neuroscience and Behavioral Health Board of the Institute of Medicine, Washington, D.C., June 10, 2004.

Dr. Cora Lee Wetherington served as the discussant in the workshop, "Sex, Drugs and No Rock 'N Roll," held at the annual meeting of the College on Problems of Drug Dependence, June 12-17, 2004, San Juan, PR. Organized by Rachel Peltier and Therese Kosten, the workshop speakers were Marilyn Carroll, Nancy Mello, Rachel Peltier and Therese Kosten.

Dr. Cora Lee Wetherington gave an invited plenary talk, "Gender Differences in Drug Abuse Across the Life Span," at the conference, "Women Across the Life Span: A National Conference on Women, Addiction and Recovery," sponsored by the Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, July 12-13, 2004, Baltimore Marriott Inner Harbor.

Drs. Cora Lee Wetherington and Shakeh Kaftarian, DESPR, co-chaired the roundtable discussion, "Drug Abuse and Psychopathology in Women: Blending Research and Practice," at the annual meeting of the American Psychological Association annual meeting, July 28-August 1, 2004.

Dr. David Shurtleff gave a presentation entitled " Research and International Activities in the Division of Basic Neuroscience and Behavioral Research" at the 2004 NIDA International Forum: Progress Through Collaboration" on June 12, 2004 at the annual meeting the College on Problems of Drug Dependence (CPDD), in San Juan, Puerto Rico.

Dr. Frank Vocci, Director, Division of Pharmacotherapies and Medical Consequences of Drug Abuse (DPMCDA), presented at the 2004 International Forum: Progress Through Collaboration, at the College on Problems of Drug Dependence (CPDD) and other parts of CPDD.

Dr. Ivan Montoya, DPMCDA, chaired a workshop at the American Psychiatric Association to discuss the topic of addiction psychiatry as a career choice in psychiatry.

Dr. Ivan Montoya participated in a consultants meeting organized by the Robert Wood Johnson School of Medicine and Dentistry to discuss the nature and extent of nicotine dependence in severely mentally ill individuals and ways to approach this issue from a public health perspective.

Dr. Ivan Montoya participated in the ASAM meeting in Washington in the symposium entitled Buprenorphine Around the World. The title of his presentation was "The Influence of Psychotherapy on Buprenorphine Treatment Outcome.

Dr. Ivan Montoya and Dr. Vocci co-chaired a consultants meeting in Rockville MD to discuss and provide guidance for the design and implementation a program in NIDA-DPMC of medications development for the treatment of cannabis dependence.

Dr. Wilson Compton presented a paper on "Marijuana Use Disorders in the United States: 1991-1992 and 2001-2002" and co-chaired a workshop on "Treatment of Patients with Drug Dependence and Psychiatric Illness" at the Annual Meeting of the American Psychiatric Association, New York, New York, May, 2004.

Dr. Wilson Compton and Bill Bukoski, DESPR, co-chaired a symposium on cutting edge methods in prevention and epidemiology, Dr. Compton presented a paper (co-authored with Dr. James Colliver) on "Using Existing National Surveys to Project Future Drug Use Among Aging Baby Boomers" and Dr. Compton served as discussant in a symposium on "Drug Abuse and Suicidal Behavior: Causation, Comorbidity, or Common Etiology" at the College on Problems of Drug Dependence, San Juan, Puerto Rico, June, 2004.

Dr. Kevin Conway, DESPR, presented a paper (co-authored with Dr. K. Merikangas) on "Epidemiology of Psychiatric and Addictive Behaviors." at the Annual Meeting of the American Psychiatric Association, New York, New York, May 4, 2004.

Drs. Elizabeth Robertson and Shakeh Kaftarian, DESPR, participated in planning a conference sponsored jointly by NIH, CDC, AHRQ and Robert Wood Johnson Foundation titled "Research Designs for Complex Multi-level Health Interventions and Programs." This conference was convened on May 4-5, 2004, in Bethesda, Maryland.

Dr. Elizabeth Robertson presented a paper titled Going to Scale: Type II Translational Research at the Prevention Leadership Conference in Snowbird, UT on April 20, 2004.

On June 14, 2004, Elizabeth Robertson, Ph.D. moderated a panel discussion at the National Forum on Evidence-based Crime and Substance Abuse meeting titled Rigorous Evidence: The Key to Progress Against Crime and Substance Abuse? Lessons from Medicine, Welfare, and Other Fields.

Dr. Elizabeth Robertson served on the planning committee for the annual National Prevention Network meeting, Cultivating the Past — Pioneering the Future, held in Kansas City, MO on August 22-25, 2004.

Dr. Elizabeth Robertson was a discussant for a panel titled Addressing Stages of Diffusion in Taking Evidence-based Programs to Scale, at the Society for Prevention Research meetings on May 28, 2004 in Quebec, Canada.

Drs. Elizabeth Robertson and Belinda Sims, NIMH, co-chaired a Scientific Dialogue/ Roundtable Discussion at the Society for Prevention Research Conference in Quebec City, Canada on May 26, 2004. The title of the Roundtable Discussion was "Allocation of Resources for School-based Prevention Interventions"." The panel of discussants included: Drs. Jonathan Caulkins, Carnegie Mellon University, E. Michael Foster, Pennsylvania State University, and Beverlie Falek, SAMHSA.

Dr. Beverly Pringle, Services Research Branch, DESPR moderated a pre-conference methodology workshop entitled Enhancing Evidence: Causal Modeling Using Observational Treatment Data—featuring grantees Andrew Morral, Ph.D.; Daniel McCaffrey, Ph.D.; and Greg Ridgeway, Ph.D., of RAND Corporation—at the NIDA-sponsored research conference on Complexities of Co-occurring Conditions: Harnessing Services Research to Improve Care for Mental, Substance Use, & Medical/Physical Disorders, June 23, 2004, Washington, DC.

Drs. Jack Stein, and Beverly Pringle, Services Research Branch, DESPR provided technical assistance to potential grantees at a NIDA-sponsored workshop for State Directors of Drug Abuse at the annual meeting of the National Association of State

Alcohol & Drug Abuse Directors.

Arnold Mills represented DESPR at the National Hispanic Science Network Summer Research Training Institute on Hispanic Drug Abuse held in Houston, Texas June 1-8, 2004.

Arnold Mills represented DESPR at a Consortium Meeting of Historical Black Colleges and Universities in Georgia hosted by Morehouse College in Atlanta, Georgia on July 30, 2004. His presentation focused on NIH grant mechanisms and fundamentals of grantsmanship.

Dr. Naimah Weinberg, DESPR, served as chair and discussant for a symposium at the May 2004 meeting of the American Psychiatric Association in New York City, entitled ADHD Subtypes and Subgroups at Risk for Substance Use Disorders, as part of the special NIDA track at this meeting.

Dr. Naimah Weinberg co-chaired a panel on epidemiology and assessment at the NIMH Workshop on the Prevention of Depression in Children and Adolescents, on June 21-22, 2004, at the Doubletree Hotel in Rockville. She also served on the planning committee for this meeting.

Dr. Eve Reider, DESPR, organized a NIDA meeting, Linking Drug Abuse and HIV Prevention inYouth, held on April 29, 2004 at the Omni Shoreham Hotel in Washington, DC.

On July 11, 2004, Dr. Lynda Erinoff, DESPR, presented on "Drug Abuse and Suicidal Behavior: An Overview" to young investigators at the Summer Research in Suicide Prevention at the University of Rochester. She also represented NIDA at the Uuniversity of Rochester R-13 meeting "Preventing Suicide and Attempted Suicide Among Women Across the Lifecourse" on July 16, 2004, in Washington, D.C.

Dr. Peter Hartsock, DESPR, participated in a meeting co-sponsored by the Center on International and Strategic Studies Task Force on HIV/AIDS and the Kaiser Family Foundation and covering two major topics: "Routine Testing: Pitting Public Concerns Against Human Rights" and "Addressing the HIV/AIDS Threat in Militaries and Peacekeeping Operations," June 17, 2004, Washington, D.C.

Dr. Shakeh Kaftarian chaired and Drs. Elizabeth Robertson and Wilson Compton were discussants at a roundtable discussion session titled "Challenges Facing Fidelity and Adaptation of Prevention Programs" at the Society for Prevention Research Conference, on May 27, 2004, in Quebec City, Canada.

Dr. Elizabeth Ginexi, DESPR, chaired a Scientific Dialogue/Roundtable Discussion at the Society for Prevention Research Conference in Quebec City, Canada on May 26, 2004. The title of the Roundtable Discussion was "Translating Basic Science Discoveries into Effective Preventive Interventions." The panel of discussants included: Drs. Elizabeth Robertson, PRB, DESPR, Kenneth Dodge, Duke University, Richard Milich, University of Kentucky, Robert Pandina, Rutgers University, John Reid, Oregon Social Learning Center, and Thomas Valente, University of Southern California.

Dr. Aria Crump, DESPR, chaired an NIH new investigator workshop in collaboration with program staff from NIMH and NIAAA for the Annual Meeting of the Society for Prevention Research in Quebec City, Canada on May 24, 2004.

Drs. Aria Crump and Dionne Jones, DESPR, convened a science meeting titled "Advancing Research to Reduce Drug Abuse and HIV/AIDS Health Disparities: Methodological Considerations" in Bethesda, Maryland on June 21-22, 2004.

Dr. Eve Reider participated in the planning of and moderated two panels for the NIMH Workshop on the Prevention of Depression in Children and Adolescents, held June 21 and 22, 3004 at the Doubletree Hotel, Rockville, MD.

Dr. William S. Cartwright, Services Research Branch, DESPR moderated a panel on cost and outcomes at Complexities of Co-occurring Conditions: Harnessing Services Research to Improve Care for Mental, Substance Use, and Medical/Physical Disorders, June 23-25, 2004, at the Marriott Wardman Park Hotel in Washington, DC.

Dr. William S. Cartwright lectured on rational budgeting at the George Mason University, School of Public Policy, July 7, 2004.

Drs. Peter Delany, Jerry Flanzer and Jack Stein, Services Research Branch, DESPR chaired the panel "Emerging Interdisciplinary Social Work Research Programs: Moving

HIV/AIDS from Research to Practice;" Dr. Jerry Flanzer presented a talk on "Social Work, HIV and NIDA's Commitment"; and Drs. Peter Delany and Jerry Flanzer led a NIDA-focused grants workshop at the HIV/AIDs 2004: The Social Work Response — the 16th Annual National Conference on Social Work and HIV/AIDS, at the Hilton Hotel, Washington, D.C, May 28-29, 2004.

Dr. Jerry Flanzer, Services Research Branch, DESPR presented NIDA's portfolio and future research interest in the application of Buprenorphine treatment as part of the panel Buprenorphine in the Primary HIV Care Setting at the Forum for Collaborative Health Research in HIV, George Washington University, Washington, DC, June 4, 2004.

Dr. Jerry Flanzer presented NIDA's portfolio and future research interests at the OBSSR/NIH sponsored Forum at the Washington, DC area, Deans of Schools of Social Work Forum, held at Catholic University, June 21, 2004.

Dr. Jerry Flanzer with Dr. James Bell of James Bell Associates, presented a poster "Intervention Services Records (ISR) Developed for the HIV/AIDS Treatment Adherence, Health Outcomes and Cost Study, at the Complexities of Co-occurring Conditions Conference, Marriott Wardman Park, Washington, D.C. June 23-25.

Dr. Jerry Flanzer, Services Research Branch, DESPR moderated a panel, Complexities of Co-Occurring Mental Illness, Substance Abuse and HIV/Hepatitis C, at the Complexities of Co-occurring Conditions Conference, Marriott Wardman Park, Washington, D.C. June 23-25, 2004.

Dr. Jerry Flanzer, Services Research Branch was a panel participant on opportunities for Mixed methods research at NIH at the OBSSR, NIH Summer Institute: The Design and Conduct of Quantitative and Mixed-method Research in Social Work and Other Health Professions, Shoreham Hotel, Washington, DC, August 5, 2004.

Dr. Thomas Hilton, Services Research Branch, DESPR, participated in a pre-conference seminar for grant applicants at the Complexities of Co-occurring Conditions Conference June 22, 2004. He also organized and chaired a workshop of the application of Rausch models at the same conference on June 23, 2004.

On August 5-11, 2004, Dr. Hilton represented NIDA at the annual Academy of Management Conference in New Orleans during which he co-chaired a workshop on applying for NIH grants and facilitated a seminar on organizational survival among public health service providers.

Dr. Dionne Jones, Services Research Branch, DESPR organized, planned and chaired a panel "Current Trends and Development in Drug Use & HIV/AIDS Research on Women and Girls" and a "Grant Development Workshop" at the Women, Girls and HIV/AIDS in Africa and the African Diaspora Conference, Spelman College, Atlanta, GA, June 10-12, 2004.

Dr. Dionne Jones made a presentation on "Research Needs and Development Opportunities at NIH" at the Women, Girls and HIV/AIDS in Africa and the African Diaspora Conference at Spelman College, Atlanta, GA, June 11, 2004.

Dr. Dionne Jones made a presentation on "Research Opportunities: 2004 and Beyond at NIH" at a NIDA-sponsored Satellite Meeting of the Caribbean Health Research Council Annual Meeting, St. Georges, Grenada, April 23, 2004.

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

Media and Education Activities

Press Releases

April 28, 2004 - **NIDA Announces 8th Annual PRISM Award Winners**
The winners of the *8th Annual PRISM Awards* were announced at The Hollywood Palladium. Presented by the Entertainment Industries Council, Inc. (EIC), in partnership with The Robert Wood Johnson Foundation (RWJF) and the National Institute on Drug Abuse, a component of the National Institutes of Health, Department of Health and Human Services (NIDA), the *PRISM Awards* recognize accurate depictions of drug, alcohol and tobacco use and addiction in television, feature film, music and comic book entertainment.

April 30, 2004 - **NIDA NewsScan #30**

- NIDA Partners With American Psychiatric Association (APA) for Research-Based Track on Drug Abuse at 2004 APA Annual Meeting
- Medication for Multiple Sclerosis May Help in Treating Cocaine Addiction
- Study Finds Bupropion May Be Effective Smoking Cessation Aid for Women
- Adopting 12-Step Philosophy May Enhance Treatment Outcomes of Individual & Group Counseling for Cocaine Addiction
- Co-Occurring Disorders Increase Risk of Suicide Attempt by Adolescents
- Examining Motivational Interviewing in Drug Abuse Therapy
- Study Finds Combination Therapy Successful for Treating Depression in Injection Drug Users
- Bupropion, Counseling May Help Youth With ADHD Stop Smoking
- Substance Abuse and Mental Illness Care Providers Should Be Prepared for High Prevalence of Severe Co-Occurring Disorders

May 4, 2004 - **New Research Study in *JAMA* shows Adult Marijuana Abuse and Dependence Increased During 1990s.**
In an article that appeared in the May 5 issue of the *Journal of the American Medical Association* (JAMA), addiction researchers at the National Institutes of Health compared marijuana use in the U.S. adult population in 1991 - 1992 and 2001 -2002. They found that the number of people reporting use of the drug remained substantially the same in both time periods, but the prevalence of marijuana abuse or dependence increased markedly. This new study showed that increases in the prevalence of abuse or dependence were most notable among young African-American men and women and young Hispanic men.

July 9, 2004 - **NIDA NewsScan #31 - Funding News**

- NIH Roadmap: Re-Engineering the Way Science Is Done
- Molecular Libraries Screening Centers Network (RFA-RM-04-017)
- Epidemiology of Drug Abuse (PA-04-100)
- Collaborative Clinical Trials in Drug Abuse (PAR-04-073)
- Research on Rural Mental Health and Drug Abuse Disorders (PA-04-061)
- Psychopharmacology of Widely Available Psychoactive Natural Products (PA-04-084)
- Enhancing State Capacity To Foster Adoption of Science-Based Practices

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(RFA-DA-05-002)

- Prescription Drug Abuse (PA-04-110)

July 19, 2004 - **NIDA NewsScan #32**

- Study Sheds New Light on Mechanism Behind Stimulant Medication for ADHD
- PET Study Highlights Mechanism Involved in Nicotine Craving
- Antiseizure Drug May Help Treat Cocaine Addiction
- Cocaine Craving Activates Different Brain Regions in Women
- Adolescent, Adult Rats Respond Differently to Nicotine and Nicotine-Related Environments

Articles of Interest

July 19, 2004, *Reuters* -- "Stronger Pot May Make Reefer Madness Real, U.S. Fears" — Interview with Nora D. Volkow, M.D.

July 22, 2004, *Nature* -- "A Hard Habit to Break" — Interview with Nora D. Volkow, M.D.

July 25, 2004, The Baltimore Sun -- "Ecstasy Research Looks for Benefits"—Interview with Glen R. Hanson Ph.D., D.D.S.

Educational Activities

DEA Museum Foundation Exhibit at One Times Square

Target America: Opening Eyes to the Damage Drugs Cause

The National Institute on Drug Abuse (NIDA) is joining several Federal and private agencies in a museum exhibit coordinated by the Drug Enforcement Administration (DEA) Museum Foundation. The exhibit, *Target America: Opening Eyes to the Damage Drugs Cause*, is housed on the first three floors of a prime location in New York City—One Times Square—from September 14, 2004 through February 1, 2005. NIDA's expertise in The *Science of Addiction* will be featured in several panels on Floor 2 of the exhibit. In addition, NIDA has developed information and graphics for a large photomural wall and a large "Memorial Wall" to individuals—famous and ordinary—who have lost their lives to drug abuse or addiction. Other agencies involved in the project include DEA, the Office of National Drug Control Policy, the Substance Abuse and Mental Health Services Administration, the State Department's Bureau of International Narcotics and Law Enforcement Affairs, the National Guard, the Association of Retired Narcotics Agents, Pokemon, and Hewlett-Packard. The entrance floor of the exhibit will feature DEA-related topics such as *Production* and *Trafficking*. Although the exhibit is strongly geared toward students, large attendance by the general public is expected because of the location. The exhibit is free, and open from 9:00 a.m. to 8:00 p.m. throughout the week.

New "Brain Power!"

This fall, NIDA will be launching the second in the Brain Power! Junior Scientists education series. The new Brain Power! was developed for use by kindergarten and first grade students. It consists of a series of five lessons that include an introduction to science, how students can become scientists, an introduction to the brain, how to keep your brain healthy and how to protect your brain. Each lesson includes classroom activities with suggestions for discussion, assessment, and extensions, as well as resources for teachers and students. Also included is a parent newsletter in both English and Spanish that can be copied and sent home. The materials will be distributed free to grades K-1 across the country.

Award for "Reconstructors"

The NIDA funded science education project "Reconstructors" received a "Best at the Conference" award at the International EdMedia Conference. This project developed an interactive and entertaining web site for middle school children on opiates. Leslie Miller, Ph.D., the PI on the project, is currently developing a similar site on club drugs.

Data and Safety Monitoring Board Guidelines

To assist grantees conducting or planning to conduct clinical trials that require monitoring by a Data and Safety Monitoring Board (DSMB), NIDA developed guidelines to establish and operate a DSMB, in accordance with NIH requirements. The purpose of the DSMB is to monitor the safety of participants and the validity of results of clinical trials that involve multiple data collection sites, large sample sizes,

or pose significant risk to the participants. Grant applicants must submit a general description of the DSMB plan as part of the research grant application. The Scientific Review Group will review the DSMB plan as part of the initial DSM plan and any comments or concerns will be included in the summary statement. A detailed DSM plan that includes a DSMB plan must be submitted to and approved by NIDA before the trial begins. The responsibility for compliance with the DSM plan rests with the grant recipient. The guidelines provide an overview of the NIH policies for data and safety monitoring, the charge of the DSMB, and methods to establish and operate a DSMB.

Several CTN protocol-training activities took place during this period for the new protocols prior to implementation.

NIDA Staff Interviews

Dr. Frank Vocci, Director, Division of Pharmacotherapies and Medical Consequences of Drug Abuse (DPMCDA) conducted an interview with Helen Pearson of Nature Magazine on May 21, 2004.

Dr. Frank Vocci conducted an interview with Marc Kaufmann of the Washington Post on June 10, 2004 regarding abuse liability of opiate analgesics.

Dr. Frank Vocci conducted a telephone interview with David Hamilton at the Wall Street Journal's San Francisco Bureau on June 25, 2004. The interview was regarding abuse resistant painkillers.

Dr. Frank Vocci conducted a telephone interview with Vince Beiser of the LA Times on June 29, 2004 regarding Ibogaine.

Dr. Frank Vocci conducted an interview with Ian Daley on July 6, 2004 regarding pharmacological and immunological treatments for cocaine dependence.

Dr. Frank Vocci conducted an interview with Eddie Dean on July 8, 2004 regarding the nicotine vaccine and smoking cessation treatments.

Dr. Frank Vocci was interviewed by Eric Hand of the Arkansas Democrat-Gazette on July 20, 2004 regarding the development of monoclonal antibodies for the treatment of PCP overdose and methamphetamine overdose.

Dr. Frank Vocci conducted a telephone interview with Christopher Whyndham of the Wall Street Journal on July 29, 2004 regarding development of vaccines for nicotine dependence and cocaine dependence.

Dr. Frank Vocci conducted an interview with Malcolm Ritter of the Associated Press on July 29, 2004 regarding medications for the treatment of cocaine dependence.

On July 31, 2004, Dr. Ro Nemeth-Coslett was interviewed by ABC World News for an upcoming story on the entertainment gaming industry's role in health.

Conferences/Exhibits

National Association of State Alcohol and Drug Abuse Directors/National Prevention Network	June 5-9, 2004
Complexities of Co-Occurring Conditions	June 23-24, 2004
American Nurses Association Biennial Convention	June 25-29, 2004
National Congress of Parents and Teachers Annual Convention	June 26-28, 2004
Association on Higher Education and Disability Annual Conference	July 13-17, 2004
American Psychological Association Annual Convention	July 28-August 1, 2004
National Prevention Network Prevention Research Conference	August 22-24, 2004
Latino Behavioral Health Institute 10th Annual Conference	September 21-23, 2004
NIDA Blending Clinical Practice and Research	September 27-28, 2004
National Association of Alcoholism and Drug Abuse Counselors	October 6-9, 2004

American Academy of Pediatrics National Conference and Exhibition	October 9-13, 2004
American Association for the Treatment of Opioid Dependence Conference	October 17-20, 2004
American Academy of Child and Adolescent Psychiatry	October 19-24, 2004
Society for the Advancement of Chicanos and Native Americans	October 21-24, 2004
Society for Neuroscience 34th Annual Meeting	October 23-28, 2004
American Public Health Association 134th Annual Meeting and Exposition	November 6-10, 2004

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Planned Meetings

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

The National Institute on Drug Abuse is organizing a research planning meeting entitled **Drug Abuse: A Workshop on Behavioral and Economic Research**. The meeting will be held October 18-20, 2004 at the Hyatt Regency Hotel in Bethesda Maryland. The conference will explore the research potential of macro-environmental, behavior economic and neuro-economic approaches to drug abuse. Meyer Glantz, Ph.D. and Yonette Thomas, Ph.D. will chair the meeting that is being organized by NIDA staff.

The National Institute on Drug Abuse (NIDA) will be sponsoring a mini-convention on **Frontiers in Addiction Research** on Friday, October 22, 2004. The mini-convention, organized by Drs. Rita Liu, David Shurtleff and Cathrine Sasek, will be held in conjunction with this year's **Society for Neuroscience (SfN) Annual meeting** at the San Diego Convention Center, San Diego, California. NIDA will bring together an exciting group of participants from a wide array of scientific disciplines to share advances and discuss future directions in the neuroscience of drug abuse and related areas.

Dr. Steven Grant is participating in the organization of a meeting of the economics of substance abuse, tentatively entitled **Drug Abuse: A Workshop on Behavioral and Economic Research** to be held in Bethesda, MD in October 2004. Dr. Grant will be chairing a session on neuroeconomics.

Dr. Steven Grant participated in the organization of and will be co-chairing a symposium entitled **Creative Directions in Imaging** at the NIDA mini-convention satellite meeting on Frontiers in Addiction Research prior the annual meeting of the Society for Neuroscience to be held in San Diego in October 2004.

Dr. Nora D. Volkow will make a presentation for the **NIH Medicine for the Public Lecture Series** on November 9, 2004. The lectures are held at the Masur Auditorium on the NIH Campus. The title of her lecture is "Addiction to Medications: What Are the Risks and Who is Vulnerable?"

On December 2-3, 2004, a meeting is planned by the Behavioral and Integrative Treatment Branch and the Services Research Branch entitled **Developing Efficacious Behavioral Therapies for Criminal Justice Involved Populations**. Drs. Cece McNamara, Lisa Onken, Melissa Racioppo, and Redonna Chandler are organizing the workshop. The purpose of the meeting is to bring together experts in behavioral treatment, criminology, and basic science to facilitate development of new treatments for drug abuse and dependence targeting criminal and juvenile justice-involved populations. Challenges and barriers to designing effective proposals within the constraints of protecting prisoners in research will be discussed.

Dr. Steven Grant will be chairing a symposium entitled **Predictors of Treatment Response and Relapse: Neurobiological Markers** at the annual meeting of the American College of Neuropsychopharmacology to be held in San Juan, Puerto Rico in December 2004.

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Dr. Steven Grant will be co-chairing a study group with Dr. Celeste Napier of Loyola University entitled **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 to be held in San Juan, Puerto Rico in December 2004.

Drs. Eve Reider and Elizabeth Robertson will host a two-day meeting on January 25 and 26, 2005 entitled **Youth with Multiple Problems: How They Got There and What to Do About It**. The meeting will be held at the Bethesda Marriott, Bethesda, MD.

Drs. Elizabeth Robertson and Eve Reider are working with Steven Hornberger of the Child Welfare League of America (CWLA) to plan a state of the science meeting entitled **Pathways To and From: Foster Care and Drug Abuse**. The meeting will take place in early winter.

National CTN Steering Committee Meetings are planned for the following dates and locations: September 29-30, 2004, Detroit, Michigan; February 7-9, 2005, San Francisco, California; and April 11-13, 2005, Raleigh-Durham, North Carolina.

The CTN Genetics Special Interest Group will hold a workshop on September 26, 2004, from 6:00-9:00 p.m. before the NIDA Blending Meeting in Detroit. The meeting will address 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? Are there ethical issues? What will CTPs do in genetics studies? How will CTPs be involved in decision-making? The meeting is open to all interested persons.

The CTN Data and Safety Monitoring Board will meet November 16-17, 2004 and March 10-11, 2005 in Rockville Maryland. The group will review the continuing progress of the CTN's protocols.

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Publications

NIDA Publications

Instituto Nacional Sobre el Abuso de Drogas Como Prevenir el Uso de Drogas en los Niños y los Adolescentes — Una guía con base científica para padres, educadores y líderes de la comunidad — Segunda Edición — Version Abreviada (Preventing Drug Use Among Children and Adolescents)
NIH Pub. No. 04-4214(Sp.)
This second edition of the "Red Book" includes updated principles, new questions, new program information, and expanded references and resources based on the latest findings from NIDA-funded prevention research. The 16 fundamental prevention principles, derived from research on effective prevention programs, are outlined. Discussions include key factors that place youth at risk for drug abuse, guidance for planning drug abuse prevention programs in the community, applying the prevention principles to programs, and describing the core elements of effective prevention programs.

A Collection of NIDA Articles That Address Research on Cocaine
NCADI NN0066
New collection features NIDA NOTES articles originally published from 1995 thru 2003. Includes titles such as "Cocaine's Effect on Blood Components May Be Linked to Heart Attack and Stroke," "Cocaine's Effects on Cerebral Blood Flow Differ Between Men and Women," "Cues for Cocaine and Normal Pleasures Activate Common Brain Sites," and "Coping Skills Help Patients Recognize and Resist the Urge to Use Cocaine."

Epidemiologic Trends in Drug Abuse, December 2003, Volume I
NIH Pub. No. 04-5364
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, December 2003, Volume II
NIH Pub. No. 04-5365
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.

Science & Practice Perspectives. Volume 2, Number 2
NIH Pub. No. 04-5356
NIDA's peer-reviewed journal for drug abuse researchers and treatment providers highlights ways in which dialogue between scientific investigators and clinical practitioners is improving drug abuse treatment and research. The Director's column in this issue calls attention to several NIDA initiatives to create links between the production of scientific knowledge and its application. The lead section focuses on buprenorphine, a newly FDA-approved medication for opioid addiction. Providers are made aware of how it works, its efficacy and safety profile, how it is used in withdrawal and maintenance treatment, and how patients should be selected, educated, and monitored during treatment. Other topics include a description of how Behavioral Couples Therapy is being used in the treatment of substance abuse, a description of a pioneer residential treatment program for parents and their children, and a report of a panel discussion featuring prevention researchers and representatives of community drug prevention coalitions.

Monitoring the Future National Results on Adolescent Drug Use

Overview of Key Findings 2003
NIH Pub. No. 04-5506
This publication provides a concise review of the findings of the Monitoring the Future Study and comparison of data from previous years.

National Survey Results from the Monitoring the Future 2003, Volume I: Secondary Students
NIH Pub. No. 04-5507
Reports on the prevalence of drug use among students in 8th-, 10th-, and 12th grades. Trends are analyzed to understand the changing drug abuse problem and to formulate appropriate prevention and treatment policies.

National Survey Results from the Monitoring the Future 2003, Volume II: College Students and Adults Ages 19-40
NIH Pub. No. 04-5508
Reviews trends in drug use by populations based on gender, college plans, regions of the country, population density, race/ethnicity, and parents' education. Trends are analyzed to understand the changing drug abuse problem and to formulate appropriate prevention and treatment policies.

Brain Power — Grades K-1
NIH Pub. No. 04-4945
Lesson modules designed to examine the effects of drugs on the brain. This curriculum lays the foundation for future scientific learning and substance abuse prevention efforts.

NIDA Notes

NIDA Notes, Volume 19 Issue 1
NIH Pub. No. 04-3478
In the Director's Column, Dr. Nora D. Volkow discusses NIDA's three-decade commitment to scientific research in drug abuse and addiction, as the Institute celebrates its 30th anniversary. Through its evolution to the world's foremost source of scientific knowledge on drug addiction, NIDA has built a basic science and research program that has produced, for example, discoveries on the brain and its molecular and neurochemical methods of communication, leading to new medications to treat drug abuse and other mental disorders. These and other research successes, initiatives, and partnerships are detailed in a 16-page insert commemorating the Institute's 30th anniversary.

The lead article examines the role of an acute dopamine surge in a part of the brain called the nucleus accumbens that suggests it may push an addicted individual to actively seek and take drugs. Research observations were made possible by use of a fast-scan cyclic voltammetry technique that measures dopamine levels hundreds of times faster than other techniques. Other Research Findings report:

- Cognitively impaired cocaine abusers derive less benefit and have higher dropout rates from cognitive-behavioral therapy than do nonimpaired abusers, challenging researchers to consider how to modify treatment for this population.
- African-American drug-using women in two tailored HIV risk prevention intervention groups reduced their risky behaviors even more than women who received the NIDA standard intervention.
- Smoking reduces levels of a key enzyme, MAO-B, throughout the body, findings that demonstrate that smoker's peripheral organs are harmed as much by cigarette smoke as are their lungs and heart.

Research News updates readers on the research studies and participant network of the National Drug Abuse Treatment Clinical Trials Network (CTN). Also noted is the availability of e-mail delivery of NIDA NOTES, whereby subscribers can receive the newsletter two weeks earlier than the print version. Bulletin Board items note the newest collaborative product of NIDA and the Community Anti-Drug Coalitions of America—Practical theorist 5: Marijuana Abuse: Using Science for an Effective Community Response. Also announced is the inauguration of the new Jacob F. Waletzky Memorial Award for Innovative Research in Drug Addiction and Alcoholism, awarded to Dr. Pier Piazza at the annual Society for Neuroscience conference in November 2003.

Advancing the Frontiers on Drug Abuse Research: NIDA Celebrates a Record Year of Achievement

NCADI #MS944
This special publication commemorates NIDA's 30th anniversary as the Federal focal point for research to increase knowledge about drug abuse, promote effective strategies to address the problem, and develop and manage a nationwide network of drug abuse prevention, treatment, and training programs. The booklet traces NIDA's 30 years of achievement in the following areas:

- assessing the Nation's drug abuse problems;
- addressing the health impacts of drug abuse;
- understanding the addicted brain and behavior; and
- preventing drug abuse and addiction

A second section of the commemorative booklet examines NIDA's efforts to develop effective addiction treatments. Research to develop new medications and to identify effective behavioral therapies is detailed. The booklet's final section explores research and practice partnerships that the Institute has had in place for several years that have helped it achieve its mission. Other partnerships are more recent. All partners will team with NIDA as it pursues the next generation of drug abuse and addiction research.

NIDA Notes, Volume 19 Issue 2
NIH Pub. No. 04-3478
In the Director's Column, Dr. Nora D. Volkow describes NIDA's Brain, Behavior, and Health Initiative, a multidisciplinary investigation of the neuroscience underlying addiction. This initiative will support research into the integrated roles of genes, proteins, brain cells, brain circuits and pathways, and behavior. We cannot understand the complex brain disease we call addiction without fully understanding the brain, Dr. Volkow says, and cannot understand the brain by looking at its parts in isolation. The Brain, Behavior, and Health Initiative provides the structure and strategy necessary to develop a comprehensive picture of biological and environmental factors that interact and lead to drug abuse, dependence, and addiction.

The lead article describes the development and initial testing of a synthetic compound that may be as effective as opioids for treatment of pain that results from injury to nerves. The compound, tested in rats, acts on cannabinoid receptors and does not cause the undesirable side effects—nausea, sedation, and depression—associated with other cannabinoids that have pain-relieving properties. Other Research Findings report:

- High school students, whose biology and chemistry curriculum teaches scientific concepts using drugs as examples, score higher on tests of their understanding of biology and chemistry than do students whose lessons did not use drug-related examples.
- Animal studies suggest that smoking is more addictive if it is begun during adolescence and that early initiation of smoking increases vulnerability to some effects of other addictive drugs.
- A new tool for evaluating a child's neurobehavioral disinhibition—a suite of emotional, behavioral, and cognitive characteristics—can predict the child's vulnerability to substance abuse later in life.
- Rats exposed before birth to MDMA (ecstasy) and tested at 21 days of age exhibit significant behavioral and neurochemical deficits compared with unexposed rats.

The Bulletin Board provides a brief discussion of NIDA-supported research into the prevalence of co-morbid substance abuse and major mental disorders among the more than 100,000 youths under age 18 in juvenile detention facilities. Among the sample of 1,829 youths ages 10 to 18, 10 percent of boys and 14 percent of girls reported both substance abuse and a mental disorder, such as major depression, psychosis, or a manic episode. The Tearoff article introduces readers to NIDA's newest Web Site, "NIDA for Teens: The Science Behind Drug Abuse." The Web site developers included a panel of teens who critiqued the content and design to help assure that the site will be appealing to their media-savvy peers.

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The CTN was featured in an article by Jamie Chamberlin in APA Online's *Monitor on Psychology* volume 35(5), May 2004. "Studying Substance Abuse in the Field" highlighted the work of Drs. James Sorensen (UCSF, California/Arizona Node), Kathleen Carroll (Yale University, New England Node), Dennis McCarty (Oregon Health Sciences University, Oregon Node), Maxine Stitzer (Johns Hopkins University, Mid-Atlantic Node), William Miller (University of New Mexico, Southwest Node), and Jose Szapocznik (University of Miami, Florida Node). The investigators state that work at the CTN is unique, covering a wide range of real-life issues in the treatment of drug abuse.

During the months May- July, six 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 - 0018 (Reducing HIV/STD Risk Behaviors: A Research Study for Men in Drug Abuse Treatment) was published and distributed throughout the CTN.

A patient recruitment brochure for CTN Protocol — 0019 (Reducing HIV/STD Risk Behaviors: A Research Study for Women in Drug Abuse Treatment) was published and distributed throughout the CTN.

A patient recruitment brochure for was translated into Spanish for CTN-0015 (Women's Treatment for Trauma and Substance Use Disorders) and was distributed throughout the Network.

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

Staff Highlights

Honors and Awards

Dr. Larry A. Seitz, DESPR, received a service award from the Society of Prevention Research at their annual meeting in Quebec City, Canada in May 2004. This award acknowledged Dr. Seitz's service to NIDA and his dedication and commitment to the field of Prevention Science.

Dr. Brandon Harvey, IRP, was appointed a research fellow in the Neural Protection and Regeneration Section, IRP.

Dr. Amy Newman, IRP, was invited by Dr. Michael Gottesman (DDIR-NIH) to participate in the NIH Focus Group on Succession Planning and Scientific Career Development.

Dr. Jonathan Katz, IRP, was appointed Guest Professor, Graduate School of Human Relations, Keio University, Tokyo, Japan, July 23 to August 6, 2004.

Staff Changes

Jag H. Khalsa, Ph.D. has been appointed as the Acting Chief of the Medical Consequences of Drug Abuse Branch within the newly formed Division of Pharmacotherapies and Medical Consequences of Drug Abuse.

Dr. Ivan Montoya was appointed Clinical Director, Medications Research & Medical Consequences of Abuse Grants in the Division of Pharmacotherapies & Medical Consequences of Drug Abuse. He will be overseeing all clinical grants in the DPMC for concurrence on DSM plans, need for a DSMB, and adverse event reporting.

Mary Ellen Michel, Ph.D. joined the CCTN as Deputy Director on June 28, 2004. Dr. Michel received her Ph.D. in neuroscience in the Anatomy Department at the University of Maryland School of Medicine. Her post-doctoral work was at NIH in NHLBI, NIA and NIDDK where she worked on blood brain barrier, cell/cell interactions and cell surface receptors including opiate receptors. In the mid-1980s she worked in industry and managed first a pre-clinical program and then a clinical trials program looking at the opiate antagonist nalmefene in a wide variety of indications, including opiate withdrawal and emergency treatment. Dr. Michel returned to NIH in 1986 and spent time as a review administrator, a program officer in the AIDS office, and on policy assignments in the Officer of the Director of NIH before directing a program in CNS trauma for NINDS. She has also worked in the National Center for Medical Rehabilitation Research at NICHD and in the Specialized Program for Translational Research in Acute Stroke at NINDS.

David S. Liu, M.D. has joined the CCTN as a Medical Officer. Dr. Liu previously worked for two years as a contractor in the CCTN office. He received his medical degree from the University of Maryland School of Medicine and an A.B. from Harvard University.

On July 1, 2004, **Mary Ann Stephens, Ph.D.** resigned from NIDA. Dr. Stephens was a program officer in the Behavioral and Integrative Treatment Branch, DPMCDA.

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Grantee Honors

Dr. James Alexander, University of Utah, received the American Psychological Association Division 43 Distinguished Contribution to Family Psychology Award on July 29, 2004.

Dr. Kathleen Brady, PI- CTN South Carolina Node, has been invited to join the Leadership Council of the Physicians and Lawyers for National Drug Policy: A Public Health Partnership (PLNDP).

Dr. Kathleen Brady was invited to present a Distinguished Psychiatrist Lecture at the 157th Annual Meeting of the American Psychiatric Association. Her lecture on *Stress and Relapse to Substance Use Disorders* was part of a collaborative session with the National Institute on Drug Abuse. Each year only a few psychiatrists are invited to make a presentation at the Annual Meeting, and it is one of the highest honors the APA can bestow a member.

Ronald Brady, CTP Director, Bridge Plaza Treatment and Rehabilitation Clinic in the CTN Long Island Node received the 2004 **J. Michael Morrison Award** at the CPDD meeting in recognition of his invention of the automated dispensing system for methadone that is currently used in 700 clinics throughout the United States and Europe. He has been perfecting the system since 1975 and has been active in addiction medicine treatment.

Dr. Twyla Hill, School of Social Work at Wichita State University, has been promoted to Associate Professor.

Dr. Kenneth Kendler served as the Fritz Redlich Fellow at the Center for the Advanced Study of the Behavioral Sciences in Stanford, CA, for the 2003-2004 academic year.

DHHS Secretary Tommy Thompson met with NIDA grantee **Dr. Andrei Kozlov** at St. Petersburg State University, St. Petersburg, Russia on July 3, 2004 to discuss AIDS research issues in Russia. Russia has the fastest growing AIDS epidemic in the world and drug abuse is its principal driver. AIDS in Russia has been designated as a major international security threat. Dr. Kozlov organized the meeting and participants included the Vice Rector and Deans of the University, the Directors of the NIH National Cancer Institute and the Fogarty International Center, and the Director of the NIAID Division of AIDS. The Secretary gave a lecture titled, "Medical Diplomacy" in which he praised the work of Dr. Kozlov and his colleagues. Follow-up meetings were held with Secretary Thompson at the U.S. Consul General in St. Petersburg.

Dr. Cathleen Lewandowski, School of Social Work at Wichita State University, has been promoted to Associate Professor.

At the annual meeting of the American Psychological Association (APA), July 28 - Aug 1, 2004, **Joshua A. Lile, Ph.D.** received the Outstanding Dissertation Award from APA's Division 28: Psychopharmacology and Substance Abuse. While on an individual predoctoral training grant with NIDA (F31 DA5934), he received his Ph.D. at Wake Forest University School of Medicine under the mentorship of Dr. Michael Nader. Dr. Lile is now on the faculty at University of Kentucky College of Medicine. The title of his award acceptance lecture was "The Reinforcing Efficacy of Psychostimulants in Rhesus Monkeys: The Role of Pharmacokinetics and Pharmacodynamics."

Dr. Rolf Loeber, University of Pittsburgh, has been appointed Distinguished Professor of Psychiatry in recognition of extraordinary levels of achievement in the

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field of psychiatry. This appointment constitutes the highest honor that the University can bestow on a member of the professoriate.

Dr. David Pollio, Associate Professor at the George Warren Brown School of Social Work, Washington University, received a joint appointment in Social Work and Psychiatry, Washington University, 2004, and the Pro Humanitate Literary Award, North American Resource Center for Child Welfare, 2004.

Dr. Elise Riley, Department of Medicine at the University of California, San Francisco, has been named a Scholar of the National Center on Minority Health and Health Disparities, 2004-2005.

Dr. Jeffrey Samet, Boston Medical Center, received an Excellence in Mentorship Award from the Association of Medical Education and Research in Substance Abuse (AMERSA), 2003.

Dr. Charles R. Schuster, PI of the CTN Great Lakes Regional Node, is this year's recipient of the Marian W. Fischman Memorial Award from Columbia University College of Physicians and Medicine. He received the award and delivered an invited lecture at a ceremony held on May 14, 2004, at Columbia University.

Dr. Arlene R. Stiffman, Director of the Comorbidity and Addictions Center at the George Warren Brown School of Social Work, Washington University, received the Outstanding Faculty Mentor Award for Doctoral Students, from the GWB School of Social Work, 2004 and the Outstanding Faculty Mentor, from the Washington University Graduate Student Senate, 2004.

Dr. Constance Weisner, Professor, University of California, San Francisco, and Senior Researcher, Kaiser Permanente, received several awards. She was re-appointed as a member of the International Expert Advisory Council on Drug Dependence and Alcohol Problems, World Health Organization, Geneva (term ending 2007). Dr. Weisner was also named as a member of the (a) Research Network on Mandated Community Treatment, funded by the John D. and Catherine T. MacArthur Foundation, 2004 - 2006; (b) MacArthur Foundation Research Network on Mental Health and the Law, 2003-2009.;(c) National Academy of Sciences, Institute of Medicine, Study on "Crossing the Quality Chasm: Adaptation to Mental Health and Addictive Disorders, 2004 - 2005; and (d) Scientific Panel for Research of the Butler Center for Research, Hazelden Treatment Center, Minnesota, 2004 - 2008.

Dr. Ken C. Winters has been promoted to Professor at the University of Minnesota.