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Research Findings - Basic Neuroscience Research

Stress-Induced Analgesia is Mediated by Endogenous Cannabinioids

Stress produces analgesia in a variety of paradigms, and opioids have long been understood to play a critical role in this process. However, NIDA grantees Andrea Hohmann, and Daniele Piomelli and their colleagues report that endogenous cannabinoids also play an important role in producing stress-induced analgesia, that is independent from the role of opioids. They found in rats that blockade of cannabinoid CB1 receptors in the periaqueductal gray (PAG) of the midbrain prevents non-opioid stress-induced analgesia. Further, increasing CB1 agonist availability in the PAG enhanced stress-induced analgesia in a CB1-receptor dependent manner. Their results indicate that cannabiniod release within the PAG mediates opioid-independent stress-induced analgesia. Hohmann, A.G., Suplita, R.L., Bolton, N.M., Neely, M.H., Fegley, D., Mangieri, R., Krey, J.F., Walker, J.M., Holmes, P.V., Crystal, J.D., Duranti, A., Tontini, A., Mor, M., Tarzia, G. and Piomelli, D. An Endocannabinoid Mechanism for Stress-induced Analgesia, Nature, 435(7045), pp. 1108-1112, 2005.

Anandamide Deactivation

The second step in the biological processing of the endogenous cannabinoid known as anandamide, following its uptake by neurons and glial cells, is hydrolysis by fatty-acid amide hydrolase (FAAH), an intracellular membrane-bound enzyme, whose crystal structure was determined in 2002. The action of this particular enzyme is believed to predominate among available lipases and amidases, since mice lacking the FAAH gene demonstrate a rate of brain hydrolytic activity about 1/100 that of wild-type mice. There is considerable research interest in studying the pharmacological and behavioral effects in animals lacking the FAAH gene, which include enhanced anandamide concentration in the brain, along with immobility, analgesia, catalepsy, and hypothermia. These latter properties are considered to be driven by CB1 receptor activation, since they are greatly reduced by prior administration of the CB1 inverse agonist SR 141716A. Recently, a pharmacological means of reducing the activity of FAAH has been studied by Dr. Danielle Piomelli and Dr. Georgio Tarzia and associates, namely, the introduction of a class of O-arylcarbamate inhibitors of FAAH activity. One of these compounds, URB 597, showed a potent IC50 inhibitory value of 5 nM toward FAAH enzymatic activity, which is supported by modeling data indicating a good fit of URB 597 into the binding cavity of FAAH. In wild-type rat brain membranes, URB 597 produced a time-dependent inhibition of tritiated anandamide hydrolysis, as well as a time-dependent increase in brain levels of anandamide, oleoylethanolamide, and palmitoylethanolamide. When the FAAH was absent, as in the FAAH null mouse, prior administration of URB 597 produced no significant increase in anandamide hydrolysis or anandamide brain levels. It also did not increase the hypothermia in FAAH null mice, produced by anandamide, and did not affect feeding behavior (satiety) in FAAH null mice, a process normally regulated by oleoylethanolamide. In the mouse intestine, the absence or presence of FAAH was not affected by URB 597 in terms of anandamide hydrolysis, but anandamide levels did not increase in the FAAH null mouse, suggesting that other enzymes may serve to regulate anandamide in the intestine, besides FAAH. The overall conclusion of this work is that synthetic inhibitors such as URB 597 can be shown to pharmacologically inhibit the action of FAAH, which is an enzyme of prime importance in the CNS for deactivating anandamide. Fegley, D., Gaetani, S., Duranti, A., Tontini, A., Mor, M., Tarzia, G. and Piomelli, D. JPET, 313(1), pp. 352-358, 2005.

Opioid Actions on Neuroimmune Processes

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In Memoriam

Chemokines (the main site of HIV action in cells) and their receptors have been implicated in the pathogenesis of neuroAIDS. NIDA supported investigators have observed that morphine regulates the expression of several key chemokine systems. Some are down regulated while others are upregulated. This indicates reciprocal actions of morphine on neuroimmune systems and may be very important in demonstrating how opiates and other drugs influence the course and action of HIV infections and neurotoxicity. Specifically, the effects of morphine on the gene expression of beta chemokines and their receptors by primary normal human astrocytes (NHA) were studied. The results show that NHA treated with morphine showed significant down regulation of the gene expression of beta chemokines, MCP-1, and MIP-1 beta, while reciprocally upregulating the expression of their specific receptors, CCR2b, CCR3, and CCR5 as detected by real-time quantitative PCR. These morphine-induced effects on NHA cells were reversed by the opioid mu receptor antagonist, naloxone. Further results indicate that morphine-induced effects are mediated via the modulation of MAPK and CREB signaling pathways. These results support the hypothesis that opiates act as co-factors in the neuropathogenesis of HIV infection. Mahajan, S.D., Schwartz, S.A., Aalinkeel, R.V., Chawda, R.P., Sykes, D.E. and Nair, M.P.N. Morphine Modulates Chemokine Gene Regulation in Normal Human Astrocytes. Clinical Immunology, 115, pp. 323-332, 2005.

The Conformation, Location, and Dynamic Properties of the Endocannabinoid Ligand Anandamide in a Membrane Bilayer

The endogenous cannabinoid ligand anandamide is biosynthesized from membrane phospholipid precursors and is believed to reach its sites of action on the CB1 and CB2 receptors through fast lateral diffusion within the cell membrane. To gain a better insight on the stereochemical features of its association with the cell membrane and its interaction with the cannabinoid receptors, the conformation, location, and dynamic properties were studied in a dipalmitoyl-phosphatidylcholine multilamellar model membrane bilayer system. By exploiting the bilayer lattice as an internal three-dimensional reference grid, the conformation and location of anandamide were determined by measuring selected inter- and intra-molecular distances between strategically introduced isotopic labels using rotational echo double resonance (REDOR) NMR method. A molecular model was proposed to represent the structural features of the anandamide/lipid system and was subsequently used in calculating the multi-spin dephasing curves. Results demonstrate that anandamide adopts an extended conformation within the membrane with its headgroup at the level of the phospholipid polar group and its terminal methyl group near the bilayer center. Parallel static 2H-NMR experiments further confirmed these findings and provided evidence that anandamide has dynamic properties similar to those of the membrane phospholipids and produces no perturbation to the bilayer. The results are congruent with a hypothesis that anandamide approaches its binding site by laterally diffusing within one membrane leaflet in an extended conformation and interacts with a hydrophobic groove formed by helices 3 and 6 of CB1 while its terminal carbon is closely positioned to a key cysteine residue in helix 6 leading to receptor activation. Tian, X., Guo, J., Yao, F., Yang, D.P. and Makriyannis, A. The Conformation, Location, and Dynamic Properties of the Endocannabinoid Ligand Anandamide in a Membrane Bilayer. Journal of Biological Chemistry, 280, pp. 29788-29795, 2005.

Pharmacological Properties of JDTic: A Novel _-Opioid Receptor Antagonist

NIDA investigators, in a recent study, have described the pharmacological properties of a novel kappa opioid receptor antagonist, (3R)-7-Hydroxy-N-{(1S)-1-{[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl] methyl}-2-methylpropyl}-1,2,3,4-tetrahydro-3-isoquinoline-carboxamide (JDTic), JDTic is the first potent _-selective opioid receptor antagonist, not derived from an opiate class of compounds. In the mouse tail-flick test, JDTic blocked antinociceptive (analgesic) activity for up to two weeks. When JDTic was administered either before the selective KOP (_)-opioid receptor agonist, enadoline, it blocked the analgesic properties of enalodine. These and other results reprted by this research team suggest that JDTic is a potent long- and orally acting selective _-opioid antagonist. Carroll, I., Thomas, J.B., Dykstra, L.A., Granger, A.L., Allen, R.M., Howard, J.L., Pollard, G.T., Aceto, M.D. and Harris, L.S. Pharmacological Properties of JDTic: A Novel _-opioid Receptor Antagonist. European Journal of Pharmacology, 501, pp. 111-119, 2004.

Flavonoid Glycosides and Cannabinoids from the Pollen of Cannabis sativa L

Chemical investigation of the pollen grain collected from male plants of Cannabis sativa L. resulted in the isolation for the first time of two flavanol glycosides from the methanol extract, and the identification of 16 cannabinoids in the hexane extract. The

two glycosides were identified as kaempferol 3-O-sophoroside and quercetin 3-o-sophoroside by spectroscopic methods including high field two-dimensional NMR experiments. The characterization of each cannabinoid was performed by GC-FID and GC-MS analyses and by comparison with both available reference cannbinoids and reported data. The identified cannabinoids were delta-9-tetrahydrocannabinol, cannabidivarin, cannabicitran, delta-9-tetrahydrocannabivarin, cannabicyclol, cannabidiol, cannabichromene, delta-9-tetrahydrocannabiorcol, cannabigerol, cannabinol, dihydrocannabinol, cannabielsoin, 6a,7-10a-trihydroxytetrahydrocannabinol, 9,10-epoxycannabitriol, 10-O-ethylcannabitriol, and 7,8-dehydro-10-O-ethylcannabitriol. These results demonstrate a diverse and large number of cannabinoids are found in *Cannabis sativa*. Research is needed to further characterize these newly discovered cannabinoids. Ross, S.A., ElSohly, M.A., Sultana, G.N.N., Mehmedic, Z., Hossain, C.F. and Chandra, S. Flavonoid Glycosides and Cannabinoids from the Pollen of *Cannabis sativa* L. Phytochemical Analysis, 16(1), pp. 45-48, 2005.

Cocaine and Development

Cocaine use during pregnancy is associated with neurobehavioral problems in school-aged children that implicate alterations in attentional processes, potentially due to impairments in the noradrenergic system. In a recent study, NIDA supported researchers report a direct, disruptive effect of cocaine on noradrenergic neurons that may provide a neurobiological basis for changes in attentional function observed, in clinical and pre-clinical investigations, in offspring exposed to cocaine in utero. In this study, rats were administered cocaine in a physiologically relevant dose during critical phases of gestation. The locus coeruleus, a brain region, was analyzed for neurite outgrowth characteristics. Results showed that cocaine inhibited locus coeruleus neurite outgrowth and development and female offspring appeared most vulnerable to such effects. Snow, D.S., Carman, H.M., Smith, J.D., Booze, R.M., Welch, M.A. and Mactutus, C.F. Cocaine-induced Inhibition of Process Outgrowth in Locus Coeruleus Neurons: Role of Gestational Exposure Period and Offspring Sex. International Journal of Developmental Neuroscience, 22(5), pp. 297-308, 2004.

THC Systems and Pain

Pain, a critical component of host defense, is one hallmark of the inflammatory response. These investigators hypothesized that pain might be exacerbated by proinflammatory chemokines. To test this hypothesis, CCR1 was cotransfected into human embryonic kidney (HEK)293 cells together with transient receptor potential vanilloid 1 (TRPV1), a cation channel required for certain types of thermal hyperalgesia. In these cells, capsaicin and anandamide induced Ca2 influx mediated by TRPV1. When CCR1:TRPV1 HEK293 cells were pretreated with proinflammatory chemokine C CL3, the sensitivity of TRPV1, as indicated by the Ca2 influx, was increased 3-fold. RT-PCR analysis showed that a spectrum of chemokine and cytokine receptors is expressed in rat dorsal root ganglia (DRG). Immunohistochemical staining of DRG showed that CCR1 is coexpressed with TRPV1 in >85% of small-diameter neurons. CCR1 on DRG neurons was functional, as demonstrated by CCL3-induced Ca2 ion influx and PKC activation. Pretreatment with CCL3 enhanced the response of DRG neurons to capsaicin or anandamide. This sensitization was inhibited by pertussis toxin, U73122, or chelerythrine chloride, inhibitors of Gi-protein, phospholipase C, and protein kinase C, respectively. Intraplantar injection of mice with CCL3 decreased their hot-plate response latency. That a proinflammatory chemokine, by interacting with its receptor on small-diameter neurons, sensitizes TRPV1 reveals a previously undescribed mechanism of receptor cross-sensitization that may contribute to hyperalgesia during inflammation. Zhang, N., Inan, S., Cowan, A., Sun, R., Wang, J.M., Rogers, T.J., Caterina, M., Oppenheim, J.J. A Proinflammatory Chemokine, CCL3, Sensitizes the Heat- and Capsaicingated Ion Channel TRPV1, Proceedings of the National Academy of Sciences, 102(19), p. 7050, 2005.

Antidepressants Attenuate Dopamine Signals and Enhance Serotonin Signals Due to the Reuptake, Accumulation and Co-Release of Serotonin and Dopamine at Dopamine Terminals

The brain's striatum receives and is rich in dopamine and serotonin neurotransmitters. After neurotransmitter release, neurotransmitter transporters take up, at their respective nerve terminals, dopamine (DA) and serotonin (5-hydroxytryptamine, 5-HT). DA is taken up by its transporters (DATs), which are expressed at the highest density in the striatum. There are far fewer serotonin transporters (SERTs) in the striatum. Although DA nerve terminals do not express SERT, they have some affinity for serotonin. Serotonin and DA terminals are often

located next to each other, but they do not normally overlap, and this anatomy provides a physical basis for the interaction of these two neurotransmitters. Recent work by Dr. Dani and his group showed, that after treatment with an anti-depressant, which inhibits SERT, DATs take up the serotonin and store it along with DA in the dopaminergic terminals. Co-release of these two neurotransmitters then occurs upon stimulation of these DA neurons. As SERT is inhibited by anti-depressants, higher concentrations of 5-HT enter into DA terminals via the extremely dense striatal DAT-mediated reuptake. As a result of this and other mechanisms there is a prolonged enhancement of the serotonin and a reduced DA signal. A consistent, parallel recording of small spontaneous signals of both 5-HT and DA indicated a co-release of these two transmitters. In addition, application of fluoxetine, an anti-depressant and DAT inhibitor, blocked the reuptake, accumulation and co-release of 5-HT in DA terminals, suggesting these were DAT-mediated events. These investigators plan to extend these studies and determine if DAT function is altered by pre-exposure to its blocking drugs. Zhou, F.M., Liang, Y., Salas, R., Zhang, L., De Biasi, M. and Dani, J.A. Corelease of Dopamine and Serotonin from Striatal Dopamine Terminals, Neuron, 46(1), pp. 65-74, 2005.

Genes Tell About Nicotine Associated Reward, Tolerance and Sensitization

Although eleven neuronal acetylcholine (ACh) receptor subunits with distinct functional properties and pharmacological characteristics have been identified in humans, until recently the identity of nicotinic receptor subtypes sufficient to elicit both the acute and chronic effects of nicotine dependence was unknown. Dr. Henry A. Lester's lab engineered mutant mice that genetically over-express alpha4 nicotinic subunits containing a single point mutation, Leu9' --> Ala9' in the pore-forming M2 domain, rendering alpha 4 receptor subunits hypersensitive to nicotine. With this genetic "knock-in" model, selective activation of alpha 4 nicotinic ACh receptors with ultra low doses of agonist recapitulated nicotine effects thought to be important in dependence, including reinforcement in response to acute nicotine administration, as well as tolerance and sensitization elicited by chronic nicotine administration. These data indicate that activation of alpha 4 receptors would be sufficient for nicotine-induced reward, tolerance, and sensitization. Genetic studies have revealed the existence of polymorphisms in genes encoding neuronal AChR alpha4 and beta2 subunits. Dr. Lester's report points to a coordinated study of polymorphisms in nAChR genes, smoking behavior, and functional characterization of mutated receptors that will shed light on our understanding of the roles of polymorphisms, and the role of the alpha 4 AChR subunit in the susceptibility to addiction. Tapper, A., McKinney, S., Nashmi, R., Schwarz, J., Deshpande, P., Labarca, C., Whiteaker, P., Collins, A. and Lester, H. Nicotine Action on _4* Receptors: Sufficient for Reward, Tolerance and Sensitization, Science, 306, pp. 1029-1032, 2004.

Hallucinogens of Three Types Increase Extracellular Glutamate in the Prefrontal Cortex

In this *in vivo* study, the indoleamine hallucinogen LSD increased glutamate efflux in rat prefrontal cortex (PFC). The dose of LSD was identical to that used in drug discrimination stimulus training, and produced maximal LSD-appropriate responding in rats. The effects of LSD were abolished by the selective 5-HT_{2A} antagonist M100907. The 5-$HT_{2A/C}$ agonist DOM, which is a phenethylamine hallucinogen, also increased glutamate efflux in rat PFC at the relevant dose. It was previously reported that phencyclidine (PCP) and ketamine also increase glutamate efflux in the PFC, though these compounds act as antagonists at the NMDA receptor. Thus, the present study provides evidence, in support of the hypothesis first presented by Aghajanian and Marek on electrophysiological grounds, that an enhanced release of glutamate is a mechanism common to indoleamine, phenethylamine, and glutamatergic hallucinogens. Muschamp, J.W., Regina, M.J., Hull, E.M., Winter, J.C. and Rabin, R.A. Lysergic Acid Diethylamide and [-]-2,5-Dimethoxy-4-methylamphetamine Increase Extracellular Glutamate in Rat Prefrontal Cortex. Brain Research, 1023, pp. 134-140, 2004.

Methamphetamine Damage to Dopamine Nerve Endings May be Due, in Part, to

Microglia are the primary immune defense cells in the brain. They safeguard and support neuronal functions. Nevertheless, excessive microglial activation can cause microglia to harm neurons. Donald M. Kuhn's group recently demonstrated that microglia, activated by methamphetamine (meth), may contribute to meth's characteristic neurotoxicity to dopamine-containing neuron terminals. They found, in mice, that: (1) Meth activates microglia in a dose-related manner and along a time

course that is coincident with damage to dopamine (DA) nerve endings, (2) Low ambient temperature prevents both the neurotoxicity and the microglial activation; (3) The microglial response to meth and the damage to DA nerve endings both occur in the striatum; (4) Drugs that are not characteristically neurotoxic (e.g., cocaine) do not mimic the effect of methamphetamine on microglia; (5) Numerous genes linked to microglia are activated within hours of meth administration, suggesting that microglial activation occurs early in the meth toxic cascade. Thomas, D.M., Francescutti-Verbeem, D.M., Liu, X. and Kuhn, D.M. Identification of Differentially Regulated Transcripts in Mouse Striatum following Methamphetamine Treatment - an Oligonucleotide Microarray Approach. Journal of Neurochemistry, 88, pp. 380-393, 2004. It was separately reported that other DA neurotoxic drugs in mice (e.g., MDMA) also produce the microglial activation. Thomas, D.M., Dowgiert, J., Geddes, T.J., Francescutti-Verbeem, D., Liu, X. and Kuhn, D.M. Microglial Activation Is a Pharmacologically Specific Marker for the Neurotoxic Amphetamines. Neuroscience Letters, 367, pp. 349-354, 2004. Kuhn and his colleagues also demonstrated that a low dosage meth regimen that makes mice tolerant to meth neurotoxicity attenuates meth-induced microglial activation. Thomas, D.M. and Kuhn, D.M. Attenuated Microglial Activation Mediates Tolerance to the Neurotoxic Effects of Methamphetamine. Journal of Neurochemistry, 92, pp. 790-797, 2005. Finally, since microglia are known to produce many of the reactive chemicals (e.g., nitric oxide, superoxide, cytokines) that mediate the neurotoxicity of the amphetamines, their activation could represent an early and essential event in the neurotoxic cascade associated with high-dose amphetamine intoxication. Thomas, D.M., Walker, P.D., Benjamins, J.A., Geddes, T.J. and Kuhn, D.M. Methamphetamine Neurotoxicity in Dopamine Nerve Endings of the Striatum Is Associated with Microglial Activation. Journal of Pharmacology and Experimental Therapeutics, 311, pp. 1-7, 2004.

Separate Dopamine Transients In The Nucleus Accumbens Are Associated With Conditioning and With the Pharmacological Effects of Cocaine

Cocaine acts as a reinforcer through its pharmacological effects on central monoaminergic systems and its administration results in the accumulation of dopamine in the nucleus accumbens. Carelli and Wightman, using fast-scan cyclic voltammetry to rapidly monitor changing dopamine signals in animals that self-administer cocaine and in those that receive it non-contingently, show that two separate dopamine signals occur. Consistent, time-locked dopamine transients occurred about 1.5 sec after each self-administered dose of cocaine, and this signal was associated with the drug-associated cues. No pharmacological effect of cocaine was observed within 10 seconds of its administration in animals given the drug non-contingently. Instead, the pharmacological effects of cocaine were observed about 40 seconds after cocaine delivery in both groups and dopamine remained elevated for at least 5 minutes afterward. The data show that this pharmacological action of cocaine occurs for an extended period of time following either contingent or non-contingent administration of the drug and that this signal is distinct from those dopamine transients that are time-locked to each lever-press in self-administering animals. Stuber, G.D., Roitman, M.F., Phillips, P.E.M., Carelli, R.M. and Wightman, R.M. Rapid Dopamine Signaling in the Nucleus Accumbens During Contingent and Noncontingent Cocaine Administration, Neuropsychopharmacology, 30, pp. 853-863, 2005.

Morphine Side Effects Are Dramatically Attenuated in Beta-Arrestin-2

Morphine is a potent analgesic, yet, like most opioid narcotics, its unwanted side effects such as constipation and respiratory suppression limit its clinical utility. Pharmacological approaches taken to preserve the analgesic properties, while eliminating the untoward side effects, have met with very limited success. Dr. Laura Bohn and her research team provide evidence that altering mu opioid receptor regulation may provide a novel approach to discriminate morphine's beneficial and deleterious effects *in vivo*. They have previously reported that mice lacking the G protein-coupled receptor regulatory protein, beta-arrestin-2 have enhanced and prolonged morphine analgesia with very little morphine tolerance. In a recent report they examine whether the side-effects of morphine treatment are also augmented in this animal model. Surprisingly, the genetic disruption of opioid receptor regulation, while enhancing and prolonging analgesia, dramatically attenuates the respiratory suppression and acute constipation caused by morphine. Raehal, K.M., Walker, J.K. and Bohn, L.M. Morphine Side Effects in {beta}-Arrestin-2 Knockout Mice, Journal of Pharmacology and Experimental Therapeutics (epub), 2005.

Dynorphin-Induced Allodynia is Prevented By a Spatial Knockout of NMDA Receptors in the Lumbar Spinal Cord Dorsal Horn (SCDH)

A single intrathecal (IT) injection of dynorphin A (1-17) (DYN) produces allodynia

(i.e., pain from stimuli that are not normally painful) in mice that is blocked by an NMDA receptor antagonist. To confirm and extend this observation, Dr. Charles Inturrisi and his colleagues used a spatial-temporal knockout (KO) of the NR1 subunits of the NMDA receptor (NR1 KO). Mechanical allodynia (von Frey), cold allodynia and thermal hyperalgesia were measured prior to and 2 to 5 days after IT DYN. DYN produced mechanical allodynia but not thermal hyperalgesia or cold allodynia in both the Control and the NR1 KO. However, while the allodynia was bilateral in the Controls, it was observed only with the contralateral paw in the NR1 KO mice. Thus, a spatial KO of the NMDA receptor, confined to one side of the SCDH, provided protection on that side from DYN-induced allodynia. These results demonstrate conclusively that postsynaptic NMDA receptors, at the level of the SCDH, are required for development of the mechanical allodynia induced by DYN. They may also offer some insight into the mechanism by which endogenous DYN mediates the allodynia that occurs following injury. South, S.M., Ohata, M., Hegarty, D., Xu, Q. and Inturrisi, C.E. Dynorphin-induced Allodynia is Prevented by a Spatial Knockout of NMDA Receptors in the Lumbar Spinal Cord Dorsal Horn, International Narcotics Research Conference, July 2005.

The Ror Receptor Tyrosine Kinase CAM-1 Is Required for ACR-16-Mediated

Communication among neurons in the nervous system is achieved by a neuron releasing a chemical substance or neurotransmitter that is detected by a neighboring neuron through a receptor. One of the major neurotransmitters in the nervous system is acetylcholine. After acetylcholine is released by a neuron, the acetylcholine signal is detected by either nicotinic or muscarinic receptors in neighboring neurons. The rewarding and addictive properties of tobacco are mediated initially by nicotine acting through nicotinic acetylcholine receptors in the central nervous system. The similarities of the neuromuscular junction of the worm, C. elegans to the vertebrate nicotinic cholinergic synapse together with the wonderful genetic tools available in c. elegans provide a powerful approach to understand the regulation of cholinergic synapses. Francis et al., identified two types of cholinergic receptors at the C. elegans neuromuscular junction by screening an RNAi library in which worms are placed into different wells and exposed to different type of RNAi. Each different RNAi type in the RNAi library selectively decreases the expression of a unique gene when taken up by the worm. The two types of cholinergic receptors that were identified are a levamisole sensitive receptor and nicotinic receptor, acr-16, which encodes a nicotinic AChR subunit homologous to the vertebrate _7 subunit. Worms lacking the *acr*-16 gene are uncoordinated and lack the fast synaptic current that is normally observed when nicotine is applied to the worm neuromuscular junction. Because worms lacking the receptor tyrosine kinase CAM-1 also show uncoordinated locomotion, Dr. Francis and his collegues tested the hypothesis that CAM-1 regulates nicotinic cholinergic transmission at the C. elegans neuromuscular junction. Dr. Francis and his colleagues show that the nicotinic receptors encoded by acr-16 are mislocalized at the neuromuscular junction and the ACR-16-dependent currents are greatly diminished. The effect of CAM-1 is selective because the response to levamisole and GABA were unaffected. In addition, the localization of vesicles and presynaptic proteins involved in the release of acetylcholine are altered in CAM-1 mutants. Dr. Francis suggests that CAM-1 acts to regulate or stabilize post-synaptic ACR-16 receptors and pre-release sites. Dr. Francis also suggest that CAM-1 action are not mediated by the kinase activity in the molecule but by other portion of the molecule because mutants lacking tyrosine kinase activity have little effect while worms completely lacking CAM-1 show the mutant phenotype. Francis, M.M., Evans, S.P., Jensen, M., Madsen, D.M., Mancuso, J., Norman, K.R. and Maricq, A.V., The Ror Receptor Tyrosine Kinase CAM-1 Is Required for ACR-16-Mediated Synaptic Transmission at the C. elegans Neuromuscular Junction, Neuron, 46(4), pp. 581-594, 2005.

Rapid Upregulation of Alpha7 Nicotinic Acetylcholine Receptors by Tyrosine Dephosphorylation

Although the tyrosine kinase activity of CAM-1 does not appear to regulate the C. elegans acr16, a nicotinic receptor homologous to the vertebrate alpha7 nicotinic receptor (see above), a recent report by Cho and his colleagues suggests that a tyrosine phosphatase, an enzyme that removes phosphate bonds from proteins regulates the expression of the rat alpha 7 nicotinic receptor. In oocytes expressing alpha 7 receptors, the size of currents elicited by nicotine was enhanced in the presence of genistein, an inhibitor of tyrosine kinase and decrease by pervandate, an inhibitor of tyrosine phosphatase activity. Genistein was found not to increase the size of the alpha7 receptor current by altering the time that the receptor-gated channel remains open nor alter the phosphorylation state of the alpha 7 nicotine receptor. Instead, the increased size of the currents elicited by nicotine in the presence of

genistein appears to be the consequence of increased insertion of alpha 7. Increased expression of the alpha 7 nicotinic receptor was shown to be increased following genistein treatment by immunobloting and alpha-bungarotoxin receptor binding. Tyrosine kinase inhibition also increased the expression of alpha7 nicotine receptors in the rat hippocampus suggesting that the increase observed is not an artifact of the Xenopus oocyte systems. The increased expression of the alpha 7 receptor by tyrosine kinase inhibition appears to be mediated by increased exocytosis of vesicles containing the alpha 7 receptor and not decreased endocytosis (turn over) of the alpha7 nicotinic receptor. A dominant negative mutant of dynamin that blocks endocytosis did not block the increased expression of the alpha7 nicotine receptor in oocytes but did block increased expression of the cystic fibrosis transmembrane conductance regulator as had previously been shown. Botulinum toxin that inhibits SNARE dependent exocytosis abrogated increased expression of the the alpha7 receptor. These results suggest that regulators of tyrosine phosphorylation may mediate the changes in number of nicotine receptors observed in animals treated with chronic nicotine. Cho, C.H., Song, W., Leitzell, K., Teo, E., Meleth, A.D., Quick, M.W. and Lester, R.A. Rapid Upregulation of alpha7 Nicotinic Acetylcholine Receptors by Tyrosine Dephosphorylation, Journal of Neuroscience, 25(14), pp. 3712-3723, 2005.

Proteome Analysis of Liver Cells Expressing a Full-Length Hepatitis C Virus (HCV) Replicon and Biopsy Specimens of Posttransplantation Liver From

Approximately 2 percent of the population in the United States is infected with hepatitis C, a blood borne virus. One of the leading causes of hepatitis C infection in the United States is intravenous drug abuse. 85% of those infected with hepatitis C will develop hepatic inflammation and fibrosis, cirrhosis, and hepatocellular carcinoma. Until recently, gene expression profiling that examines the expression of all the mRNAs in liver cells has been used to examine the host response and has been used to predict the clinical outcome of hepatitis C infection. One of the difficulties of this approach is that mRNA expression does not always correspond to the pattern of expression of proteins in the same cells. To overcome this problem, Dr. Michael Katze at the University of Washington in collaboration with Dr. Richard Smith at Pacific Northwest Laboratory have developed highly sensitive methods to assay all the proteins, the proteome, of a liver cell line, Huh-7.5 in the presence or absence of a replicating full length length HCV genome. In their analysis they observed changes in the level of more than 4,200 proteins in this cell line, including HCV replicon proteins, using multidimensional liquid chromatographic (LC) separations coupled to mass spectrometry. Dr. Katze and his colleagues were able to extend this analysis to liver biopsy material from HCV-infected patients. Dr. Katze and his colleagues identified 1500 proteins from less than 2 microgram of liver biopsy tissue. Analysis of both the huh-7 cells in the presence of the full HCV genome and liver biopsies of livers infected with HCV suggests that HCV alters lipid metabolism that may contribute to a state of oxidative stress in infected cells. The ability to analyze the proteome from limited amounts of biopsied liver samples is a technological breakthrough that permits evaluation of clinical significance of changes in protein expression levels associated with HCV infection. Jacobs, J.M., Diamond, D.L., Chan, E.Y., Gritsenko, M.A., Qian, W., Stastna, M., Baas, T., Camp, D.G., Carithers, R.L. Jr., Smith, R.D. and Katze, M.G. Proteome Analysis of Liver Cells Expressing a Full-length Hepatitis C Virus (HCV) Replicon and Biopsy Specimens of Posttransplantation Liver from HCV-infected Patients, Journal of Virology, 79(12), pp. 7558-7569, 2005.

A Mouse Model For Study of Systemic HIV-1 Infection, Antiviral Immune Responses, and Neuroinvasiveness

HIV readily infects humans and some non-human primates such as chimpanzees but species specific barriers prevent infection in other animals such as mice. A mouse model of HIV infection would have great utility because mice are cheaper than chimpanzees to maintain, the immune system is well characterized, and the mouse is a genetically tractable model system. Attempts so far to genetically engineer transgenic mice expressing key proteins involved in HIV infection such as CD4, CCR4, CXCR4, cyclin T1 have failed to produce a mouse host susceptible to HIV infection. Dr. Volsky and his colleagues have adopted a different strategy in which the HIV virus envelope is altered instead of altering the host to produce a mouse model of HIV infection. The gp80 envelope from ecotropic murine leukemia virus, a retrovirus that infects only rodents was used to replace coding region of gp120 in HIV-1 to produce a productive infection in mouse lymphocytes (white cells) but not in human lymphocytes. Dr. Volsky and his colleagues made two chimeric viruses, one based on a backbone of clade B NL4-3 (EcoHIV) and EcoNDK on a backbone of clade D NDK. Dr. Volsky and his colleagues then showed that intravenous inoculation of p24 EcoHIV, the genetically modified virus, infected nervous tissue, macrophages, spleen

cells, and lymphocytes. The EcoHIV virus infection was replication competent because co-culturing of infected spleen cells with uninfected spleen cells resulted in the uninfected spleen cells becoming infected. In response to infection with the EcoHIV virus the mice mount a humoral response by producing antibodies against tat and gag, two HIV proteins. Although Dr. Volsky and his colleagues did not observe an overt disease in the mice infected with the chimeric virus, mice infected with EcoNDK showed expression of the chimeric virus in the brain associated with increased host expression of IL-1, MCP-1, and STAT-1. Increased expression of IL-1, MCP-1, and STAT-1 are associated with HIV dementia. The successful development of chimeric mouse HIV virus model of HIV infection provides an extremely useful model to study HIV pathogenesis, and a model to develop vaccines and other therapeutics. The model also provides a means for investigator to analyze the interaction of drugs of abuse and HIV infection. Potash, M.J., Chao, W., Bentsman, G., Paris, N., Saini, M., Nitkiewicz, J., Belem, P., Sharer, L., Brooks, A.I. and Volsky, D.J. A Mouse Model for Study of Systemic HIV-1 Infection, Antiviral Immune Responses, and Neuroinvasiveness, Proceedings of the National Academy of Sciences, 102(10), pp. 3760-3765, 2005.

Shank Expression is Sufficient to Induce Functional Dendritic Spine Synapses in Aspiny Neurons

In the mammalian nervous system most excitatory inputs are received by glutamate receptors located on dendritic spines at post-synaptic densities. The post synaptic density is composed of glutamate receptors, PSD-95, shank, homer, guanylate associated kinase, and cystoskeletal protein. Shank proteins couple glutamate receptors to the cytoskeleton and intracellular signaling molecules. A key question is whether shank plays a role in the formation of dendritic spines and the maturation of excitatory synapses. This is an important question for drug abuse research because drugs of abuse alter the number of dendritic spines. Dr. Worley and his colleagues have now shown that shank is both necessary and sufficient to induce spine formation. Expression of RNAi against shank expression in hippocampal neurons reduces the number of dendritic spines. In aspiny cerebellar granule cells transfection of shank into these cells induces dendritic spines. To determine the function of different domains in the shank3 protein, Worley and his colleague deleted various portions of the shank gene and then transfected the mutant shank gene into aspiny cerebellar granule cells. Deletion of the PSD and homer domains in the shank gene prevented the shank protein from being targeted to dendrites, a necessary condition for forming dendritic spines. Worley and his colleagues also report that the ankyrin repeats in the SH3 region of shank and the cortactin binding site are required for spine maturation. The ankyrin repeats in the SH3 region of shank appears to regulate only spine enlargement while the cortacting-site regulates head enlargement and retraction of spines. The formation of spines induced by transfection of shank is associated with the recruitment of glutamate receptors and the formation of functional synapses. Glutamate receptor blockers reduced the number of spines induced by shank suggesting that the release of glutamate from presynaptic terminals is required for the formation of spines induced by shank. The results reported by Dr. Worley and colleagues suggest that shank3 and glutamate are essential for the maturation and formation of synapses. Roussignol, G., Ango, F., Stefano, R., Tu, J.C., Sala, C., Worley, P.F., Bockaert, J.L. and Fagni, L. Shank Expression is Sufficient to Induce Functional Dendritic Spine Synapses in Aspiny Neurons, Journal of Neuroscience, 25(14), pp. 3560 -3570, 2005.

Regulation of Dopaminergic Transmission and Cocaine Reward By The Clock Gene

Molecular mechanisms regulating circadian rhythms regulate responses to cocaine. Previous work conducted by Jay Hirsh and his colleagues in fruit flies has shown that mutations in Period, Clock, Cycle, and Doubletime genes, regulating circadian rhythms, also alters cocaine's sensitizing effects. Subsequent work by Abarca and his colleagues showed that mutant mice lacking the period 1 gene do not sensitize to repeated administration of cocaine whereas mutant mice lacking the period-2 gene become hyper-responsive to repeated cocaine injection. Similarly, knockout mice lacking the period 1 gene showed a complete lack of cocaine reward while mice lacking the period 2 gene showed enhanced cocaine reward. In the June 28 issue of the Proceeding of the National Academy Science, Dr. Eric Nestler's laboratory led by Dr. Colleen McClung in collaboration with Dr. Joseph Takashi and Dr. Frank White now establish the role of the circadian rhythm gene, Clock, in regulating cocaine reward behavior. Clock mutant mice show increased activity to novel environments and have elevated activity throughout the dark/light cycle, especially at the beginning of the light cycle and the beginning of the dark cycle. Increased locomotor activity was

associated with increased firing of dopamine neurons in the brain's ventral tegmental area (VTA) in clock mutant mice as compared to wild type mice. Although sensitization to cocaine is unaffected in the clock mutants, the clock mutants show increased place preference conditioning to lower doses of cocaine than wild type mice. This suggests that cocaine is more rewarding in clock mutant mice. The clock gene is expressed in dopamine neurons in the VTA that mediates the rewarding effects of cocaine. Because the clock gene is a transcription factor, the Nestler lab examined whether the clock mutant mice affected the expression of other genes. Clock mutants showed increased expression of tyrosine hydroxylase the rate-limiting enzyme for dopamine biosynthesis, and reduced expression of the beta-1 subunit of the GABAA receptor was observed. Decreased expression of the beta-1 subunit of the GABAA receptor which has previously been shown to inhibit the excitability of dopamine neurons may mediate the increased firing of dopamine neurons. Increased firing of dopamine VTA neurons in the clock mutant is also associated with decreased expression of a voltage-gated potassium channel. At the same time, the increase in the NR1 subunit of the AMPA receptor in VTA neurons of the clock mutants were observed by Dr. McClung and her colleagues. Previous work has suggested that upregulation of the NR1 subunit of the AMPA receptor increases the rewarding properties of cocaine. In conclusion, this work not only shows the role of circadian rhythm genes in regulating the effects of cocaine but also shows the power of fruit fly genetics to identify new pathways that mediate the effects of drugs of abuse in vertebrates. McClung, C.A., Sidiropoulou, K., Vitaterna, M., Takahashi, J.S., White, F.J., Cooper, D.C. and Nestler, E.J. Regulation of Dopaminergic Transmission and Cocaine Reward by the Clock Gene, Proceedings of the National Academy of Sciences, 102(26), pp. 9377-9381, 2005.

S-Nitrosylated GAPDH Initiates Apoptotic Cell Death by Nuclear Translocation Following Siah1 Binding

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is well known for its role in metabolizing glucose. More recently, work has shown that translocation of GAPDH to the nucleus is associated with cell death and cytotoxicity (degree to which a substance is poisonous to cells). Hara and his colleague now report the signaling mechanism by which GAPDH translocates to the nucleus and causes cell death. Hara and his colleague show that nitrosylation of GAPDH by nitric oxide synthase, an enzyme activated by stress, cause GAPDH to bind Siah1 (Sevenless in absentia homologue1), a ubiquitin E3 ligase and translocate to the nucleus. The binding of nitrosylated GAPDH to Siah1 decreases the rate of degredation of Siah1 in the nucleus, thereby increasing the amount and activity of Siah1 in the cell nucleus. The stabilization of Siah1 by GAPDH and increased activity cause increased ubiquination of nuclear proteins leading to increased degradation of nuclear proteins and cell death. To test the role of GAPDH in cell death, a macrophage cell lines was depleted of GAPDH using RNAi and stimulated with lipopolysacharide (LPS) that activates nitric oxide synthase. Depletion of GAPDH prevented cell death induced by LPS. Furthermore, Hara and his colleague's further show that depletion of GAPDH or Siah1 using RNAi prevents glutamate mediated cell death in cerebellar granule cells. Inhibitors of GAPDH nitrosylation by inhibitors of MAOB such as deprenyl not only have significant implications for the treatment of neurodegenerative diseases but also for treating the neurotoxic effects of MDMA and methamphetamine. Hara, M.R., Agrawal, N., Kim, S.F., Cascio, M.B., Fujimuro, M., Ozeki, Y., Takahashi, M., Cheah, J.H., Tankou, S.K., Hester, L.D., Ferris, C.D., Hayward, S.D., Snyder, S.H. and Sawa, A. S-nitrosylated GAPDH Initiates Apoptotic Cell Death by Nuclear Translocation Following Siah1 Binding, Nature Cell Biology, 7, pp. 665-674, 2005.

Regulation of Drug Reward by Cyclic-Amp Response Element-Binding Protein: Evidence For Two Functionally Distinct Subregions of the Ventral Tegmental Area

The cyclic-AMP response element (CRE) is present in the promoter region of cAMP-responsive genes. When the CRE binding protein (CREB) is activated by phosphorylation, it binds to the CRE and increases expression of those genes. Many groups have shown that CREB is activated in several brain regions following exposure to drugs of abuse. In this study, Olson et al., show that morphine upregulates CREB in the ventral tegmental area (VTA), a very important brain structure for drug abuse. More specifically, they went on to show that active CREB expressed in two different regions of the VTA produces opposite effects on drug reward. This is unusual since the VTA has traditionally been treated as a single structure. They found that these two sub-regions of the VTA contained differential proportions of two types of neurons, those that produce Gamma-Aminobutryic Acid (GABA) and those that produce dopamine. These differential cell populations may account for opposing responses

they observed in the two regions. Specifically, they found that in the sub-region containing predominantly dopamine cells, the induced CREB expression made a threshold dose of cocaine or morphine aversive, while they were rewarding when expressed in the sub-region containing fewer dopamine cells and more GABA cells. They further confirmed that the dopamine cells are projecting to the nucleus accumbens shell, which has been shown by others previously. These findings suggest that studies on addiction involving the VTA may need to consider sub-regions of the VTA since this study clearly shows differential responses to morphine as it relates to CREB activity. Olson, V.G., Zabetian, C.P., Bolanos, C.A., Edwards, S., Barrot, M., Eisch, A.J., Hughes, T., Self, D.W., Neve, R.L., and Nestler, E.J. Regulation of Drug Reward by cAMP Response Element-binding Protein: Evidence for Two Functionally Distinct Subregions of the Ventral Tegmental Area, Journal of Neuroscience, 25(23), pp. 5553-5562, 2005.

μ-Opioid Receptor and CREB Activation are Required for Nicotine Reward

Understanding the molecular and genetic mechanisms that underlie the addictive properties of nicotine is important for creating successful treatments for smoking cessation, but these mechanisms are currently poorly delineated. Dr. Blendy and her colleagues have recently found that exposure to an environment previously associated with rewarding properties of nicotine results in an increase of CREB phosphorylation similar to that seen following nicotine administration, and this response is absent in mu opioid receptor knock-out (MOR-/-) mice. Administration of a single dose of the mu opioid antagonist, naloxone, blocks both the conditioned molecular response (CREB phosphorylation) and the conditioned behavioral response (nicotine reward) in a place preference paradigm. In related experiments, this group also found that repeated nicotine administration results in increased expression of the mu opioid receptors. In mice with a mutated CREB gene, however, expression of the mu receptor is abrogated as well as the rewarding properties of nicotine. These data suggest that activation of both the endogenous opioid system and CREB are critical for the expression of conditioned nicotine reward. This effect may also be seen in other substances of abuse, but has yet to be examined. Walters, C.J., Cleck, J.N., Kuo, Y-C. and Blendy, J.A. Mu-opioid Receptor and CREB Activation are Required for Nicotine Reward, Neuron, 46, pp. 933-943, 2005.

Remote Control of Behavior Through Genetically Targeted Photostimulation of Neurons

Dr. Miesenbock and his colleagues have recently published the first use of genetically encoded phototriggers for defining the neuronal substrates of specific behaviors in invertebrates. The ionotropic purinoreceptor P2X2, not normally expressed in the fly, was ectopically expressed in circumscribed groups of neurons in the Drosophila CNS so that broad illumination of flies evoked action potentials only in genetically designated target cells. Illumination of "caged" agonists of the P2X2 receptor causes the agonist to be released and bind to the receptor, thereby acting as a phototrigger. Flies harboring the phototriggers in different sets of neurons responded to laser light with behaviors specific to the sites of phototrigger expression. Photostimulation of neurons in the giant fiber system elicited the characteristic escape behaviors of jumping, wing beating, and flight; photostimulation of dopaminergic neurons caused changes in locomotor activity and locomotor patterns. These responses reflected the direct optical activation of central neuronal targets rather than from confounding visual input. These experiments demonstrate that encodable phototriggers provide non-invasive control interfaces for studying the connectivity and dynamics of neural circuits, for assigning behavioral content to neurons and their activity patterns, and, potentially, for restoring information corrupted by injury or disease. The capacity to remote-control genetically delineated sets of neuronal targets promises to open many new possibilities for the analysis of neural circuits and the search for the cellular substrates of behavior. The strategy developed by Dr. Meisenbock and his colleagues for two systems of neurons and their associated behaviors, i.e., the Giant Fiber system and escape movements and the dopaminergic system and locomotion, can be extended immediately to screens of existing collections of enhancer trap lines (or mosaic offspring in which expression of the phototrigger is restricted to smaller subsets of neurons) and other behaviors. Examples include searches for the neuronal signals guiding different forms of movement, courtship, mating, aggression, feeding, grooming, learning, and sleep and wakefulness, as well as the neural symbols representing reward and punishment, expectation, and categories of generalization. Lima, S.Q. and Miesenbock, G. Remote Control of Behavior Through Genetically Targeted Photostimulation of Neurons, Cell, 121, pp. 141-152, 2005.

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

Research Findings - Basic Behavioral Research

Learned Inhibition of Cocaine Seeking

It has long been known that cues predictive of drug administration, "conditioned excitors," acquire conditioned incentive value through classical conditioning. Such cues can serve to motivate drug-seeking behavior and they are one source of drug craving in human drug abusers. Treatments aimed at reducing the incentive value of conditioned excitors through the use of extinction procedures have proved only modestly successful in reducing drug seeking in animal models and craving in humans. Additional treatments with proven efficacy could be useful in reducing the motivation for drugs among drug addicts. Recently published research by NIDA grantee Stanley Weiss has described a conditioned inhibition procedure that offers some hope of eventually being translated into effective drug abuse treatments. "Conditioned inhibitors," unlike excitors, predict the absence (or unavailability) of drug. In Weiss' study, rats were trained to self-administer cocaine by pressing a lever in the presence of a tone or a clicking sound. Once rats were responding reliably, a light was introduced along with the tone, (or the click, in a counterbalanced design), and in the presence of the light/tone compound, responding did not result in cocaine administration. That is, the light was trained as a conditioned inhibitor since it signaled the absence of an otherwise expected injection of cocaine. To evaluate its ability to inhibit responding, the light was then presented during test sessions with the drug-paired auditory stimulus (e.g., click) that had previously been established as a conditioned excitor. Whereas the click occasioned vigorous responding when presented alone, the simultaneous presentation of the light attenuated responding in the presence of the click. Thus, the animals had learned that the light predicted the absence of an otherwise expected drug administration and withheld responding when it was presented. These results suggest that conditioned inhibitors might effectively neutralize the stimuli (conditioned excitors) that occasion drug seeking. Moreover, by suppressing stimulus-elicited drug craving, a conditioned inhibitor could attenuate drug seeking and avert relapse. Kearns, D.N., Weiss, S.J., Schindler, C.W., and Panlilio, L.V. Conditioned Inhibition of Cocaine Seeking in Rats. Journal of Experimental Psychology: Animal Behavior Processes, 31, pp. 247-253, 2005.

Inhibition of Dopaminergic and Serotonergic Reuptake During Gestation Has a Variety of Effects on Maternal Behavior in the Rat

Psychostimulants, antidepressants, anti-anxiety medications, and some antipsychotics all inhibit reuptake of one or more of the catecholmine neurotransmitters. Dr. Josephine Johns previously showed that gestational exposure to cocaine alters several aspects of maternal behavior and oxytocin levels in the rat, but it was not known whether this effect was mediated by cocaine-induced inhibition of catecholamine reuptake, or which neurotransmitters were involved. In this study, she systematically tested specific reuptake blockers of dopamine and serotonin during gestation, alone or in combination, to determine the effect of long-term reuptake inhibition on maternal behavior, postpartum aggression towards an intruder ("maternal aggression"), and oxytocin levels. Rat dams were treated throughout gestation with amfonelic acid, fluoxetine, or a combination of both at various doses, to investigate effects of reuptake inhibition of dopamine and serotonin systems, respectively. The more appetitive aspects of maternal behavior (nesting, licking, touching), and general activity of the dams, were increased by a low dose of amfonelic acid, a high dose of fluoxetine, or the high dose combination, more than other treatments. Maternal aggression was decreased by amfonelic acid and somewhat increased by fluoxetine. The results for crouching behavior were complex, but overall suggested both dopaminergic and serotonergic involvement. Dopamine uptake inhibition had a strong

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effect on hippocampal oxytocin levels, while receptor dynamics appeared to be more strongly affected by serotonin uptake inhibition. Dr. Johns is continuing her examination of oxytocin levels and receptor expression, which as recent studies suggest, may have a greater role in maternal care in humans than previously thought. Since pregnant women frequently take drugs (e.g. antidepressants, cocaine) that induce long-term reuptake inhibition of dopamine and/or serotonin, it is important to understand the effects of such drugs on behavior and biochemistry. The quantitative measures in this study indicate that long-term reuptake inhibition of dopamine or serotonin, or both, has specific and complex effects on different aspects of maternal behavior. The overall conclusion is that these treatments do not impair maternal behavior per se, but they alter it in a variety of ways that can further our understanding of alterations in human maternal behavior after perinatal exposure to drugs with the same mechanism of action. Johns, J.M., Joyner, P.W., McMurray, M.S., Elliott, D.L., Hofler, V.E., Middleton, C.L., Knupp, K., Greenhill, K.W., Lomas, L.M. and Walker, C.H. The Effects of Dopaminergic/serotonergic Reuptake Inhibition on Maternal Behavior, Maternal Aggression, and Oxytocin in the Rat. Pharmacology, Biochemistry and Behavior. July 1, 2005 [Epub ahead of print].

Repeated Exposure to the Abused Inhalant Toluene Alters GABAA and Glutamate Receptor Subunit Expression In Specific Brain Regions

Toluene is a commonly abused solvent found in many industrial and commercial products. The neurobiological effects of toluene remain unclear, but there is increasing evidence that many of them, like those of ethanol, are mediated by GABA and glutamate receptors. The purpose of a recent set of experiments by Dr. Steketee and his colleagues was to examine the effects of repeated toluene inhalation on the protein levels of specific subunits for $GABA_A$, NMDA and AMPA receptors. Rats were exposed to toluene vapors (8000 ppm) or air for 10 days (30 min/day) in a protocol previously devised in Dr. Steketee's laboratory. Consistent with their previous findings, toluene exposure produced significant sedation and ataxia, mild body tremors, jerking of the legs, and nose twitching. They determined the levels of $GABA_A$ _1, NMDA NR1 and NR2B, and AMPA GluR1 and GluR2/3 receptor subunit levels in discrete brain regions. Toluene increased $GABA_A$ _1, NR1, NR2B and GluR2/3 subunits in the medial prefrontal cortex and decreased $GABA_A$ _1 and NR1 subunits in the substantia nigra compacta. It produced modest increases in $GABA_A$ _1 subunits in the striatum, as well as slight decreases in the ventral tegmental area. NR2B subunit levels were also slightly increased within the nucleus accumbens. These studies show that toluene differentially alters levels of specific GABAergic and glutamatergic receptor subunits in a regionally selective manner. The authors discuss the similarities and differences between their findings and those from studies on other drugs of abuse and alcohol. The neurobehavioral and pharmacological effects of toluene appear similar to those of classical CNS depressants such as ethanol, but regulation of the $GABA_A$ _1 subunit in this study was less widespread than that produced by ethanol. However, the pattern of changes in expression suggests that repeated toluene administration might regulate GABAA receptors to significantly alter dopaminergic transmission within brain areas important as neuroanatomical substrates for the effects of drugs of abuse. The authors also suggest that these toluene-induced changes in $GABA_A$ and glutamate receptor subunits might underlie the previously observed cross-sensitization to cocaine produced by toluene exposure. Williams, J.M., Stafford, D. and Steketee, J.D. Effects of Repeated Inhalation of Toluene on Ionotropic GABA A and Glutamate Receptor Subunit Levels in Rat Brain. Neurochemistry International, 46, pp. 1-10, 2005.

Conditioned Withdrawal From Nicotine Decreases Activity of Brain Reward Systems

Scripps Research Institute investigators studied intracranial self-stimulation thresholds in nicotine-dependent rats before and after they were presented with a light/tone conditioned stimulus and injected with the nicotinic receptor antagonist dihydro-beta-erythroidine (DhβE) on four consecutive days. On the test day, the rats were presented the conditioned stimulus but this time injected with saline. DbβE elevated reward thresholds, (indicated by increased self-stimulation thresholds) by steady increments on each successive conditioning day, suggesting a potentiation of the degree of nicotine withdrawal as the motivational significance increased. On the test day, by contrast, the reward thresholds were increased by the conditioned stimuli alone, providing the first evidence that conditioned nicotine withdrawal can occur following withdrawal-paired cues and suggesting that decreases in brain reward function may bring about a fundamental source of craving that continually contributes

to the intransigence of smoking. Kenny, P.J. and Markou, A. Conditioned Nicotine Withdrawal Profoundly Decreases the Activity of Brain Reward Systems. The Journal of Neuroscience, 25(26), pp. 6208-6212, 2005.

Cigarette Smoking May Selectively Enhance Spatial Working Memory and Attentional Deficits in Schizophrenia

High rates of cigarette smoking (upwards of 90% by some estimates) among schizophrenic patients compared to the general population (approximately 23%) have long been recognized. A neuropsychological battery of tests was administered to 25 smokers with schizophrenia and an equal number of controls, all of whom met the criteria of smoking more than 15 cigarettes per day, expired breath levels of carbon monoxide more that 10 ppm, and plasma cotinine levels greater than 150 ng/mL. The tests were administered at smoking baseline, after overnight abstinence, and after smoking reinstatement across three test weeks during which the subjects were pretreated with the nonselective nicotinic receptor antagonist mecamylamine. Abstinence reduced scores on a continuous performance test in both groups, whereas visuospatial memory was impaired in the schizophrenic group only and this effect was reversed when smoking was once again allowed. The enhanced scores on the two tests in the schizophrenic group during reinstatement were blocked by mecamylamine. Results from these studies suggest an explanation for high rates of smoking among schizophrenics, and may contribute to strategies for developing pharmacotherapies to treat both cognitive deficits and nicotine dependence in schizophrenia. Sacco, K.A., Termine, A., Seyal, A., Dudas, M.M., Vessicchio, J.C., Krishman-Sarin, S., Jatlow, P.I., Wexler, B.E. and George, T.P. Effects of Cigarette Smoking on Spatial Working Memory and Attentional Deficits in Schizophrenia: Involvement of Nicotinic Receptor Mechanisms. Archives of General Psychiatry, 62, pp. 649-659, 2005.

Validity and Reliability of the Fagerstrom Test for Nicotine Dependence in PTSD Smokers

Rates of smoking among individuals with psychiatric conditions are greater than rates seen in the general population, yet little is known about the psychometric properties of commonly used nicotine dependence instruments among psychiatric smokers. This study examined the reliability, validity, and factor structure of the Fagerstrom Test for Nicotine Dependence (FTND) among psychiatric smokers. With respect to the validity analyses, the FTND was correlated at statistically significant levels with biological and psychological measures of dependence. Results revealed that the FTND had good test-retest reliability, convergent validity, and discriminant validity. A factor-analytic examination converged on a two-factor solution, reflecting two correlated but separate processes related to nicotine dependence. The psychometric profile of the FTND in this study was at least as good as that found in psychometric studies of the FTND with nonpsychiatric smokers, validating use of the FTND with this population. Buckley, T.C., Mozley, S.L., Holohan, D.R., Walsh, K., Beckham, J.C. and Kassel, J.D. A Psychometric Evaluation of the Fagerstrom Test for Nicotine Dependence in PTSD Smokers. Addictive Behaviors, 30(5), pp. 1029-1033, 2005.

Preclinical "Binge" Model of Inhalant Abuse for Studying Prenatal Exposure Effects

Dr. Scott Bowen at Wayne State University has developed a binge model for exposing animals to abused inhalants. In his static exposure chambers, animals receive high concentrations of solvents over relatively brief exposure periods, mimicking the typical pattern of solvent abuse in humans. Previous exposure paradigms have employed long-term, relatively low levels of inhalant treatment, but with this model, the investigator attempts to produce repeated and rapidly resolved high-peak blood solvent concentrations. Recently he has used this procedure to study the teratogenic impact of toluene exposure during gestational days eight through 20 in the rat. Solvent abuse in adolescent females of childbearing age is a concern because rates of first-time solvent use among young people between 18 and 25 rose 243% during the 1990s and toluene-related embryopathy and malformations have been reported, with high levels of exposure linked to gross morphological teratogenicity. Moreover, follow-up evaluations reveal developmental delays and language impairment, among other neurological pathologies, and retardation in physical growth. In the present study, timed-pregnant females were exposed twice per day for 15 min to either 8000 (L) or 12,000 (H) ppm toluene. There was also an "air-only" control group (C) that was placed in the chambers twice daily for an equal amount of time. Pups were assessed on measures of early neonatal growth, perinatal outcome, and neurobehavioral development. From whole litter assessments of reflex development, strength and motor coordination, the investigators note a greater number of weaker pups in the

highest dose group on post-natal (PN) day 16 (i.e., close to half the animals from the H group were at or below the 25th percentile of the C group). There were also significant effects of solvent exposure on negative geotaxis, with longer latencies for both concentration groups on PN days 6-8. On PN1, H litters weighed significantly less than the other two groups. However, between PN12-21, H pups gained relatively more weight than control animals, showing "catch up" growth. The authors also observed a dose relationship for gross malformations, external soft tissue malformations, number of pups classified as "runts", and neonatal mortality: The percentage of litters affected by these three kinds of outcomes was 12.5, 29.4 and 52.9 for the CF, L and H exposure conditions, respectively. These differences were seen with similar maternal weights and maternal weight gains across the three groups. There were also no significant between group differences in total litter size or mean gestational length. It appears that this procedure, using high dose, binge exposure conditions, may better reproduce the key pharmacodynamic features of inhalant abuse in humans and provide a more valid characterization of toluene embryopathy than studies employing longer, lower dose exposure. Bowen, S.E., Batis, J.C., Mohammadi, M.H. and Hannigan, J.H. Abuse Pattern of Gestational Toluene Exposure and Early Postnatal Development in Rats. Neurotoxicology and Teratology, 27, pp. 105-116, 2005.

A Metabotropic Glutamate Receptor 5 Antagonist Suppresses Cocaine Intake, Subjective Effects and Relapse

Ionotropic glutamate receptors have been implicated in the behavioral effects of cocaine in animal studies. For example, these receptors are involved in cocaine self-administration, reinstatement of drug seeking, and behavioral sensitization. Recently, an important role for metabotropic glutamate receptors (mGluRs) has been identified, following reports that mice lacking the mGluR5 subtype do not self-administer cocaine; and that a selective mGluR5 antagonist (2-methyl-6(phenyethynyl)-pyridine or MPEP) attenuates cocaine self-administration at doses not affecting food reinforced operant behavior. While these observations suggest that MPEP may be acting as a functional cocaine antagonist, these prior studies have been conducted in rodent models. The present study by Dr. Roger Spealman and colleagues examined MPEP effects on squirrel monkeys responding for i.v. cocaine, and compared these effects with the NMDA antatongist, dizocilpine. Animals self-administered cocaine under a second-order schedule and were then withdrawn so that responses were no longer reinforced by i.v. cocaine. Once responding on the drug lever was extinguished (i.e., responding on the lever no longer produced cocaine injections), drug seeking was measured following a cocaine "priming" injection to reinstate the behavior. In a separate study, monkeys were trained to discriminate cocaine from saline by making responses on a drug- or saline-appropriate lever, after injection of either the drug or the vehicle. Other animals were observed following MPEP or dizocilpine to assess antagonist effects on a number of spontaneous behaviors including locomotion, object exploration, foraging, self-grooming, and vocalizations. The data show that pretreatment with either 0.1 to 1.0 mg/kg MPEP, or 0.003 to 0.03 mg/kg dizocilpine, to animals responding for 0.1 to 0.3 mg/kg cocaine, produced dose-related decreases in response rates. When MPEP pretreatment was tested before cocaine priming in animals extinguished from lever pressing, with either 0.3 or 1.0 mg/kg cocaine as the prime, both 0.3 and 1.0 mg/kg MPEP significantly attenuated reinstatement. However, higher doses of MPEP were required to reduce seeking primed with 1.0 mg/kg cocaine, suggesting that the cocaine-antagonist effects of this mGluR5 drug are surmountable. Surmountable antagonism was also observed for the attenuation of discriminative cue properties of cocaine, as MPEP produced an overall rightward shift in the cocaine dose-response function in this paradigm. In contrast, the NMDA antagonist had little effect on drug seeking in the test for reinstatement, and rather than blocking discriminative cue properties of cocaine, had either no effect or enhanced cocaine discrimination. Behavioral observations revealed that MPEP significantly reduced overall locomotion but was without effects on foraging, exploration or grooming, whereas dizocilpine had no behavioral effects except that it increased muscle resistance. As MPEP did not disrupt spontaneous behavior, and also did not disrupt operant responding in drug discrimination testing, this mGluR5 antagonist may be a promising candidate to explore for the treatment of cocaine addiction. Moreover, the observed differences between this antagonist and dizocilpine suggest that the observed antagonism is independent from MPEP's interaction with the glutamate NMDA receptor. Lee, B., Platt, D.M., Rowlett, J.K., Adewale, A. and Spealman, R.D. Attenuation of Behavioral Effects of Cocaine by the Metabotropic Glutamate Receptor 5 Antagonist 2-methyl-6-(phenylethynyl)-pyridine in Squirrel Monkeys: Comparison with Dizocilpine. The Journal of Pharmacology and Experimental Therapeutics, 312, pp. 1232-1240, 2005.

Heavy Marijuana Smoking in Adolescents is Associated With Reduced Motivation

In A Laboratory Measure Of "Work" Dr. Scott Lane and his colleagues have developed a computer based "work" task that uses progressive ratio (PR) schedules of reinforcement with money, to assess motivation in the laboratory. In this procedure, subjects have the option of responding on the PR schedule, which increases number of responses required to receive monetary reward over sequential segments of the experimental session, or switching to a fixed time (FT) schedule that delivers money without a work requirement. However, the FT schedule delivers less money than the PR, so it is advantageous to continue to "work" on the PR schedule. Early session switching to the non-work, FT option is considered an indication of reduced motivation. Previously, these researchers have found that adults smoking marijuana in the laboratory show reduced motivation on this task. Until the present study, however, the task had not been used to assess motivation in adolescent subjects who may be especially vulnerable to the cognitive and motivational effects of THC. In this study, 14-18 years who regularly smoked marijuana (at least 4 days/wk) and met DSM-IV criteria for marijuana abuse or dependence (MJ+) were compared with a control group of 14-18 year olds who reported no current illicit drug use (MJ-). The dependent measures assessed were: largest PR completed in the increasing sequence of greater response requirements, and percent earnings from the non-work option. The data indicate that control subjects completed a larger average PR on both test days, and as expected, the MJ+ group derived proportionally more earnings from the FT option. Pearson correlation coefficients were calculated to examine the relationship between urinary cannabinoid levels and these behavioral measures. While there was no relationship between drug concentration and the largest PR completed, a significant correlation was detected between the biochemical measure and percent of earnings from the FT option. These findings are consistent with "amotivational" effects of marijuana as previously reported from this laboratory. However, the authors caution that other variables might have contributed to these behavioral differences (e.g., socio-demographic, past marijuana use by control subjects, attention, efficacy of the reinforcer, etc.). Lane, S.D., Cherek, D.R., Pietras, C.J. and Steinberg, J.L. Performance of Heavy Marijuana-smoking Adolescents on a Laboratory Measure of Motivation. Addictive Behaviors, 30, pp. 815-828, 2005.

Deficits in Memory Induced by the Cannabinoid _9-THC Can be Reversed by Treatment With a GABAA Antagonist

Recent studies in brain slices have indicated that one important effect of cannabinoids is to modulate the release of the inhibitory neurotransmitter GABA from neural terminals. Indeed, a large proportion of brain cannabinoid receptors (CB1 receptors) are located on GABAergic terminals, especially in brain areas that are important for learning and memory. Dr. Aaron Lichtman and his colleagues hypothesized that the memory disrupting effects of the exogenous cannabinoid _9-tetrahydrocannabinol (_9-THC) are mediated by its effect on GABA release. They tested this hypothesis by evaluating whether GABA antagonists would ameliorate the behavioral effects of _9-THC-induced deficits seen on two different tests of working memory in the mouse. That is, if _9-THC disrupts working memory by decreasing GABA release, then a GABA antagonist should counteract the disruption. The two memory tests they used were the Morris water maze task and an alternating T-mast task. The first of these requires spatial memory, whereas the second task relies on the animal remembering its previous action. The two tasks also differ in motivation (escape vs. hunger) and in the reinforcer provided (safety platform vs. food reward), and in several other respects. Thus, by using both tasks, the investigators were able to assess cognitive processes per se, and control, to some extent, for motoric or motivational factors. They found that the GABAA antagonist bicuculline completely reversed the deficits in the water maze task resulting from _9-THC treatment and also blocked the disruptive effects of _9-THC in the T-maze task. They also tested the GABAB antagonist CGP 36742 in the first task and found no effect. Furthermore, bicuculline did not reverse non-mnemonic effects of _9-THC, including analgesia, hypothermia, or catalepsy. These results support the hypothesis that activation of GABAA receptors plays a critical role in _9-THC-induced memory impairment and is the first demonstration that GABAA receptors appear to play a necessary role in _9-THC-induced memory impairment in whole animals. This study furthers our understanding of how cannabinoids modulate memory and could lead to improved strategies for treating cannabis-related disorders. Varvel, S.A, Anum, E., Niyuhire F., Wise L.E. and Lichtman, A. H. _9-THC-induced Cognitive Deficits in Mice are Reversed by the GABAA Antagonist Bicuculline. Psychopharmacology, 178, pp. 317-327, 2005.

Decreased Motivation to Obtain Cocaine Following Extended Access: Effects

of Sex and Ovarian Hormones

As described in the September 2004 Director's Report to Council, Drs. Wendy Lynch and Jane Taylor reported sex differences in cocaine self-administration (1.5 mg/kg/infusion) under a 24-hour access procedure in which rats received four 10-min discrete trials per hour for seven days -- a procedure which produces escalation of cocaine intake in a binge-abstinence pattern. Drs. Lynch and Taylor found that compared to males, females self-administered more cocaine, self-administered for longer periods of time, and exhibited greater disruption in the diurnal control over cocaine intake. In an assessment of long-term changes in cocaine motivation, conducted following a 10-day forced abstinence period, females exhibited an increase in motivation for cocaine as measured by behavior under a progressive ratio schedule, whereas males did not. (Lynch, W.J. and Tavlor, J.R. Sex Differences in the Behavioral Effects of 24-hr Access to Cocaine Under a Discrete Trial Procedure. Neuropsychopharmacology, 29, pp. 943-951, 2004). In a recent follow-up study, these researchers examined more immediate changes in cocaine motivation by testing 1, 2, and 3 days following the 7-day discrete trial procedure. Whereas males showed no change in cocaine motivation over the three test days, as assessed by progressive ratio performance, females exhibited a marked reduction in motivation. By comparing ovariectomized females with and without estrogen replacement, the researchers found that estrogen modulated the motivation for cocaine. Taken together, these two studies indicate that at 1, 2, 3, and 10 days following seven days of high access to cocaine, males exhibit no change in cocaine motivation, whereas females exhibit a reduction at 1, 2, and 3 days, and an increase at 10 days. These outcomes, along with earlier research using variations of the 24-hr discrete trials procedure with only male rats, illustrate male-female differences in the development and time course of cocaine motivation during and following extended access to cocaine. These data add to a growing body of human and animal literature indicating sex differences in cocaine addiction. Lynch, W.J. and Taylor, J.R. Decreased Motivation Following Cocaine Self-administration Under Extended Access Conditions: Effects of Sex and Ovarian Hormones. Neuropsychopharmacology, 30, pp. 927-935, 2005.

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

Research Findings - Behavioral and Brain Development Research

Quantitative Analysis of Diffusion Tensor Orientation: Theoretical Framework

Dr. Andrew Alexander and colleagues of the University of Wisconsin-Madison have developed a series of visual and quantitative tools for representing the coherence and directional organization of white matter tracts in the human brain. These authors have also shown that the methods developed are sensitive to changes in the structural organization caused by infiltrative disease. Wu, Y-C., Field, A.S., Chung, M.K., Badie, B. and Alexander, A.L., Magnetic Resonance in Medicine. 52, pp. 1146-1155, 2004.

Marijuana Impairs Growth Mid-gestation Fetuses

Dr. Yasmin Hurd and her colleagues analyzed the growth rate in fetuses that had been exposed to marijuana in utero and compared their growth with non-exposed fetuses. In a sample of 44 exposed and 95 non-exposed fetuses analyzed at gestational ages of from 17 to 22 weeks it was found that the exposed fetuses had significantly reduced body weight and foot length, even when the data were adjusted to account for maternal alcohol consumption and smoking (tow other factors that can impair fetal development). These findings provide evidence of a negative impact of marijuana on intrauterine growth in human fetuses. Hurd, Y.L., Wang, X., Anderson, V., Beck, O., Minkoff, H., and Dow-Edwards, D. Neurotoxicology and Teratology. 27(2), pp. 221-229, 2005.

fMRI Response to Spatial Working Memory in Adolescents with Comorbid Marijuana and Alcohol Use Disorders

Dr. Susan Tapert and her colleagues compared the brain activation patterns of 15 adolescents that had used both marijuana and alcohol (MAUD participants) with those of 15 adolescents that had used only alcohol (AUD) and 19 adolescents that had used neither while performing a spatial working memory task. The results showed that, even though the 3 groups of adolescents had similar performance on the task, MAUD adolescents showed less activation in the inferior frontal and temporal regions than the AUD and the control groups, and more activation in dorsolateral prefrontal regions and deactivation in the anterior cingulate cortex than the control group. These findings suggest that marijuana use in adolescents may cause deficits in attentional mechanisms and evoke compensatory responses in areas that subserve spatial working memory. Schweinsburg, A.D., Schwiensburg, B.C., Cheung, E.H., Brown, G.G., Brown, S.A. and Tapert, S.F. Drug and Alcohol Dependence. 79, pp. 201-210, 2005.

Heritability of Substance Dependence in a Native American Population

This study estimated the heritability of substance dependence and associated symptoms in a sample of Southwest California (Mission) Indians. Dependence diagnoses for alcohol, marijuana, stimulants and a measure of regular tobacco usage, any drug dependence or tobacco usage were obtained. Heritability estimates were calculated using variance component methods, as implemented in SOLAR. In this population, marijuana dependence (0.38) and regular tobacco use (0.43), alcohol dependence (0.29), and stimulant dependence (0.25) showed evidence for moderate genetic influences as determined by heritability estimates. The authors conclude that marijuana dependence, regular tobacco usage and composite phenotypes constructed from alcohol dependence symptoms for antisocial problems, drinking severity and withdrawal generally have patterns of familial aggregation, suggesting that they can be successfully used for linkage analysis in this Southwest California Indian sample.

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Wilhelmsen, K.C. and Ehlers, C. Heritability of Substance Dependence in a Native American Population. Psychiatric Genetics, 15(2), pp. 101-107, 2005.

Patterns of Polydrug Use among Ketamine Injectors in New York City

Polydrug use is an important public health issue since it has been linked to significant adverse health outcomes. Recently, club drugs, including ketamine and other drugs used in dance/rave scenes, have been identified as key substances in new types of polydrug using patterns. While seemingly a self-explanatory concept, "polydrug" use constitutes multiple drug using practices that may impact upon health risks. Ketamine, a club drug commonly administered intranasally among youth for its disassociative properties, has emerged as a drug increasingly prevalent among a new hidden population of injection drug users (IDUs). Using an ethno-epidemiological methodology, the researchers interviewed 40 young (< 25 years old) ketamine injectors in New York during 2000-2002 to describe the potential health risks associated with ketamine and polydrug use. Findings indicate that ketamine was typically injected or sniffed in the context of a polydrug using event. Marijuana, alcohol, PCP, and speed were among the most commonly used drugs during recent ketamine using events. Polydrug using events were often quite variable regarding the sequencing of drug use, the drug combinations consumed, the forms of the drug utilized, and the modes of administrating the drug combinations. The investigators suggest that future research should be directed towards developing a more comprehensive description of the risks associated with combining ketamine with other drugs, such as drug overdoses, the transmission of bloodborne pathogens such as HIV and HCV, the short- and long-term effects of drug combinations on cognitive functioning, and other unanticipated consequences associated with polydrug use. Lankenau, S.E. and Clatts, M.C. Patterns of Polydrug Use among Ketamine Injectors in New York City. Substance Use and Misuse, 40, pp. 1381-1397, 2005.

Neurocognitive Consequences of Marijuana in Young Adults for Whom Pre-Drug Use Performance is Known

This report examined effects of current and past regular use of marijuana among young adults for whom pre-drug use performance had been ascertained in a prospective, longitudinal study. A total of 113 young adults (17-21 years of age), assessed since infancy, were evaluated using neurocognitive tests for which commensurate measures were obtained prior to the initiation of marijuana smoking (i.e., 9-12 years of age). Marijuana users, determined by urinalysis and self-report, were categorized as light (<5 joints per week) and heavy (³5 joints per week) current users and former users, the latter having used the drug regularly in the past (³1 joint per week) but not for at least 3 months. A third of the participants were using marijuana on a regular basis at the time of assessment, with half being heavy users. Among former, regular users, approximately half had been smoking 5 or more joints per week. Overall IQ, memory, processing speed, vocabulary, attention, and abstract reasoning were assessed. After accounting for potentially confounding factors and pre-drug performance in the appropriate cognitive domain, current regular heavy users did significantly worse than non-users in overall IQ, processing speed, and in immediate and delayed memory. In contrast, the former marijuana smokers did not show any cognitive impairments. The authors conclude that residual marijuana effects are evident beyond the acute intoxication period in current heavy users after taking into account pre-drug performance, but similar deficits are no longer apparent 3 months after cessation of regular use, even among former heavy using young adults. The investigators suggest caution in interpreting and generalizing the results, pointing out that the average length of time of regular use was relatively short (i.e., slightly over 2 _ years). They also note that the literature is inconclusive regarding associations between lifetime duration of former use and cognitive functioning. Fried, P.A., Watkinson, B., and Gray, R. Neurocognitive Consequences of Marijuana - A Comparison with Pre-Drug Performance. Neurotoxicology and Teratology, 27, pp. 231-239, 2005.

Prenatal Tobacco Exposure and Offspring Smoking in Early Adolescence

In this prospective study of a birth cohort of 567 14-year-olds, investigators at the University of Pittsburgh examined relationships among trimester-specific prenatal tobacco exposure (PTE), offspring smoking, and other correlates of adolescent smoking. Average age of the adolescents was 14.8 years (range: 13.9-16.6 years). Approximately half of the sample was female, and about half was African-American. Data on maternal tobacco and other substance use were collected both prenatally and postnatally. Fifty-one percent of the mothers were prenatal smokers and 53% smoked when their children were 14 years old. PTE in the third trimester significantly predicted offspring smoking (ever/never, smoking level, age of onset) when

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demographic and other prenatal substances were included in the analyses. PTE remained a significant predictor of the level of adolescent smoking when maternal and child psychological characteristics were added to the model. When more proximal measures of the child's smoking were included in the model, including mother's current smoking and friends' smoking, PTE was no longer significant. Significant predictors of adolescent smoking at age 14 were female gender, Caucasian race, child externalizing behavior, maternal anxiety, and child depressive symptoms. The authors conclude that although direct effects of PTE on offspring smoking behavior have previously been reported from this study and by others, by early-adolescence, this association was not significant in this sample after controlling for the more proximal covariates of adolescent smoking such as mother's current smoking and peer smoking. They also note that many of the reports in the literature that indicate a relationship between PTE and offspring smoking have been retrospective or have not included important variables such as other prenatal substance exposures, maternal and child psycho-social characteristics, mother's current smoking, and friends' smoking. Cornelius, M.D., Leech, S.L., Goldschmidt, L. and Day, N.L. Is Prenatal Tobacco Exposure a Risk Factor for Early Adolescent Smoking? Neurotoxicology and Teratology, 27, pp. 667-676, 2005.

School Performance of Children with Gestational Cocaine Exposure

Researchers from the University of Pennsylvania have reported results on school performance in a sample of children exposed to cocaine in utero. At the completion of fourth grade, a total of 135 children (62 with gestational cocaine exposure and 73 without) who were enrolled at birth and followed prospectively, were evaluated using report card data, standardized test results, teacher and parent report, and natal and early childhood data. Successful grade progression was defined as completing grades 1 through 4 without being retained. Cocaine-exposed and control children were similar in school performance (all p³0.10): successful grade progression (71% cocaine-exposed vs. 84% control), Grade Point Average (2.4±0.8 vs. 2.6±0.7), reading below grade level (30% vs. 28%), and standardized test scores below average (reading [32% vs. 35%], math [57% vs. 44%], science [39% vs. 36%]). Children with successful progression, regardless of cocaine exposure, had higher Full Scale IQ and better home environments. The researchers conclude that in this inner-city cohort, cocaine-exposed and control children had similar poor school performance, with better home environment and higher Intelligence Quotient associated with an advantage for successful grade progression, regardless of gestational cocaine exposure. Hurt, H., Brodsky, N.L., Roth, H., et al. School Performance of Children with Gestational Cocaine Exposure. Neurotoxicology and Teratology, 27, pp. 23-211, 2005.

Prenatal Drug Exposure and Selective Attention in Preschoolers

Based on research conducted at Case Western Reserve University, a recent report focused on selective attention in a large, polysubstance cocaine-exposed cohort of 4-year-olds and their at-risk comparison group. Maternal pregnancy use of cocaine and use of cigarettes were both associated with increased commission errors, interpreted as indicative of inferior selective attention. Severity of maternal use of marijuana during pregnancy was positively correlated with omission errors, suggesting impaired sustained attention. Substance exposure effects were independent of maternal postpartum psychological distress, birth mother cognitive functioning, current caregiver functioning, other substance exposures, and child concurrent verbal IQ. Noland, J.S., Singer, L.T., Short, E.J., et al. Prenatal Drug Exposure and Selective Attention in Preschoolers. Neurotoxicology and Teratology, 27, pp. 429-438, 2005.

Relative Ability of Biologic Specimens and Interviews to Detect Prenatal Cocaine

Exposure University of Florida researchers recruited women in a labor and delivery service, enrolling all consenting patients with a history of prenatal cocaine use and the next admission with no recorded use. During the immediate postpartum period, private, structured interviews were carried out to obtain details of prenatal cocaine use and to identify a priori exclusion criteria (other illicit drug use, high alcohol use and chronic illnesses and medications). Amniotic fluid, cord blood, infant urine, meconium, and maternal hair were also collected. All specimens were blindly analyzed with respect to exposure, using gas chromatography/mass spectrometry. Of 115 subjects, 46 had one or more biologic specimens positive for cocaine metabolites and five admitted prenatal use, but had negative specimens. Of these 51 identified as users by any method, 38 admitted, 32 were positive for urine, 28 for hair, and 25 for meconium. Of the 38 admitters, 87% had positive specimens. Of the 77 denying use, 17% were positive. Urine was most frequently positive in identified users, 67%

overall and 62% of users who denied. Hair was next, positive in 65% of all users and 50% of users who denied. Of the 13 subjects who denied use but were positive on at least one specimen, four were identified solely by urine, two only by hair and one only by meconium. Self-report identified five users with all negative specimens. The authors conclude that although no one method identified all users, the single method that maximally identified users was detailed history taken by experienced interviewers. Eyler, F.D., Behnke, M., Wobie, K., Garvan, C.W. and Tebbett, I. Relative Ability of Biologic Specimens and Interviews to Detect Prenatal Cocaine Use. Neurotoxicology and Teratology, 27, pp. 677-687, 2005.

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

Research Findings - Clinical Neuroscience Research

Recognition and Management of Complications of New Recreational Drug Use

Social use of illicit drugs in clubs and large dance parties (i.e., raves) is an escalating cultural trend. Such recreational drug use is associated with several medical complications, both acute and chronic. Although few, if any, of the drugs currently used in recreational situations are truly new, their patterns and context of use have changed (substantially in some instances). For some of these substances, a cultural repackaging of the drug experience has resulted in various medical disorders that have previously gone undocumented. This review by Hopkins researchers aims to help treating physicians recognize and manage complications associated with the use of new drugs in clubs, including methylenedioxy-methamphetamine, ephedrine, gamma-hydroxybutyrate, gamma-butyrolactone, 1,4-butanediol, flunitrazepam, ketamine, and nitrites. The article also alerts researchers to specific toxic effects of club-drugs on which more basic information is needed. Ricaurte, G.A. and McCann, U.D. Lancet, 7, pp. 2137-2145, 2005.

Interaction of Executive Functions, Sensation Seeking, and HIV Serostatus and its Effect on the Risky Sexual Practices of Drug Abusers

From a public health standpoint, identifying factors that contribute to risky sexual practices among substance-dependent individuals is critical, particularly in the context of HIV infection. Investigators from the University of Illinois, Chicago, examined the contributions of executive neurocognitive functions, sensation seeking, and HIV serostatus to predict risky sexual practices among poly-substance abusers with a history of cocaine or cocaine/heroin (speedballing). HIV+ (n=109) and HIV- (n=154) substance-dependent individuals were assessed using three neurocognitive tasks of executive functions: Stroop reaction time, delayed non-matching to sample, and the Iowa Gambling Task. Sensation seeking was assessed using the Sensation Seeking Scale-V. Greater sensation seeking was associated with more risky sexual practices among HIV+ participants, particularly among those who performed best on the Iowa Gambling Task. The findings indicate that continued risk behavior among HIV+ drug users may be driven by sensation seeking (a personality trait common among drug users); however, the impact of executive functions is less clear. Gonzalez, R., Vassileva, J., Bechara, A., Grbesic, S., Sworowski, L., Novak, R.M., Nunnally, G. and Martin, E.M. J. International Neuropsychological Society 11, pp. 121-131, 2005.

Enlarged Striatum in Abstinent Methamphetamine Abusers: A Possible Compensatory Response

Since so little is known about structural brain abnormalities associated with methamphetamine (METH) abuse, Dr. Linda Chang and colleagues at University of Hawaii evaluated METH-dependent subjects for possible morphometric changes. They focused on the striatum of recently abstinent METH abusers, to determine whether morphometric changes, if any, were related to cognitive performance, and to evaluate if there might be sex-by-METH interactions on morphometry. Structural MRI was performed in 50 METH and 50 comparison subjects withage range and gender controlled. Quantitative morphometric analyses were performed in the subcortical gray matter, cerebellum and corpus callosum (CC). Neuropsychological tests were also performed in 44 METH and 28 comparison subjects. All METH users, regardless of gender, showed an enlarged putamen and GP when compared to controls. Additionally, female METH users displayed a larger mid-posterior CC. Although METH users had normal cognitive function, those with smaller striatal structures reported greater cumulative METH usage and had poorer cognitive performance. Since METH

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subjects with less cumulative METH usage had larger striatal structures and had relatively normal cognitive performance, the enlarged putamen and GP might represent a compensatory response to maintain function. Possible mechanisms for the striatal enlargement include glial activation and inflammatory changes associated with METH-induced injury. Chang, L., Cloak, C., Patterson, K., Grob, C., Miller, E.N. and Ernst, T. Biol Psychiatry, 157, pp. 967-974, 2005.

Response Inhibition Deficits Associated with Chronic Methamphetamine Abuse

It is known that chronic methamphetamine (METH) abuse is associated with cerebral deficits, involving frontal/basal-ganglia regions that are important for inhibitory control. Researchers from UCLA used the Stop-Signal Task to measure response inhibition in 11 abstinent METH abusers (5-7 days abstinent) and two groups of control subjects who did not use METH (14 tobacco smokers and 29 non-smokers). Stop-signal reaction time (SSRT), which indicates the latency to inhibit an initiated motor response, was significantly longer for METH abusers than for either control group. In contrast, the METH abusers did not differ from either group on Go trial reaction time (RT) or number of discrimination errors, which reflect motor speed and decision-processes, respectively. In this study, METH abuse was therefore associated with a specific deficit in inhibiting a pre-potent response. The authors speculate that future research could examine whether SSRT is different for METH abusers who respond to treatment compared to those who do not. If such differences are established then response inhibition may serve as a marker for investigating METH abuse in basic science and clinical trials. Monterosso, J.R., Aron, A.R., Cordova, X., Xu, J. and London, E.D. Drug Alcohol Depend.79, pp. 273-277, 2005.

Repeated Psychological Stress Testing in Stimulant-Dependent Patients

Decreasing response to stress has been one goal of interventions aimed at reducing relapse to substances of abuse. A laboratory stress test that can be repeated would be helpful in testing the efficacy of interventions in decreasing the response to stress before more extensive trials are begun. The effects of two types of psychological stress tests, the Trier Social Stress Test (TSST) and a stress imagery test, on psychological, physiological, and hormonal responses (salivary cortisol and DHEA) were examined when each test was given twice to cocaine (COC)- or methamphetamine (METH)-dependent human subjects, 24 of whom completed at least one session. The stress imagery test produced significant changes in several of the subjective response measures in both first and second sessions, including several measures of negative affect and a craving measure. The TSST produced significant changes only in the second session. The stress imagery protocol showed better replicability across two sessions. COC users and METH users did not respond similarly in their craving responses. Reported craving for METH after stress testing showed decreases or much smaller increases compared to that for cocaine. Neither stress test significantly increased salivary cortisol or DHEA, and changes in hormone concentrations were not related to subjective responses. These results suggest that stress imagery testing procedures may be useful as provocative tests of stress-induced affect and stimulant drug craving. Although less convincing because of the heterogeneity of the subjects, they also suggest that HPA axis responsivity is not clearly linked to acute stress-induced stimulant craving or affective response. Harris, D.S., Reus, V.I., Wolkowitz, O.M., Mendelson, J.E. and Jones R.T. Prog Neuropsychopharmacol Biol Psychiatry 29, pp. 669-677, 2005.

Imaging Brain Mu-Opioid Receptors in Abstinent Cocaine Users Over Time and in Relation to Craving

Cocaine (coc) treatment upregulates brain mu-opioid receptors (mOR) in animals. Human data regarding this phenomenon are limited. These researchers have previously used positron emission tomography (PET) with [11C]-carfentanil to show increased mOR binding in brain regions of 10 coc-dependent men after 1 and 28 days of abstinence. Regional brain mOR binding potential (BP) was measured with [11C]carfentanil PET scanning in 17 coc users over 12 weeks of abstinence on a research ward and in 16 healthy control subjects. Results demonstrate that mOR BP was increased in the frontal, AC, and LTC after 1 day of abstinence. mOR BP remained elevated in the first two regions after 1 week and in the AC and AFC after 12 weeks. Increased binding in some regions at 1 day and 1 week was positively correlated with self-reported cocaine craving. mOR BP was significantly correlated with percentage of days coc was used and the amount of coc used per day during the 2 weeks prior to admission and with urine benzoylecgonine concentration at the first PET scan. These results suggest that chronic coc use influences endogenous opioid systems in the human brain and might explain mechanisms of coc craving and reinforcement.

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Gorelick, D.A., Kim, Y.K., Bencherif, B., Boyd, S.J., Nelson, R., Copersino, M., Endres, C.J., Dannals, R.F. and Frost, J.J. Biological Psychiatry, 15, pp. 573-582, 2005.

Brain Activity in Cigarette Smokers Performing a Working Memory Task: Effect of Smoking Abstinence

When smokers who are nicotine-dependent abstain from cigarette smoking, working memory deficits occur. An understanding of the neural substrates of such impairments may help to understand how nicotine affects cognition. The aim of researchers at UCLA, was to identify abnormalities in the circuitry that mediates working memory in nicotine-dependent subjects after they initiate abstinence from smoking. BOLD fMRI was used to study eight smokers while they performed a letter version of the N-Back working memory task under satiety (/=14 hours abstinence) conditions. Task-related activity in the DLPFC showed a significant interaction between test session (satiety, abstinence) and task load (1-back, 2-back, and 3-back). This interaction reflected that task-related activity in the satiety condition was relatively low during performance of the 1-back task but greater at the more difficult task levels, whereas task-related activity in the abstinence condition was relatively high at the 1-back level and did not increase at the more difficult task levels. It is concluded that neural processing related to working memory in the left DLPFC is less efficient during acute abstinence from smoking than at smoking satiety. Xu, J., Mendrek, A., Cohen, M.S, Monterosso, J., Rodriguez, P., Simon, S.L., Brody, A., Jarvik, M., Domier, C.P., Olmstead, R., Ernest, M. and London, E. Biological Psychiatry. 15, pp. 143-150, 2005.

Hepatitis C Augments Cognitive Deficits Associated with HIV Infection and Methamphetamine

Researchers from UCLA examined the contribution of hepatitis C virus (HCV) infection to neurocognitive dysfunction in individuals with comorbid HIV infection or methamphetamine (METH) dependence. Neurocognitive functioning was examined in 430 study participants who were either normal controls or had HCV infection, HIV infection, history of METH dependence, or combinations of these factors as risks for cognitive deficits. Rates of global and domain-specific neuropsychological (NP) impairment increased with the number of risk factors. HCV serostatus was a significant predictor of NP performance both globally and in the areas of learning, abstraction, and motor skills, with trends in speeded information processing and delayed recall. HCV serostatus did not predict scores in attention/working memory or verbal fluency. It is concluded that HCV infection contributes to the neuropsychological deficits observed among HIV-infected and stimulant-dependent populations. Cherner, M., Letendre, S., Heaton, R.K., Durelle, J., Marquie-Beck, J., Gragg, B., Grant, I. and HIV Neurobehavioral Research Center Group. Neurology, 26, pp. 1343-1347, 2005.

Effects of Methamphetamine Dependence and HIV Infection on Cerebral Morphology

Researchers at UCLA examined the separate and combined effects of methamphetamine dependence and HIV infection on brain morphology. Morphometric measures obtained from magnetic resonance imaging of methamphetamine-dependent and/or HIV+ participants and their appropriate age- and education-matched comparison groups were analyzed. Main effects of age, HIV infection, METH dependence, and the interactions of these factors were examined in analyses of cerebral gray matter structure volumes. Independent of the effect of age, HIV infection was associated with reduced volumes of cortical, limbic, and striatal structures. There was also some evidence of an interaction between age and HIV infection such that older HIV+ participants suffered disproportionate loss. METH dependence was surprisingly associated with basal ganglia and parietal cortex volume increases, and in the nucleus accumbens there appeared to be a larger effect in younger methamphetamine abusers. Neurocognitive impairment was associated with decreased cortical volumes in HIV+ participants but with increased cortical volumes in METH-dependent participants. Results suggest significant brain structure alterations associated with both HIV infection and METH. The regional patterns of the changes associated with these factors were distinct but overlapping, and the effects on brain volumes were opposing. Although the results of the present study provide little information about the specific mechanisms leading to the unexpected methamphetamine effects, they may be related to glial activation or neuritic growth, both of which have been associated with methamphetamine exposure in animal studies. The findings have implications for the interpretation of brain morphological findings in METH+/HIV+ individuals, a group whose numbers are unfortunately increasing. Jernigan, T.L., Gamst, A.C., Archibald, S.L., Fennema-Notestine, C.,

Mindt, M.R., Marcotte, T.L., Heaton, R.K., Ellis, R.J. and Grant, I. American Journal of Psychiatry, 162, pp. 1461-1472, 2005.

Sleep Quality Deteriorates In Two Weeks Following Abstinence From Smoked Cocaine

Stickgold, Hobson and associates at Harvard found that sleep quality - duration, efficiency, and onset latency, but not subjective report - deteriorated over 15 days following abstinence from a binge session of smoked cocaine. The subjects were non-treatment-seeking cocaine abusers who participated in an inpatient study of binge use followed by two-week abstinence. Polysomnography assessed sleep quality and confirmed a steadily decreasing sleep quality, phenomena reported by others. There was not, however, evidence of REM rebound that has been reported by other studies which may be due to the hospital setting in this study or other factors. The main limitation in this study was the small number of subjects (though more than other studies), requiring replication. Nevertheless, sleep disturbances are likely one source of relapse in those trying to quit. Pace-Schott, E.F., Stickgold, R., Muzur, A., Wigren, P.E., Ward, A.S., Hart, C.L, Clarke, D., Morgan, A. and Hobson J.A.. Psychopharmacology 179, pp. 873-883, 2005.

Significant Association of the _4 Subunit of the Nicotine Acetylcholine Receptor with Nicotine Dependence

M.D. Li and colleagues studied over 2000 subjects from more than 600 families with three measures of smoking severity (heaviness, quantity, and dependence) and demonstrated association with at least two (of six studied) single nucleotide polymorphisms (SNPs). However, different SNPs were associated in different ethnic groups (African Americans and European Americans). Furthermore, in female African Americans on SNP was significantly associated with all three nicotine dependence measures. The _2 subunit of the nACHR gene was also examined but no association was found. This study is believed to be the first to confirm a genetic role of the CHRNA4 gene, separately in African and European American samples as well as indicate that such an association may be sex-specific as well. Li, M.D., Beuten, J., Ma, J.Z., Payne, T.J., Lou, X.-Y., Garcia, V., Duenes, A.S., Crews, K.M. and Elston, R.C. Human Molecular Genetics, 14, pp. 1211-1219, 2005.

Genetic Linkages For Cocaine Dependence and Related Traits

Gelernter at Yale University and associates reported significant linkage (lod score = 4.66) for an empirically-derived symptom cluster entitled, "Heavy use, cocaine predominant," at position 104.7 on Chromosome 12 for European Americans only. For African Americans there was a significant peak at 52.9 on Chromosome 3 for the cluster entitled, "Moderate cocaine and opiate use." Two suggestive peaks (lod ~2.5) were found for European Americans for cocaine dependence and for "Heavy use, cocaine predominant" at 52.9 on Chromosome 3. For African Americans for whom cocaine induced paranoia (CIP), there was a significant peak (lod = 3.65) at location 117.4 on Chromosome 9. These data demonstrate differences in genotype vulnerabilities among ethnic groups while pointing to chromosomal regions for further study into the genetic basis of drug abuse vulnerability. Gelernter, J., Panhuysen, C., Weiss, R., Brady, K., Hesselbrock, V. Rounsaville, B., Poling, J., Wilcox, M., Farrer, L. and Kranzler, H.R. American Journal of Medical Genetics Part B (Neuropsychiatric Genetics), 136B, pp. 45-52, 2005.

Cholinergic Muscarinic Receptor Predisposes To Drug Dependence and Other Psychiatric Disorders

Gelernter at Yale University and associates studied six markers and 38 ancestry-informative markers in a sample of 871 subjects including controls and individuals with diagnoses of drug dependence, alcohol dependence and/or major depressive syndrome. Using a conventional case-control design some of the markers were marginally significant which did not hold up when corrected for multiple testing. However, regression analysis did identify specific alleles, genotypes, and haplotypes that were associated with risk for each disorder. The authors concluded that variation in the cholinergic muscarinic receptor predisposes to the disorders under investigation. Allele interaction demonstrated increased risk for alcohol and drug dependence while not for affective disorders indicating counteracting forces. Luo, X., Kranzler, H.R., Zuo, L., Wang, S., Blumberg, H.P. and Gelernter, J. HMG Advance Access, July 2005.

Increased DAT Availability Associated With 9-Repeat of the SLC6A3 Gene

Gelernter and associates at Yale University determined that homozygotes with 9

repeats of a 40-base-pair segment in the 3' untranslated region of the SLC6A3 gene together with heterozygotes (with a 10-repeat segment) compared to 10-repeat homozygotes had less dopamine transporter available in both the caudate and putamen when corrected for age and as determined by SPECT. In addition there was a left/right asymmetry with more availability in the left putamen and (marginally) caudate. These data replicate a previous study by these investigators but differ from others with possible differences due to diagnosis, methodology, or ethnic composition. The repeat is not in the coding region rendering the cause for the differences to be unknown-possibly affecting gene expression, being in linkage equilibrium with another gene variant, or related to other polymorphism as yet unknown. Van Dyck, C.H., Malison, R.T., Jacobsen, L.K., Sebyl, J.P., Staley, J.K., Laruell, M., Baldwin, R.M., Innis, R.B. and Gelernter, J. Journal of Nuclear Medicine, 46, pp. 745-751, 2005.

fMRI Brain Activation during Cocaine Self-Administration in Humans

Risinger and colleagues at the Medical College of Wisconsin used BOLD fMRI to determine pattern of brain activation during cocaine self-administration in order to identify those sites associated with drug-induced high and craving as measures of reward and motivation. Non-treatment seeking cocaine-dependent subjects chose both when and how often to administer i.v. cocaine within a medically supervised self-administration procedure. Both functional magnetic resonance imaging (fMRI) data and real-time behavioral ratings were acquired during the 1-h self-administration period. Drug-induced HIGH was found to correlate negatively with activity, in limbic, paralimbic, and mesocortical regions including the nucleus accumbens (NAc), inferior frontal/orbitofrontal gyrus (OFC), and anterior cingulate (AC), while CRAVING correlated positively with activity in these regions. This study provides the first evidence in humans that changes in subjective state surrounding cocaine self-administration reflect neural activity of the endogenous reward system. Risinger, R.C., Salmeron, B.J., Ross, T.J., Amen, S.L., Sanfilipo, M., Hoffmann, R.G., Bloom, A.S., Garavan, H. and Stein, E.A. Neuroimage 26, pp. 1097-1108, 2005.

Neural Activation Patterns of Methamphetamine-Dependent Subjects during Decision Making Predict Relapse

Paulus and colleagues at the University of California, San Diego investigated whether BOLD functional magnetic resonance imaging (fMRI) shortly after drug cessation could predict relapse in stimulant-dependent individuals. Treatment-seeking methamphetamine-dependent males (N = 46) were scanned using fMRI while performing a 2 choice prediction task 3 to 4 weeks after cessation of drug use. Of the 40 subjects who were followed up a median of 370 days, 18 relapsed and 22 did not. fMRI activation patterns in right insular, posterior cingulate, and temporal cortex obtained early in recovery correctly predicted 20 of 22 subjects who did not relapse and 17 of 18 subjects who did. A Cox regression analysis revealed that the combination of right middle frontal gyrus, middle temporal gyrus, and posterior cingulate activation best predicted the time to relapse. In contrast, behavioral performance on the task was not predictive of relapse. This investigation demonstrates that fMRI can be used to predict relapse in substance-dependent individuals. Paulus, M.P., Tapert, S.F. and Schuckit, M.A. Archives of General Psychiatry 62, pp. 761-768, 2005.

Methamphetamine Users in Sustained Abstinence - A Proton Magnetic Resonance Spectroscopy Study

Nordahl and colleagues at the University of California, Davis measured cerebral metabolite levels using magnetic resonance spectroscopy imaging techniques in early abstinent vs long term (at least one year) methamphetamine users and healthy controls. MRS measured N-acetylaspartate-creatine and phosphocreatine (NAA/Cr), choline-creatine and phosphocreatine (Cho/Cr), and choline-N-acetylaspartate (Cho/NAA) ratios were obtained in the anterior cingulate cortex as well as in the primary visual cortex, which served as a control region. The absolute values of Cr did not differ between controls and methamphetamine users. Methamphetamine users had abnormally low NAA/Cr levels within the anterior cingulate cortex, regardless of the time spent abstinent. No NAA/Cr group differences were observed in the primary visual cortex ($F(2,33) = 0.29$; $P = .75$). The Cho/NAA values for the anterior cingulate cortex were abnormally high in the methamphetamine users who recently initiated abstinence were at normal levels in long-term abstinent methamphetamine users. Results are consistent with adaptive changes following cessation of methamphetamine use in the anterior cingulate. Nordahl, T.E, Salo, R., Natsuaki, Y., Galloway, G.P., Waters, C., Moore, C.D., Kile, S. and Buonocore, M.H. Archives of General Psychiatry 62, pp. 444-452, 2005.

Lack of Hippocampal Volume Change in Long-Term Heavy Cannabis Users

Yurgelun-Todd and colleagues at McLean Hospital used structural MRI to investigate the effect of chronic cannabis smoking on the morphology of the hippocampus. Structural MRI was performed on 22 older, long-term cannabis users (reported a mean [SD] of 20,100 [13,900] lifetime episodes of smoking) and 26 comparison subjects with no history of cannabis abuse or dependence. When compared to control subjects, smokers displayed no significant adjusted differences in volumes of gray matter, white matter, cerebrospinal fluid, or left and right hippocampus. Moreover, hippocampal volume in cannabis users was not associated with age of onset of use nor total lifetime episodes of use. These findings are consistent with recent literature suggesting that cannabis use is not associated with structural changes within the brain as a whole or the hippocampus in particular. Tzilos, G.K., Cintron, C.B., Wood, J.B.R., Simpson, N.S., Young, A.D., Pope, H.G. and Yurgelun-Todd, D.A. American Journal on Addictions 14, pp. 64-72, 2005.

Cognitive Impairment in Acute Cocaine Withdrawal

Beversdorf and colleagues at Ohio State University investigated whether in human substance abusers early in cocaine withdrawal there are impairments in a range of cognitive flexibility tasks known to be sensitive to changes in noradrenergic tone. Twelve patients acutely withdrawing from cocaine were compared with gender-, age-, and estimated premorbid intelligence-matched control subjects on tests of cognitive flexibility as well as verbal fluency, verbal memory, spatial memory, and attention. As predicted, impairments were found on the cognitive flexibility tasks, especially in the Anagram Generation task. Impairments also were present in verbal fluency and verbal memory but not spatial memory or attention. These results suggest that cognitive flexibility impairment may relate to the increased noradrenergic activation recently described in cocaine withdrawal. Impairments on verbal tasks may also relate to an impaired flexibility in the search of semantic network. These results are consistent with studies showing treatment benefits for propranolol patients in cocaine withdrawal. Further research will explore whether impaired cognitive flexibility related to altered noradrenergic tone could serve as a mechanism for this treatment response. Kelley, B.J., Yeager, K.R., Pepper, T.H. and Beversdorf, D.Q. Cognitive and Behavioral Neurology 18, pp. 108-112, 2005.

Shape Changes of the Corpus Callosum in Abstinent Methamphetamine Users

Renshaw and colleagues at McLean Hospital used structural MRI to evaluate structural changes of the corpus callosum (CC) in abstinent methamphetamine (MA) users. Shape and size of the CC in 27 MA users were compared to those of 18 healthy comparison subjects. To define the local curvature and width of the CC, medial model-based shape analysis was performed using CC skeletons extracted from 41-distance map. To define the local displacement of the CC, a boundary model-based shape analysis was performed. In addition, the size of regional areas of the CC was measured. In the medial model-based shape analysis, increased curvature in the genu (curvature angle difference=4.1') and decreased width in posterior midbody (width difference=0.77 mm) and isthmus area (width difference=0.86 mm) of the CC were observed in MA users relative to healthy comparison subjects. In the boundary model-based shape analysis, significant displacement was observed in MA users where there were differences in shape/width patterns by the medial model-based shape analysis. There were no differences in the size of regional areas of the CC between groups. Findings suggest that MA use is associated with regional changes in interhemispheric white matter tracts, which connect frontal and parietal cortices and that these frontal and parietal abnormalities may underlie clinical manifestations of MA abuse. Oh, J.S., Lyoo, I.K., Sung, Y.H., Hwang, J., Kim, J., Chung, A., Park, K.S., Kim, S.J., Renshaw, P.F. and Song, I.C. Neuroscience Letters 384, pp. 76-81, 2005.

Impaired Perception of Self-Motion (Heading) in Abstinent Ecstasy and Marijuana Users

Bechara and colleagues at the University of Iowa used a laboratory task to determine whether chronic use of MDMA and THC can impair cognitive processes that help direct our safe movement, and therefore can increase the risk of driving accidents. The study participants were grouped according to their drug use history into 2 groups: MDMA/THC user, and users of THC alone. Perception of self-motion, or heading, from optical flow patterns was assessed using stimuli comprising random dot ground planes presented at three different densities and eight heading angles. On each trial, subjects reported if direction of travel was to the left or the right. Results showed impairments in both drug groups, with the MDMA/THC group performing the worst. The finding that these psychoactive agents adversely affect heading perception, even

in recently abstinent users, raises potential concerns about MDMA use and driving ability. Rizzo, M., Lamers, C.T., Sauer, C.G., Ramaekers, J.G., Bechara, A. and Andersen, G.J. Psychopharmacology 179, pp. 559-566, 2005.

Increased Risk-Taking Decision-Making But Not Altered Response to Punishment in Stimulant-Using Young Adults

Paulus and colleagues at the University of California, San Diego investigated whether increased risky behavior is evident in stimulant-na•ve subjects. Stimulant-using (but not dependent) young adults non-stimulant using subject performed a "risky gains" decision-making task. On each trial, the numbers 20, 40, and 80 are presented individually in ascending order. Subjects press a button to receive the displayed number in points. The 20 is always associated with a gain of 20 points (safe response). There is a chance that waiting to select a 40 or 80 will result in punishment of 40 or 80 points, respectively (risky response). All subjects made fewer risky responses immediately following punished trials ($p < .001$). Stimulant-users made more risky responses than never-users overall ($p < .02$) but showed the same inhibition effect of punishment on next-trial risky responding. Risk-taking in the task correlated with measures of sensation seeking and impulsivity, but not other personality measures, anxiety, or tendency toward alcohol use disorders. One caveat is that because this task requires selection from a sequence of individual options presented according to a fixed schedule, rather than allowing deliberation between simultaneously available options, the risky gains task may model a different sort of risk-taking than other tasks. Nonetheless, the results are consistent with the hypothesis that stimulant-users show increased risk-taking but are not less sensitive to punishments than controls. Leland, D.S. and Paulus, M.P. Drug and Alcohol Dependence 78, pp. 83-90, 2005.

Regional Cerebral Blood Flow Responses to Smoking in Tobacco Smokers after Overnight Abstinence

Zubieta, Domino and colleagues at the University of Michigan used PET to determine the effects of cigarette smoking on brain regional function in a group of chronic smokers on cerebral blood flow (CBF). Nineteen tobacco smokers were studied after about 12 hours of smoking abstinence. Regional CBF (rCBF) measures were obtained with PET and [O-15] H2O in six consecutive scans. Two average-nicotine-yield (1.0 mg) and one denicotinized (0.08 mg) research cigarettes with similar tar yields (9.5 mg and 9.1 mg, respectively) were smoked in a double-blind design, preceded and followed by baseline scans. The rCBF effects of smoking were compared to baseline measures and between cigarettes, as well as to subjective ratings of craving for cigarettes. Smoking the first cigarette of the day resulted in increases in rCBF in the visual cortex and the cerebellum and reductions in the anterior cingulate, the right hippocampus, and the ventral striatum, including the nucleus accumbens. Cigarette craving scores correlated with rCBF changes in the dorsal anterior cingulate and right hippocampus. Less pronounced effects were observed with the second cigarette and the denicotinized cigarette. Smoking affects rCBF not only in areas of the brain rich in nicotinic cholinergic receptors but also in areas implicated in the rewarding effects of drugs of abuse. Furthermore, craving for a cigarette in chronic smokers was correlated with rCBF in the right hippocampus, an area involved in associating environmental cues with drugs, and in the left dorsal anterior cingulate, an area implicated in drug craving and relapse to drug-seeking behavior. Zubieta, J.K., Heitzeg, M.M., Xu, Y..J, Koeppe, R.A., Ni, L.S., Guthrie, S. and Domino, E.F. American Journal of Psychiatry 162, pp. 567-577, 2005.

Dissociation of Inhibition from Error Processing Using a Parametric Inhibitory Task During Functional Magnetic Resonance Imaging

Paulus and colleages at the University of California, San Diego used fMRI to investigate brain activation patterns involved in inhibition, the process that overrides and reverses the execution of a thought, action, or emotion, and is important in daily life. Sixteen healthy volunteers performed a parametrically modulated motor inhibition task during functional magnetic resonance imaging. Two results were observed: (1) increased error-related anterior cingulate cortex activation and, (2) increased inferior frontal gyrus and medial prefrontal cortex activation during inhibition, irrespective of errors. Thus, the parametric nature of the task elucidated a functional dissociation of brain structures involved in motor inhibition from those involved in error processing. Additionally, this task allowed the identification of unique areas of increased activation within specific subregions of the anterior cingulate cortex related to errors made during trials with a high (dorsal anterior cingulate cortex) and low (ventral anterior cingulate cortex) inhibitory load. Matthews, S.C., Simmons, A.N., Arce, E. and Paulus M.P. Neuroreport 16, pp. 755-760, 2005.

Investment Behavior And The Negative Side Of Emotion

Bechara and colleagues at the University of Iowa investigated whether dysfunction in neural systems subserving emotion can lead, under certain circumstances, to more advantageous decisions. In this study normal participants, patients with stable focal lesions in brain regions related to emotion (target patients), and patients with stable focal lesions in brain regions unrelated to emotion (control patients) made 20 rounds of investment decisions. Target patients made more advantageous decisions and ultimately earned more money from their investments than the normal participants and control patients. When normal participants and control patients either won or lost money on an investment round, they adopted a conservative strategy and became more reluctant to invest on the subsequent round, these results suggest that they were more affected than target patients by the outcomes of decisions made in the previous rounds. These results suggest that brain dysfunction may paradoxically result in improved performance in decision-making tasks under certain conditions. Shiv, B., Loewenstein, G., Bechara, A., Damasio, H. and Damasio, A.R. Psychological Science 16, pp. 435-439, 2005.

Decisions Under Uncertainty: Probabilistic Context Influences Activation of Prefrontal and Parietal Cortices

Huettel and colleagues at Duke University used BOLD fMRI to investigate patterns of brain activity when decisions are made under uncertainty, that is, with limited information about their potential consequences. Previous neuroimaging studies of decision-making have implicated regions of the medial frontal lobe in processes related to the resolution of uncertainty. However, a different set of regions in dorsal prefrontal and posterior parietal cortices has been reported to be critical for selection of actions to unexpected or unpredicted stimuli within a sequence. In the current study, authors induced uncertainty using a novel task that required subjects to base their decisions on a binary sequence of eight stimuli so that uncertainty changed dynamically over time (from 20 to 50%), depending on which stimuli were presented. Activation within prefrontal, parietal, and insular cortices increased with increasing uncertainty. In contrast, within medial frontal regions, as well as motor and visual cortices, activation did not increase with increasing uncertainty. Authors conclude that the brain response to uncertainty depends on the demands of the experimental task. When uncertainty depends on learned associations between stimuli and responses, as in previous studies, it modulates activation in the medial frontal lobes. However, when uncertainty develops over short time scales as information is accumulated toward a decision, dorsal prefrontal and posterior parietal contributions are critical for its resolution. The distinction between neural mechanisms subserving different forms of uncertainty resolution provides an important constraint for neuroeconomic models of decision-making. These results also may aid the interpretation of recent studies showing anatomical changes in parietal cortical structures and activation in methamphetamine users. Huettel, S.A., Song, A.W. and McCarthy, G. Journal of Neuroscience 25, pp. 3304-3311, 2005.

Superior Temporal Gyrus and Insula Provide Response and Outcome-Dependent Information During Assessment and Action Selection in a Decision-Making Situation

Paulus and colleagues at the University of California, San Diego used BOLD fMRI to investigate whether distinct neural systems may contribute differentially during various stages within a decision-making situation. This study investigated whether neural activation during assessment or action selection is critically dependent on previous outcomes or actions. Twelve healthy, right-handed subjects (6 females) played a Rock Paper Scissors (RPS) computer game during functional magnetic resonance imaging. Bilateral insula and medial prefrontal cortex (including the anterior cingulate) were specifically engaged during the assessment and action selection stages of decision-making, whereas bilateral superior frontal gyrus and right inferior parietal lobule activated more during the outcome. Two regions of activation within the bilateral superior temporal gyrus activated only when the previous outcome was a win. Moreover, right insula and superior temporal gyrus were active more when the subject switched responses relative to staying with the same choice made on the previous trial. These findings support the hypothesis that distinct neural systems underlie different stages of the decision-making process. Furthermore, the superior temporal gyrus may play an important role in integrating previous actions and successful outcomes into one's decision-making strategy. These results may be directly related to recent findings by the same investigators that decreased activation in these regions predict relapse in methamphetamine abusers. Paulus, M.P., Feinstein, J.S., Leland, D. and Simmons, A.N. Neuroimage 25, pp. 607-615, 2005.

Body Mass Predicts Orbitofrontal Activity during Visual Presentations of High-Calorie Foods

Yurgelun-Todd and colleagues at McLean Hopsital used BOLD fMRI to investigate the relationship between weight status and reward-related brain activity in normal weight humans. Orbitofrontal and anterior cingulate cortex activity as measured by fMRI in 13 healthy, normal-weight adult women as they viewed images of high-calorie and low-calorie foods, and dining-related utensils. Body mass index correlated negatively with both cingulate and orbitofrontal activity during high-calorie viewing, negatively with orbitofrontal activity during low-calorie viewing, and positively with orbitofrontal activity during presentations of nonedible utensils. With greater body mass, activity was reduced in brain regions important for evaluating and modifying learned stimulus-reward associations, suggesting a relationship between weight status and responsiveness of the orbitofrontal cortex to rewarding food images. Killgore, W.D.S. and Yurgelun-Todd, D.A. Neuroreport 16, pp. 859-863, 2005.

Electrophysiological Correlates of Reward Prediction Error Recorded in the Human Prefrontal Cortex

Bechara and colleagues at the University of Iowa investigated used electrophysiological recordings to directly determine neuronal activity in the ventral medial prefrontal cortex during risky behavior. They recording directly from prefrontal depth electrodes in a rare neurosurgical patient while he performed the Iowa Gambling Task, and concurrently measured behavioral, autonomic, and electrophysiological responses. Authors found a robust alpha-band component of event-related potentials that reflected the mismatch between expected outcomes and actual outcomes in the task, correlating closely with the reward-related error obtained from a reinforcement learning model of the patient's choice behavior. The finding implicates this brain region in the acquisition of choice bias by means of a continuous updating of expectations about reward and punishment. Oya, H., Adolphs, R., Kawasaki, H., Bechara, A., Damasio, A. and Howard, M.A. Proceedings National Academy of Sciences, USA 102, pp. 8351-8356, 2005.

Emotion-Modulated Performance and Activity in left Dorsolateral Prefrontal Cortex

Miller and colleagues at the University of Illinois used BOLD functional MRI (fMRI) to examine the relationship between processing of pleasant and unpleasant stimuli and activity in prefrontal cortex in normal healthy subjects. Twenty volunteers identified the colors in which pleasant, neutral, and unpleasant words were printed, Pleasant words prompted more activity bilaterally in dorsolateral prefrontal cortex (DLPFC) than did unpleasant words, In addition, pleasant words prompted more activity in left than in right DLPFC. Response speed to pleasant words was correlated with DLPFC activity. These data directly link positive affect to enhanced prefrontal activity, providing some of the first fMRI evidence supporting models of emotional valence and frontal brain asymmetry based on electroencephalography (EEG). Herrington, J.D., Mohanty, A., Koven, N.S., Fisher, J.E., Stewart, J.L., Banich, M.T., Webb, A.G, Miller, G.A. and Heller, W. Emotion 5(2), pp. 200-207, 2005.

Reinstatement of Conditioned Fear in Humans Is Context Dependent and Impaired in Amnesia

LaBar and Phelps at New York University used a contextual reinstatement procedure to assess the contributions of environmental cues and hippocampal function in the recovery of conditioned fear following extinction in humans. They showed context specificity in the recovery of extinguished skin conductance responses after presentations of an auditory unconditioned stimulus, and that fear recovery did not generalize to an explicitly impaired conditioned stimulus. In addition, the context dependency of fear recovery was replicated using a shock as an unconditioned stimulus. Two amnesic patients failed to recover fear responses following reinstatement in the same context, despite showing initial fear acquisition. These results extend the known functions of the human hippocampus and highlight the importance of environmental contexts in regulating the expression of latent fear associations. LaBar, K.S. and Phelps, E.A. Behavioral Neuroscience 119, pp. 677-686, 2005.

fMRI Sensitization to Angry Faces

Breiter and colleagues used BOLD fMRI to map the neural substrates of responses to facial expressions of anger and evaluated the motivational salience of these stimuli. During functional magnetic resonance imaging, angry and neutral faces were

presented to human subjects. Across experimental runs, signal adaptation was observed. Whereas fearful faces have reproducibly evoked response habituation in amygdala and prefrontal cortex, angry faces evoked sensitization in the insula, cingulate, thalamus, basal ganglia, and hippocampus. Complementary offline rating and key-press experiments determined an aversive rank ordering of angry, fearful, neutral, and happy faces and revealed behavioral sensitization to the angry faces. Subjects rated angry faces, in contrast to other face categories such as fear, as significantly more likely to directly inflict harm. Furthermore, they rated angry faces as significantly less likely to produce positive emotional outcomes than the other face categories. Together these data argue that angry faces, a directly aversive stimulus, produce a sensitization response. These studies form the basis for studying whether drug abusers have altered responses to social stimuli. Strauss, M.M., Makris, N., Aharon, I., Vangel, M.G., Goodman, J., Kennedy, D.N., Gaslc, G.P. and Breiter, H.C. Neuroimage 26, pp. 389-413, 2005.

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

Research Findings - Epidemiology and Etiology Research

Lifetime Prevalence and Age-of-Onset Distributions' of DSM-IV Disorders in the National Comorbidity Survey Replication

This study estimated lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the recently completed National Comorbidity Survey Replication. This nationally representative face-to-face household survey, conducted between February 2001 and April 2003, used the fully structured World Health Organization World Mental Health Survey version of the Composite International Diagnostic Interview. Participants were 9282 English-speaking respondents aged 18 years and older. Results indicated the following lifetime prevalence estimates: anxiety disorders (28.8%), mood disorders (20.8%), impulse-control disorders (24.8%), substance use disorders (14.6%), and any disorder (46.4%). The median age of onset is much earlier for anxiety (11 years) and impulse-control (11 years) disorders than for substance use (20 years) and mood (30 years) disorders. Half of all lifetime cases start by age 14 years and three-fourths by age 24 years. Later onsets are mostly of comorbid conditions, with estimated lifetime risk of any disorder at age 75 years (50.8%) only slightly higher than observed lifetime prevalence (46.4%). Lifetime prevalence estimates are higher in recent cohorts than in earlier cohorts and have fairly stable inter-cohort differences across the life course that vary in substantively plausible ways among socio-demographic subgroups. These findings indicate that about half of Americans will meet the criteria for a DSM-IV disorder sometime in their life, with first onset usually in childhood or adolescence. Interventions aimed at prevention or early treatment need to focus on youth. Kessler, R.C., Berglund, P., Demler, O., Jin, R., and Walters, E.E. Lifetime Prevalence and Age-of-onset Distributions' of DSM-IV Disorders in the National Comorbidity Survey Replication. Archives of General Psychiatry 62, pp. 593-602, 2005.

Prevalence and Treatment of Mental Disorders: 1990 to 2003

Although the 1990s saw enormous change in the mental health care system in the United States, little is known about changes in the prevalence or rate of treatment of mental disorders. This study examined trends in the prevalence and rate of treatment of mental disorders among people 18 to 54 years of age during the past decade. Data from the National Comorbidity Survey (NCS) were obtained in 5388 face-to-face household interviews conducted between 1990 and 1992, and data from the NCS Replication were obtained in 4319 interviews conducted between 2001 and 2003. Anxiety disorders, mood disorders, and substance-abuse disorders that were present during the 12 months before the interview were diagnosed with the use of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). Treatment for emotional disorders was categorized according to the sector of mental health services, psychiatry services, other mental health services, general medical services, human services, and complementary-alternative medical services. Results indicated that the prevalence of mental disorders did not change during the decade (29.4 percent between 1990 and 1992 and 30.5 percent between 2001 and 2003, P=0.52), but the rate of treatment increased. Among patients with a disorder, 20.3 percent received treatment between 1990 and 1992 and 32.9 percent received treatment between 2001 and 2003 (P<0.001). Overall, 12.2 percent of the population 18 to 54 years of age received treatment for emotional disorders between 1990 and 1992 and 20.1 percent between 2001 and 2003 (P<0.001). Only about half those who received treatment had disorders that met diagnostic criteria for a mental disorder. Significant increases in the rate of treatment (49.0 percent between 1990 and 1992 and 49.9 percent between 2001 and 2003) were limited to the sectors of general medical services (2.59

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times as high in 2001 to 2003 as in 1990 to 1992), psychiatry services (2.17 times as high), and other mental health services (1.59 times as high) and were independent of the severity of the disorder and of the sociodemographic characteristics of the respondents. Despite an increase in the rate of treatment, these findings indicate that most patients with a mental disorder do not receive treatment. Continued efforts are needed to obtain data on the effectiveness of treatment in order to increase the use of effective treatments. Kessler, R.C., Demler, O., Frank, R.G., Olfson, M., Pincus, H.A., Walters, E.E., Wang, P., Wells, K.B., and Zaslavsky, A.M., Prevalence and Treatment of Mental Disorders, 1990 to 2003. New England Journal of Medicine, 352, pp. 2515-2523, 2005.

Initial Treatment Contact after First Onset of Mental Disorders in the National Comorbidity Survey Replication

This study investigated patterns and predictors of failure and delay in making initial treatment contact after first onset of a mental disorder in the United States from the recently completed National Comorbidity Survey Replication. This nationally representative face-to-face household survey, conducted between February 2001 and April 2003, used the fully structured World Health Organization World Mental Health Survey version of the Composite International Diagnostic Interview. Participants were 9282 English-speaking respondents aged 18 years and older. Cumulative lifetime probability curves show that the vast majority of people with lifetime disorders eventually make treatment contact, although more so for mood (88.1%-94.2%) disorders than for anxiety (27.3%-95.3%), impulse control (33.9%-51.8%), or substance (52.7%-76.9%) disorders. Delay among those who eventually make treatment contact ranges from 6 to 8 years for mood disorders and 9 to 23 years for anxiety disorders. Failure to make initial treatment contact and delay among those who eventually make treatment contact are both associated with early age of onset, being in an older cohort, and a number of socio-demographic characteristics (male, married, poorly educated, racial/ethnic minority). These findings indicate that failure to make prompt initial treatment contact is a pervasive aspect of unmet need for mental health care in the United States. Interventions to speed initial treatment contact are likely to reduce the burdens and hazards of untreated mental disorder. Wang, P.S., Berglund, P., Olfson, M., Pincus, H.A., Wells, K.B., and Kessler, R.C. Failure and Delay in Initial Treatment Contact after First Onset of Mental Disorders in the National Comorbidity Survey Replication. Archives of General Psychiatry 62, pp. 603-613, 2005.

Patterns and Predictors of Attention-Deficit/Hyperactivity Disorder Persistence into Adulthood: Results from the National Comorbidity Survey Replication

This study examined correlates of persistence of childhood cases into adulthood using a retrospective assessment of childhood ADHD, childhood risk factors, and a screen for adult ADHD. Participants were a sample of 3197 18-44 year old respondents from the National Comorbidity Survey Replication (NCS-R). Blinded adult ADHD clinical reappraisal interviews were administered to a sub-sample of respondents. Multiple Imputation (MI) was used to estimate adult persistence of childhood ADHD. Logistic regression was used to study retrospectively reported childhood predictors of persistence. Potential predictors included socio-demographics, childhood ADHD severity, childhood adversity, traumatic life experiences, and comorbid DSM-IV child-adolescent disorders (anxiety, mood, impulse-control, and substance disorders). The results identified 36.3% of respondents as meeting DSM-IV criteria for current ADHD. Childhood ADHD severity and childhood treatment significantly predicted persistence. Controlling for severity and excluding treatment, none of the other variables significantly predicted persistence even though they were significantly associated with childhood ADHD. These findings identified no modifiable risk factors for adult persistence of ADHD. Further research, ideally based on prospective general population samples, is needed to search for modifiable determinants of adult persistence of ADHD. Kessler, R.C., Adler, L.A., Barkley, R., Biederman, J., Conners, C.K., Faraone, S.V., Greenhill, L.L., Jaeger, S., Secnik, K., Spencer, T., Ustun, T.B., and Zaslavsky, A.M., Patterns and Predictors of Attention-Deficit/Hyperactivity Disorder Persistence into Adulthood, Results from the National Comorbidity Survey Replication. Biological Psychiatry 57, pp. 1442-1451, 2005.

Costs of Attention Deficit-Hyperactivity Disorder (ADHD) in the US

The objective of this study is to provide a comprehensive estimate of the cost of ADHD by considering the healthcare and work loss costs of persons with ADHD, as well as those costs imposed on their family members. Excess per capita healthcare

(medical and prescription drug) and work loss (disability and work absence) costs of treated ADHD patients (ages 7 years-44 years) and their family members (under 65 years of age) were calculated using administrative claims data from a single large company, work loss costs are from disability data or imputed for medically related work loss days. Excess costs are the additional costs of patients and their family members over and above those of comparable control individuals. The excess costs of untreated individuals with ADHD and their family members were also estimated. All per capita costs were extrapolated using published prevalence and treatment rates and population data, the prevalence of persons with ADHD was based upon the literature. Results indicated that the total excess cost of ADHD in the US in 2000 was $31.6 billion. Of this total, $1.6 billion was for the ADHD treatment of patients, $12.1 billion was for all other healthcare costs of persons with ADHD, $14.2 billion was for all other healthcare costs of family members of persons with ADHD, and $3.7 billion was for the work loss cost of adults with ADHD and adult family members of persons with ADHD. These findings indicate that the annual cost of ADHD in the US is substantial. Both treated and untreated persons with ADHD, as well as their family members, impose considerable economic burdens on the healthcare system as a result of this condition. Birnbaum, H.G., Kessler, R.C., Lowe, S.W., Secnik, K., Greenberg, P.E., Leong, S.A., and Swensen, A.R. Costs of Attention Deficit-Hyperactivity Disorder (ADHD) in the US, Excess Costs of Persons with ADHD and their Family Members in 2000. Current Medical Research and Opinion 21, pp. 195-205, 2005.

Trends in Suicide Ideation, Plans, Gestures, and Attempts in the United States: 1990-1992 to 2001-2003

This study provides nationally representative trend data on suicidal ideation, plans, gestures, attempts, and their treatment. Data came from the 1990-1992 National Comorbidity Survey and the 2001-2003 National Comorbidity Survey Replication. These surveys asked identical questions to 9708 people aged 18 to 54 years about the past year's occurrence of suicidal ideation, plans, gestures, attempts, and treatment. Trends were evaluated by using pooled logistic regression analysis. Face-to-face interviews were administered in the homes of respondents, who were nationally representative samples of US English-speaking residents. Results indicated no significant changes occurred between 1990-1992 and 2001-2003 in suicidal ideation (2.8% vs 3.3%, P=.43), plans (0.7% vs 1.0%, P=.15), gestures (0.3% vs 0.2%, P=.24), or attempts (0.4%-0.6%, P=.45), whereas conditional prevalence of plans among ideators increased significantly (from 19.6% to 28.6%, P=.04), and conditional prevalence of gestures among planners decreased significantly (from 21.4% to 6.4%, P=.003). Treatment increased dramatically among ideators who made a gesture (40.3% vs 92.8%) and among ideators who made an attempt (49.6% vs 79.0%). These findings indicate a dramatic increase in treatment, but no significant decrease occurred in suicidal thoughts, plans, gestures, or attempts in the United States during the 1990s. Continued efforts are needed to increase outreach to untreated individuals with suicidal ideation before the occurrence of attempts and to improve treatment effectiveness for such cases. Kessler, R.C., Berglund, P., Borges, G., Nock, M., and Wang, P.S., Trends in Suicide Ideation, Plans, Gestures, and Attempts in the United States, 1990-1992 to 2001-2003. JAMA 293, pp. 2487-2495, 2005.

Prevalence, Severity, and Comorbidity of 12-month DSM-IV Disorders in the National Comorbidity Survey Replication

This study estimated the 12-month prevalence, severity, and comorbidity of DSM-IV anxiety, mood, impulse control, and substance disorders in the recently completed US National Comorbidity Survey Replication. This nationally representative face-to-face household survey, conducted between February 2001 and April 2003, used the fully structured World Health Organization World Mental Health Survey version of the Composite International Diagnostic Interview. Participants were 9282 English-speaking respondents aged 18 years and older. Results indicated the following 12-month prevalence estimates: anxiety (18.1%), mood (9.5%), impulse control (8.9%), substance (3.8%), and any disorder (26.2%). Of 12-month cases, 22.3% were classified as serious, 37.3% moderate, and 40.4% mild. Fifty-five percent carried only a single diagnosis, 22% had 2 diagnoses, and 23% had 3 or more diagnoses. Latent class analysis detected 7 multivariate disorder classes, including 3 highly comorbid classes representing 7% of the population. These findings indicate that mental disorders are widespread, and that serious cases are concentrated among a relatively small proportion of cases with high comorbidity. Kessler, R.C., Chiu, W.T., Demler, O. and Walters, E.E. Prevalence, Severity, and Comorbidity of 12-month DSM-IV Disorders in the National Comorbidity Survey Replication. Archives of General

Psychiatry 62, pp. 617-627, 2005.

Twelve-month Use of Mental Health Services in the United States: Results from the National Comorbidity Survey Replication

This study provided data on patterns and predictors of 12-month mental health treatment in the United States from the recently completed National Comorbidity Survey Replication. Of the 12-month cases, 41.1% received some treatment in the past 12 months, including 12.3% treated by a psychiatrist, 16.0% treated by a nonpsychiatrist mental health specialist, 22.8% treated by a general medical provider, 8.1% treated by a human services provider, and 6.8% treated by a complementary and alternative medical provider (treatment could be received by > 1 source). Overall, cases treated in the mental health specialty sector received more visits (median, 7.4) than those treated in the general medical sector (median, 1.7). More patients in specialty than general medical treatment also received treatment that exceeded a minimal threshold of adequacy (48.3% vs 12.7%). Unmet need for treatment is greatest in traditionally underserved groups, including elderly persons, racial-ethnic minorities, those with low incomes, those without insurance, and residents of rural areas. These findings indicate that most people with mental disorders in the United States remain either untreated or poorly treated. Interventions are needed to enhance treatment initiation and quality. Wang, P.S., Lane, M., Olfson, M., Pincus, H.A., Wells, K.B., and Kessler, R.C. Twelve-month Use of Mental Health Services in the United States - Results from the National Comorbidity Survey Replication. Archives of General Psychiatry 62, pp. 629-640, 2005.

Epidemiological Risk Estimates of Cocaine Dependence for the United States, 2000-2001

This paper presents new estimates for the risk of becoming cocaine dependent within 24 months after first use of the drug, and study subgroup variation in this risk. The study estimates are based on the National Household Survey on Drug Abuse conducted during 2000-2001, with a representative sample of U.S. residents aged 12 years and older (n = 114,241). A total of 1081 respondents were found to have used cocaine for the first time within 24 months prior to assessment. Between 5 and 6% of these recent-onset users had become cocaine dependent since onset of use. Excess risk of recent cocaine dependence soon after onset of cocaine use was found for female subjects, young adults aged 21-25 years, and non-Hispanic Black/African-Americans. The use of crack-cocaine and taking cocaine by injection was associated with having become cocaine dependent soon after onset of use. These epidemiologic findings help to quantify the continuing public health burden associated with new onsets of cocaine use in the 21st century. O'Brien, M.S. and Anthony, J.C. Risk of Becoming Cocaine Dependent, Epidemiological Estimates for the United States, 2000-2001. Neuropsychopharmacology 30, pp. 1006-1018, 2005.

Developmental Trajectories of Offending Predict Alcohol Use, Drug Use, and Depressive Symptoms

This longitudinal study examined the validity of differing offending pathways and the prediction from the pathways to substance use and depressive symptoms for 204 young men. Findings from this study indicated good external validity of the offending trajectories. Further, substance use and depressive symptoms in young adulthood (i.e., ages 23-24 through 25-26 years) varied depending on different trajectories of offending from early adolescence to young adulthood (i.e., ages 12-13 through 23-24 years), even after controlling for antisocial propensity, parental criminality, demographic factors, and prior levels of each outcome. Specifically, chronic high-level offenders had higher levels of depressive symptoms and engaged more often in drug use compared with very rare, decreasing low-level, and decreasing high-level offenders. Chronic low-level offenders, in contrast, displayed fewer systematic differences compared with the two decreasing offender groups and the chronic high-level offenders. The findings supported the contention that varying courses of offending may have plausible causal effects on young adult outcomes beyond the effects of an underlying propensity for crime. Wiesner, M., Kim, H.K. and Capaldi, D.M. Developmental Trajectories of Offending, Validation and Prediction to Young Adult Alcohol Use, Drug Use and Depressive Symptoms. Development and Psychopathology 17, pp. 251-270, 2005.

Cocaine Use and the Occurrence of Panic Attacks

This study uses the case-crossover method to estimate the magnitude of excess occurrence of panic attacks during months of cocaine use vs. months of no cocaine use, motivated by a prior estimate that cocaine users have three-fold excess risk of

panic attack. The epidemiologic case-crossover method is a powerful tool for research on suspected hazards of illegal drug use, the advantage being a subject-as-own-control approach that constrains stable individual-level susceptibility traits. The self-report data on cocaine and panic are from assessments of a nationally representative sample of 1071 recent panic cases age 18 years or older identified as part of the National Household Surveys on Drug Abuse conducted in the United States during 1994-1997. Based on case-crossover estimates, cocaine use is associated with a three- to- four-fold excess occurrence of panic attack (estimated relative risk (RR) = 3.3, p = 0.049, 95% confidence interval, 1.0, 13.7). Year-by-year, the RR estimates from four independent yearly replicates (1994-1997) are 5.0, 2.0, 3.0, and 3.0. While there are several important limitations, this study adds new evidence about a previously reported suspected causal association linking cocaine use to occurrence of panic attacks, and illustrates advantages of the epidemiologic case-crossover approach and new directions in research on hazards of illegal drug use. O'Brien, M.S., Wu, L.T. and Anthony, J.C. Cocaine Use and the Occurrence of Panic Attacks in the Community: A Case-crossover Approach. Substance Use & Misuse 40, pp. 285-297, 2005.

Early Onset Inhalant Use and Risk for Opiate Initiation

This study examined a hypothesized link from early onset inhalant use to later use of opiates by young adulthood, with data from an epidemiological sample of 2311 first graders who entered an urban mid-Atlantic public school system in 1985 or 1986 (49.8% male, 67.1% ethnic minority), and who were studied longitudinally to young adulthood. An estimated 9% had initiated inhalant use before the age of 14 and at follow-up in young adulthood an estimated 3% (n = 66) of the sample had tried opiates at least once. Youth who used inhalants prior to age 14 were twice as likely to initiate opiate use, as compared to those who had never tried. Statistical adjustment for other covariates attenuated but did not dissolve this relationship. These findings help confirm previously reported evidence that the use of inhalants might be an early marker of vulnerability for future involvement with illegal drugs such as heroin, but an exploratory analysis suggests that there may be no direct inhalants-opiate link once a general early onset susceptibility trait is taken into account. Storr, C.L., Westergaard, R. and Anthony, J.C., Early Onset Inhalant Use and Risk for Opiate Initiation by Young Adulthood. Drug and Alcohol Dependence, 78, pp. 253-261, 2005.

Early Violent Death among Delinquent Youth

This study compared mortality rates for delinquent youth with those for the general population, controlling for differences in gender, race/ethnicity, and age. This prospective longitudinal study examined mortality rates among 1829 youth (1172 male and 657 female) enrolled in the Northwestern Juvenile Project, a study of health needs and outcomes of delinquent youth. Participants, 10 to 18 years of age, were sampled randomly from intake at the Cook County Juvenile Temporary Detention Center in Chicago, Illinois, between 1995 and 1998. The sample was stratified according to gender, race/ethnicity (African American, non-Hispanic white, Hispanic, or other), age (10-13 or >= 14 years), and legal status (processed as a juvenile or as an adult), to obtain enough participants for examination of key subgroups. The sample included 1005 African American (54.9%), 296 non-Hispanic white (16.2%), 524 Hispanic (28.17%), and 4 other-race/ethnicity (0.2%) subjects. Data on deaths and causes of death were obtained from family reports or records and were then verified by the local medical examiner or the National Death Index. For comparisons of mortality rates for delinquents and the general population, all data were weighted according to the racial/ethnic, gender, and age characteristics of the detention center, these weighted standardized populations were used to calculate reported percentages and mortality ratios. Mortality ratios were calculated by comparing the sample's mortality rates with those for the general population of Cook County, controlling for differences in gender, race/ethnicity, and age. Results indicated that sixty-five youth died during the follow-up period. All deaths were from external causes. As determined by using the weighted percentages to estimate causes of death, 95.5% of deaths were homicides or legal interventions (90.1% homicides and 5.4% legal interventions), 1.1% of all deaths were suicides, 1.3% were from motor vehicle accidents, 0.5% were from other accidents, and 1.6% were from other external causes. Among homicides, 93.0% were from gunshot wounds. The overall mortality rate was greater than 4 times the general-population rate. The mortality rate among female youth was nearly 8 times the general-population rate. African American male youth had the highest mortality rate (887 deaths per 100 000 person-years). These findings indicate that early violent death among delinquent and general-population youth affects racial/ethnic minorities disproportionately and should be addressed, as are other health disparities. Future studies should identify the most promising

modifiable risk factors and preventive interventions, explore the causes of death among delinquent female youth, and examine whether minority youth express suicidal intent by putting themselves at risk for homicide. Teplin, L.A., McClelland, G.M., Abram, K.M., and Mileusnic, D. Early Violent Death among Delinquent Youth: A Prospective Longitudinal Study. Pediatrics 115, pp. 1586-1593, 2005.

Early Parenting Practices and Subsequent Risk of Trying Cannabis

This study estimated the extent to which parental monitoring, parental involvement and reinforcement, and coercive parental discipline during primary school might exert a durable influence on the risk of transitioning into an early stage of youthful cannabis onset. Data come from a prospective study of first-graders who entered an urban public school system in the middle 1980s. Parenting was assessed in fourth grade, and cannabis experiences were evaluated during periodic assessments from middle childhood through young adulthood. Results indicated that the estimated risk of the first chance to try cannabis peaked around 16 to 18 years of age. Lower parental involvement and reinforcement and higher coercive parental discipline were associated modestly with a greater risk of cannabis exposure opportunity through the years of adolescence and into early adulthood (parental involvement and reinforcement, adjusted relative risk, 1.4, 95% confidence interval, 1.1-1.7, parental discipline, adjusted relative risk, 1.3, 95% confidence interval, 1.1-1.5). These findings indicate that certain parenting practices in the mid-primary school years may have a durable impact, perhaps helping to shield youths from having a chance to try cannabis throughout adolescence and into young adulthood. Chen, C.Y., Storr, C.L., and Anthony, J.C. Influences of Parenting Practices on the Risk of Having a Chance to Try Cannabis. Pediatrics 115, pp. 1631-1639, 2005.

Gender/Racial Differences in "Jock" Identity, Dating, and Adolescent Sexual Risk

Despite recent declines in overall sexual activity, sexual risk-taking remains a substantial danger to US youth. Existing research points to athletic participation as a promising venue for reducing these risks. Linear regressions and multiple analyses of covariance were performed on a longitudinal sample of nearly 600 Western New York adolescents in order to examine gender- and race-specific relationships between "jock" identity and adolescent sexual risk-taking, including age of sexual onset, past-year and lifetime frequency of sexual intercourse, and number of sexual partners. After controlling for age, race, socioeconomic status, and family cohesion, male jocks reported more frequent dating than nonjocks but female jocks did not. For both genders, athletic activity was associated with lower levels of sexual risk-taking, however, jock identity was associated with higher levels of sexual risk-taking, particularly among African American adolescents. Future research should distinguish between subjective and objective dimensions of athletic involvement as factors in adolescent sexual risk. Miller, K.E., Farrell, M.P., Barnes, G.M., Melnick, M.J. and Sabo, D. Gender/racial Differences in Jock Identity, Dating, and Adolescent Sexual Risk. Journal of Youth and Adolescence 34, pp. 123-136, 2005.

Nicotine Phenotypes based on Withdrawal Discomfort, Response to Smoking, and Ability to Abstain

Smoking is often viewed as a comprehensive phenotype rather than a complex set of traits involving intermediate phenotypes. To explore this issue in a laboratory setting, researchers tested 69 smokers stratified on depression, nicotine dependence, and gender. On the third day of an initial withdrawal period, participants were tested for differences in uncued and cued craving and withdrawal. On the fourth day, participants were exposed to a controlled dose of smoke and assessed for physiological and hedonic effects and reduction of craving and withdrawal. Following resumption of smoking for at least a week, participants were then tested on their ability to abstain for an 11-day interval. During the withdrawal test, high-depressed smokers and men exhibited elevated craving and withdrawal scores overall, whereas no differences emerged for dependence. Cue exposure produced significant increases in craving but not withdrawal. During the smoke-exposure test, men were significantly more likely than women, and high-depressed smokers more likely than low-depressed smokers, to show evidence of experiencing pleasurable "buzzes." High-dependent smokers showed significant increases in diastolic blood pressure, possibly suggestive of greater sensitivity to nicotine. During the quit test, high-dependent smokers had more difficulty abstaining than low-dependent smokers, and women more than men, no differences emerged based on depression. Independently of group membership, inability to abstain was predicted by increased anxiety, depression, and difficulty concentrating in response to cue exposure. These findings provide support for the existence of phenotypes that can be distinguished by withdrawal

symptomatology (primarily driven by depression) and ability to remain abstinent (primarily driven by dependence). Pomerleau, O.F., Pomerleau, C.S., Mehringer, A.M., Snedecor, S.M., Ninowski, R. and Sen, A. Nicotine Dependence, Depression, and Gender: Characterizing Phenotypes Based On Withdrawal Discomfort, Response to Smoking and Ability to Abstain. Nicotine & Tobacco Research 7, pp. 91-102, 2005.

Accuracy of Offspring Assessment Based on Parental Smoking Status

This study investigated the accuracy of offspring assessments of parental smoking status among 116 parents and 151 adult children (276 parent-child dyads) who provided data on both their own and their parents' smoking status. All currently smoking and all ex-smoking parents were correctly classified as ever-smokers by their offspring (n = 79 and 100, respectively). Of the 97 offspring who reported on never-smoking parents, 88 correctly classified their parents as never-smokers. Thus, sensitivity for detecting ever-smoking in parents was 100%, and specificity, 91%. Because all incorrect classifications involved never-smoking parents, further analyses focused on this group. Too few parents were misclassified to permit testing of parental characteristics. Offspring who misclassified their parents were significantly older than those who did not, neither sex nor smoking status of the offspring was associated with the increased likelihood of misclassification. No significant differences were discovered for dyadic factors (concordance/discordance for sex, parent-offspring age difference). Overall, these results support the utility of proxy reports of parental smoking phenotype by adult informants when self-report is unavailable. Pomerleau, C.S., Snedecor, S., Ninowski, R., Gaulrapp, S., Pomerleau, O.F. and Kardia, S.L.R. Differences in Accuracy of Offspring Assessment Based On Parental Smoking Status. Addictive Behaviors 30, pp. 437-441, 2005.

Validation of Retrospective Reports of Early Smoking Experiences

Initial sensitivity to the pharmacological effects of a drug may affect patterns of future use and dependence for a wide variety of drugs. Retrospective reports of sensations experienced upon early experimentation, however, may be limited by recall bias based on time elapsed and subsequent experiences. To validate reports of early experiences with nicotine, this study investigated 34 smokers who had contributed retrospective data on early experiences with smoking. Half had reported experiencing a buzz from smoking their first cigarette (the "yes" group), the other half had not (the "no" group). To simulate initial sensitivity to nicotine, participants were asked to remain abstinent from smoking for 5 days to allow for the dissipation of tolerance. They then participated in a laboratory session in which they were re-exposed to nicotine in an unfamiliar form (nicotine nasal spray) and asked to indicate pleasurable responses by depressing a foot pedal if and when they experienced a "pleasurable buzz." Smokers in the "yes" group were marginally more likely to be male. The two groups did not differ significantly on age or race. The "yes" group smoked significantly more cigarettes/day than the "no" group. When the two groups were compared for response to nasal spray following 5 days' abstinence, smokers in the "yes" group were marginally more likely to have signaled experiencing at least one pleasurable buzz and rated "pleasurable sensation from spray" on a 100-mm visual analogue scale administered 10 min after nicotine dosing significantly higher than were those in the "no" group. To the extent that several days' abstinence can serve as a model for initial sensitivity to nicotine, our findings validate retrospective reports of pleasurable sensations upon early smoking experimentation. Pomerleau, O.F., Pomerleau, C.S., Mehringer, A.M., Snedecor, S.A. and Cameron, O.G. Validation of Retrospective Reports of Early Experiences with Smoking. Addictive Behaviors 30, pp. 607-611, 2005.

Timing of Entry into Fatherhood in Young, At-Risk Men

The timing of first fatherhood was examined in a sample of 206 at-risk, predominantly White men, followed prospectively for 17 years. An event history analysis was used to test a model wherein antisocial behavior, the contextual and familial factors that may contribute to the development of antisocial behavior, and common correlates of such behavior, including academic failure, substance use, and early initiation of sexual behaviors, lead both directly and indirectly to an early transition to fatherhood. Having a mother who was younger at first birth, low family socioeconomic status, poor academic skills, failure to use condoms, and being in a cohabitating or marital relationship predicted entry into fatherhood. Pears, K.C., Pierce, S.L., Kim, H.K., Capaldi, D.M. and Owen, L.D. The Timing of Entry into Fatherhood in Young, At-risk Men. Journal of Marriage and the Family 67, pp. 429-447, 2005.

Personality Factors Contributing to Comorbidity

The authors investigated the role of personality traits in accounting for comorbidity in common psychiatric and substance use disorders. 7588 participants in a population-based twin registry in Virginia were interviewed with the SCID to determine lifetime diagnoses of common psychiatric and substance use disorders, and completed self-report questionnaires to determine dimensions of neuroticism, extraversion, and novelty seeking. Of note, neuroticism accounted for the highest proportion of comorbidity within internalizing (mood and anxiety) disorders (20-45%) and between internalizing and externalizing (antisocial and substance use) disorders (19-88%). Variation in neuroticism and novelty seeking each accounted for a modest proportion (10-12% and 7-14%, respectively) of the comorbidity within externalizing disorders. Extraversion contributed negligibly. Although rates of disorders differed among the genders, the patterns of comorbidity accounted for by personality were similar in males and females. These findings extend previous research on personality and psychiatric disorder by using a population-based sample and by quantifying the proportion of comorbidity explained by personality dimension. Given that comorbidity among psychiatric and substance use disorders is extremely common, these findings can help refine our understanding of those underlying traits that put individuals at risk for multiple later disorders, regardless of gender, particularly the role of neuroticism. Khan, A.A., Jacobson, K.C., Gardner, C.O., Prescott, C.A. and Kendler, K.S. Personality and Comorbidity of Common Psychiatric Disorders. British Journal of Psychiatry, 186, pp. 190-196, 2005.

Association of Early Adolescent Problem Behavior with Adult Psychopathology

The authors investigated whether the association between adolescent problem behavior and adult substance use and mental health disorders was general, such that adolescent problem behavior elevates the risk for a variety of adult disorders, or outcome-specific, such that each problem behavior is associated specifically with an increased risk for disorders clinically linked to that behavior (e.g., early alcohol use with adult alcohol abuse). A population-based group of 578 male and 674 female twins reported whether they had ever engaged in, and the age of initiation of, five adolescent problem behaviors: smoking, alcohol use, illicit drug use, police trouble, and sexual intercourse. Participants also completed a structured clinical interview at both ages 17 and 20 covering substance use disorders, major depressive disorder, and antisocial personality disorder. Each problem behavior was significantly related with each clinical diagnosis. The association was especially marked for those who had engaged in multiple problem behaviors before age 15. Among those with four or more problem behaviors before age 15, the lifetime rates of substance use disorders, antisocial personality disorder, and major depressive disorder exceeded 90%, 90%, and 30% in males and 60%, 35%, and 55% in females, respectively. The association between the clinical diagnoses and adolescent problem behavior was largely accounted for by two highly correlated factors. This study suggests that early adolescent problem behavior identifies a subset of youth who are at an especially high and generalized risk for developing adult psychopathology. McGue, M. and Iacono, W.G. The Association Of Early Adolescent Problem Behavior With Adult Psychopathology. American Journal of Psychiatry. 162(6), pp. 1118-1124, 2005.

Coping Factors Mediating the Association between Childhood ADHD and Adolescent Cigarette Use

The authors sought to examine the possible role of coping factors in the relationship between childhood attention deficit hyperactivity disorder (ADHD) and higher rates of later cigarette use. Subjects were 142 adolescents who had been diagnosed with ADHD in childhood, and 100 adolescent controls without ADHD. Adolescents were interviewed regarding cigarette use and parental support, while parents were interviewed regarding coping skills; both parents and adolescents were interviewed with standardized instruments to determine psychiatric diagnoses (ADHD and CD). Results indicated that subjects with childhood ADHD smoked more frequently, had fewer adaptive coping skills, and lower parental support compared with controls. Reduced coping and support partially mediated the association between ADHD and smoking. Persistence of ADHD (which could be related to reduced coping skills) and adolescent conduct disorder (which often relates to poor parental support) were also important in the model. As noted by the authors, the model accounted for 30% of the variance in smoking, and other variables need to be included to explicate these relationships further. However, if confirmed, these findings point to coping behaviors as possible targets for preventive intervention with ADHD youth at risk for cigarette use. Molina, B.S., Marshal, M.P., Pelham, W.E. Jr. and Wirth, R.J. Coping Skills and Parent Support Mediate The Association Between Childhood Attention-Deficit/Hyperactivity Disorder And Adolescent Cigarette Use. Journal of Pediatric

Psychology 30(4), pp. 345-357, 2005.

Child Psychopathology and Early Substance Use

This study examined the relationships between childhood externalizing and internalizing disorders and early substance use and abuse, in a large community-based sample of twins of both genders, at ages 11 and 14. The sample was composed of twins participating in the Minnesota Twin Family Study, an epidemiological sample of twins and their families representative of the largely-Caucasian population of Minnesota. A total of 699 twin girls and 665 twin boys participated at both time-points. Twins participated in in-person, life-time diagnostic assessments of the following childhood DSM III-R externalizing and internalizing disorders at age 11: conduct disorder, oppositional defiant disorder, attention deficit hyperactivity disorder, major depressive disorder and in addition, for girls only, overanxious disorder and separation anxiety disorder. At ages 11 and 14, substance use and abuse were assessed. Consistent with the literature, externalizing disorders at age 11, particularly conduct and oppositional disorders, were related to substance use and abuse in both boys and girls, at ages 11 and 14. Among the internalizing disorders, only major depression among girls at age 11 showed a relationship to substance use and abuse at age 14. These findings can help refine populations that may benefit from interventions for early substance abuse. King, S.M., Iacono, W.G. and McGue, M. Childhood Externalizing and Internalizing Psychopathology in the Prediction of Early Substance Use. Addiction, 99, pp. 1548-1559, 2004.

Heritability of Cigarette Smoking and Family Dysfunction in Women

Previous studies using adoption samples have found that the impact of genetic risk factors on alcoholism in women have a stronger influence when there is a history of conflict in the family. The authors of this study investigated a similar impact on cigarette smoking in a population-based twin sample. A sample of 1676 female twins from a population-based registry provided data on maximum lifetime cigarette smoking and family dysfunction assessed as the mean report of up to four informants (twin, co-twin, mother, father). Using a variety of statistical approaches and models, the hypothesis was not confirmed; on the contrary, the heritability (proportion of variance due to genetic factors) of cigarette smoking was reduced at higher levels of family dysfunction, and unique environmental factors became more significant. Further work, with different populations and substances, is needed; in the meantime, the authors caution against a broad assumption that adverse childhood environments always increase heritability. Kendler, K.S., Aggen, S.H., Prescott, C.A., Jacobson, K.C. and Neale, M.C. Level of Family Dysfunction and Genetic Influences on Smoking in Women. Psychological Medicine, 34, pp. 1263-1269, 2004.

Partitioning Common and Specific Influences on Drug Use and Abuse

Previous studies of the genetic epidemiology of drug abuse have generally modeled drug use and drug abuse and dependence separately. However, the authors of this paper note that drug use disorders are contingent on drug use (one cannot develop the disorder without first using the drug) and so they apply a model that can partition the genetic and environmental influences into those that are common to both stages and those that are stage-specific. Using the SCID, data on use and abuse/dependence of cannabis, cocaine, sedatives, stimulants and any illicit drug were obtained from 1191 male and 934 female Caucasian twin pairs in the Mid-Atlantic Twin Registry. Results provide evidence for both genetic, shared environmental and unique environmental influences that are common to illicit drug use and abuse/dependence, and factors that are specific to abuse/dependence. Similarities among different types of drugs and between both sexes were noted in the patterns of risk influences. Thus, it is likely that there are some genetic and environmental factors that influence both drug use and abuse/dependence regardless of the drugs used or gender of the user, and that there are other factors that operate specifically to predispose to abuse and dependence once use has onset. Agrawal, A., Neale, M.C., Jacobson, K.C., Prescott, C.A. and Kendler, KS. Illicit Drug Use and Abuse/Dependence: Modeling of Two-Stage Variables Using the CCC Approach. Addictive Behaviors 30(5), pp. 1043-1048, 2005.

Effectiveness of Highly Active Antiretroviral

Therapy among IDU with Late-Stage HIV Highly active antiretroviral therapy (HAART) has been shown to be effective in different populations, but data among injection drug users are limited. HIV-infected IDUs recruited into the Acquired Immunodeficiency Syndrome Link to Intravenous Experiences (ALIVE) Study as early as 1988 were tested semiannually to identify their first CD4-positive T-lymphocyte cell count below 200/ll; they were followed for mortality through 2002. Visits were

categorized into the pre-HAART (before mid-1996) and the HAART eras and further categorized by HAART use. Survival analysis with staggered entry was used to evaluate the effect of HAART on AIDS-related mortality, adjusting for other medications and demographic, clinical, and behavioral factors. Among 665 participants, 258 died during 2,402 person-years of follow-up. Compared with survival in the pre-HAART era, survival in the HAART era was shown by multivariate analysis to be improved for both those who did and did not receive HAART (relative hazards .25, 0.06 and 0.33, respectively; $p < 0.001$). Inferences were unchanged after restricting analyses to data starting with 1993 and considerations of lead time bias and human immunodeficiency viral load. The annual CD4-positive T-lymphocyte cell decline was less in untreated HAART-era participants than in pre-HAART-era participants as well, suggesting that changing indications for treatment may have contributed to improved survival and that analyses restricted to the HAART era probably underestimate HAART effectiveness. These findings suggest that treatment can work in this and other populations where reduced access may have occurred from a general reluctance by clinicians to provide treatment due to concerns about adherence and the potential development of resistant virus that might be transmitted to others. Research is needed to develop and improve approaches for reaching HIV-infected IDUs to offer and monitor effective antiretroviral treatment. Vlahov, D., Galai, N., Safaeian, M., Galea, S., Kirk, G., Lucas, G. and Sterling, T. Effectiveness of Highly Active Antiretroviral Therapy among Injection Drug Users with Late-Stage Human Immunodeficiency Virus Infection. Amer J Epidemiol, 161, pp. 999-1012, 2005.

The Effect of HIV Infection on Overdose Mortality

This prospective cohort study sought to quantify the association of HIV infection with overdose mortality and explore the potential mechanisms. A total of 1927 active IDUs who were HIV seronegative at baseline, of whom 308 later HIV seroconverted, were followed semi-annually for death from 1988 to 2001. Survival analyses using marginal structural and standard Cox models were used to evaluate the effect of HIV infection on the risk of overdose mortality. The study found that overdose death rates were higher in HIV-seropositive than HIV-seronegative drug users: 13.9 and 5.6 per 1000 person-years, respectively ($P < 0.01$). The hazard ratio (HR) was 2.54 [95% confidence interval (CI) 1.47, 4.38] for the marginal structural model and 2.06 (95% CI 1.25, 3.38) for the standard Cox model, both adjusted for demographics, drug injection characteristics, alcohol abuse, substance abuse treatment, and sexual orientation. Adjusting for possible time-varying mediators (i.e. drug use, medical conditions and healthcare access) in extended marginal structural models reduced the effect of HIV on overdose mortality by 30% (HR 1.82, 95% CI 1.01, 3.30). Abnormal liver function was associated with a higher risk of overdose mortality (HR 2.00, 95% CI 1.05, 3.84); adjustment for this further reduced the effect of HIV on overdose mortality. These findings indicate that HIV infection is associated with a higher risk of overdose mortality. Drug use behavior, systematic disease and liver damage associated with HIV infection appeared to account for a substantial portion of this association. Wang, C., Vlahov, D., Galaia, N., Colea, S., Bareta, J., Pollinia, R., Mehtaa, S., Nelson, K. and Galea, S. The Effect of HIV Infection on Overdose Mortality. AIDS, 19, pp. 935-942, 2005.

Prospective Evaluation of Community-Acquired Acute-Phase Hepatitis C Virus Infection

More than two-thirds of hepatitis C virus (HCV) infections in Western countries are caused by injection drug use, but prospective clinical data regarding the most common mode of HCV acquisition are rare, in part because acute-phase HCV infection is usually asymptomatic. To characterize acute-phase HCV infection, 179 HCV antibody negative injection drug users were prospectively evaluated; 62 (34%) of these patients had seroconverted. Twenty of the participants who seroconverted had long-term follow-up with consistent monthly sampling before and after seroconversion, allowing detailed study. The first indication of HCV infection was the presence of HCV RNA in serum, which preceded elevation of alanine transaminase levels and total bilirubin levels to more than or equal to 2 times baseline in 45% and 77% of patients, respectively. No subjects had jaundice. The median time from initial viremia to seroconversion was 36 days (range, 32 46 days). In one instance, viremia was detected 434 days before seroconversion. However, in no other case was HCV RNA detected >63 days before seroconversion. In subjects with viral persistence, a stable level of HCV RNA in the blood was noted in some subjects within 60 days after the initial detection of viremia, but in others, it was not apparent until >1 year later. In subjects with long-term viral clearance, HCV became persistently undetectable as early as 94 and as late as 620 days after initial viremia. These data underscore the

importance of nucleic acid screening of blood donations to prevent HCV transmission and of long-term follow-up to ascertain whether there is viral persistence, at least among injection drug users. Cox, A., Netski, D., Mosbruger, T., Sherman, S., Strathdee, S., Ompad, D., Vlahov, D., Chien D., Shyamala, V., Ray, S. and Thomas, D. Prospective Evaluation of Community-Acquired Acute-Phase Hepatitis C Virus Infection. Clin Infectious Diseases, 40, pp. 951-958, 2005.

Drug Use and HIV Risk Practices of Secondary and Primary Needle Exchange Users

This study examined HIV risk practices associated with secondary needle exchange, obtaining needles from a needle exchange program (NEP) through others who attend in person. Data were analyzed from NEP logs, a survey and HIV testing from 901 drug injectors who (a) always visited NEPs themselves to get needles (primary-only NEP users), (b) obtained at least some NEP needles by having others exchange for them (mixed/secondary NEP users), and (c) obtained no needles from an NEP. About 22% of 40,000 NEP visits involved secondary exchanges, and these accounted for over half of all needles exchanged. In multiple logistic regression analyses, primary-only needle exchange was significantly associated with lower levels of receptive needle sharing, backloading, sharing other injection equipment and lending used needles, and positively associated with obtaining drug treatment. Mixed/secondary needle exchange was associated with less receptive needle sharing and a greater likelihood of drug treatment. Secondary exchange facilitated HIV risk reduction but the salutary effects of NEPs were attenuated in mixed/ secondary exchangers. Huo, D., Bailey, S., Hershow, R. and Ouellet, L. Drug Use and HIV Risk Practices of Secondary and Primary Needle Exchange Users. AIDS Educ Prev. (2), pp. 170-184, April 7, 2005.

Attitudes of Emergency Medical Service Providers Towards Naloxone Distribution Programs

Training and distributing naloxone to drug users is a promising method for reducing deaths associated with heroin overdose. Emergency Medical Service (EMS) providers have experience responding to overdose, administering naloxone, and performing clinical management of the patient. Little is known about the attitudes of EMS providers toward training drug users to use naloxone. An anonymous survey was conducted of 327 EMS providers to assess their attitudes toward a pilot naloxone program. Of 176 who completed the survey, the majority were male (79%) and Caucasian (75%). The average number of years working as an EMS provider was 7 (SD = 6). Overall attitudes toward training drug users to administer naloxone were negative, with 56% responding that this training would not be effective in reducing overdose deaths. Differences in attitudes did not vary by gender, level of training, or age. Providers with greater number of years working in EMS were more likely to view naloxone trainings as effective in reducing overdose death. Provider concerns included drug users' inability to properly administer the drug, program condoning and promoting drug use, and unsafe disposal of used needles. The study concludes that incorporating information about substance abuse and harm reduction approaches in continuing education classes may improve the attitudes of providers toward naloxone training programs. Tobin, K., Gaasch, W., Clarke, C., MacKenzie, E. and Latkin, C. Attitudes of Emergency Medical Service Providers Towards Naloxone Distribution Programs. J Urban Health, 82(2), pp. 296-302, 2005.

The Effect of Serostatus on HIV Risk Behavior Change Among Women

Sex Workers in Miami, Florida HIV prevention and risk reduction are especially salient and timely issues for women, particularly among those who are drug-involved or who exchange sex for drugs or money. Studies suggest that HIV-prevention measures can be effective with highly vulnerable women, and have the potential to produce significant reductions in risk behaviors among both HIV-negative and HIV-positive women. Within this context, this paper examines risk behaviors and HIV serostatus among 407 drug-involved women sex workers in Miami, Florida, and investigates the effects of participation in HIV testing, counseling, and a risk-reduction intervention on subsequent behavioral change among this population. Overall, at follow-up, the HIV-positive women were 2.4 times more likely than the HIV-negative women to have entered residential treatment for drug abuse, 2.2 times more likely to have decreased the number of their sex partners, 1.9 times more likely to have decreased the frequency of unprotected sex, 1.9 times more likely to have reduced their levels of alcohol use, and 2.3 time more likely to have decreased their crack use. These data support the importance of HIV testing and risk-reduction programs for drug-involved women sex workers. Inciardi, J., Surratt, H., Kurtz, S. and Weaver, J. The Effect of Serostatus on HIV Risk Behavior Change Among Women Sex Workers in Miami, Florida. AIDS Care, 17 (Supplement 1): S88-S101, June 2005.

Racial/Ethnic Disparities in Injection Drug Use in Large US Metropolitan Areas

Because Blacks and Latinos bear a disproportionate burden of injection-related health problems compared with whites, this investigation sought to examine and describe black/white and Latino/white disparities in injecting drugs in 94 US metropolitan statistical areas (MSAs) in 1998. Using US Census data and three databases documenting injectors' use of different healthcare services (drug treatment, HIV counseling and testing, and AIDS diagnoses), researchers calculated database-specific black/white and Latino/white disparities in injecting in each MSA and created an index of black/white and Latino/white disparities by averaging data across the three databases. They found that the median black/white injecting disparity in the MSAs ranged from 1.4 to 3.7 across the three databases; corresponding median Latino/white injecting disparities ranged from 1.0 to 1.1. Median black/white and Latino/white index disparity values were 2.6 and 1.0, respectively. The findings suggest that, although whites were the majority of injectors in most MSAs, database-specific and index black/white disparity scores indicate that blacks were more likely to inject than whites. While database-specific and index disparity scores indicate that Latinos and whites had similar injecting rates, they also revealed considerable variation in disparities across MSAs. Future research would help to understand the causes of these disparities, including racial/ethnic inequality and discrimination, and to identify their contributions to the disproportionate burden of injection-related health problems borne by blacks and Latinos. Cooper, H., Friedman, S., Tempalski, B., Friedman, R. and Keem, M. Racial/Ethnic Disparities in Injection Drug Use in Large US Metropolitan Areas. Ann Epidemiol, 15, pp. 326-334, 2005.

Respondent-Driven Sampling to Recruit MDMA Users: A Methodological Assessment

Recruiting samples that are more representative of illicit drug users is an on-going challenge in substance abuse research. Respondent-driven sampling (RDS), a new form of chain-referral sampling, is designed to eliminate the bias caused by the non-random selection of the initial recruits and reduce other sources of bias (e.g. bias due to volunteerism and masking) that are usually associated with regular chain-referral sampling. This study provides a methodological assessment of the application of RDS among young adult MDMA/ecstasy users in Ohio. The results show that the sample compositions converged to equilibrium within a limited number of recruitment waves, independent of the characteristics of the initial recruits (i.e. seeds). The sample compositions approximated the theoretical equilibrium compositions, and were not significantly different from the estimated population compositions-with the exception that White respondents were over-sampled and Black respondents were under-sampled. The effect of volunteerism and masking on the sampling process was found not to be significant. Though identifying productive seeds and improving the referral rate are significant challenges when implementing RDS, the findings demonstrate that RDS is a flexible and robust sampling method. RDS has the potential to be widely employed in studies of illicit drug-using populations. Wang, J., Carlson, R., Falck, R., Siegal, H., Rahman, A. and Li, L. Respondent-Driven Sampling to Recruit MDMA Users: A Methodological Assessment. Drug and Alcohol Depend, 78, pp. 147-157, 2005.

Drug Sharing Among Heroin Networks: Implications for HIV and Hepatitis B and C Prevention

Qualitative and quantitative findings from the baseline survey of a longitudinal, socially focused blood-borne disease intervention study among 611 heroin IDUs in Denver indicate that high risk injection practices-the sharing of contaminated drug solution in particular-often occur as a consequence of how heroin is obtained, the quantity obtained and the setting where it is injected. Contamination occurs if a contaminated syringe is used to liquefy and apportion the shared drug. In a cohort of 304 heroin injecting networks, there was at least one member who, when asked to describe their last injection, reported dividing the drug as a liquid (82%), using a reservoir of water that syringes had been rinsed in to mix drugs (67%), using a common cooker (86%)-a proxy for drug sharing-and beating a shared cotton filter (58%). In contrast, only 22% reported syringe sharing. Variables associated with various injection practices included location of the last injection episode, quantity of drug injected, dope sickness, and years injecting. When compared to those who injected in a safe setting, those in an unsafe location had almost three times the odds (OR = 2.9; 95% CI: 1.9, 4.6) of being part of an injection episode where there was cooker sharing; and the smaller the quantity of heroin (²1/4 gram v. >1/4 gram) present at the episode, the greater the odds that cooker sharing occurred (OR = 1.8;

95% CI: 1.2, 2.6). Use of a used, unbleached syringe to prepare shared drugs had twice the odds of occurring in "unsafe" v. safe settings (OR = 2.2; 95% CI: 1.3, 4.0) and in episodes in which a participant was dopesick (OR = 2.1; 95% CI: 1.2, 3.6). In summary, this study found that risky injection practices occur within an injection process that is, in part, a response to a structurally imposed risk environment. The findings indicate that reducing the blood-borne disease risks embedded within this process requires interventions designed to mitigate the environmental factors that influence it, including syringe accessibility, law enforcement strategies and the settings where IDUs inject drugs. Koester, S., Glanz, J. and Baron, A. Drug Sharing Among Heroin Networks: Implications for HIV and Hepatitis B and C Prevention. AIDS and Behavior, 9(1), pp. 27-39, 2005.

"Long-Term" and "New" IDUs in a Declining HIV/AIDS Epidemic in Rio de Janeiro, Brazil

A substantial decline of HIV prevalence has been observed in injection drug users (IDUs) from Rio de Janeiro, in recent years. Differential characteristics and behaviors of new (injecting for <6 years) and long-term (>= 6 years) injectors may help to understand recent changes and to implement appropriate prevention strategies. Between October 1999 and December 2001, 609 active/ex-IDUs were recruited from different communities, interviewed, and tested for HIV. Contingency table analysis and t-tests were used to assess differences between new and long-term injectors. Multiple Logistic Regression was used to identify independent predictors of HIV serostatus for long-term and new injectors. HIV prevalence was found to be 11.7% for 309 long-term injectors (95% CI 8.1- 15.3) and 4.3% for 300 new injectors (95% CI 2.0-6.6). New injectors reported having engaged in treatment and having received syringes from needle exchange programs (NEPs) more frequently than long-term injectors in the last 6 months, but sharing behaviors remained frequent and even increased vis-a`-vis long-term injectors. For male new injectors, "sexual intercourse with another man" was found to be the sole significant risk factor for HIV infection (Adj OR=8.03; 95% CI 1.52-42.48). Among male long-term injectors, ÔÔto have ever injected with anyone infected with HIV'' (Adj OR=3.91; 95% CI 1.09-14.06) and to have ÔÔever been in prison'' (Adj OR=2.56; 95% CI 1.05-6.24) were found to be significantly associated with HIV infection. New injectors are seeking help in drug treatment centers or needle exchange programs. They differ from long-term injectors in terms of their risk factors for HIV infection and have lower prevalence levels for HIV. Such differences may help to understand the recent dynamics of HIV/AIDS in this population and highlight the need to reinforce new injectors' help-seeking behavior and to reduce current unacceptably high levels of unprotected sex and syringe sharing in new injectors despite attendance of prevention/treatment programs. Hacker, M., Friedman, S., Telles, P., Teixeira, S., Bongertz, V., Morgado, M. and Bastosi, F. The Roles of "Long-Term" and "New" IDUs in a Declining HIV/AIDS Epidemic in Rio de Janeiro, Brazil. Subst Use & Misuse, 40, pp. 99-123, 2005.

Challenges to Research on HIV/AIDS Among Migrant and Immigrant Hispanic Populations in the U.S.

Migrant populations in the U.S. have been found to be at risk for HIV/AIDS. The growth in immigrant and migrant Hispanic populations increases the need to enhance understanding of influences on their HIV-risk behaviors. Four challenges to conducting research among these populations have been identified: (1) the need to use multilevel theoretical frameworks; (2) the need to differentiate between Hispanic subgroups; (3) challenges to recruitment and data collection; and (4) ethical issues. This article describes how two studies of Hispanic immigrants and migrants in the New York area addressed these challenges. One study focused on new immigrants from Mexico, the Dominican Republic, El Salvador, Honduras and Guatemala, and a second study focused on Puerto Rican drug users. Both studies incorporated qualitative and quantitative methods to study these hard-to-reach populations. Continued research to understand socio-cultural and contextual factors affecting drug abuse and HIV risk among mobile and migrant populations is crucial to developing sustainable and effective intervention programs. Deren, S., Shedlin, M., Decena, C. and Mino, M. Challenges to Research on HIV/AIDS Among Migrant and Immigrant Hispanic Populations in the U.S. J Urban Health, 82(2), Spplt 3: 13-25, 2005.

Predictors of High Rates of Suicidal Ideation Among Drug Users

Several studies have attempted to understand the link among substance abuse, depression, and suicidal ideation (SI). Assessment of this link is important to develop specific interventions for persons in substance abuse treatment. This association was tested among 990 drug users in and out of treatment with significant criminal justice histories from two NIDA-sponsored studies. The Diagnostic Interview Schedule and

Substance Abuse Module assessed DSM-III-R depression, number of depression criteria met, antisocial personality disorder (ASPD), and substance use disorders. Compared with men, women were twice as likely to report depression (24% vs. 12%), whereas men were nearly twice as likely to report ASPD (42% vs. 24%). High rates of SI were found, with women more likely than men to report thoughts of death (50% vs. 31%), wanting to die (39% vs. 21%), thoughts of committing suicide (47% vs. 33%), or attempting suicide (33% vs. 11%); 63% of women and 47% of men reported at least one of these suicidal thoughts or behaviors. Male and female ideators were more likely than nonideators to report depressed mood and to meet criteria for depression, ASPD, and alcohol use disorders. Male ideators were more likely than male nonideators to meet criteria for cocaine use disorders. Using logistic regression, SI among men was predicted by alcohol use disorder (OR - 1.60), ASPD (OR - 1.59), and number of depression criteria (OR _ 9.38 for five criteria). Among women, SI was predicted by older age, marital status, alcohol use disorder (OR - 2.77), and number of depression criteria (OR - 9.12 for five criteria). These original findings point out the need to discuss suicidal thoughts among depressed drug users for early treatment and prevention. Cottler, L., Campbell, W., Krishna, V., Cunningham-Williams, R. and Abdallah, A. Predictors of High Rates of Suicidal Ideation Among Drug Users. J Nerv Ment Dis,193, pp. 431-437, 2005.

Knowledge of Hepatitis among Active Drug Injectors at a SEP

IDUs are at high risk for contracting and spreading viral hepatitis through nonsterile injection practices, unprotected sexual contact, and unsanitary living conditions. This study sought to characterize hepatitis knowledge, prior testing, and vaccination history among IDUs at a New York City syringe exchange program (SEP). IDU subjects generally had a poor understanding of viral hepatitis transmission and prevention. They also had low vaccination rates: only 8% reported receiving hepatitis A vaccine and 11% hepatitis B vaccine. These findings suggest that educating IDUs about risky behaviors and medical preventive interventions, such as vaccines for hepatitis A and B and treatment for hepatitis C, may help prevent disease and reduce transmission. Stronger linkages between health-care centers and SEPs, drug treatment programs, and other service delivery centers where IDUs are encountered may promote hepatitis education and vaccination. Carey, J., Perlman, D., Friedmann, P., Kaplan, W., Nugent, A., Deutscher, M., Masson, C. and Des Jarlais, D. Knowledge of Hepatitis among Active Drug Injectors at a SEP. J Subst Abuse Treat, 29, pp. 47-53, 2005.

Use of Electronic Debit Cards in Longitudinal Data Collection with Geographically Mobile Drug Users

This study sought to assess the use of electronic debit (ATM) cards in conducting longitudinal research with geographically mobile ("urban nomad") drug users. Young illicit drug users with recent travel history were street-recruited from the Lower East Side area of New York City. Multiple efforts were made to develop rapport and positive relationships between participants and the study. Honoraria were paid through electronic debit cards usable at ATMs countrywide. Participants were encouraged to complete follow-up interviews in person if they were in New York City, or by telephone if elsewhere. Follow-up rates from two other recent cohort studies of young drug users in New York were used to compare with those from this study. 139 participants were recruited between 2001-2002. They had traveled extensively, averaging 31 trips per participant to different cities during the prior 3 years. Telephone follow-up interviews were obtained from participants in over 200 different cities/towns. The follow-up rates were 81% at 6 months and 71% at 12 months, substantially higher than corresponding rates in the comparison studies. The use of electronic debit cards, combined with other efforts to develop positive relationships and rapport with participants, led to high rates of continued study participation. Debit cards appear to be a useful and promising approach to conduct longitudinal research with geographically mobile populations. Des Jarlais, D., Perlis, T. and Settembrino, J. The Use of Electronic Debit Cards in Longitudinal Data Collection with Geographically Mobile Drug Users. Drug and Alcohol Depend, 77, pp. 1-5, 2005.

Barriers to Health and Social Services for Street-Based Sex Workers

Homelessness, poverty, drug abuse and violent victimization faced by street-based women sex workers create needs for a variety of health and social services, yet simultaneously serve as barriers to accessing these very services. Researchers utilized interview (n = 586) and focus group (n = 25) data to examine the service needs and associated barriers to access among women sex workers in Miami, Florida. Women most often reported acute service needs for shelter, fresh water, transportation, crisis intervention, and drug detoxification, as well as long-term needs

for mental and physical health care, drug treatment, and legal and employment services. Barriers included both structural (e.g., program target population, travel costs, office hours, and social stigma) and individual (e.g., drug use, mental stability, and fear) factors. Bridging these gaps is tremendously important from a public health perspective given the disease burden among this population. The findings support additional efforts to improve service staff training and outreach and to reduce marginalization and stigma in this population through peer education, empowerment, and accessing care and treatment. Kurtz, S., Surratt, H., Kiley, M. and Inciardi, J. Barriers to Health and Social Services for Street-Based Sex Workers. J Health Care for the Poor and Underserved, 16, pp. 345-361, 2005.

Post-Circuit Blues: Motivations and Consequences of Crystal Meth Use among Gay Men in Miami

Miami, Florida was at the vanguard of the rise of circuit parties and attendant club drug use--especially ecstasy, GHB, and ketamine-in the 1990s. Crystal methamphetamine, a drug of abuse among gay men for some years on the West coast, gradually moved east toward the end of the decade and recently became prevalent in Miami. This paper reports the results of focus group research into the motivations and consequences of crystal use among gay men in this new setting. Loneliness, fears about physical attractiveness due to aging and illness, and desires to lose sexual inhibitions were common motivations for using the drug. Continued use of crystal was often described as the cause of lost friendships, employment and long-term relationships, as well as sexual behaviors that put men at risk for HIV and other sexually transmitted infections. Implications for drug and sexual risk prevention interventions are discussed. Kurtz, S. Post-Circuit Blues: Motivations and Consequences of Crystal Meth Use Among Gay Men in Miami. AIDS Behav., 9(1), pp. 63-72, 2005.

The Social Structural Production of HIV Risk among IDUs

In this paper, researchers discuss the increasing appreciation for and need to understand how social and structural factors shape HIV risk. Drawing on a review of recently published literature, they describe the social structural production of HIV risk associated with injecting drug use. They use an inclusive definition of the HIV Ôrisk environment' as the space, whether social or physical, in which a variety of factors exogenous to the individual interact to increase vulnerability to HIV. Factors identified as critical in the social structural production of HIV risk associated with drug injecting include cross-border trade and transport links; population movement and mixing; urban or neighborhood deprivation and disadvantage; specific injecting environments (including shooting galleries and prisons); the role of peer groups and social networks; the relevance of Ôsocial capital' at the level of networks, communities and neighborhoods; the role of macro-social change and political or economic transition; political, social and economic inequities in relation to ethnicity, gender and sexuality; the role of social stigma and discrimination in reproducing inequity and vulnerability; the role of policies, laws and policing; and the role of complex emergencies such as armed conflict and natural disasters. The researchers argue that the HIV risk environment is a product of interplay in which social and structural factors intermingle but where political-economic factors may play a predominant role; moreover, Ôstructural HIV prevention' implies community actions and structural changes within a broad framework concerned to alleviate inequity in health, welfare and human rights. Rhodes, T., Singer, M., Bourgois, P., Friedman, S. and Strathdee, S. The Social Structural Production of HIV Risk among IDUs. Social Science and Medicine, 61, pp. 1026-1044, 2005.

Herpes Simplex Virus 2 and Syphilis Among Young Drug Users in Baltimore, Maryland

To examine the sex specific seroprevalence and correlates of herpes simplex virus 2 (HSV-2) and syphilis among a cohort of young drug users, researchers recruited drug users aged 15-30 years old who used heroin, cocaine, or crack between October 1999 and August 2002. Baseline interviews gathered information on socio-demographics, drug use and sexual behaviors. Serum was tested at baseline for HSV-2 and syphilis seroreactivity. For each sexually transmitted infection (STI), infected and non-infected participants were stratified by sex and compared using x2, Mann-Whitney tests, and logistic regression. The study found that, of the 543 participants recruited, 42.4% were female and 39.3% were African-American. The seroprevalence of STIs among females and males, respectively, were HSV-2: 58.7% and 22.0%; syphilis: 4.3% and 0.3%. In multivariate models, older age, African-American race, having over 30 lifetime sex partners, current HIV infection and previous incarceration were independently associated with HSV-2 infection among males. For females, older age,

African-American race, sex trade, and daily heroin use were independently associated with HSV-2. For females, only a self reported previous syphilis diagnosis was associated with current syphilis seroreactivity in multivariate analyses. Examination of this cohort revealed a particularly high seroprevalence of HSV-2 and syphilis, especially among female drug users. Few infected participants had been previously diagnosed with these infections. Plitt, S., Sherman, S., Strathdee, S. and Taha, T. Herpes Simplex Virus 2 and Syphilis Among Young Drug Users in Baltimore, Maryland. Sex Transm Inf., 81, pp. 248-253, 2005.

Drinking Restraint and Alcohol Outcomes Among COAs

A subsample from a longitudinal study on children of alcoholics (COAs) (COAs, n= 189; controls, n=192), including participants with complete data from two relevant collection periods (Time 3, Mean age = 15.1 and Time 4, Mean age = 20.3), was included in this study on associations among parent alcoholism, early drinking restraint, and alcohol-related outcomes. Findings replicate and extend previous cross-sectional literature by replicating the main effects of drinking restraint as a risk factor for subsequent drinking for controls. However, for COAs, drinking restraint was protective against subsequent alcohol use. Furthermore, participants at the extreme levels of drinking restraint were least likely to develop alcohol dependence. Trim, R.S. and Chassin, L. Drinking Restraint, Alcohol Consumption, and Alcohol Dependence Among Children of Alcoholics. Stud Alcohol, 65, pp. 122-125, 2004.

Resilience, Internalizing Symptomology, and Positive Affect in a Community Sample of Children of Alcoholics

This sample was part of a larger longitudinal study of non-Hispanic Caucasian and Hispanic adolescents and their families (N=216 children of alcoholics [COAs], N=201 non COAs] recruited through court records, HMO well being evaluations, and community telephone surveys. Computer assisted interviews were conducted three times at yearly interviews. A subset of COAs performing at high and average levels of competence levels in multiple domains were identified. However, in comparison to matched controls, fewer COAs performed in a highly competent manner, and more performed in a low-competent manner for both the conduct/rule-abiding and academic competence domains. No significant differences were found between COAs and controls in the domain of social competence. For both COAs and controls, high competence was associated with fewer internalizing symptoms and the endorsement of positive affect. These findings suggest that behavioral resilience is not associated with psychological costs but is associated with decreased internalizing and increased positive affect. The authors conclude that efforts to encourage competent performance in COAs should be associated with decreased internalizing symptomatology and increased positive affect, serving to increase positive mental health for COAs. Carle, A.C. and Chassin L. Resilience in a Community Sample of Children of Alcoholics: Its Prevalence and Relation to Internalizing Symptomatology and Positive Affect. Applied Developmental Psychology, 25, pp. 577-595, 2005.

Homogeneity and Heterogeneity of Drug Use Patterns Within and Between Hispanic Students in the U.S

Data from the Monitoring the Future study were used to compare trends in and correlates of marijuana use, cocaine use, and heavy alcohol use for adolescents of Mexican American, Puerto Rican, Cuban, and other Latin American heritage in the United States. Data from nationally representative samples of eighth-grade Hispanic students who participated in the Monitoring the Future study during the years 1991-2002 (n=24,235) were analyzed. This study found that drug use differed considerably according to ethnic group on language first spoken, parental education, urbanicity, and region. In addition, drug use was significantly higher among boys and adolescents of almost all Hispanic ethnicities who did not live with both parents. The study findings suggest that the heterogeneity in drug use patterns among adolescents of different Hispanic ethnicities should be considered in the development and targeting of prevention programs. Delva, J., Wallace, J.M., O'Malley, P.M., Bachman, J.G., Johnston, L.D. and Schulenberg, J.E. American Journal of Public Health, 95(4), pp. 696-702, April 2005.

The Relationship Between College Fraternity/Sorority Membership and Substance Use

Nationally representative probability samples of US high school seniors (modal age 18 years) were followed longitudinally across two follow-up waves during college (modal ages 19/20 and 21/22). The longitudinal sample consisted of 10 cohorts (senior years of 1988 97) made up of 5883 full-time undergraduate students, of whom 58% were

women and 17% were active members of fraternities or sororities. Analysis of the longitudinal data revealed that active members of fraternities and sororities had higher levels of heavy episodic drinking, annual marijuana use and current cigarette smoking than non-members at all three waves. Although members of fraternities reported higher levels than non-members of annual illicit drug use other than marijuana, no such differences existed between sorority members and non-members. Heavy episodic drinking and annual marijuana use increased significantly with age among members of fraternities or sororities relative to non-members, but there were no such differential changes for current cigarette use or annual illicit drug use other than marijuana. These findings indicate that the higher rates of substance use among US college students who join fraternities and sororities predate their college attendance, and that membership in a fraternity or sorority is associated with considerably greater than average increases in heavy episodic drinking and annual marijuana use during college. These findings have important implications for prevention and intervention efforts aimed toward college students, especially members of fraternities and sororities. McCabe, S.E., Schulenberg, J.E., Johnston, L.D., O'Malley, P.M., Backman, J.G. and Kloska, D.D. Selection and Socialization Effects of Fraternities and Sororities on US College Student Substance Use: A Multi-cohort National Longitudinal Study, Addiction, 100, pp. 512-524, 2005.

Substance Use Disorders Among Adolescents Who Use Marijuana and Inhalants

This study examined the association between the use of inhalants, marijuana, and other drugs and recent DSM-IV substance use disorders among adolescents aged 12-17 years. Data were drawn from 2000 to 2001 National Household Surveys on Drug Abuse. Adolescents aged 12-17 years who reported having ever used an illicit drug in their lifetime were categorized into four mutually exclusive groups: inhalant users (16%), marijuana users (53%), inhalant and marijuana users (16%), and other drug users (15%). Logistic regression models were used to estimate associations with recent substance use diagnoses among lifetime adolescent drug users (N= 10,180). Analyses revealed that 31% of lifetime drug users reported having never used marijuana. One half of these atypical drug users were predominantly nonmedical users of pain relievers. Adolescents who used inhalants or other drugs but not marijuana were least likely to report multidrug use. Adolescents who reported using both inhalants and marijuana were most likely to use three or more classes of drugs (73%) and to receive a diagnosis of past year alcohol (35%) and drug (39%) abuse or dependence. These findings suggest that among lifetime adolescent drug users, those who use both inhalants and marijuana are at very high risk for alcohol and drug use disorders, underscoring the importance of early-targeted interventions. Wu, L.T., Pilowsky, D.J. and Schlenger, E.W. High Prevalence of Substance Use Disorders Among Adolescents Who Use Marijuana and Inhalants. Drug and Alcohol Dependence, 78(1), pp. 23-32, April 2005.

Parent Occupation, Education, and Smoking and Adult Offspring Smoking

This study includes 603 families that have been followed for a period of 25 years (86.7% and 81.7% of the children's mothers and fathers, respectively, had an educational level of 12th grade or higher; 77.5% of the youth had a mother and/or father belonging to the white-collar occupational class. The two objectives include: (1) examining the independent associations between two components of parental SES (educational attainment and blue-collar/white-collar occupational status) and adult offspring smoking; and (2) examining the intervening factors between parental educational achievement, parental occupational status, and prenatal smoking, and smoking in their adult offspring. Findings suggest that parental blue-collar status, low parental educational achievement, and parental smoking were related to adult offspring smoking. This link was mediated by parent - child relationship, which in turn was mediated by smoking in late adolescence with respect to adult offspring smoking. Both components of parental SES (low educational achievement and blue-collar status) predict smoking in their adult offspring, although the respective pathways were somewhat different. Specifically, parental education showed a direct pathway to adult offspring smoking, whereas the parental occupation pathway was mediated by smoking in late adolescence. Parental blue-collar (versus white-collar) occupational status was associated with less parent-child mutual attachment (e.g., greater parent-child conflict, less identification with the parent), and lower parental educational aspirations for their children. Interestingly, weaker parent-child bond was associated with smoking in late adolescence, which was the most powerful predictor of adult offspring smoking. Fagan, P., Brook, J.S., Rubenstone, E. and Zhang, C. Parental Occupational, Education, and Smoking as Predictors of Offspring Tobacco Use in Adulthood: A Longitudinal Study. Addictive Behaviors, 30, pp. 517-529, 2005.

Coping Styles and Stress from Adolescence to Adulthood Among COAs

This study used a longitudinal design to examine the development of coping styles over adolescence, continuity in these coping styles, the impact of coping on adult stress and substance use, and differences in coping between children of alcoholics and their peers. The sample of 340 adolescents were followed from 11 to 23 years of age. Small to moderate effect sizes suggested inter-individual continuity in coping over time, such that those higher than their peers in planful or cognitive-avoidant coping at one point in time were likely to be higher than their peers at another point in time as well. Significant intra-individual change over time was found in the normative trends in coping, as well as inter-individual differences among adolescents in their coping trajectories. Individual trajectories of both planful and cognitive-avoidant coping showed mean decrements over time, suggesting an average decrease over adolescence. Adolescent coping continued to modestly predict coping styles in young adulthood. Adolescent planful coping predicted greater active coping in adulthood, whereas adolescent avoidant cognitive coping predicted greater avoidant coping in adulthood. The relation between transition-related stress that may be somewhat controllable and alcohol use was exacerbated by greater avoidant coping. However, a marginally significant interaction between major life events, which tend to be uncontrollable, and drug use was buffered by greater avoidant coping. This suggests that avoidant coping may be more useful for uncontrollable as opposed to controllable stressors. COAs reported less planful coping and more cognitive-avoidant coping in adolescence as well as less active coping in young adulthood. Hussong, A.M. and Chassin, L. Stress and Coping Among Children of Alcoholic Parents through the Young Adult Transition. Development and Pyschopathology, 16, pp. 985-1006, 2004.

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

Research Findings - Prevention Ressearch

Children in EIFC Had Fewer Failed Placements than Children in Regular Foster Care

From the early 1980s through the mid-1990s, children under age 6 were the fastest growing segment of the U.S. foster care population. These children are at exceptionally high risk for poor outcomes across many domains, including risk for substance use and abuse. The Early Intervention Foster Care (EIFC) program was designed to improve reunification and adoption outcomes for foster children in this age range. Children receive individual therapy, and birth parents or other permanent placement families receive intensive parent training. The program emphasizes concrete encouragement for prosocial behavior, consistent, nonabusive limit setting to address disruptive behavior, and close supervision of the child in order to create the optimal environmental conditions for developmental progress, including a responsive and consistent caregiver and a predictable daily routine. To test the efficacy of the EIFC, the Oregon Department of Human Services Child Welfare identified 3-6 year old foster care children in need of a new foster placement. Eligible participants were randomly assigned to the intervention (EIFC, n = 47) or regular foster care comparison (RFC, n = 43). Families were assessed at entry, 3 to 5 weeks after entering their new foster care placement and at 3-month intervals over 24 months. Of the 90 children, 54 were placed permanently. Although they entered permanent placement at equal rates, experiences varied greatly. Placements failed for 36% of RFC children compared to only 10% of EIFC children. The number of placements prior to the study was significantly related to failed placements for children in RFC but not for children in EIFC. Permanent placement success rate was 64% for RFC and 90% for EIFC. Fisher, P.A., Burraston, B. and Pears, K. The Early Intervention Foster Care Program: Permanent Placement Outcomes From a Randomized Trial. Child Maltreatment, 10, pp. 61-71, 2005.

Pre- and Post-HAART Risk Behaviors of Youth Living with HIV

This study examined transmission behaviors among youth living with HIV (YLH), pre- and post-HAART (Highly Active Antiretroviral Therapy). Two cohorts were recruited: (1) 349 YLH during 1994 to 1996 and (2) 175 YLH during 1999 to 2000, after the wide availability of HAART. The cross-sectional data were drawn from 2 different cohorts of YLH collected at 2 different points in time, 1 pre- and the other post-introduction of HAART. Differences in sexual and substance-use risk acts and quality of life were examined. The post-HAART YLH were more likely to engage in unprotected sex (odds ratio [OR] =1.96; p<.05) and substance use (marijuana OR=2.36; p<.01; hard drugs OR=2.80; p<.01), to be more emotionally distressed OR=1.64; p<.05), and to have lower self-reported quality of life than were pre-HAART YLH. Lightfoot, M., Swendeman, D., Rotheram-Borus, M.J., Comulada, W.S. and Weiss R. Risk Behaviors of Youth Living with HIV: Pre- and Post-HAART. American Journal of Health Behavior, 29(2), pp. 162-171, 2005.

HIV Predictors of Sexual Transmission Risk Behaviors among HIV-Positive Young Men

Reduction in the incidence of high-risk sexual behaviors among HIV-positive men is a priority. This study examined the roles of current substance use and delinquency-related variables, and more distal demographic and psychosocial variables as predictors of serious high-risk sexual behaviors among 248 HIV-positive young males, aged 15 - 24 years. Demographics (ethnicity, sexual orientation and poverty) and background psychosocial factors (coping style, peer norms, emotional distress, self-

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esteem and social support) predicted recent problem behaviors (delinquency, common drug use and hard drug use), which in turn predicted recent high-risk sexual behaviors. Hard drug use and delinquency were found to predict sexual risk behaviors directly, as did lower self-esteem, being White and being gay/bisexual. Negative peer norms strongly influenced delinquency and substance use and positive coping predicted less delinquency. In turn, less positive coping and negative peer norms exerted indirect effects on sexual transmission risk behavior through delinquency and hard drug use. Results suggest targeting hard drug use, delinquency, maladaptive peer norms, dysfunctional styles of escaping stress and self-esteem in the design of intervention programs for HIV-positive individuals. Stein, J.A., Rotheram-Borus, M.J., Swendeman, D. and Milburn, N.G. AIDS CARE-Psychological and Socio-Medical Aspects of AIDS/HIV, 17(4), pp. 433-442, 2005.

Schools and Homes In Partnership (SHIP): Long-Term Effects of a Preventive Intervention Focused on Social Behavior and Reading Skill in Early Elementary School

This paper reports a randomized controlled trial of the effects of behavioral parenting skills training, social skills training, and supplemental reading instruction on the social behavior of early elementary school children (K through 3). Children were selected on the basis of teacher-rated aggressive behavior or reading-skill deficits. The intervention was delivered over a 2-year period and follow-up data were collected for two additional years. There were 162 in the intervention group and 165 in the control group; 171 Hispanic children and 158 European-American; 153 female. The intervention affected only two of eight measures of child functioning: 1) parent daily reports of antisocial behavior ($p=.04$), and 2) parent ratings of coercive behavior ($p=0.02$). There was evidence that parents of boys in the intervention condition displayed significantly greater declines in their rated use of coercive discipline than did parents of boys in the control condition. Smolkowski, K., Biglan, A., Barrera, M., Taylor, T., Black, C. and Blair, J. Prevention Science, 6(2), pp. 113-125, 2005.

Evaluation of a High School Peer Group Intervention for At-Risk Youth

The purpose of this paper is to examine the effectiveness of Reconnecting Youth, a prevention program for at-risk high school youth. Data are from a large, independently evaluated effectiveness trial in two diverse urban school districts. A total of 1,218 students participated; 50% were male; average age was 15. They tested whether positive efficacy trial effects could be replicated, and whether any negative behavioral effects occur when clustering high-risk youth. Although mixed program effects were observed at immediate post-intervention, only negative effects were found at 6-month follow-up. These effects included less optimal scores on measures of Grade Point Average (GPA), anger, school connectedness, conventional peer bonding, and peer high-risk behaviors. Overall, they found little support for the use of this social-influence model intervention aimed at increasing school connectedness for high-risk youth. Further, this study provides evidence that clustering high-risk youth in preventive interventions has the potential for iatrogenic effects. Cho, H.S., Hallfors, D.D. and Sanchez, V. Journal of Abnormal Child Psychology, 33(3), pp. 363-374, 2005.

Peer Influence is an Important Mediator for Smoking

Mediation analyses were conducted on a middle school student population (2,554 treatment and 1,723 control) data where students were exposed to Project ALERT (a social influence-based school prevention program), to examine the mechanisms by which program effects on past month cigarette use and alcohol misuse were achieved. Results for cigarettes showed that all hypothesized mediating variables were significant mediators of ALERT's effect on intentions to smoke and past month cigarette use, with peer influence being the strongest. Results for alcohol point to positive beliefs about the consequences of drinking as an important mediator for alcohol misuse. Taken together, the findings highlight an avenue for program improvement through increased impact on peer influence to use alcohol and drugs. Orlando, M., Ellickson, P.L., McCaffrey, D.F., and Longshore, D.L. Mediation Analyses of a School-based Drug Prevention Program: Effects of Project ALERT. Prevention Science, 6(1), pp. 35-46, 2005.

Adolescents' Beliefs About Harm of Substance Use on Future Aspirations

One consistently reported protective factor in terms of adolescent drug use risk is bonding to school. This study examined the dynamic relationship between school bonding, beliefs about the deleterious effects of substance use on future aspirations, and subsequent substance use (cigarettes, alcohol, marijuana) among a sample of

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1065 middle school students. The students participated in a larger prevention study, but represented the control condition, which received no intervention. The students were in 6th or 7th grade at the initial survey and they provided data on three additional occasions over a 2-year period. Mediation models showed that beliefs about the risks of substance use on future aspirations were a significant mediator of the relationship between school bonding and subsequent substance use. That is, adolescent's perceptions about the risks associated with substance use on future aspirations explained part of the reason why poor school bonding predicts subsequent substance use. Further analyses suggested that students who were characterized by a consistently poor bond to school were less likely to perceive that substance use would have deleterious effects on the attainment of future goals. In addition, a strong intra-individual effect of school bonding indicated that as a student became more or less bonded to his/her school, the belief that substance use may harm his/her future also changed in a similar fashion. By implementing on-going school-based programs that foster strong school bonds, adolescents may be more likely to perceive that substance use will impact the attainment of future goals, and as a result, they may be less likely to use substances. Henry, K.L., Swaim, R.C., and Slater, M.D. Intraindividual Variability of School Bonding and Adolescents' Beliefs About the Effect of Substance Use on Future Aspirations. Prevention Science, 6, pp. 101-112, 2005.

Risky Products Elicit More Arousal and Memory than Non-risky Products

This article reports on two studies designed to measure whether the mere presence of a risky product in a message elicits greater attention and arousal in young adults. Participants for both studies (n = 42) were recruited from undergraduate communication courses at a large Midwestern university. The average age of the participants was 20 and 42.9% of them were male. In the first study, participants viewed and rated 30 pictures of risky (alcohol, tobacco, drugs, condoms) and nonrisky (soda, juice, food) products while heart rate and skin conductance were measured. In the second study, participants viewed and rated 30 risky and nonrisky product words. Results indicated that the risky pictures and words elicited more emotional and physiological arousal than nonrisky pictures and words. Both risky pictures and words were remembered better than nonrisky pictures and words. However, there was little evidence to suggest that risky products elicited more attention than nonrisky products. Instead, the results showed that risky products might be identified more quickly than nonrisky products. Overall these two studies suggest that the mere presence of a risky product either pictorial or verbal elicits more arousal and more memory, but not more attention. These findings could have practical application for designing effective health campaign messages. The arousal elicited by risky products results in the automatic allocation of resources to storage, and as a result, the risky products are remembered better than the nonrisky products. However, because messages that contain representations of risky products may require more resources to process they may be more likely to result in cognitive overload. Lang, A., Chung, Y., Lee, S., and Zhao, X. It's the Product: Do Risky Products Compel Attention and Elicit Arousal in Media Users? Health Communications, 17, pp. 283-300, 2005.

School Prevention Coordinators Influence Selection of Evidence-based Curricula

In 1999 a written survey of substance abuse prevention coordinators (N=1593) in public schools that served students in grades 5-8 indicated that 47.5% of districts used at least one evidence-based curriculum (EBC) in their middle schools. Coordinators reported they had the greatest input in decisions about curricula. In a multivariate analysis of factors positively associated with district-level decisions to adopt EBC programs, significant factors included input from a state prevention group, use of information disseminated by NIDA or CSAP, use of local needs assessment data, consideration of research showing which curricula are effective, and allocation of a greater proportion of the coordinator's time to substance use prevention activities. The conclusion is that state and federal agencies should increase their efforts in disseminating information about EBC programs, targeting in particular the district substance use prevention coordinator. Rohrbach, L.A., Ringwalt, C.R., Ennett, S.T. and Vincus, A.A. Factors Associated With Adoption of Evidence-based Substance Use Prevention Curricula in US School Districts. Health Education Research, 2, pp. 1-13, 2005.

School-based Prevention Implemented Via School-Extension Collaboration

Despite availability of empirically supported school-based prevention programs, adoption and implementation fidelity of such programs appear to be low. To investigate school adoption and implementation processes, Project ALERT a program

identified as evidence-based, was replicated by using Cooperative Extension Specialists as implementers. Interviews with school personnel revealed: 1) schools were not aware of evidence-based programs until Extension approached them; 2) schools afraid to eliminate DARE; 3) teachers were unlikely to implement with fidelity; 4) implementation of theory-based prevention was not consistent with school views of curriculum delivery; and 5) schools believed Project ALERT via Cooperative Extension personnel was an advantage over teacher delivery, but only 3 of the 8 schools sustained the model. Their article discusses potential for Extension as a national implementation system, the value of qualitative inquiry to study processes of adoption, and issues related to the selection and implementation of evidence-based programs. St. Pierre, T.L. and Kaltreider, L. Tales of Refusal, Adoption, and Maintenance: Evidence-based Substance Abuse Prevention Via School-Extension Collaboration. American Journal of Evaluation, 25(4), pp. 479-491, 2005.

Community Organizing to Prevent Youth Drug Use and Violence

Multiple studies have demonstrated that community organizing is an effective method to influence public health problems. Understanding and documenting the community organizing process is critical for dissemination. The DARE Plus Project is a multi-component, community-wide intervention to reduce drug use and violent behaviors among adolescents, using classroom, family, and community organizing strategies. This paper describes the community organizing methods and process results of 8 adult and youth action teams, and suggests that community organizing is an effective method for engaging community members in prevention efforts around youth drug use and violence. Bosma, L.M., Komro, K.A., Perry, C.L., Veblen-Mortenson, and Farbakhsh, K. Community Organizing to Prevent Youth Drug Use and Violence: The DARE Plus Project. Journal of Community Practice, 13(2), pp. 5-19, 2005.

Quality of Implementation: Developing Measures Crucial to Understanding the Diffusion of Preventive Interventions

As prevention programs become disseminated, the most serious threat to effectiveness is maintaining the quality of implementation intended by the developers. This paper presents a methodology for measuring quality of implementation in school settings and presents data from a pilot study designed to test several of the proposed components. These methods included assessments of adherence, quality of process, the positive or negative valence of adaptations, teachers' attitudes and teachers' understanding of program content. This study was conducted with 11 teachers who had varying degrees of experience with teaching Life Skills Training (LST). Observation and interview data were collected during visits to schools. Results suggest that quality of implementation can be measured through observation and interview. Teachers varied in adherence and quality of program delivery. All teachers made adaptations to the program. Experienced teachers were more likely to adhere to the curriculum, deliver it in a way that was more interactive and engaging to students, communicate the goals and objectives better, and make positive adaptations. The field can use these findings as the basis for exploring strategies for measuring and improving quality of implementation. Dusenbury, L., Brannigan, R., Hansen, W.B., Walsh, J. and Falco, M. Quality of Implementation: Developing Measures Crucial to Understanding the Diffusion of Preventive Interventions. Health Education Research, 20(3), pp. 308-313, 2005.

Key Informant Assessments of Community Readiness Benefits Prevention Trial

Researchers and practitioners have found that communities vary greatly in their interest and willingness to try new prevention strategies. In this study key informant readiness was assessed via interviews conducted with community members in 16 U.S. communities (8 treatment, 8 control), in a group-randomized trial of a community and school media intervention, prior to and following the intervention. Project staff asked community members to identify people in their community who were the most knowledgeable or influential relative to the issue of substance use. Recruitment was stratified to represent a broad spectrum of society, with at least one person in each community representing the perspectives of schools, law enforcement, human services, and the general community. Results indicated that the intervention itself influenced community knowledge of effort and improved prevention leadership quality and community climate supportive of prevention efforts. The authors suggest that key informant community readiness assessments have a valuable role to play in evaluating randomized community trials. Key informant readiness assessments provide formative insights into community dynamics, offer a basis for matching community assignment to condition, and they offer a tool that can be used directly with community activists in coalition-building in a workshop setting. Finally, key

informant assessments can be used as a means of assessing outcomes at the community level to supplement individual-level behavioral and attitudinal outcomes. Slater, M.D., Edwards, R.W., Plested, B.A., Thurman, P.J., Kelly, K.J., Comello, M.L.G., and Keefe, T.J. Using Community Readiness Key Informant Assessments in a Randomized Group Prevention Trial: Impact of a Participatory Community-Media Intervention. Journal of Community Health, 30, pp. 39-53, 2005.

Opinion of Indian Youth Used as Basis for Prevention Program

This article discusses the findings of Focus Group Discussions (FGD) that were conducted as a formative assessment for a project titled "Mobilizing Youth for Tobacco Related Initiatives in India", a randomized, multi-component, school-based trial to prevent and control tobacco use among youth in India. Forty-eight FGDs were conducted with students (N=435) in 6th and 8th grades in 6 schools in Delhi, India. Key findings include: 1) students in government schools self-reported as "consumers" of tobacco, whereas students in private schools reported as "commentators"; 2) parents and peers have a strong influence on youth tobacco use; 3) chewing gutkha is considered less harmful and more accessible than smoking cigarettes; 4) schools are not promoting tobacco control activities; and 5) students were enthusiastic about the role government should play in tobacco control. Mishra, A., Arora, M., Stigler, M.H., Komro, L.A., Srinath Reddy, K., and Perry, C.L. Indian Youth Speak About Tobacco: Results of Focus Group discussions with School Students. Health Education & Behavior, 32(3), pp. 363-379, 2005.

Substance Use is a Robust Predictor of Adolescent Recidivism

How well does substance use predict adolescent recidivism? When the Cox proportional hazards model was applied to officially recorded first re-arrest of 505 juvenile offenders, a best-fitting complex multivariate model indicated that: (a) parent reports that youth "often" uses substances more than doubles first re-arrest risk, (b) averaged youth/parent substance use reports predict recidivism better than a single source, (c) parent or youth denial of youth's substance use predicts recidivism, (d) age at first arrest does not predict recidivism, (e) non-White/non-Asians have a 79% a higher recidivism risk than other adjudicated youth, (f) parent-reported delinquency predicts recidivism with declining accuracy over time, and (g) substance use robustly predicts recidivism despite prior reported delinquency, gender, ethnicity, age, follow-up time, or data source. Stoolmiller, M. and Blechman, E.A. Criminal Justice and Behavior, 32(3), pp. 302-328, 2005.

Spirituality Is Not Protective against Violence Perpetration and Drug Use Among Youth at Continuation High Schools

This paper presents the results of a 1-year prospective study of violence perpetration, drug use, and spirituality among continuation high school youth. Data are reported on a sample of 501 adolescents from 19 continuation high schools located in a five-county region of Southern California. Age of participants at baseline was 14 to 19 years (M=16.8, SD=0.9). Participants were 57% male, with an ethnic distribution of 34% White, 49% Latino, 5% African American, 7% Asian). Analyses were undertaken to identify independent variables that predicted violence perpetration, drug use, or spirituality at 1-year follow-up. Spirituality was found to predict later violence perpetration and drug use as a single predictor. However, it failed to predict violence or drug use in models that also included six other variables. It is possible that current measures of spirituality predict later violence perpetration and drug use as a result of tapping attitudes about morality. Controlling for baseline spirituality, male gender, low morality of drug use, violence perpetration, and drug use predicted later spirituality. Spirituality appears to be affected by drug use and violence, but not the converse. The protective influence of spirituality is not supported, at least as currently measured. Sussman, S., Skara, S., De Calice, P., Hoffman, B. and Dent, C.W. Spirituality as a 1-Year Prospective Predictor of Violence Perpetration and Drug Use Among Youth at Continuation High Schools. Journal of Applied Social Psychology, 35(1), pp. 80-99, 2005.

Parents' Beliefs Synergistically Affect Children's Drinking

This research examined whether mother's and father's beliefs about their children's alcohol use had cumulative self-fulfilling effects on their children's future drinking behavior. Researchers analyzed longitudinal data from 115 seventh-grade children and their mothers and fathers. Questionnaire data were collected at two points in time 12 months apart. At the first time point, researchers measured parents' beliefs about their child's alcohol use, the child's alcohol use and intentions to use and other risk and protective factors for substance use. At the second time point, child's recent

alcohol use was measured. Findings suggest that the inaccurate portion (e.g., overestimation or underestimation) of parent's beliefs about their children's behavior at time 1 uniquely accounted for variance in a model predicting alcohol use at time 2. Mothers' beliefs that overestimated children's alcohol use more strongly predicted time 2 alcohol use when father's beliefs also overestimated time 2 use, a process the authors call synergistic accumulation. However, synergistic accumulation did not occur when parents' beliefs underestimated children's alcohol use. Madon, S., Guyll, M., Spoth, R. and Willard, J. Self-Fulfilling Prophecies: The Synergistic Accumulative Effect of Parents' Beliefs on Children's Drinking Behavior. Psychological Science, 15(12), pp. 837-845, 2004.

The Role of Neglect and Harsh Parenting in the Development of Childhood Aggression

Multimethod and multisource indices were used to measure social disadvantage, denial of care neglect, supervisory neglect, and punitive discipline in a sample of 218 disadvantaged families with children ages 4 to 8 years. The goal was to understand the effects of neglectful parenting, poor supervision, and punitive parenting on the development of children's aggression. A replication of the hypothesized theoretical model from prior research was tested. The results established the role of care neglect, supervisory neglect, and punitive parenting as mediators of the role of social disadvantage in the development of children's aggression. That is, the direct path from social status to aggression was rendered nonsignificant after entering the intervening mechanisms. Findings further highlight the importance of distinguishing between the two subtypes of neglect (care neglect and supervisory neglect) and the need to consider the role of harsh discipline when attempting to understand the effects of parenting in the development of aggression. Knutson, J.K., DeGarmo, D., Koeppl, G. and Reid, J.B. Care Neglect, Supervisory Neglect, and Harsh Parenting in the Development of Children's Aggression: A Replication and Extension. Child Maltreatment, 10, pp. 92-107, 2005.

Noncollege Students May Be More Important Targets for Prevention Programs than College Students

Youth who transition from high school to college face a set of challenges that can impact their drug use behaviors. Noncollege-bound youth who move out of their parents' homes also experience several of the same changes and risk factors following high school, although much less research has focused on them. This study examined transitions in alcohol, cigarette, and marijuana use and alcohol- and marijuana-related problems from late adolescence through young adulthood. Men and women who attended college were compared to their peers who did not in order to determine if the situational/socialization effects of college are unique during this developmental period. Prospective data from a community sample were collected at ages 18, 21, and 30 years from a college group (n = 326, 172 females, 154 males) and a noncollege group (n = 221, 109 females, 112 males). Analyses revealed that 18 year olds who transitioned out of high school, regardless of college status, reported higher levels of substance use than their peers who were still in high school. In addition, noncollege students compared to college students reported higher levels of cigarette and marijuana use in adolescence, emerging adulthood, and young adulthood and higher levels of alcohol- and marijuana-related problems in adolescence and young adulthood. Latent growth curve analyses revealed that college status was related to lower levels of alcohol and marijuana problems at age 18, greater increases from ages 18 to 21, and greater decreases from ages 21 to 30 even after controlling for level and growth in use. Overall the findings suggest that noncollege students may be a more important target group than college students from drug use prevention efforts during emerging adulthood. White, H.R., Labouvie, E.W. and Papadratsakis, V. Changes in Substance Use During the Transition to Adulthood: A Comparison of College Students and their Noncollege Age Peers. Journal of Drug Issues, 35, pp. 281-306, 2005.

Higher Impulsivity Related to Fewer Negative Expectancies and More Marijuana Use

The current study evaluated a model of marijuana use by examining the relationship between a distal risk factor (impulsivity) and a proximal risk factor (marijuana use expectancies) and marijuana use. An impulsive personality style has been identified as both a risk factor and a predictor of substance use and abuse. Marijuana expectancies, or evaluations of marijuana's expected effects (positive, negative, or neutral) have emerged as a strong predictor of marijuana use. Estimated probabilities and subjective evaluations of personally expected marijuana effects, along with impulsivity and frequency of marijuana use, were assessed in a sample of 337 college

undergraduates (248 females, 89 males, average age of 20.84 years). Tests of mediation indicated that negative expectancies were a significant mediator for both males and females. That is, participants who were higher on impulsivity had fewer negative expectancies and in turn used more marijuana. Vangsness, L., Bry, B.H. and LaBouvie, E.W. Impulsivity, Negative Expectancies, and Marijuana Use: A Test of the Acquired Preparedness Model. Addictive Behaviors, 30, pp. 1071-1076, 2005.

Effective Community Collaboration

This article discusses one solution to a significant challenge in prevention research: bridging the divide between scientists and communities in the implementation and study of prevention programs. The tribal participatory research approach was developed to facilitate culturally centered prevention research in American Indian and Alaska Native communities. To produce meaningful and lasting results at the level of the community, prevention research frequently requires investigators to reevaluate the boundaries that have traditionally separated them from the subjects of their investigations. This paradigm describes new tools and techniques to facilitate collaboration between researchers and communities while maintaining scientific rigor. This approach is discussed within the broader context of community-based participatory research, and increasingly prevalent paradigm in the prevention field. Fisher, P.A. and Ball, T.J. Balancing Empiricism and Local Cultural Knowledge in the Design of Prevention Research. Journal of Urban Health, 82(2) supplement 3, pp. 44-55, 2005.

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

Participating in Family Activities Results in Less Drug Use

Dr. Nancy Petry and colleagues at University of Connecticut Health center examined data from 150 adults who had been randomized into a contingency management intervention in which completion of client elected goals received tangible reinforcement. The client selected the type of goals in which they participated during the twelve-week treatment period. People who engaged in at least three family-related activities per week were engaged in treatment longer, were abstinent for more weeks, and reported greater reductions in family conflict than people who engaged in fewer family related goals. Lewis, M.W. and Petry, N, Drug Alcohol Dependence, pp. 267-271, August 2005.

Financial Incentives for Participating in Drug Abuse Treatment Research Does Not Appear to Impact Participants Negatively

Dr. David Festinger and colleagues at the Treatment Research Institute randomly assigned drug abuse outpatients to receive payments of $10, $40, or $70 in one of two modalities, cash or gift certificate, for attending a research follow-up assessment session six months after treatment. Participants who attended received a randomly determined incentive and were then scheduled for a appointment 3 days later to detect new instances of drug use. New drug use and perceptions of coercion by participants were not affected by either the magnitude or the mode of the incentives, as had been commonly assumed. Higher incentives ($40, & $70) significantly improved the chance that a participant would attend the follow-up rates over the 10$ condition. Festinger, D.S., Marlowe, D.B., Croft, J.R., Dugosh, K.L., Mastro, N.K., Lee, P.A., Dematteo, D.S. and Patapis, N.S. Drug & Alcohol Dependence, pp. 275-281, June 2005.

Efficacy of Dose and Contingency Management Procedures in LAAM-Maintained Cocaine-Dependent Patients

Dr. Oliveto and colleagues at Yale University randomly assigned opioid and cocaine dependent participants (N=140) to one of the following in a 12 week clinical trial: 1) LAAM (30,30,39mg/MWF) with contingency management; 2) LAAM (30,30,39mg/MWF) without contingency management; 3) LAAM (100, 100,130mg/MWF) with contingency management; and 4) LAAM (100, 100, 130mg/MWF) without contingency management. Urine samples were collected 3 times per week. In contingency management, each urine negative for both opioids and cocaine resulted in a voucher worth a certain monetary value that increased for consecutively drug free urines. Vouchers were exchanged for mutually agreed upon goods and services. The groups did not differ on retention and baseline characteristics. Abstinence from both opioids and cocaine was greatest in the high dose LAAM plus contingency management group. However, contingency management procedures were not as effective in reducing cocaine use at the lower dose of LAAM. The results suggest that an efficacious maintenance dose may be necessary for contingencies to be effective in facilitating both opioid and cocaine abstinence in this dually dependent population. Oliveto, A., Poling, J., Sevarino, K.A., Gonsai, K.R., McCance-Katz, E.F., Stine, S.M. and Kosten, T.R. Drug and Alcohol Dependence, 79(2), pp. 157-165, August 1, 2005.

Moderators of Effects of Motivational Enhancements to Cognitive Behavioral Therapy

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In Memoriam

Dr. Rosenblum and colleagues at the Institute for Treatment and Services Research, National Development and Research Institutes, Inc, in New York, conducted a study in which patient treatment matching hypotheses were tested for substance users randomly assigned to a group cognitive behavioral therapy (CBT; n=114) or a group motivational intervention (GMI; n=116). Treatment was scheduled twice weekly for 10 weeks. Using a patient attribute by treatment interaction design with a 15 week follow up, the study predicted that alexithymia, antisocial personality disorder, and network support for alcohol and drug use would be associated with less substance use for CBT subjects and that hostility and lower motivation would be associated with less substance use for GMI subjects. Three of the hypothesized moderators were empirically supported: alexithymia, network support for alcohol, and antisocial personality disorder. The results indicate the use of assessing specific patient attributes to better inform treatment recommendations. Rosenblum, A., Cleland, C., Magura, S., Mahmood, D., Kosanke, N. and Foote, J. American J. Drug and Alcohol Abuse. 31(1), pp. 35-38, 2005.

Cocaine Dependence and PTSD: A Pilot Study of Symptom Interplay and Treatment Preferences

Cocaine dependence and posttraumatic stress disorder (PTSD) frequently co-occur; however, little is known about patients' perceptions of symptom connectedness and preferences for treatment. Dr. Sudie Back and colleagues at the Medical University of South Carolina, conducted a preliminary investigation of patients' perceptions of symptom interplay and their preferences regarding concurrent or sequential models of psychotherapy, therapy format, and treatment modalities. Participants were 23 individuals with comorbid cocaine dependence and PTSD. The majority (95.5%) reported a functional relationship between cocaine use and PTSD symptoms. Improvement in PTSD symptoms was typically (63.3%) associated with a decrease in cocaine use, and a worsening of PTSD symptoms was associated with an increase in cocaine use. In contrast, improvement/deterioration in cocaine use was not significantly related to subsequent improvement/deterioration in PTSD symptoms. This finding suggests that changes in PTSD symptoms may be an important risk factor to consider among individuals with comorbid cocaine dependence and PTSD. Approximately 41% preferred a concurrent model of therapy in which the cocaine use and PTSD were treated simultaneously in therapy. These findings highlight the functional relationship between these two disorders and have direct implications for treatment interventions. Back, S.E., Brady, K.T., Jaanimagi, U. and Jackson, J.L. Addict Behavior, June 9, 2005.

Anxiety Disorders among Patients with Co-occurring Bipolar and Substance Use Disorders

Dr. Kolodziej and colleagues at Harvard and Boston University examined the prevalence and nature of anxiety disorder among treatment seeking patients diagnosed with current bipolar and substance use disorders, and investigated the association between anxiety disorders and substance use. Among 90 participants diagnosed with bipolar disorder I (n=75, 78%) or II (n=15, 22%), 43 (48%) had a lifetime anxiety disorder, with posttraumatic stress disorder (PTSD) occurring most frequently (n=21, 23%). They found that those with PTSD, but not with the other anxiety disorders assessed, began using drugs at an earlier age and had more lifetime substance use disorders, particularly cocaine and amphetamine use disorders, than those without PTSD. Most participants with PTSD were women, sexual abuse was the most frequently reported index trauma, and the mean age of the earliest index trauma occurred before the mean age of initiation of drug use. These findings highlight the heterogeneity of dually diagnosed patients, and the importance of further investigating the ramifications of a trauma history among those who are diagnosed with bipolar and substance use disorders. Kolodziej, M.E., Griffin, M.L., Najavits, L.M., Otto, M.W., Greenfield, S.F. and Weiss, R.D. Drug and Alcohol Dependence, In Press, Corrected Proof Available Online May 3, 2005.

Behavioral Treatment Approaches for Methamphetamine Dependence and HIV-Related Sexual Risk Behaviors Among Urban Gay and Bisexual Men

Dr. Shoptaw and colleagues evaluated the efficacy of four behavioral drug abuse treatments for reducing methamphetamine use and sexual risk behaviors in methamphetamine-dependent gay and bisexual men. Participants (N=162) were assigned to 16 weeks of one of four behavioral treatments: standard cognitive behavioral therapy (CBT), contingency management (CM), combined cognitive behavioral therapy and contingency management (CBT+CM) and a culturally tailored cognitive behavioral therapy (GCBT). CM and CBT+CM conditions were statistically

better than CBT during treatment in retention, in longest period of consecutive urine samples negative for methamphetamine metabolites, and in the Treatment Effectiveness Score. GCBT significantly reduced unprotected receptive anal intercourse during the first four weeks of treatment. Between-group differences found during treatment, disappeared at follow-up with overall reductions in outcomes sustained to one-year. The authors conclude that among high-risk methamphetamine-dependent GBM, drug abuse treatments produced significant reductions in methamphetamine use and sexual risk behaviors. Drug abuse treatments merit consideration as a primary HIV prevention strategy for this population. Shoptaw, S., Reback, C.J., Peck, J.A., Yang, X., Rotheram-Fuller, E., Larkins, S., Veniegas, R.C. Freese, T.E. and Hucks-Ortiz, C. Drug and Alcohol Dependence, 9, pp. 125-134, 2005.

Brief Motivational Intervention for Adolescent Smokers in Medical Settings

Investigators from Brown University conducted a study designed to determine the efficacy of two brief behavioral interventions for smoking cessation in adolescents treated in a hospital outpatient clinic or Emergency Department. Patients aged 14-19 years (N=85) were randomly assigned to receive either one session of motivational interviewing (MI) or standardized brief advice (BA) to quit smoking. Patients were proactively screened and recruited and not seeking treatment for smoking. Follow-up assessments were conducted at 1, 3, and 6 months post-intervention. Adolescents in both conditions reported smoking reductions at all three follow-ups. Those in the MI group also showed reduced cotinine levels at 3 months, unlike those in BA, and both groups showed reduced cotinine levels at 6 months. Overall, abstinence rates were low and did not differ between groups at 1 or 3 months. At 6 months, self-report data indicated that abstinence rates were significantly higher for the MI group than the BA group, but this difference was not confirmed biochemically. Groups did not differ in biochemically confirmed abstinence at any follow-up. The low rates of abstinence found are consistent with findings from other adolescent smoking cessation trials, which have generally effected only minimal change even among treatment-seeking adolescents. Colby, S.M., Monti, P.M., O'Leary, Tevyaw, T. Barnett, N.P., Spirito, A., Rohsenow, D.J., Riggs, S. and Lewander, W. Addictive Behaviors, 30, pp. 865-874, 2005.

Smoking Stage of Change and Interest in an Emergency Department-based Intervention

This study sought to assess the prevalence and predictors of smoking stage of change and interest in an ED-initiated smoking intervention. Patients in an emergency department were interviewed immediately before discharge from the ED or transfer to an inpatient floor. Among those interviewed, 581 (40%) were current smokers, 117 (21%) were in precontemplation stage, 241 (43%) were in contemplation stage, and 197 (36%) were in preparation stage. Sixty-two percent endorsed at least "somewhat" agreement that smoking counseling should be provided in the ED, while nearly one half (49%) agreed to stay 15 extra minutes to do so. Fifty-nine percent of treating physicians/nurses screened patients for smoking status, however only 8% of patients reported receiving information about quitting. The findings indicate that most smokers have at least some desire to change and appear interested in ED smoking cessation counseling. Due to limited efforts in the ED, efforts may be better spent on counseling patients who are receptive and ready to change. Boudreaux, E.D., Baumann, B.M., Friedman, K. and Ziedonis, D.M. Acad Emerg Med, 12, pp. 211-218, 2005.

Intentions to Quit Smoking Change Over Short Periods of Time

This study intended to assess the stability of intention to quit smoking over a 30-day period. One-hundred and fifteen US and Swedish smokers were randomized to complete Stage of Change (SOC) or ladder scales of intentions to quit at either 0, 7, 14 and 30 days or at 0 and 30 days in the absence of intervention. The results indicate that measures of intention to quit are often unstable over short periods of time. The results also indicate the four-assessment group had more progression in intention to quit than the two-assessment group, indicating that repeated measurement can influence intention outcomes. Hughes, J.R., Keely, J.P., Fagerstrom, K.O. and Callas, P.W. Addictive Behaviors, 30, pp. 653-662, 2005.

Distress Tolerance and Early Smoking Lapse

This paper discusses the theoretical and clinical implications of distress tolerance in smoking cessation. Whereas past work on smoking relapse has largely addressed the role of withdrawal symptoms and negative affect, the model presented by Brown et

al. emphasizes that the way in which one reacts to the discomfort of nicotine withdrawal is a more promising avenue of investigation. Development of a specialized and novel behavioral distress tolerance treatment for early smoking lapsers is proposed. Brown, R.A., Lejuez, C.W., Kahler, C.W., Strong, D.R. and Zvolensky, M.J. Clin Psychol Rev, 6, pp. 713-733, 2005.

The Effects of a Prison Smoking Ban on Smoking Behavior and Withdrawal Symptoms

This study investigated symptoms of distress and nicotine dependence as predictors of nicotine withdrawal symptoms among 188 incarcerated male smokers during a mandated smoking ban. Participants were assessed at three time periods: baseline, 4 days after the smoking ban, and 1 month after the smoking ban. Most smokers (76%) continued to smoke following the smoking ban. Smokers after the ban were more nicotine dependent and reported more withdrawal symptoms than participants that quit. An interaction was found such that distressed smokers had the highest level of nicotine withdrawal. The authors surmise that the low compliance with the smoking ban was due to low motivation to enforce the ban on the part of prison employees, since they were affected by the ban as well. These results have implications for how smoking bans are instituted in prison settings. Cropsey, K.L. and Kristeller, J.L. Addictive Behaviors, 30, pp. 589-594, 2005.

Acceptance of Nicotine Dependence Treatment Among Currently Depressed Smokers

Dr. Haug and colleagues at the University of California, San Francisco conducted this study to examine specific characteristics of psychiatric outpatients with depressive disorders who either accepted or refused available smoking cessation treatment. The sample (N=154) participated in a repeated contact experimental condition where they received a stage-based expert system program to facilitate treatment acceptance and were then offered smoking treatment, consisting of behavioral counseling, nicotine patch, and bupropion. Acceptors (N=53) were defined as those accepting behavioral counseling and pharmacological treatment at some point during the 18-month study, whereas refusers (N=101) received only the expert system. The number of days to treatment acceptance was significantly predicted by stage of change, with those in preparation entering treatment more quickly than contemplators or precontemplators. The variables most strongly associated with accepting treatment were current use of psychiatric medication and perceived success for quitting. Severity of depressive symptoms, duration of depression history, and history of recurrent depression were not related to treatment acceptance. The authors suggest that the findings have implications for the psychiatric assessment and treatment of smokers in clinical settings. Psychiatric medication may play a significant role in smoking cessation treatment acceptance by currently depressed smokers. Haug, N.A., Hall, S.M., Prochaska, J.J., Rosen, A.B., Tsoh, J.Y., Humfleet, G., Delucchi, K., Rossi, J.S., Redding, C.A. and Eisendrath, S. Nicotine and Tobacco Research, 7, pp. 217-224, 2005.

Contingency Management and Cognitive-Behavioral Treatment for Adolescent Marijuana Abuse Shows Promise

Investigators at the University of Vermont published data on an initial sample of 19 adolescents participating in a Stage-I treatment-development study targeting marijuana abuse and associated behavior problems. Adolescents participated in a 14-week treatment consisting of incentives for adolescent abstinence, parent involvement in delivering contingencies, clinic-delivered incentives to parents for participation in treatment, and individual cognitive-behavioral treatment for adolescents. The results suggest that families had high levels of participation in treatment, and that abstinence from marijuana increased significantly from treatment entry to completion (improving from 37% abstinence to 74% abstinence). This study reports on a unique combination of two behavioral interventions found to be beneficial in treating drug abuse-contingency management and family involvement-and demonstrates that the two can be efficacious in treating adolescent marijuana abuse. Kamon, J., Budney, A. and Stanger, C. Journal of the American Academy of Child and Adolescent Psychiatry, 44, pp. 513-521, 2005.

Researchers Should Evaluate Costs of Treatment in Addition to Efficacy and Effectiveness

Recognizing the role of cost in the availability and dissemination of treatments for drug abuse and related co-morbidities, Dr. William Fals-Stewart of the Research Triangle Institute and colleagues published guidelines to assist clinical researchers in

including cost evaluations in their studies. Using marriage and family treatments as a model, the authors outline user-friendly guidelines to identify and define key constructs (i.e., cost, benefit, effectiveness), and offer recommendations of how to assess and analyze these constructs. This paper serves as a valuable tool in equipping researchers to design comprehensive studies of drug abuse treatment. Fals-Stewart, W., Yates, B. T. and Klosterman, K. Journal of Family Psychology, 19, pp. 28-39, 2005.

Ecologically Based Family Therapy Reduces Drug Abuse among Substance Abusing Runaway Adolescents

Dr. Natasha Slesnick, recently joining the faculty at Ohio State University, and colleague Jillian L. Prestopnik, report on the efficacy of a family-based behavioral treatment for substance abuse among runaway teens. Substance-abusing teens were recruited at a homeless shelter, and 124 were randomly assigned to receive Ecologically Based Family Therapy (EBFT) or to receive services as usual (SAU). Teens receiving EBFT had significantly greater reductions in substance use than did teens receiving SAU, with those reporting a history of physical or sexual victimization achieving even better outcomes in EBFT. Other areas of functioning (psychiatric diagnoses, delinquent behaviors, family functioning, knowledge of HIV risk, etc.) improved significantly for teens receiving either EBFT or SAU. These results suggest that a family-based behavioral treatment has potential to improve substance abuse among a high-risk population of runaway teens, and that there may be several avenues to intervening in other areas of functioning. Slesnick, N. and Prestopnik, J. L. Journal of Adolescence, 28, pp. 277-298, 2005.

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Research Findings - Research on Pharmacotherapies for Drug Abuse

Desipramine Treatment for Cocaine Dependence in Buprenorphine- or Methadone-treated Patients: Baseline Urine Results as Predictor of Response

Dr. Tom Kosten and colleagues at Yale University examined the prognostic importance of baseline urines for cocaine in a randomized, placebo-controlled, twelve-week clinical trial in 165 opioid- and cocaine-dependent patients who were treated with desipramine in combination with buprenorphine or methadone. Patients with a cocaine-positive urine at baseline had significantly fewer cocaine-free urines than those with a negative urine at baseline. The group with cocaine-positive urines at baseline showed a treatment effect of desipramine. This effect was significant in patients maintained on buprenorphine, but not on methadone. Kosten, T., Sofuoglu M., Poling J., Gonsai K., and Oliveto, A. Am. J. Addiction, 14(1), pp. 8-17, Jan-Feb 2005.

Immunotherapy for the Treatment of Drug Abuse

Dr. Tom Kosten at Yale and Dr. Michael Owens at University of Arkansas have summarized the present status of preclinical and clinical studies on immunotherapies (using both active and passive immunization) for drugs of abuse. Antibody therapy in the area of drug abuse treatment research is designed primarily to prevent drugs of abuse from entering the central nervous system. Because antibodies remain primarily in the circulatory system, they have no apparent CNS side effects. Antibodies have two immediate clinical applications in drug abuse treatment, to treat drug overdose and reduce relapse. Active immunization with vaccines has been tested preclinically for cocaine, heroin, methamphetamine and nicotine. There have been Phase 2 clinical trials with one cocaine vaccine and three nicotine vaccines in humans. Passive immunization with high affinity monoclonal antibodies has been tested preclinically for cocaine, methamphetamine, nicotine and PCP. The specificity of the antibodies, lack of abuse liability, minimal side effects, and long-lasting protection against drug use offer a major therapeutic benefit over small molecule agonists and antagonists. Immunotherapies could also be used in combination with other antiaddiction medications and enhance behavioral therapies. Kosten, T. and Owens, S.M. Pharmacology and Therapeutics 13, July 2005.

Vaccine Pharmacotherapy for the Treatment of Cocaine Dependence

Dr. Martell and colleagues at Yale University evaluated the safety, immunogenicity and clinical efficacy of a cocaine vaccine (TA-CD) in an open label, fourteen week, dose-escalation study in eighteen cocaine dependent subjects, of which sixteen completed the study. Ten subjects received four-100 microgram injections (totaling 400 micrograms) and eight subjects received five 400 microgram injections (totaling 2000 micrograms). There were no serious adverse events and the vaccine was well tolerated. The 2000 microgram total dose group had a significantly higher antibody titer response as compared to the 400 microgram dose group. The 2000 microgram dose group maintained more cocaine-free urines than those in the 400 microgram dose group. Despite relapse in both groups, most subjects reported an attenuation of cocaine's euphoric effects at the six month follow-up time points (63% in the 400 microgram dose group and 100% in the 2000 microgram dose group). Cocaine specific antibodies persisted at least six months. Martell, B.A., Mitchell, E., Poling, J., Gonsai, K. and Kosten, T.R. Biological Psychiatry, 58(2), pp. 158-164, July 2005.

Methadone Versus Buprenorphine With Contingency Management or

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Performance Feedback for Cocaine and Opioid Dependence

Although buprenorphine can now be prescribed for opioid agonist maintenance treatment outside of narcotic treatment programs, treatment guidelines for patients with co-occurring cocaine and opioid dependence are not available. Dr. Schottenfeld and other investigators at Yale carried out a 24 week clinical trial in 162 subjects to compare the effects of buprenorphine and methadone and evaluate the efficacy of combining contingency management (CM) with maintenance treatment for patients with a comorbidity of cocaine and opioid dependence. Cocaine and opioid dependent subjects were provided manual-guided counseling and randomly assigned in a double-blind design to receive daily sublingual buprenorphine (12-16 mg) or methadone (65-85 mg po) and to CM or performance feedback. It was found that subjects treated with methadone remained in treatment significantly longer and achieved significantly longer periods of sustained abstinence and a greater proportion of drug-free tests compared with subjects who received buprenorphine. Subjects receiving CM achieved significantly longer periods of abstinence and a greater proportion of drug-free tests during a period of escalating voucher compared with those who received performance feedback, but there were no significant differences between groups in these variables during the entire 24 week study. The conclusion drawn from this study is that methadone may be superior to buprenorphine for maintenance treatment of patients with co-occurring cocaine and opioid dependence. Combining methadone or buprenorphine with CM may improve treatment outcome. Schottenfeld, R.S., Chawarski, M.C., Pakes, J.R., Pantalon, M.V., Carroll, K.M. and Kosten, T.R. American Journal of Psychiatry 162, pp. 340-349, Feb 2005.

Effect of Nicotine Replacement Therapy on Post-cessation Weight Gain and Nutrient Intake: A Randomized Controlled Trial of Postmenopausal Female Smokers

This study of 94 postmenopausal female smokers evaluated the effect of nicotine replacement therapy (NRT) and hormone therapy (HT) on change in weight, energy intake, and physical activity during 2 weeks of smoking abstinence. Women, stratified by current use of HT, were randomized to nicotine or placebo patch. After 2 weeks of abstinence, women on nicotine patch had significantly larger increases in total caloric and fat intake than women on placebo patch and a trend toward larger increases in carbohydrates (total and sweet). Conversely, the nicotine group had less weight gain, 0.47 kg, than the placebo group, 1.02 kg ($F=10.31$, $p=0.002$). No effects were observed for hormone therapy. It appears that in short-term smoking abstinence, postmenopausal women on NRT gain less weight than do women on placebo, in spite of consuming more calories. This may be beneficial in the critical first 1-2 weeks of tobacco cessation, especially in light of postmenopausal weight gain. Allen, S.S., Hatsukami, D., Brintnell, D.M. and Bade, T. Effect of Nicotine Replacement Therapy on Post-cessation Weight Gain and Nutrient Intake: A Randomized Controlled Trial of Postmenopausal Female Smokers. Addict. Behav., 30, pp. 1273-1280, 2005.

Utility of Lead-in Period in Cocaine Dependence Pharmacotherapy Trials

The authors examined whether drug use behaviors during a 2-week lead-in for a pharmacotherapy trial were predictive of retention in treatment and of the level of cocaine use during the subsequent 12 weeks of treatment. Fifty cocaine dependent patients were grouped based on: (1) principal route of cocaine administration: intranasal versus smoking, and (2) level of cocaine use during the 2-week lead-in: high versus low. Results indicate that level of cocaine use during the 2-week lead-in was a significant predictor of cocaine use during the subsequent 12 weeks of treatment. Patients with reported higher level of use during the lead-in period were more likely to continue using cocaine during the treatment. Patients who used smoking as their primary route of cocaine use were more likely to drop out early in the treatment. Findings of this study suggest that route and level of cocaine use during lead-in be used as a covariate in models testing treatment effect. Bisaga, A., Aharonovich, E., Garawi, F., Levin, F. R., Rubin, E., Raby, W. N. et al. Utility of Lead-in Period in Cocaine Dependence Pharmacotherapy Trials. Drug Alcohol Depend., 77, pp. 7-11, 2005.

Tobacco Abstinence Symptom Suppression: The Role Played by the Smoking-related Stimuli that are Delivered by Denicotinized Cigarettes

This study was designed to clarify the impact of smoking-related stimuli on tobacco withdrawal, and to explore the duration of their ability to suppress withdrawal in smokers. Three double-blind, within-subjects, Latin square-ordered, 5-day conditions in which participants smoked nicotinized, denicotinized or no cigarettes. Subjective, physiological and performance measures were collected daily and compliance with

study conditions was verified objectively. Smoking-related stimuli are sufficient for suppressing some symptoms of tobacco abstinence over a 5-day period [i.e. Questionnaire of Smoking Urges (QSU) factor 1, 'Desire for sweets', 'Hunger' and 'Urges to smoke'], while in this study a combination of nicotine and smoking-related stimuli suppressed other symptoms (i.e. 'Difficulty concentrating', 'Increased eating', 'Restlessness' and 'Impatient'). These results indicate that, while some tobacco abstinence symptoms may be suppressed with nicotine, suppressing others may also require strategies that address the absence of smoking-related stimuli. Buchhalter, A.R., Acosta, M.C., Evans, S.E., Breland, A.B. and Eissenberg, T. Tobacco Abstinence Symptom Suppression: The Role Played by the Smoking-related Stimuli that are Delivered by Denicotinized Cigarettes. Addiction, 100, pp. 550-559, 2005.

Modafinil Influences the Pharmacokinetics of Intravenous Cocaine in Healthy Cocaine-Dependent Volunteers

To determine if modafinil, a putative treatment for cocaine dependence, influences the pharmacokinetics of intravenous cocaine in otherwise healthy cocaine-dependent volunteers. Cocaine 20 or 40 mg was administered intravenously on consecutive days over 1 minute at baseline and after modafinil administration at each of two dosages of 400 and 800 mg/day for 7 days. Twelve subjects completed the clinical protocol. Compared with baseline, the cocaine peak plasma concentration was decreased after both the 20 and 40 mg cocaine infusions, but the reduction was only statistically significant after the 40 mg cocaine infusion ($p < 0.01$ after modafinil 400 mg/day; $p < 0.05$ after modafinil 800 mg/day). The area under the cocaine plasma concentration-time curve from 0 to 180 minutes (AUC180) was significantly decreased by modafinil administration ($p < 0.01$ and $p < 0.001$ for modafinil 400 and 800 mg/day, respectively, for the cocaine 20mg dose; $p < 0.001$ for the cocaine 40 mg dose at both modafinil levels). There were no significant changes in total AUC, clearance or elimination half-life of cocaine. This study did not find evidence for a harmful pharmacokinetic interaction between modafinil and cocaine. In contrast, long-term administration of modafinil significantly decreased systemic exposure to cocaine during the first 180 minutes following intravenous cocaine administration. Donovan, J.L., DeVane, C.L., Malcolm, R.J., Mojsiak, J., Chiang, C.N., Elkashef, A. et al. Modafinil Influences the Pharmacokinetics of Intravenous Cocaine in Healthy Cocaine-dependent Volunteers. Clin.Pharmacokinet., 44, pp. 753-765, 2005.

Screening and Intervention for Alcohol and Illicit Drug Abuse: A Survey of Internal Medicine Housestaff

This study attempts to determine how internal medicine housestaff screen and intervene for problematic alcohol and illicit drug use, as well as identify factors correlating with favorable practices. A cross-sectional survey was administered to 93 medical housestaff. Of 64 (69%) respondents, 94% reported routinely screening new patients for alcohol or illicit drug use, while only 52% routinely quantified alcohol consumption and 28% routinely used a screening instrument. Housestaff were unfamiliar with national guidelines and felt unprepared to diagnose substance use disorders, particularly prescription drug abuse. Most routinely counseled patients with alcohol (89%) or illicit-drug problems (91%), although only a third of these patients were referred for formal treatment. More thorough screening practices were associated with greater treatment optimism, while favorable referral practices were associated with greater optimism about 12-step program benefit and difficulty with management. These findings suggest areas to be addressed in residency curricula on substance abuse. Gunderson, E.W., Levin, F.R. and Smith, L. Screening and Intervention for Alcohol and Illicit Drug Abuse:A Survey of Internal Medicine Housestaff. J. Addict. Dis., 24, pp. 1-18, 2005.

Dronabinol and Marijuana in HIV+ Marijuana Smokers: Acute Effects on Caloric Intake and Mood

The aim of this study was to compare dronabinol (0, 10, 20, 30 mg p.o.) and marijuana [0.0, 1.8, 2.8, 3.9% Delta(9)-tetrahydrocannabinol (THC)] in two samples of HIV+ marijuana smokers: those with (n=15) and those without (n=15) a clinically significant loss of muscle mass (<90% body cell mass/height), which is one component of AIDS wasting. Mood, physical symptoms, self-selected food intake, cardiovascular data, and cognitive task performance were measured before and repeatedly after dronabinol and marijuana administration in eight 7-h sessions. Marijuana and dronabinol were administered in randomized order using a within-subject, staggered, double-dummy design. As compared to placebo, (1) marijuana (1.8, 2.8, 3.9% THC) and the lower dronabinol doses (10, 20 mg) were well tolerated (e.g., few physical symptoms, significant increases in ratings of "good drug effect") in both groups of participants; the highest dose of dronabinol (30 mg) was poorly

tolerated in a subset of participants; (2) marijuana and dronabinol significantly increased caloric intake in the low bioelectrical impedance analysis (BIA) group but not in the normal BIA group; and (3) drug effects on cognitive performance were minor. These data suggest that for experienced marijuana smokers with clinically significant muscle mass loss, both dronabinol (at acute doses at least four to eight times the current recommendation) and marijuana produce substantial and comparable increases in food intake without producing adverse effects. Haney, M., Rabkin, J., Gunderson, E. and Foltin, R.W. Dronabinol and Marijuana in HIV+ Marijuana Smokers: Acute Effects on Caloric Intake and Mood. Psychopharmacology (Berl), Online First, March 19, 2005.

Reinforcing Effects of Oral Delta(9)-THC in Male Marijuana Smokers in a Laboratory Choice Procedure

Oral Delta-9-tetrahydrocannabinol (Delta(9)-THC; Marinol) is medically available for the treatment of nausea associated with cancer chemotherapy and for wasting syndromes related to HIV/AIDS. Little is known about its reinforcing effects. This study was conducted to characterize the reinforcing effects of oral Delta(9)-THC in experienced marijuana smokers under controlled laboratory conditions. Ten healthy male marijuana users completed this 17-day residential study. On days 2, 6, 10, and 14, at 0900 h, participants received a "sample" oral dose of Delta(9)-THC (0, 10, 20 mg) and an alternative reinforcer, a $2 voucher (redeemable for cash at study's end). Over the next 3 days, they had 11 opportunities to self-administer either the sampled dose of Delta(9)-THC or to receive a $2 voucher. Participants chose active Delta(9)-THC (10 and 20 mg) more often than placebo (< two selections vs approximately four selections, respectively). However, they chose active Delta(9)-THC on less than 50% of choice opportunities. Both active Delta(9)-THC doses produced significant increases in "positive" subjective effects, impaired psychomotor performance, and increased heart rate, relative to the placebo conditions. These data indicate that oral Delta(9)-THC may have modest abuse liability in experienced marijuana smokers. Hart, C.L., Haney, M., Vosburg, S.K., Comer, S.D. and Foltin, R.W. Reinforcing Effects of Oral Delta(9)-THC in Male Marijuana Smokers in a Laboratory Choice Procedure. Psychopharmacology (Berl), Online First, April 14, 2005.

Reducing Harm Caused by Tobacco: Research Findings from the University of Minnesota

Researchers from the University of Minnesota Transdisciplinary Tobacco Use Research Center have spent the past 5 years exploring ways to evaluate exposure to tobacco toxins in smokers and nonsmokers and reduce the associated health risks. This article discusses research into the health effects associated with smokers reducing the number of cigarettes they consume and using lower-tar cigarettes, modified tobacco products, and smokeless tobacco. Researchers found little, if any, benefit to products that promise less exposure to cancer-causing tobacco toxins. Hecht, S. and Hatsukami, D. Reducing Harm Caused by Tobacco. Research Findings from the University of Minnesota. Minn. Med., 88, pp. 40-43, 2005.

Co-morbidity of Smoking in Patients with Psychiatric and Substance Use Disorders

This article reviews cigarette smoking in patients with psychiatric disorders (PD) and substance use disorders (SUD). Rates of smoking are approximately 23% in the U.S. population but approximately two- to four-fold higher in patients with PD and SUD. Many remaining smokers have had repeated smoking cessation failures, possibly due to the presence of co-morbid PD and SUDs. There is modest, evidence-based support for effective treatment interventions for nicotine addiction in PD and SUD. Further research is needed to increase our understanding of nicotine addiction in PD and SUD and develop more effective treatment interventions. Kalman, D., Morissette, S.B. and George, T.P. Co-morbidity of Smoking in Patients with Psychiatric and Substance Use Disorders. Am.J.Addict., 14, pp. 106-123, 2005.

Inhibition of CYP2D6 Activity by Bupropion

The purpose of this study was to assess the effect of bupropion on cytochrome P450 2D6 (CYP2D6) activity. Twenty-one subjects completed this repeated-measures study in which dextromethorphan (30-mg oral dose) was administered to smokers at baseline and after 17 days of treatment with either bupropion sustained-release (150 mg twice daily) or matching placebo. Subjects quit smoking 3 days before the second dextromethorphan administration. To assess CYP2D6 activity, urinary dextromethorphan/dextrorphan metabolic ratios were calculated after an 8-hour urine collection. Thirteen subjects received bupropion, and 8 received placebo. In those

receiving active medication, the dextromethorphan/dextrorphan ratio increased significantly at the second assessment relative to the first (0.012 +/- 0.012 vs. 0.418 +/- 0.302; P < 0.0004). No such change was observed in those randomized to placebo (0.009 +/- 0.010 vs. 0.017 +/- 0.015; P = NS). At baseline, all subjects were phenotypically extensive CYP2D6 metabolizers (metabolic ratio <0.3); after treatment, 6 of 13 subjects receiving bupropion, but none of those receiving placebo, had metabolic ratios consistent with poor CYP2D6 metabolizers. Bupropion is therefore a potent inhibitor of CYP2D6 activity, and care should be exercised when initiating or discontinuing bupropion use in patients taking drugs metabolized by CYP2D6. Kotlyar, M., Brauer, L.H., Tracy, T.S., Hatsukami, D.K., Harris, J., Bronars, C.A. et al. Inhibition of CYP2D6 Activity by Bupropion. J. Clin. Psychopharmacol., 25, pp. 226-229, 2005.

Spontaneous Smoking Cessation During Pregnancy Among Ethnic Minority Women: A Preliminary Investigation

This study examined the postpartum relapse rates and characteristics of pregnant women who stopped smoking without professional intervention. Baseline characteristics of women who spontaneously quit were compared to women who continued to smoke. Women who spontaneously quit were also randomized to a psychotherapy relapse prevention treatment, or to usual care. The sample was ethnically diverse, containing 141 low-income women who were predominantly Hispanic, 23% (n=33) of whom spontaneously quit smoking. The variables that significantly differentiated between "spontaneous quitters" and ongoing smokers were entered into a regression analysis, which revealed that higher self-confidence, smoking fewer cigarettes per day, and younger age accounted for 25% of the variance in spontaneous cessation. Adding the psychotherapy intervention conferred no additional protection against relapse in this subgroup of spontaneous quitters. The six-month abstinence rate of 36% is similar to that found in Caucasian and higher-income populations. These results extend research with pregnant smokers to a new population and may have implications for healthcare providers and policy makers. Morasco, B.J., Dornelas, E.A., Fischer, E.H., Oncken, C. and Lando, H.A. Spontaneous Smoking Cessation During Pregnancy Among Ethnic Minority Women: A Preliminary Investigation. Addict. Behav. In Press, Corrected Proof Available Online May 24, 2005.

Reinstatement of Morphine-Conditioned Reward is Blocked by Memantine

Protection of abstinent individuals from relapse is the main goal of drug dependence treatment. Relapse is frequently precipitated by exposure to small doses of the drug of abuse or exposure to the environment that was previously associated with the drug. Mice exposed to morphine (10 mg/kg) in a unique test-box environment display a conditioned place preference for this environment. Such preference can be extinguished by subsequent pairing of physiological saline administration with the same environment. Once extinguished, the original place preference can be reinstated after a priming dose (1-2.5 mg/kg) of morphine is given. However, mice treated with 7.5 (but not 3.75) mg/kg of memantine (the glutamate/NMDA receptor antagonist) during the extinction phase were insensitive to morphine's ability to reinstate the place preference 2 days after extinction conditionings. Effect of memantine was also observed when priming dose of morphine was given 21 days after extinction conditionings. In contrast, morphine's ability to reinstate conditioned response was not affected by treatment with 10 mg/kg of chlordiazepoxide, 0.5 mg/kg of LSD-25, or 1 mg/kg of morphine given during extinction conditionings. A separate experiment demonstrated that memantine (7.5 mg/kg) treatment did not affect learning. The authors show for the first time that memantine treatment during extinction conditionings may abolish the ability of drug-related cues to evoke reinstatement, suggesting that this NMDA receptor antagonist can be useful in preventing relapse in opioid dependent individuals. Popik, P., Wrobel, M. and Bisaga, A. Reinstatement of Morphine-Conditioned Reward is Blocked by Memantine. Neuropsychopharmacology, Advance Online Publication, May 1, 2005.

Cigarette Smoking Among Marijuana Users in the United States

The vast majority of drug users smoke cigarettes. Most use marijuana and no other illicit drug. The investigators analyzed adult responses to the 1997 NHSDA (n = 16,661) to explore relationships between marijuana use and cigarette smoking. Multivariate analyses controlled for other illicit drug use and other potential covariates. Nearly three-quarters of current marijuana users (74%) smoked cigarettes. Compared to nonusers, the adjusted odds of being a smoker were 5.43 for current marijuana users, 3.58 for past year marijuana users, and 2.02 for former marijuana users. Odds for cigarette smoking among current poly-drug users, compared to nonusers, were 2.3 to 1. Level of cigarette smoking was directly

associated with frequency of marijuana use. Nationwide, an estimated 7 million adults smoke both substances and are at increased risk for respiratory illnesses and mortality. Cigarette smoking is a major co-morbidity of marijuana use and smoking cessation should be addressed among marijuana users in addition to their other illicit drug involvement. Richter, K.P., Kaur, H., Resnicow, K., Nazir, N., Mosier, M.C.and Ahluwalia, J.S. Cigarette Smoking Among Marijuana Users in the United States. Subst.Abus., 25, pp. 35-43, 2005.

An Evaluation of the Reinforcing Effects of Memantine in Cocaine-dependent Humans

The purpose of this double-blind, outpatient study was to evaluate the reinforcing and subjective effects of the uncompetitive N-methyl-d-aspartate (NMDA) antagonist memantine in cocaine-dependent humans. Eight participants (two females, six males) completed this study which consisted of three blocks of seven sessions; each block tested a different dose of memantine. During the first two sessions of each block, participants "sampled" the memantine capsule (10, 20, or 30mg) and the placebo capsule that were available for the next five sessions. During the five subsequent sessions, participants had an opportunity to self-administer either the active or placebo capsule. Memantine was not reinforcing and subjective-effects ratings were not altered as a function of dose. Results suggest that these doses of memantine do not have abuse liability in cocaine-dependent individuals. Vosburg, S.K., Hart, C.L., Haney, M. and Foltin, R.W. An Evaluation of the Reinforcing Effects of Memantine in Cocaine-dependent Humans. Drug Alcohol Depend., 79, pp. 257-260, 2005.

The Integration of Tobacco Dependence Treatment and Tobacco-free Standards into Residential Addictions Treatment in New Jersey

New Jersey was the first state to implement a licensure standard for all residential addiction treatment programs to assess and treat tobacco dependence in the context of entirely tobacco-free facilities (including grounds). A program evaluation of the first year of the policy (2001-2002) assessed the impact on programs, clients, and staff. At 1-year follow-up, all 30 residential programs surveyed provided some tobacco dependence treatment and 50% had tobacco-free grounds. Eighty-five percent of the programs accepted the state's offer to provide free NRT, reaching more than 2,326 clients. Seventy-seven percent of all clients were smokers, and 65% of the smokers reported they wanted to stop or cut down tobacco use. Forty-one percent of the smokers reported that they did not use any tobacco during their entire residential stay. There was no increase in irregular discharges, or reduction in proportion of smokers among those entering residential treatment, compared with prior years. Licensure standards regulation can be an effective mechanism for increasing the quantity and quality of tobacco dependence treatment in residential addictions programs. Williams, J.M., Foulds, J., Dwyer, M., Order-Connors, B., Springer, M., Gadde, P. et al. The Integration of Tobacco Dependence Treatment and Tobacco-free Standards into Residential Addictions Treatment in New Jersey. J. Subst. Abuse Treat., 28, pp. 331-340, 2005.

Increased Nicotine and Cotinine Levels in Smokers with Schizophrenia and Schizoaffective Disorder is Not a Metabolic Effect

It has been hypothesized that smokers with schizophrenia take in more nicotine per cigarette than smokers without this disorder. This study examines this phenomenon by comparing the serum nicotine and cotinine levels in smokers with either schizophrenia or schizoaffective disorder compared to control smokers without mental illness. Serum cotinine and nicotine levels of smokers with schizophrenia or schizoaffective disorder were 1.3 times higher than control smokers (cotinine 291 versus 227 ng/mL; $p=0.0115$; nicotine 28 versus 21 ng/mL; $p<0.001$) despite smoking a similar number of cigarettes per day. Similar serum 3'-hydroxycotinine (3HC) to cotinine ratios in both groups indicate that this difference was not due to differences in the rate of metabolism of nicotine or cotinine. By examining serum nicotine and 3HC/cotinine ratios in addition to cotinine, this study expands upon previous research that relied on cotinine as an indirect indicator for nicotine intake. Our data support the hypothesis that the increased serum nicotine and cotinine levels observed are attributable to an increased nicotine intake per cigarette in smokers with schizophrenia as compared to those without mental illness. Williams, J.M., Ziedonis, D.M., Abanyie, F., Steinberg, M.L., Foulds, J. and Benowitz, N.L. Increased Nicotine and Cotinine Levels in Smokers with Schizophrenia and Schizoaffective Disorder is Not a Metabolic Effect. Schizophr. Res, In Press, Corrected Proof Available Online, June 14, 2005.

Assessing Missing Data Assumptions in Longitudinal Studies: An Example

Using A Smoking Cessation Trial

Due to the chaotic nature of the clinical disorder, longitudinal data analysis in substance abuse research is plagued by missing values. To obtain an unbiased estimation on intervention effects, different longitudinal modeling strategies require various assumptions on the patterns and mechanisms of missing data. By defining missingness as intermittent missingness (occasional omission) and dropout (premature withdrawal), this article demonstrates statistical ways for assessing missing data assumptions using evidence from a clinical trial. Within the framework of multiple imputation, intermittent missing data are imputed first so that dropouts can be isolated and treated specifically. A computational tool called "pattern reduction resampling" is proposed to simplify missing data methods when the number of intra-subject repeated measures is large. To test whether missingness patterns are nondifferential across treatment conditions, a formal testing approach treats indicators of missingness as a special type of repeated measures (e.g., 0: intermittent missing, 1: observed, and 2: dropout missing). After reviewing the idea of ignorability for missing data and of classifying missingness mechanisms into subcategories, the article provides an example for assessing common assumptions on missingness mechanisms and how these assumptions affect model selection for significance testing. A carbon monoxide longitudinal data set in a smoking cessation study is used for illustration. Yang, X. and Shoptaw, S. Assessing Missing Data Assumptions in Longitudinal Studies: An Example Using a Smoking Cessation Trial. Drug Alcohol Depend., 77, pp. 213-225, 2005.

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

Research Findings - Research on Medical Consequences of Drug Abuse

Disorders of Glucose Metabolism Among HIV-infected Women

Abnormal glucose metabolism in HIV-infected patients has largely been attributed to the use of protease inhibitors. However, most studies of glucose metabolism in HIV-infected patients have focused on men or have lacked appropriate control groups. Authors assessed the factors associated with previously diagnosed diabetes among 620 middle-aged women with or at risk for HIV infection. For a subset of 221 women without previously diagnosed diabetes, we performed an oral glucose tolerance test (OGTT) to measure glucose and insulin levels, and we assessed factors associated with abnormal glucose tolerance, insulin resistance, and insulin secretion. Thirteen percent of the women in the present study had previously diagnosed diabetes. Among women without previously diagnosed diabetes who underwent an OGTT, 6% had previously undiagnosed diabetes, and 12% had impaired glucose tolerance (IGT). According to multivariate analysis, factors that were associated with previously diagnosed diabetes included current methadone treatment, body mass index of >or =25, family history of diabetes, and physical inactivity. Factors that were independently associated with an abnormal result of an OGTT (i.e., a result consistent with IGT or diabetes) included age >or =50 years, family history of diabetes, physical inactivity, and a high number of pack-years of smoking. Factors independently associated with insulin resistance included waist circumference, Hispanic ethnicity, physical inactivity, and, among HIV-infected women, use of HAART that did not include protease inhibitors. Factors associated with lower levels of insulin secretion included current opiate use (i.e., methadone or heroin) and older age. The authors conclude that abnormal glucose metabolism is highly prevalent among middle-aged women with or at risk for HIV infection, particularly women who use opiates. Screening for diabetes in the HIV primary care setting should occur for women who have classic risk factors for diabetes, rather than solely for women who are taking PIs. Interventions that target modifiable risk factors, including obesity and physical inactivity, are also warranted. Howard, A.A., Floris-Moore, M., Arnsten, J.H., Santoro, N., Fleischer, N., Lo, Y. and Schoenbaum, E.E. Disorders of Glucose Metabolism Among HIV-infected Women. Clin Infect Dis. 40(10), pp. 1492-1499, 2005.

Depressive Symptoms, Quality of Life, and Neuropsychological Performance in HIV/AIDS: The Impact of Gender and Injection Drug Use

Limited attention has been paid to the potential impact of gender and injection drug use (IDU) on mood, quality of life, and neuropsychological performance in human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). Several studies that describe the natural history of HIV/AIDS in terms of mental health and neuropsychological ability have focused solely on men or have excluded injection drug users. Women and injection drug users are two groups for whom the incidence of HIV infection is increasing. Additionally, the National Academy of Sciences recently recommended that studies concerned with health-related research include males and females, and that researchers analyze their data for gender differences. The goals of the current study were to investigate possible relationships between HIV and IDU status and depressive symptoms, quality of life, and neuropsychological performance in women and men matched for age, race, and education. Overall, women reported more depressive symptoms than men, and this gender difference was most evident in women who were both infected with HIV and who were also injection drug users. Women and HIV-infected individuals reported the poorest quality of life scores. Women outperformed men on a measure of verbal memory and HIV(-) participants outperformed HIV(+) participants on a measure of perceptual speed. Finally, gender

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and HIV status interacted such that uninfected women performed the best, and infected men performed the worst, on a test of verbal memory. A better understanding of how men and women with different drug use profiles respond to HIV/AIDS may substantially improve survival, as well as aspects of daily functioning, of affected individuals. Thus, further study and development of treatment protocols targeted at including women and IDU are needed. Wisniewski, A.B., Apel, S., Selnes, O.A., Nath, A., McArthur, J.C., Dobs, A.S. Depressive Symptoms, Quality of Life, and Neuropsychological Performance in HIV/AIDS: The Impact of Gender and Injection Drug Use. J Neurovirol. 11(2), pp. 138-143, 2005.

Young Drug Abusers May be Predisposed to Developing Early Onset Rrain Aging Changes and Dementia

Drug abuse is a major problem worldwide. The incidence of drug-related deaths attributed to opiate abuse is increasing annually. Apart from routine examination, little is known of the neuropathology of drug abuse. Authors of the present study and others, have shown previously that drug abuse is associated with microglial activation. They hypothesized that neuroinflammation might lead to premature neurodegeneration in drug abusers. They investigated the brains of young opiate abusers (n = 34, all <40 years) for the presence of proteins associated with neurodegenerative diseases and compared them with the brains of age-matched, non-drug users (n = 16) all of whom died suddenly. Detailed immuno-histochemical analysis of the hippocampus, brainstem and basal ganglia for hyperphosphorylated tau, beta-amyloid, beta-amyloid precursor protein (betaAPP) and ubiquitin demonstrated an excess of AT8-positive neurofibrillary tangles (NFT) in the drug abusers. These were not only more prevalent in the drug abusers than in controls (44%vs. 19%) but also involved more brain areas. In controls NFT were confined to the entorhinal cortex whereas in drug users they were also found in the subiculum, temporal neocortex, nucleus basalis of Meynert and the locus coeruleus. Virtually no amyloid plaques were present but betaAPP positivity was again much more common in drug abusers than controls (73%vs. 20% in the brainstem and 59%vs. 23% in the temporal lobe). There is no suggestion that these drug abusers had displayed major cognitive impairment although detailed neuropsychological assessment is difficult in this subject group. Likely causes of hyperphosphorylated tau deposition in drug abuse include hypoxic-ischaemic injury, microglial-associated cytokine release and possibly drug-associated neurotoxicity or hepatitis. Head injury, which is another major risk factor, does not appear to have contributed to our findings. Genetic factors also merit consideration. It is unclear at present how much of the hyperphosphorylated tau detected in these young drug abusers represents a transitory phenomenon. Ramage, S.N., Anthony, I.C., Carnie, F.W., Busuttil, A., Robertson, R. and Bell, J.E. Hyperphosphorylated tau and Amyloid Precursor Protein Deposition is Increased in the Brains of Young Drug Abusers. Neuropathol Appl Neurobiol. 31(4), pp. 439-448, 2005.

Morphine Exacerbates HIV-1 Viral Protein gp120 Induced Modulation of Chemokine Gene Expression in U373 Astrocytoma Cells

HIV-1 affects microglia and astroglia, which subsequently contributes to the neurodegenerative changes. Viral proteins cause neurotoxicity by direct action on the CNS cells or by activating glial cells to cause the release of cytokines, chemokines or neurotoxic substances. Opioid abuse has been postulated as a cofactor in the immunopathogenesis of human immunodeficiency virus (HIV) infection and AIDS. HIV-induced pathogenesis is exacerbated by opiate abuse and the synergistic neurotoxicity is a direct effect of opiates on the CNS. Chemokines and their receptors have been implicated in the pathogenesis of neuroAIDS. Herein, authors describe the effects of morphine and/or gp120 on the expression of the genes for the beta-chemokine MIP-1beta and its receptors CCR3 and CCR5 by the U373 cells that are a human brain-derived astrocytoma/glioblastoma cell line. Results indicate that treatment of U373 cells with morphine significantly downregulated the gene expression of the beta chemokine, MIP-1 beta, while reciprocally upregulating the expression of its specific receptors, CCR3 and CCR5 suggesting that the capacity of mu-opioids to increase HIV-1 co-receptor expression may promote viral binding, trafficking of HIV-1-infected cells, and enhanced disease progression. Additionally, opiates can enhance the cytotoxicity of HIV-1 viral protein gp120 via mechanisms that involve intracellular calcium modulation resulting in direct actions on astroglia, making them an important cellular target for HIV-opiate interactions. Mahajan, S.D., Aalinkeel, R., Reynolds, J.L., Nair, B.B., Fernandez, S.F., Schwartz, S.A. and Nair, M.P. Morphine Exacerbates HIV-1 Viral Protein gp120 Induced Modulation of Chemokine Gene Expression in U373 Astrocytoma Cells. Curr HIV Res. 3(3), pp. 277-288, 2005.

Cocaine Modulates Dendritic Cell-specific C Type Intercellular Adhesion Molecule-3-grabbing Nonintegrin Expression by Dendritic Cells in HIV-1 Patients

Authors report that cocaine may act as cofactor in HIV pathogenesis by increasing dendritic cell-specific C type ICAM-3-grabbing nonintegrin (DC-SIGN) expression on dendritic cells (DC). Their results show that cocaine-using, long-term nonprogressors and normal progressors of HIV infection manifest significantly higher levels of DC-SIGN compared with cocaine-nonusing long-term nonprogressors and normal progressors, respectively. Furthermore, in vitro HIV infection of MDC from normal subjects cultured with cocaine and/or HIV peptides up-regulated DC-SIGN, confirming their *in vivo* finding. Cocaine, in synergy with HIV peptides, also up-regulates DC-SIGN gene expression by MDC. Furthermore, the cocaine-induced effects were reversed by a D1 receptor antagonist demonstrating the specificity of the reaction. These results indicate that cocaine exacerbates HIV infection by up-regulating DC-SIGN on DC and these effects are mediated via dysregulation of MAPKs. These data are the first evidence that cocaine up-regulates the expression of DC-SIGN on DC. A better understanding of the role of DC-SIGN in HIV infection may help to design novel therapeutic strategies against the progression of HIV disease in the drug-using population. Nair, M.P., Mahajan, S.D., Schwartz, S.A., Reynolds, J., Whitney. R., Bernstein, Z., Chawda, R.P., Sykes, D., Hewitt, R. and Hsiao, C.B. Cocaine Modulates Dendritic Cell-specific C Type Intercellular Adhesion Molecule-3-grabbing Nonintegrin Expression by Dendritic Cells in HIV-1 Patients. J Immunol. 174(11), pp. 6617-6626, 2005.

Influence of Depression and HIV Serostatus on the Neuropsychological Performance of Injecting Drug Users

Depression is common in injecting drug users (IDUs), a group at significant risk for HIV infection. Moreover, both HIV infection and depression have been shown to adversely effect neurocognitive abilities. Understanding the effects of depression and HIV infection on the neurocognitive functioning of drug users is essential for appropriate management and/or treatment of these deficits in this population. Therefore, the purpose of the present study was to investigate the effects of depression and HIV status on cognitive functioning in 100 male and female IDUs. Participants were categorized into three groups of depression severity based on their scores on the Beck Depression Inventory: no depression, mild depression, and moderate to severe depression. The effects of depression and HIV serostatus as well as their interaction were assessed. Results indicated that regardless of serostatus, those with moderate to severe depression had lower scores on cognitive measures. These findings suggest that although depression contributes to poor neuropsychological performance in IDUs, this effect was not exacerbated by HIV infection. The finding also illustrates the importance of addressing depression-related neurocognitive deficits in IDUs. Waldrop-Valverde, D., Ownby, R.L. and Kumar, M. Influence of Depression and HIV Serostatus on the Neuropsychological Performance of Injecting Drug Users. Psychiatry Clin Neurosci. 59(4), pp. 372-378, 2005.

Humoral Immune Response in Acute Hepatitis C Virus Infection

There is little information on the timing, magnitude, specificity, and clinical relevance of the antibody response to acute hepatitis C virus (HCV) infection. Authors investigated the specificity, titer, and neutralizing potential of antibody responses to acute infection by examining 12 injection drug users before, during, and after infection. Seroconversion was defined as incident detection of HCV-specific antibodies by using a commercially available enzyme-linked immuosorbent assay (ELISA). HCV protein-specific antibody responses were measured using recombinant antigens in an ELISA. For neutralization assays, plasma was incubated with human immunodeficiency virus (HIV)-HCV H77 or control HIV-murine leukemia virus (MLV) pseudotype virus and then allowed to infect Hep3B hepatoma cells. The mean time to HCV seroconversion was 6 weeks after the onset of viremia. Antibody responses to nonstructural proteins were detected before responses to the structural proteins, and antibodies to both were primarily restricted to the immunoglobulin G1 (IgG1) subclass. The maximum median end point titers for antibody responses to structural and nonstructural proteins were 1:600 and 1:6400, respectively. Antibodies that neutralized a retroviral pseudotype bearing HCV 1a envelope glycoproteins were detected at seroconversion in only 1 subject and at 6-8 months after seroconversion in 3 subjects. The delayed appearance of neutralizing antibodies was consistent with the late development of antibodies specific for the viral envelope glycoproteins, which are believed to mediate virus neutralization. The humoral immune response to acute HCV infection is of relatively low titer, is restricted primarily to the IgG1 subclass, and

is delayed. A better understanding of why production of neutralizing antibody is delayed may improve efforts to prevent HCV infection. Netski, D.M., Mosbruger, T., Depla, E., Maertens, G., Ray, S.C., Hamilton, R.G., Roundtree, S., Thomas, D.L., McKeating, J. and Cox, A. Humoral Immune Response in Acute Hepatitis C Virus Infection. Clin Infect Dis. 41(5), pp. 667-675, 2005.

Liver Enzyme Values in Injection Drug Users with Chronic Hepatitis C

Liver enzymes fluctuate in chronic hepatitis C virus infection. However, the range that can be attributed to the course of hepatitis C virus (versus an intercurrent cause of hepatitis) is unknown. The aim of the present study was to characterize the range of liver enzyme values as a function of the upper limit of normal (ULN) of the assay among persons chronically infected with hepatitis C virus. One thousand and fifty-nine hepatitis C virus chronically infected individuals with >/=5 semi-annual evaluations. Alanine aminotransferase and aspartate aminotransferase levels were prospectively obtained. Potential causes of elevations were examined using serologic testing. Among 1059 individuals, 11,463 enzyme measurements were obtained over 6.5 years, of which 63.5% were <1.25x ULN, 26.5% were 1.25-2.5x ULN, 8.3% were 2.5-5x ULN, and 1.6% were 5-10x ULN; only 0.2% were >10x ULN. Elevations >10x ULN were transient, the alanine aminotransferase/aspartate aminotransferase ratio tended to be different at the time of the elevation compared to before and after and 24% were associated with acute viral hepatitis. On the other hand, subjects with elevations 5-10x ULN tended to have elevated levels throughout follow-up and only 8% were associated with acute viral hepatitis. Liver enzymes fluctuate up to 5x ULN in most hepatitis C virus-infected persons; clinicians should seek alternate explanations for those with higher alanine aminotransferase or aspartate aminotransferase levels, especially among hepatitis C virus-infected persons with greater than 10-fold elevations. Mehta, S.H., Netski, D., Sulkowski, M.S., Strathdee, S.A., Vlahov, D. and Thomas, D.L. Liver Enzyme Values in Injection Drug Users with Chronic Hepatitis C. Dig Liver Dis. June 9, 2005 [Epub ahead of print].

HCV Therapeutic Success Increases, Yet HIV/HCV Coinfected IDUs Significantly Less Likely to Receive HCV Therapeutic Benefits

Although hepatic manifestations of opportunistic infections are now rare, chronic HCV is found in approximately one-third of HIV-infected individuals. The severity of HCV-related liver disease is greater in those with HIV than in those uninfected. Among HIV-HCV-coinfected individuals, advanced immunosuppression has been associated with more severe liver disease, supporting the hypothesis that reversal or prevention of immunosuppression with ART will slow the progression of HCV disease. However, effective ART use may also contribute to liver disease as most protease inhibitors have been associated with metabolic abnormalities, hyperlipidemia, and decreased insulin sensitivity, which themselves have been linked to hepatic steatosis. The objective of this study was to ascertain the prevalence and severity of hepatic steatosis among patients coinfected with HIV and HCV who have been taking antiretroviral therapy (ART); to investigate if steatosis is associated with more advanced liver disease, and to identify factors that might contribute to the process. Steatosis was assessed among a randomly selected subset of HIV-HCV-coinfected patients who had received at least 2 years of ART in a cohort study at the Johns Hopkins University HIV clinic. The results of liver histology were assessed in 112 patients, 74% of whom were taking ART at the time of biopsy. In multivariate analysis, steatosis was independently associated with Caucasian race, weight > 86 kg, hyperglycemia, and stavudine use. Patients with steatosis also were more likely to have greater hepatic fibrosis and necroinflammatory activity. Steatosis was observed in 40% of HIV-HCV-coinfected patients with extensive ART exposure and was associated with more severe HCV-related liver disease. Metabolic abnormalities (excess weight and hyperglycemia) and stavudine use were modifiable risk factors for steatosis in this population. Authors conclude that the disparity between HIV/HCV infected IDUs who are significantly less likely to be eligible for HCV therapy becomes more compelling as the success of HCV therapy increases. The investigators plan further analysis to assess the relationship(s) of clinical and socioeconomic covariates and treatment eligibility. Sulkowski, M.S., Mehta, S.H., Afdhal, N.H., Moore, R.D., Thomas, D.L., Torbenson, M., Brinkley, S., Mirel, L., Chaisson, R.E., Moore, R.D. and Sulkowski, M.S. Hepatic Steatosis and Antiretroviral Drug Use Among Adults Coinfected with HIV and Hepatitis C Virus. AIDS. 19(6), pp. 585-592, March 24, 2005. The critical significance of this work is in defining the burden of liver disease among HCV-infected IDUs, and thereby identify and target medical needs for anti-HCV therapy. Additional data regarding eligibility and actual acceptance of therapy among population groups will yield fundamental information with respect to the delivery of HCV therapy to IDUs. The data supports and expands upon recently published

preliminary findings from the study by the authors Mehta, S.H., Thomas, D.L., Torbenson, M., Brinkley, S., Mirel, L., Chaisson, R.E. and Sulkowski, M.S. The Effect of Antiretroviral Therapy on Liver Disease Among Adults with HIV and Hepatitis C Coinfection. Hepatology. 41(1), pp. 123-131, January 2005.

CD8+ Cell Responses to Hepatitis C Virus (HCV) in the Liver of Persons with HCV-HIV Coinfection Versus HCV Monoinfection

Cellular immune responses are difficult to detect in the peripheral blood of persons with chronic hepatitis C virus (HCV) infection. Authors of the present study sought to determine whether T cell responses were present in the liver of patients with human immunodeficiency virus (HIV) and HCV coinfection. T cells were expanded from liver-biopsy samples from 10 patients coinfected with HIV and HCV (median CD4(+) cell count, 456 cells/mm(3)) and 8 patients infected with HCV alone. CD8(+) cell responses were detected by use of a modified enzyme-linked immunospot (ELISpot) assay with recombinant vaccinia virus, and CD4(+) cell responses were detected by use of ELISpot with recombinant HCV proteins core, nonstructural (NS) 3, and NS5. Intrahepatic CD8(+) cell responses to HCV were detected in 7 of 10 patients coinfected with HCV and HIV (median frequency, 638 spot-forming cells [sfc]/1 x 10(6) cells) and were similar to those observed in patients singly infected with HCV (7/8; median, 647 sfc/1 x 10(6) cells). Intrahepatic HCV-specific CD4(+) cell responses were also comparable in both groups and correlated with the intrahepatic CD8(+) cell responses (r=0.59; P=.03). HCV-specific CD8(+) cell responses are present in the liver of persons with chronic HCV infection even when they are coinfected with HIV; these correlate with intrahepatic HCV-specific CD4(+) cell responses. Alatrakchi, N., Graham, C.S., He, Q., Sherman, K.E. and Koziel, M.J. CD8+ Cell Responses to Hepatitis C Virus (HCV) in the Liver of Persons with HCV-HIV Coinfection Versus HCV Monoinfection. J Infect Dis., 191(5), pp. 702-709, 2005.

Antigen-specific Immune Responses and Liver Histology in HIV and Hepatitis C Cinfection

The objective of this study was to test the hypothesis that antigen-specific interferon (IFN) gamma responses are correlated with milder liver disease in subjects coinfected with HIV-1 and hepatitis C virus (HCV). Cellular immune responses were studied in a cohort with HIV/HCV coinfection (n = 107) who underwent liver biopsy. Authors measured HCV-specific and recall responses in peripheral blood mononuclear cells using IFNgamma and interleukin (IL)-10 ELISpots, and correlated these immune responses with liver histology. The relationship of immunologic, virologic and clinical variables to inflammation and fibrosis was modeled using recursive partitioning. There were significant negative correlations between inflammatory scores and IFNgamma production in response to the HCV proteins core, NS5 and summed HCV responses. Lower fibrosis scores were also correlated with higher IFNgamma production in response to NS5 and summed HCV proteins. Higher IFNgamma production in response to Candida was significantly associated with lower inflammatory and fibrosis scores. In multivariable models, factors associated with severe fibrosis were lower IFNgamma responses to Candida and summed HCV proteins. Factors associated with severe inflammation were detectable HIV viral load and lower HCV viral load, while predictors of mild inflammation included undetectable HIV viral load and higher IFNgamma response to Candida. In this cohort of subjects coinfected with HIV and HCV, antigen-specific IFNgamma responses are correlated with milder inflammation and fibrosis. Immunological responses best predicted severity of fibrosis, while clinical variables and recall antigen responses best predicted severity of inflammation. Graham, C.S., Wells, A., Liu, T., Sherman, K.E., Peters, M., Chung, R.T., Bhan, A.K., Andersen, J., Koziel, M.J. and ACTG 5071 Study Team. Antigen-specific Immune Responses and Liver Histology in HIV and Hepatitis C Coinfection. AIDS.19(8), pp. 767-773, 2005.

Prediction of Hepatic Fibrosis in HIV/HCV Co-infected Patients Using Serum Fibrosis Markers: The SHASTA Index

The aim of this study was to examine if serum fibrosis biomarkers could accurately identify the stage of liver disease amongst hepatitis C (HCV) and HIV co-infected patients. One hundred and thirty seven HIV/HCV co-infected persons were randomly selected from the Johns Hopkins HIV Clinic cohort. Ninety five had complete testing for fibrosis markers in sera collected at the time of liver biopsy. Biopsies were scored according to Ishak modified histological activity index (F0 no fibrosis to F6 cirrhosis). Fibrosis was evaluated against alanine aminotransferase (ALT), aspartate aminotransferase (AST), AST to platelet ratio (APRI), albumin, total bilirubin, hyaluronic acid (HA) and YKL-40. Sixty nine (73%) had no or minimal portal fibrosis (F0-2) and were compared with remaining subjects (F3-6). Fibrosis scores > or =F3

were found 27 times more often in persons with HA levels >86 ng/ml and 5.5 times more often in persons with HA levels 41-86 ng/ml. Less substantial associations were detected with levels of albumin <3.5 g/dl (OR 4.85) and AST >60 iu (OR 5.91). All 35 subjects who had favorable results of HA, albumin, and AST had minimal fibrosis (F0-2). Amongst HIV/HCV co-infected patients, serum testing for HA, albumin, and AST (SHASTA Index) was able to accurately stage mild and advanced fibrosis. Kelleher, T.B., Mehta, S.H., Bhaskar, R., Sulkowski, M., Astemborski, J., Thomas, D.L., Moore, R.E. and Afdhal, N.H. Prediction of Hepatic Fibrosis in HIV/HCV Co-infected Patients Using Serum Fibrosis Markers: The SHASTA Index. J Hepatol. 43(1), pp. 78-84, 2005.

Respiratory Effects of Marijuana and Tobacco Use in a U.S. Sample

Although a number of studies have examined the respiratory impact of marijuana smoking, such studies have generally used convenience samples of marijuana and tobacco users. The current study examined respiratory effects of marijuana and tobacco use in a nationally representative sample while controlling for age, gender, and current asthma. Analysis of the nationally representative third National Health and Nutrition Examination Survey (NHANES III). U.S. households. A total of 6,728 adults age 20 to 59 who completed the drug, tobacco, and health sections of the NHANES III questionnaire in 1988 and 1994. Current marijuana use was defined as self-reported 100+ lifetime use and at least 1 day of use in the past month. Self-reported respiratory symptoms included chronic bronchitis, frequent phlegm, shortness of breath, frequent wheezing, chest sounds without a cold, and pneumonia. A medical exam also provided an overall chest finding and a measure of reduced pulmonary functioning. Marijuana use was associated with respiratory symptoms of chronic bronchitis (P=.02), coughing on most days (P=.001), phlegm production (P=.0005), wheezing (P<.0001), and chest sounds without a cold (P=.02). The impact of marijuana smoking on respiratory health has some significant similarities to that of tobacco smoking. Efforts to prevent and reduce marijuana use, such as advising patients to quit and providing referrals for support and assistance, may have substantial public health benefits associated with decreased respiratory health problems. Moore, B.A., Augustson, E.M., Moser, R.P. and Budney, A.J. Respiratory Effects of Marijuana and Tobacco Use in a U.S. Sample. J Gen Intern Med. 20(1), pp. 33-37, 2005.

Gender Effects Following Repeated Administration of Cocaine and Alcohol in Humans

Use of cocaine, alcohol, and the two drugs simultaneously is common and the risk of morbidity and mortality associated with these drugs is widely reported. This double-blind, placebo-controlled, randomized study examined gender differences in response to administration of these drugs alone and in combination. Current users of cocaine and alcohol (n = 17) who met diagnostic criteria (DSM-IV) for cocaine dependence and alcohol abuse or dependence (not physiologically dependent on alcohol) and who were not seeking treatment for substance use disorders gave voluntary, written, informed consent to participate in three drug administration sessions:1) four doses of intranasal cocaine (1 mg/kg every 30 min) with oral alcohol (1 g/kg following the initial cocaine dose and a second drink at +60 min (120 mg/kg) calculated to maintain a plasma alcohol concentration of approximately 100 mg/dL; 2)four doses of cocaine and alcohol placebo; 3) cocaine placebo and alcohol. Pharmacokinetics were obtained by serial blood sampling, physiological measurements (heart rate and blood pressure) were obtained with automated equipment, and subjective effects were assessed using visual analog scales over 480 min. Responses to cocaine, alcohol, and cocaine-alcohol were equivalent by gender for most measurements. Women had higher heart rates following alcohol administration (p = .02). Women consistently reported higher ratings for "Feel Good", a measure of overall mental/physical well-being, for all study conditions, reaching statistical significance for cocaine (p = .05) and approaching significance for alcohol administration (p = .1). Women showed equivalent responses to drug administration with the exception of perception of well-being, which was significantly increased for women. These findings may have implications for differential risk for acute and chronic toxicity in women. McCance-Katz, E.F., Hart, C.L., Boyarsky, B., Kosten, T. and Jatlow, P. Gender Effects Following Repeated Administration of Cocaine and Alcohol in Humans. Subst Use Misuse. 40(4), pp. 511-528, 2005.

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

Research Findings - Services Research

Organizational Factors Influence Adoption of Naltrexone

Three surveys of outpatient substance abuse treatment centers in Connecticut, Massachusetts, Rhode Island, Maine, Vermont, and New Hampshire were conducted in 1997 (N-281), 1999 (N=235), and 2001 (N=246) to examine organizational characteristics that influenced the adoption of naltrexone. Structural equation modeling with manifest variables was used to assess predictors related to the use of naltrexone. Use of naltrexone increased over time from 14% in 1997 to 25% in 2001. In 1997, programs funded by managed care were more likely, and clinics that provided only substance abuse services were less likely to use psychiatric medication and naltrexone. In subsequent years, counselor education level and organization size also was associated with increased use of naltrexone. Fuller, B.E., Rieckmann, T, McCarty, D., Smith, K.W. and Levine, H. Adoption of Naltrexone to Treat Alcohol Dependence. Journal of Substance Abuse Treatment, 28, pp. 273- 280, 2005.

Emergency Departments Offer Opportunities to Identify Cocaine Abusers and Enroll Them in Treatment

This study examined 145 patients with cocaine-associated chest pain, aged 18-60 years, with low to moderate risk for acute coronary syndrome who were screened (urinalysis and/or self-report) from among 1,343 chest-pain patients presenting for emergency department (ED) treatment who agreed to be screened for cocaine (94% response rate). Responses on standardized and validated instruments were used to examine demographic and clinical characteristics. Half of the cocaine using patients met criteria for substance abuse or dependence in the past three months, primarily cocaine or alcohol dependence; on the other hand, a substantial proportion surprisingly did not meet abuse or dependence criteria and reported infrequent cocaine use. Approximately one-half of the entire chest-pain sample reported substantial symptoms of depression. Substance use frequency and consequences, depression, and psychological distress were significantly more severe among those with past three-month substance use diagnoses; however, most socio-demographic characteristics were not associated with substance use diagnoses. Findings regarding diversity in alcohol and drug involvement, current level of psychological functioning, depressive symptomatology, and interest in treatment services provide useful information for designing ED-based interventions for this population. Because cocaine-related chest-pain was shown to be manifest among patients with no history of frequent substance abuse, ER staff should consider discussing alcohol and cocaine usage with all chest-pain patients, and discourage cocaine use when mentioned. For those presenting a history of cocaine use, patients should be provided on-the-spot counseling and referral for substance abuse treatment, as their brush with myocardial infarction appears to increase in motivation to be treated. Booth, B.M., Weber, J.E., Walton, M.A., Cunningham, R.M., Massey, L., Thrush, C.R. and Maio, R.F. Characteristics of Cocaine Users Presenting to an Emergency Department Chest Pain Observation Unit. Academic Emergency Medicine, 12(4), pp. 329-37, 2005.

Modified Work-Release Therapeutic Community is Superior to Standard Work-Release

This study examined the effects of 6-month work-release transitional therapeutic community treatment on the drug use and employment rates of 945 prisoners in the Delaware corrections system. Participants were followed for up to 5 years after release. A comparison group (N=374) received standard 6-month work-release supervision. Abstinence rates were 32.2% in the treatment group and 9.9% in the

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no-treatment group, and the treatment group had a higher overall proportion of time free of drug use. Time-to-relapse was a mean of 28.8 months in the treatment group versus 13.2 months in the no-treatment group. Relapse was defined as any use of any drug and was confirmed by urinalysis. Positive effects were seen even for those who did not complete treatment. The treatment group had a significantly higher rate of employment after leaving work release (54.6%) than did the no-treatment group (45.4%). Treatment during the transitional period between prison and community showed substantial and persistent benefits even for a cohort marked with extensive criminal history, low rates of marital bonds, and substantial unemployment. Butzin, C.A., Martin, S.S. and Inciardi, J.A. Treatment During Transition From Prison to Community and Subsequent Illicit Drug Use. Journal of Substance Abuse Treatment, 28, pp. 351- 358, 2005.

Perceived Deterrence Related to Drug Court Outcomes

This study examined individuals' expectations that they would be rewarded or sanctioned appropriately for their participation in drug court, and the impact this expectation had on outcomes including reduction in drug use and criminal recidivism. Perceived-deterrence theory provides the conceptual framework for this study and posits that, the likelihood an offender will engage in drug use or illegal activity is influenced by the perceived certainty of being detected for infractions or recognized for accomplishments, the perceived certainty of receiving sanctions for infractions or rewards for accomplishments, and the anticipated magnitude of the sanctions and rewards. Perceived deterrence of 225 offenders participating in three different drug courts was examined. Exploratory cluster analysis on longitudinal perceived deterrence scores yielded five subtypes of drug offenders characterized either by consistently elevated perceived-deterrence scores, consistently moderate scores, consistently low scores, increasing scores, or decreasing scores. The best outcomes were associated with consistently elevated scores, whereas the worst outcomes were associated with scores that declined over time as the participants became accustomed to the drug court program. The correlational design does not permit inferences of causality; however, the results lend credence to perceived deterrence as a potential explanatory mechanism for the effects of drug courts. Marlowe, D.B., Festinger, D.S., Lee, P.A. and Patapis, N.S. Perceived Deterrence and Outcomes in Drug Court. Behavioral Sciences and the Law, 23(2), pp. 183-198, 2005.

Need-Based Syringe Dispensation May Reduce Syringe Reuse

Numerous papers about the effectiveness of syringe exchange programs (SEPs) have been published, but only a few identify operational characteristics of the SEPs they study or assess which of those characteristics are associated with optimal HIV risk reduction among clients. The objective of this study was to examine whether different syringe dispensation policies were associated with client-level injection-related HIV risk. Injection drug users (IDUs) were recruited at 23 SEPs in California in 2001 (n = 531). SEPs were classified by their executive directors as to whether they provided a strict one-for-one syringe exchange, gave a few extra syringes above the one-for-one exchange, or distributed the amount of syringes based upon need as opposed to how many syringes were turned in by the clients. Injection-related risk was compared by SEP program type. In multivariate logistic regression analysis, clients of distribution-based programs had lower odds of reusing syringes (adjusted odds ratio = 0.43; 95% CI = 0.27, 0.71) when adjusting for confounding variables. There were no statistical differences with regards to distributive or receptive syringe sharing by dispensation policy. It is concluded that SEPs that base syringe dispensation policy upon need may facilitate reductions in reuse of syringes. Kral, A.H., Anderson, R., Flynn, N.M. and Bluthenthal, R.N. Injection Risk Behaviors Among Clients of Syringe Exchange Programs With Different Syringe Dispensation Policies. Journal of Acquired Immune Deficiency Syndrome, 37(2), pp. 1307-1312, 2004.

Chemically Dependent Youth Benefit from Psychiatric Services

Many adolescents with alcohol and drug problems have mental health co-morbidities. The literature suggests that patients entering chemical dependency (CD) treatment with co-occurring problems have less successful outcomes, including treatment dropout and relapse. Researchers examine the impact of psychiatric services on treatment initiation, retention, and alcohol and drug abstinence outcomes for adolescents in CD treatment. Participants were 419 adolescents aged 12-18 years who were seeking treatment at four CD programs of a nonprofit, managed care, group model health system. A parent or guardian for each adolescent also participated. Participants were surveyed at intake and at 6 months and the researchers were exposed to clinical and administrative data pertaining to their diagnoses for CD and psychiatric utilization. Six-month response rates were 91% for

adolescents and 93% for parents. Fifty-five percent of the patients with treatment intakes had at least one psychiatric diagnosis in addition to a substance use disorder. Compared with matched controls, patients with CD intakes had higher rates of depression, anxiety, eating disorders, attention deficit hyperactivity disorder, conduct disorder, and conduct disorder including oppositional defiant disorder. Thirty-one percent of the full sample had psychiatric visits in the 6 months after intake; among those with a psychiatric diagnosis, 54% had a psychiatric visit. Girls and those with higher Youth Self-Report internalizing scores were more likely to have a psychiatric visit (OR = 2.27, $p < 0.001$ and OR = 1.05, $p < 0.0001$, respectively). Adolescents receiving psychiatric services were more likely to be abstinent from both alcohol and drugs than those not receiving these services (OR = 1.57, 95% CI = 0.98-2.5) and more likely to be alcohol abstinent (OR = 1.68, 95% CI = 1.00-2.85). Those adolescents at co-located clinics had higher odds of abstinence from both alcohol and drugs (OR = 1.57, 95% CI = 1.03-2.39) and drugs (OR = 1.84, 95% CI = 1.87-2.85) and of returning after intake to initiate CD treatment (OR = 2.28, 95% CI = 1.44-3.61, $p < 0.001$) than others. The results demonstrate the need for psychiatric treatment of adolescents in CD treatment and highlight the importance of their receiving such services. Sterling, S. and Weisner, C. Chemical Dependency and Psychiatric Services for Adolescents in Private Managed Care: Implications for Outcomes. Alcoholism: Clinical and Experimental Research, 25(5), pp. 801-809, 2005.

Effectiveness of Post-Discharge Monitoring in Sustaining Addiction Recovery

Using data from quarterly interviews conducted over a 2-year period in which 448 post-discharge recovering addicts were randomly assigned to either an assessment only condition or to a Recovery Management Checkup (RMC) condition, investigators looked at the frequency, type, and predictors of transitions between points in the relapse, treatment reentry, and recovery cycle. The results indicated that about one-third of the participants transitioned from one point in the cycle to another each quarter; 82% transitioned at least once, 62% multiple times. People assigned to RMC were significantly more likely to return to treatment sooner and receive more treatment. The probability of transitioning to recovery was related to drug use severity, problem orientation, desire for help, self-efficacy, self-help involvement, and recovery environment at the beginning of the quarter and the amount of treatment received during the quarter. These findings support the conceptualization of addiction as a chronic condition and demonstrate the need for and effectiveness of post-discharge monitoring and checkups. The methods in this study also provide a simple but replicable method for learning more about the multiple pathways that individuals travel along before achieving a prolonged state of recovery. Scott, C.K., Dennis, M.L. and Foss, M.A. Utilizing Recovery Management Checkups to Shorten the Cycle of Relapse, Treatment Reentry, and Recovery. Drug & Alcohol Dependence, 78(3), pp. 325-338, 2005.

Discussion Groups Facilitate Recruitment into Treatment for MSMs

Drug-using men who have sex with men (MSM) are at high risk of acquiring or transmitting HIV infection. Efforts to change behaviors in this population have been hampered by difficulties in recruiting drug-using MSM into behavioral interventions. This study sought to develop an effective strategy for recruiting drug-using MSM into behavioral interventions that consist of motivational interviewing alone or motivational interviewing plus contingency management. MSM were recruited through advertising and community outreach into groups to discuss party drugs, party burnout, and sexual behavior, with the intervention subsequently described and enrollment offered in the group setting. Many more eligible MSM responded to advertisements for the discussion groups than advertisements for the interventions, and 58% of those who participated in the discussion groups volunteered for counseling. Men who entered counseling reported high levels of drug use and sexual activity and were racially and ethnically diverse. Only 35% were willing to accept drug treatment. Results demonstrate that a two-stage strategy in which drug-using MSM are first recruited into discussion groups before they are offered a behavioral intervention can be an effective way to induce voluntary acceptance of an intervention employing a behavioral risk-reduction approach. Kanouse, D.E., Bluthenthal, R.N., Bogart, L., Iguchi, M.Y., Perry, S., Sand, K. and Shoptaw, S. Recruiting Drug-using Men Who Have Sex With Men into Behavioral Interventions: A Two-Stage Approach. Journal of Urban Health, 82 (1 Suppl 1), pp. i109-i119, 2005; Epub 2005.

Cash Benefits Associated with Lower Risk Behavior Among Homeless and Marginally Housed

To address the widespread debate about the role of public assistance to the urban

poor, this study identified characteristics of individuals receiving cash assistance and explored the link between cash subsidies and risk behavior. From 1999 to 2000, a representative sample of homeless and marginally housed (HMH) adults living in San Francisco was recruited and interviewed about subsidies, shelter, jail, and drug use. Among 1,156 adults, 87% were ever homeless, 22% currently injected drugs, and 14% were HIV positive. Sixty percent of participants reported that most of their income came from subsidies [mostly subsidized (MS)]. The MS had lower odds of receiving any income from selling drugs or trading sex. Adjusting for HIV infection, the MS had higher odds of sleeping in a hotel [odds ratio (OR) =_2.39] or shelter (OR =_1.61) compared to the street. The MS had lower odds of injection drug use (OR =_0.69) and recent incarceration (OR=_O.77). Among San Francisco's homeless, being MS was positively associated with having shelter and negatively associated with injection drug use and incarceration. These data suggest that government subsidies are associated with positive health behaviors among the urban poor. Riley, E.D., Moss, A.R., Clark, R.A., Monk, M.L. and Bangsberg, D.R. Cash Benefits are Associated with Lower Risk Behavior Among the Homeless and Marginally Housed in San Francisco. Journal of Urban Health, 82(1), pp. 142-150, 2005.

Brief Motivational Intervention May Facilitate Abstinence From Heroin and Cocaine

Brief intervention is effective for alcohol misuse, but not adequately tested in the clinical setting with drug using patients. This study tested the impact of a single, structured encounter targeting cessation of drug use, conducted by peer educators with out-of-treatment cocaine and heroin users screened in the context of a routine medical visit. A randomized, controlled trial was conducted in inner-city teaching hospital outpatient clinics with 3- and 6-month follow-up by blinded observers. Drug abstinence was documented by hair testing. Analysis was limited to enrollees with drug-positive hair at baseline. Among 23,669 patients screened from May 1998 to November 2000, 1,232 (5%) were eligible, and 1,175 enrolled. Enrollees (mean age 38 years) were 29% female, 62% were non-Hispanic Black, 23% were Hispanic, and 46% were homeless. Among those with positive hair test at entry, the follow-up rate was 82%. The intervention group was more likely to be abstinent than the control group for cocaine alone (22.3% vs. 16.9%), heroin alone (40.2% vs. 30.6%), and both drugs (17.4% vs. 12.8%), with adjusted OR of 1.51-1.57. Cocaine levels in hair were reduced by 29% for the intervention group and only 4% for the control group. Reductions in opiate levels were similar (29% vs. 25%). The authors conclude that brief motivational intervention may help patients achieve abstinence from heroin and cocaine. Bernstein, J., Bernstein, E., Tassiopoulos, K., Heeren, T., Levenson, S. and Hingson, R. Brief Motivational Intervention at a Clinic Visit Reduces Cocaine and Heroin Use. Drug and Alcohol Dependence, 77, pp. 49-59, 2005.

Low-cost Contingent Rewards Effective in Reducing Cocaine Use By Methadone Clients

Both behavioral (low-cost contingency rewards) and cognitive (relapse prevention counseling) interventions have shown promise in helping engage opiate-dependent clients in treatment. In this study, researchers examined the effectiveness of combining contingent rewards with a cocaine-specific relapse prevention counseling module. Sixty-one cocaine-using methadone clients (60% male, 74% Hispanic/20% Caucasian) were randomly assigned to one of four treatment conditions to participate in the eight-week intervention and eight-week follow-up period. Conditions included specialized counseling on cocaine abuse (COCA) with or without contingent rewards (stars for clean urines, attending sessions, etc. redeemable for prizes valued to $25); methadone treatment as usual with or without contingent rewards. Using analysis of variance (ANOVA), differences in cocaine use and treatment retention were examined. Both contingent reward conditions were significantly related to reductions in cocaine use during and upon completion of treatment. The COCA intervention also showed substantial reductions in use even without rewards when compared to the no-COCA/no-Reward group. Moreover, the COCA counseling module was positively related to six-month retention rates regardless of reward contingency. Though results support the value of low-cost contingent rewards for changing the behavior of methadone clients. Though encouraging, the power for this study was limited. Rowan-Szal, G.A., Bartholomew, N.G., Chatham, L.R. and Simpson, D.D. A Combined Cognitive and Behavioral Intervention for Cocaine-Using Methadone Clients. Journal of Psychoactive Drugs, 37(1) pp. 75-84, 2005.

Compromises to Cultural/Ethical Issues and Maintenance of Research Integrity

A study of American Indian youth illustrates competing pressures between research

and ethics. A stakeholder/researcher team developed three plans to protect subjects. The first allowed youths to skip potentially upsetting interview sections. The second called for those flagged for abuse or suicidality to receive referrals, emergency 24-hour clinical backup, or both. The third, based on the community's desire to promote service access, included giving youths a list of service resources. Interviewers gave referrals to those flagged as having mild problems, and reported ones with serious problems to supervisors for clinical backup. The youths seldom chose to skip sections, so data integrity was not compromised. They did have more problems than expected (e.g., one in three had thought about suicide, one in five had attempted, and one in four reported abuse), so service agencies were not equipped to respond. Researchers must accept the competing pressures and find ethically appropriate compromises that will not undermine research integrity. Stiffman, A.R., Striley, C.W., Brown, E., Limb, G. and Ostmann, E. Cultural and Ethical Issues Concerning Research on American Indian Youth. Ethics and Behavior, 15(1), pp. 1-14, 2005.

High Lifetime Benefit-Cost Ratio For Chronic Disease Model of Drug Abuse Treatment

Several studies have examined the benefits and costs of drug treatment; however, they have typically focused on the benefits and costs of a single treatment episode. Although beneficial for certain analyses, the results are limited because they implicitly treat drug abuse as an acute problem that can be treated in one episode. Researchers developed a Monte Carlo simulation model that incorporates the chronic nature of drug abuse. The model represents the progression of individuals from the general population aged 18-60 with respect to their heroin use, treatment for heroin use, criminal behavior, employment, and health care use. Three model scenarios are presented for an increase in the probability of going to treatment, an increase in the treatment length of stay, and a scenario in which drug treatment is not available so that the impact on results may be examined. The benefit-cost ratio of treatment from the chronic disease model (37.72) exceeds the benefit-cost ratio from the acute care model (4.86). The chronic care model characterizes the dynamics of heroin use and captures the notion of heroin use as a chronic recurring condition. Similar models can be developed for other chronic diseases, such as diabetes, mental illness, or cardiovascular disease. Zarkin, G.A., Dunlap, L.J., Hicks, K.A. and Mamo, D. Benefits and Cost Of Methadone Treatment: Results From A Lifetime Simulation Model. Health Economics. Published on line May 5, 2005. http://www3.interscience.wiley.com/cgi-bin/jissue/77002049

Family Drug Court has Higher Engagement and Completion Rates than Other Court Assisted Treatment Services

A geographical comparison-group design was used to examine the effectiveness of the Pima County (Arizona) Court Assisted Treatment Services (CATS) program and its drug court intervention. The study compared summary statistics for the volunteers to family drug court (n=33) with a treatment-refusal group (n=42) and a treatment-as-usual group (n=45) from a matched geographical area. The family drug court group had higher engagement and completion rates of residential treatment than the comparison groups. In addition, the family drug court group had fewer parental rights severed, a higher percentage of permanency decisions reached within one year, earlier permanency decisions, and a higher percentage of children placed with their parents. The results suggest that further study of family court as a treatment of choice is warranted. Ashford, JosŽ B., Treating Substance-abusing Parents: A Study of the Pima County Family Drug Court Approach, Juvenile and Family Court Journal, Fall. pp. 27-33, 2004.

Drug Treatment Services as Providers of Hepatitis C Virus Treatment

(HCV) is the most prevalent blood-borne infectious disease in the U.S., especially among drug users, and co-infection with HIV is common. Because drug users are often medically underserved, drug treatment units are important sites of opportunity for providing services for these infectious diseases. Given the commonalities in the routes of transmission of HIV and HCV, and the fact that many drug treatment units have established an infrastructure to provide HIV services, some have suggested integrating HCV services into those already established for HIV. Using data collected in a telephone survey with 89 drug treatment units throughout the U.S., the researchers examined the extent to which drug treatment units have expanded their HIV services to include those for HCV, and the extent to which this expansion was facilitated by having HIV services in place. Overall, a greater proportion of methadone maintenance than drug-free treatment units provided services for HIV and HCV. The majority of units in both modalities that provided HIV and HCV-related services expanded their HIV service delivery to include similar HCV services, and one third

expanded all of their HIV services. A large number with an HIV service infrastructure, however, did not facilitate this expansion, often because the units wanted to emphasize differences in the two viral infections. Policy makers and individual treatment units need to develop strategies that capitalize on existing infrastructures while maintaining the distinction between HIV and HCV primary and secondary prevention efforts. Strauss, S.M., Astone, J.M., DesJarlais, D.C. and Hagan, H. Integrating Hepatitis C Services Into Existing HIV Services: The Experiences of a Sample of U.S. Drug Treatment Units, AIDS Patient Care STDS, 19(2), pp. 78-88, 2005.

Interagency Collaboration in Developing Opioid Agonist Programs for Inmates

This paper briefly reviews the empirical literature and describes the development of a unique inter-agency collaboration between community treatment providers, researchers, and the criminal justice system to implement treatment and research on opioid agonist treatment for inmates leaving prison and returning to their community. The authors clearly articulate the problem of inadequate treatment and relapse to drug use for individuals with heroin addiction prior to incarceration. They suggest prisons provide an opportunity to engage individuals with heroin addiction histories in treatment, including opioid agonist programs. They describe the steps necessary for the development of an opioid agonist program within a prison setting followed by on-going treatment in the community. In addition, they detail logistical issues related to conducting research in a prison-based setting and offer recommendations for developing and implementing opioid agonist programs in other prison-based settings and conducting research. Kinlock, T.W., Schwartz, R.P. and Gordon, M.S. The Significance of Interagency Collaboration in Developing Opioid Agonist Programs for Inmates. Corrections Compendium, pp. 6-30.

Juvenile Offenders at Increased Risk for HIV Infection

The purpose of this study was to examine the prevalence, multiple correlates, and gender differences in chlamydia and gonorrhea infections among adolescents incarcerated in a youth detention center in the southern region of the United States. STD screening was conducted on 1816 youth, ages 10-18, as they entered the facility. Rates of undiagnosed chlamydia were 24.7% for incarcerated girls and 8.1% for boys. Gonorrhea was detected in 7.3% of the girls and 1.5% of the boys. Only youth 13 years or older were asked to complete a survey: 763 assented to participate, and 690 gave permission to link their STD test results to their survey responses. The majority of the juveniles who participated in the study were African American (89%) and male (67%). Predictors of STD positivity differed for boys and girls. Demographic characteristics (gender, race, and age) account for 52% of the total variance in STD infections; youths' behavior (alcohol use, sex under the influence of alcohol, history of STD and sexual risk reduction strategy) accounts for about one-third of the total variance, psychological (sexual abuse, alcohol and drug expectancies) and family variables (family structure/living arrangements, supervision and monitoring, parental involvement, family communication) account for 8.6% (boys) and 7.2% (girls) of the total variance. An approach that considers psychological and social influences on adolescent sexual behavior is useful for identifying potential risk and protective factors of adolescent STD/HIV risk that are amenable to intervention. Robertson, A.A., Baird-Thomas, C., St. Lawrence, J.S. and Pack, R. Predictors of Infection with Chlamydia or Gonorrhea in Incarcerated Adolescents. Sexually Transmitted Diseases, 32(2), pp. 115-122, 2005.

Managed Care Delivers Outpatient Treatment for Adolescent Substance Abuse

This study assessed the impact of managed care on publicly funded adolescent substance abuse treatment by comparing differences in service utilization and outcomes across prospective samples from two states: Oregon, which uses managed care practices in service financing and delivery, and Washington, which does not. One hundred and six adolescents from Washington and 94 from Oregon, who entered outpatient substance abuse treatment in 1998 and 1999, completed self-report surveys about their substance use before and after receiving treatment (follow-up rate = 75 percent). In addition, clinical chart reviews conducted at the 6-month follow-up assessed the type and amount of treatment these adolescents received during the study period. Results showed that service utilization and treatment outcomes were comparable across the two state samples, suggesting that managed care is capable of delivering substance abuse treatment services of comparable quality to state-administered substance abuse treatment services. Carlson, M.J., Gabriel, R.M., Deck, D.D., Laws, K.E. and D'Ambrosio, R. The Impact Of Treatment:

Service Use And Six-Month Outcomes In Oregon and Washington. Medical Care Research Review, 62(3), pp. 320-38, 2005.

Legal Pressure Negatively Affects Methamphetamine Treatment Outcomes

With the increase in the prevalence of methamphetamine (MA) use and the associated social costs (such as crime and child abuse and neglect), a growing number of MA users are mandated to substance abuse treatment via the criminal justice system (CJS) and/or child protective service (CPS) agencies. Empirical evidence remains sparse about treatment outcomes, specifically for MA users who report that their treatment admission occurred under such pressures. This analysis uses natural history interview data from 350 clients treated for MA use in Los Angeles County to examine clients' self-reported CJS/CPS pressure to enter treatment, comparing background and treatment characteristics and selected treatment outcomes across groups defined by existence of such perceived pressure and source of pressure. Approximately half the clients reported legal pressure to enter the index (used for sampling) treatment episode. Those reporting pressure were younger, less likely to have received residential treatment, and had longer treatment episodes than those not reporting pressure. Outcomes (treatment completion, relapse within 6 months, time to relapse, and percentage of days with MA use in 24 months following treatment) did not differ significantly in simple comparisons between the pressured and nonpressured groups; however, when client and treatment characteristics were controlled, the short term outcome of relapse within 6 months was worse for those reporting legal pressure. Outcomes did not differ by source of pressure. Brecht, M. L., Anglin, M. D. and Dylan, M. Coerced Treatment for Methamphetamine Abuse: Differential Patient Characteristics and Outcomes. American Journal of Drug and Alcohol Abuse, 31, pp. 337-356, 2005.

Role of Dental Professionals and Tobacco Treatment

This review article discusses tobacco use and dependence, effective treatments, and the role of the dental professional. Tobacco dependence is discussed as a chronic condition characterized by a vulnerability to relapse that persists for years. The need for ongoing rather than acute care is highlighted. Effective treatments for tobacco exist, and a brief clinical intervention can make a difference. Dental professionals are favorably positioned to encourage tobacco cessation treatments since more than 50 percent of smokers see a dentist during the year. It is recommended that every dental patient who uses tobacco be offered at least one of the effective treatments available. In so doing, dental professionals can play an important role in primary prevention of adverse health effects and can have an important public health impact by helping to counter tobacco use. Walsh, M.M. and Ellison, J.A. Treatment of Tobacco Use and Dependence: The Role of the Dental Professional. Journal of Dental Education, 69(5), pp. 522-537, 2005.

Medical Outreach Improves Regular Use of Medical Care Among Unstably-Housed HIV-Infected Individuals

One hundred sixty-one cross-sectional interviews were conducted prior to and after establishing a medical outreach program in single room occupancy hotels. Participants' mean age was 42 years; 58% were men, 95% minority, and 59% active substance users. The postintervention group was more likely to have a regular health care provider ($p = 0.02$), and to take Pneumocystis carinii pneumonia prophylaxis ($p = 0.03$) and antiretroviral medication ($p = 0.02$) than the pre-intervention group. Quality of care was more positively perceived in the postintervention group ($p = 0.001$). On multivariate analysis, the postintervention group remained more likely to have a regular provider (OR = 5.3, $p = 0.02$), take antiretroviral medication (OR = 5.7, $p = 0.02$), and have a better perception of quality of care (OR = 4.9, $p = 0.003$). A medical outreach program targeting unstably housed HIV-infected individuals was associated with increased use of regular medical care and improved perceived quality of care. Cunningham, C.O., Shapiro, S., Berg, K.M., Sacajiu G. and Paccione J. An Evaluation of a Medical Outreach Program Targeting Unstably Housed HIV Infected Individuals. Journal of Health Care for the Poor and Underserved, 16, pp. 127-138, 2005.

Treatment for HCV-Infected Patients Complicated by Substance Abuse and Psychiatric Comorbidity

Despite the high prevalence of hepatitis C virus (HCV) infection among drug users enrolled in methadone maintenance treatment programs, few drug users are being treated with combination therapy. Researchers developed a pilot program to integrate care for HCV infection with substance abuse treatment in a setting of maintenance

treatment with methadone. This on-site, multidisciplinary model of care includes comprehensive screening and treatment for HCV infection, assessment of eligibility, counseling with regard to substance abuse, psychiatric services, HCV support groups, directly observed therapy, and enhanced linkages to a tertiary care system for diagnostic procedures. This approach has led to high levels of adherence with liver biopsy, and substantial rates of initiation of antiviral therapy. Two cases illustrate the successful application of this model to patients with HCV infection complicated by active substance abuse and psychiatric comorbidity. Litwin, A.H., Soloway, I. and Gourevitch, M.N. Integrating Hepatitis C Services with Methadone Maintenance Treatment: Challenges and Opportunities. Clinical Infectious Diseases, 40, pp. 339-345 2005.

Medical Service Use among Patients with HIV and Substance Abuse Disorders

HIV-infected persons with a substance abuse disorder enrolled in a randomized trial of a case management intervention (N=190) were interviewed about their backgrounds, housing status, income, alcohol and drug use problems, health status and depressive symptoms at study entry. Electronic medical records were used to assess medical service use. During a two-year period, 71% were treated in the emergency department, 64% had been hospitalized and the sample averaged 12.9 ambulatory care visits. Homelessness was associated with high utilization of emergency department and inpatient services; drug use severity was associated with higher inpatient and ambulatory care service use; and alcohol use severity was associated with greater use of emergency medical services. Homelessness and substance abuse exacerbate the health care needs of HIV-infected persons and result in increased use of emergency department and inpatient services. Interventions are needed that target HIV-infected persons with substance abuse disorders particularly those that increase entry and retention in outpatient health care and thus decrease reliance on acute hospital-based services. Masson, C.L., Sorensen, J.L., Phibbs, C.S. and Okin, R.L. Predictors of Medical Service Utilization Among Individuals with Co-occurring HIV Infection and Substance Abuse Disorders. AIDS Care, 16(6), pp. 744-755, 2004.

Case Management for Substance Abusers with HIV/AIDS: Lessons from a Clinical Trial

The many problems experienced by substance abusers with HIV/AIDS have prompted development and testing of new models of service delivery. This study tested the efficacy of case management with HIV-infected substance abusers (70% male, 52% heterosexual, 42% Caucasian, 43% African American) in a general hospital setting. Ninety-two subjects were randomly assigned to treatment as usual -- hospital-based brief contact with referrals for intervention as requested; while 98 subjects were assigned to weekly case management which included both hospital-based and community visits. Regardless of SA treatment length, the duration for both conditions was 12 months. The study found negative results. The results demonstrate the need for caution in interpreting positive reports from demonstration projects that do not have a comparison condition. Taking into account the results of this study, clinicians may want to be cautious about undertaking case management with this population unless they are clearly focused on achievable outcomes and engage in this effort being fully aware of both the power of case management intervention and its limitations. Sorensen, J.L. and Masson, C.L. Case Management for Substance Abusers with HIV/AIDS: Lessons from a Clinical Trial. Directions in Rehabilitation Counseling, 15, pp. 193-201, 2004.

Unmet Adult Need For Substance Abuse Treatment

This study presents a method for estimating the size and cost of eliminating unmet need for substance abuse treatment services among adults who have clinically significant substance use disorders, and applies the approach to Massachusetts' information. Unmet treatment needs were derived using a statewide household telephone survey of 7,251 Massachusetts residents aged 19 and older conducted in 1996-1997, and an index of treatment mix and cost information from state and Medicaid financial data. The study estimates that 39,450 adult state residents (0.81% of the total sample) had a clinically significant past-year untreated substance use disorder. Providing substance abuse treatment and outreach services to them would have required an additional cost of approximately 109 million dollars (17 dollars per capita), of which the state's payer of last resort, the Massachusetts Department of Public Health Bureau of Substance Abuse Services (BSAS), would need to fund 31 million dollars (5 dollars per capita). The share paid by BSAS (28%) would represent an increase of 42% over its current spending. This paper quantifies an important but sometimes overlooked objective of managed care: to improve access for substance

abusers who need but do not seek treatment. Shepard, D.S., Strickler, G.K., McAuliffe, W.E., Beaston-Blaakman, A., Rahman, M. and Anderson, T.E. Unmet Need For Substance Abuse Treatment Of Adults In Massachusetts. Administrative Policy in Mental Health. 32(4), pp. 403-26, 2005.

Reconsidering Evaluation of Addiction Treatment

Historically, addiction treatments have been delivered and evaluated under an acute-care format. Fixed amounts or durations of treatment have been provided and their effects evaluated 6-12 months after completion of care. The explicit expectation of treatment has been enduring reductions in substance use, improved personal health and social function, generally referred to as 'recovery'. In contrast, treatments for chronic illnesses such as diabetes, hypertension and asthma have been provided for indeterminate periods and their effects evaluated during the course of those treatments. Here the expectations are for most of the same results, but only during the course of continuing care and monitoring. The many similarities between addiction and mainstream chronic illnesses stand in contrast to the differences in the ways addiction is conceptualized, treated and evaluated. This paper builds upon established methods of during-treatment evaluation developed for the treatment of other chronic illnesses and suggests a parallel evaluation system for out-patient, continuing-care forms of addiction treatment. The suggested system retains traditional patient-level, behavioral outcome measures of recovery, but suggests that these outcomes should be collected and reported immediately and regularly by clinicians at the beginning of addiction treatment sessions, as a way of evaluating recovery progress and making decisions about continuing care. The researchers refer to this paradigm as 'concurrent recovery monitoring' and discuss its potential for producing more timely, efficient, clinically relevant and accountable evaluations. McLellan, A.T., McKay, J.R., Forman, R., Cacciola, J. and Kemp, J. Reconsidering the Evaluation of Addiction Treatment: From Retrospective Follow-up to Concurrent Recovery Monitoring. Addiction, 100(4), pp. 447-458, 2005.

Language Preference Effect on Program Effectiveness

This study examines whether language preference, as an indicator of acculturation, moderates the effects of a culturally-grounded substance use prevention intervention for Mexican and Mexican-American middle school students (N=2,146) in Phoenix, Arizona. The main hypothesis is that levels of program effectiveness would vary based on the language preference of the students and the specific culturally-grounded version of the intervention to which they were assigned. The researchers found that matching language preference to particular versions of the intervention did not influence substance use related program outcomes, but overall program effects (intervention versus control) did vary by language preference. English-language dominant participants, considered the most at-risk sub-group, demonstrated more desirable outcomes if they received the intervention while Spanish dominant and bilingual participants did not demonstrate significant differences between the intervention and control groups. Spanish dominant respondents had low substance use rates at baseline that remained relatively unchanged throughout the experiment. The higher initial use rates of English dominant students increased in the control group while they remained unchanged or decreased among students exposed to any version of the intervention. The program appeared to strengthen existing protective effects of Spanish language use among less acculturated students and decreased or weakened risks associated with higher acculturation among English dominant students. Marsiglia, F.F., Kulis, S., Wagstaff, D.A., Elek, E. and Dran, D. Acculturation Status and Substance Use Prevention With Mexican and Mexican American Youth. Journal of Social Work Practice in the Addictions, 5, 1/2, pp. 85-111, 2005.

Effectiveness of Highly Regarded Adolescent Substance Abuse Treatment Programs

This study conducted the first systematic evaluation of the quality of highly regarded adolescent substance abuse treatment programs in the United States. An advisory panel of 22 experts defined 9 key elements of effective treatment for adolescent substance abuse based on a review of the literature. In-depth telephone and written surveys were conducted with 144 highly regarded adolescent substance abuse treatment programs identified by panel members and by public and private agencies. There was a 100% response rate to the initial interviews, and a 65% response rate to the follow-up surveys. The open-ended survey responses were coded by defining 5 components deemed to be crucial in addressing each of the 9 key elements, and quality scores were calculated overall and for each of the 9 key elements. Out of a possible total score of 45, the mean score was 23.8 and the median was 23. Top-quartile programs were not more likely to be accredited. The majority of programs

scored at least 4 of a possible 5 on only 1 of the 9 key elements (qualified staff). The elements with the poorest-quality performance were assessment and treatment matching, engaging and retaining teens in treatment, gender and cultural competence, and treatment outcomes. Most of the highly regarded programs surveyed are not adequately addressing the key elements of effective adolescent substance abuse treatment. Expanded use of standardized assessment instruments, improved ability to engage and retain youths, greater attention to gender and cultural competence, and greater investment in scientific evaluation of treatment outcomes are among the most critical needs. Expanding awareness of effective elements in treating adolescents will lead the way to program improvement. Brannigan, R., Schackman, B.R., Falco, M. and Millman, R.B. The Quality of Highly Regarded Adolescent Substance Abuse Treatment Programs: Results of an In-depth National Survey. Archives of Pediatric Adolescence Medicine, 158, pp. 904-909, 2004.

Infectious Disease-Related Cost-Utility Analysis

The purpose of this review is to understand infectious disease-related cost-utility analyses by describing published analyses, examining growth and quality trends over time, examining factors related to quality, and summarizing standardized results. The review identified 122 cost-utility analyses and 352 cost-utility ratios. Pharmaceutical interventions were most common (47.5%); three author groups accounted for 42.8% of pharmaceutical ratios. High-volume journals (three or more published cost-utility analyses) published higher quality analyses than low-volume journals ($p<0.001$). Use of probabilistic sensitivity analysis and discounting at 3% were more frequently found in the years after the US Public Health Service Panel on Cost-Effectiveness in Health and Medicine recommendations ($p<0.01$). Median ratios varied from US$13,500/quality-adjusted life year (QALY) for immunizations to US$810,000/QALY for blood safety. Publication of infectious disease cost-utility analyses is increasing. The results of cost-utility analyses have important implications for the development of clinical guidelines and resource allocation decisions. More trained investigators and better peer-review processes are needed. Stone, P.W., Schackman, B.R., Neukermans, C.P., Olchanski, N., Greenberg, D., Rosen, A.P. and Neumann, P.J. A Synthesis of Cost-Utility Analysis Literature in Infectious Disease. Lancet Infectious Disease, 5, pp. 383-391, 2005.

Syringe Access and HIV Risk Among IDUs

This study compares syringe re-use and receptive syringe sharing among two groups of injection drug users (IDUs). They are: 1) IDUs with legal over-the-counter pharmacy access and limits on syringes that can be purchased, exchanged or possessed, and 2) IDUs without legal over-the-counter pharmacy access, but unlimited access to syringes through Syringe Exchange Programs (SEPs). Three questions are addressed: (1) Does residing in an area with no legal syringe possession increase the likelihood of police contact related to possessing drug paraphernalia? (2) Among direct SEP users, is the use of more permissive SEPs associated with less likelihood of syringe re-use and receptive syringe sharing? (3) Among non-SEP users, is residing in an area with pharmacy access associated with lower likelihood of syringe re-use and receptive syringe sharing? The study utilized a quantitative survey of IDUs recruited from SEPs, subject nomination, and outreach methods. Multivariate analyses compared police contact, syringe re-use and receptive syringe sharing among IDUs recruited in three cities. Findings revealed that police contact was associated independently with residing in the area with no legal possession of syringes. Among SEP users, those with access to SEPs without limits had lower syringe re-use but not lower syringe sharing; and among non-SEP users, no significant differences in injection risk were observed among IDUs with and without pharmacy access to syringes. Greater legal access to syringes, if accompanied by limits on the number of syringes that can be exchanged, purchased and possessed, may not have the intended impacts on injection-related infectious disease risk among IDUs. Bluthenthal, R.N., Malik, M.R., Grau, L.E., Singer, M., Marshall, P. and Heimer, R. Sterile Syringe Access Conditions and Variations in HIV Risk Among Drug Injectors in Three Cities. Addiction, 99(9), pp. 1136-1146, 2004.

Antiretroviral Therapy, Hepatitis C Virus, and AIDS Mortality Among the Homeless and Marginally Housed

Mortality has declined in most HIV-infected populations yet remains high among those with barriers to accessing antiretroviral (ARV) therapy. This study examined predictors of death in a group of HIV-infected homeless persons in San Francisco. Between 1996 and 2002, quarterly interviews and blood draws were conducted. Hazards of death were determined based on the number of months during the previous 6 months that any of the following occurred: any ARV, drug use, hepatitis C

virus (HCV) status, and housing status. Among 330 participants, 65% were HCV-seropositive at baseline, 85% received ARV during the study period, and there were 57 deaths (5.3 per 100 person-years). Compared with having none of the prior 6 months on therapy, the risk of death was not significantly reduced for individuals on 1-to-5 months of therapy (hazard ratio [HR] = 0.82, 95% confidence interval [CI]: 0.43-1.57), but the risk of death was reduced 62% for those on ARV therapy for 6 months (HR = 0.38, CI: 0.19-0.76). Housing status and HCV status were not significant predictors of death. HIV is the major cause of death in this population, whereas the impact of HCV infection on death seems to be minimal. Sustained ARV treatment significantly reduces the risk of death among the homeless. Riley, E.D., Bangsberg, D.R., Guzman, R., Perry, S. and Moss, A.R. Antiretroviral Therapy, Hepatitis C Virus, and AIDS Mortality Among San Francisco's Homeless and Marginally Housed. Journal of Acquired Immune Deficiency Syndrome, 38, pp. 191-195, 2005.

Hair Testing and Self-Report of Cocaine Use

This study identified predictors of non-disclosure of cocaine use among individuals who self-reported heroin use during a medical care encounter. The study design was a prospective comparison of self-report of cocaine use among heroin users and hair analysis for cocaine. Participants were patients presenting for a health care visit who were willing to self-report use of heroin and were not engaged in any form of drug treatment. They were selected from four health care clinics at an academic, inner-city hospital. Measures included: 1) Self-report using standardized instruments: the Drug Addiction Severity Test (DAST), the Addiction Severity Index (ASI), and quantity/frequency questions for heroin and cocaine use; 2) biochemical evidence: analysis of hair for cocaine and opiate levels. Among 336 heroin users who tested positive for cocaine in hair, 34.2% did not report their recent cocaine use. The mean cocaine level for discordant individuals was significantly lower than for concordant individuals (109.6 ng/10 mg vs. 470.57 ng/10 mg; $p < 0.0001$). Multivariate predictors of disclosure included opiate and cocaine levels in hair, and the ASI drug severity subscore. Although self-report has been validated for treatment system patients, almost one-third of the out-of-treatment heroin users in this medical clinic study failed to disclose concomitant cocaine use. The likelihood of non-disclosure was greatest for heavy users of heroin and light users of cocaine. Confirmation of self-report with biochemical analysis may be necessary in the medical setting to improve both clinical care and research validity. Tassiopoulos, K., Bernstein, J., Heeren, T., Levenson, S., Hingson, R. and Bernstein, E. Hair Testing and Self-Report of Cocaine Use by Heroin Users. Addiction, 99, pp. 590-597, 2004.

Testable Gateway Provider Model for Youth Service Access

Enhancing the functioning of parents, teachers, juvenile justice authorities, and other health and mental health professionals who direct children and adolescents to services is a major mental health services concern. The Gateway Provider Model is an elaborated testable subset of the Network-Episode Model (NEM; B. A. Pescosolido and C. A. Boyer, 1999) that synthesizes it with Decision (D. H. Gustafson, et al., 1999) and organizational theory (C. Glisson, 2002; C. Glisson and L. James, 1992, 2002). The Gateway Provider Model focuses on central influences that affect youth's access to treatment, i.e., the individual who first identifies a problem and sends a youth to treatment (the "gateway provider"); and the need those individuals have for information on youth problems and relevant potential resources. Preliminary studies by the authors show that providers' perception of need, their knowledge of resources, and their environment are related to the decision to offer or refer to services, supporting key aspects of the Model. Stiffman A.R., Pescosolido B. and Cabassa L. Building a Model to Understand Youth Service Access: The Gateway Provider Model. Mental Health Services Research, 6(4), pp. 189-198, 2004.

Mental Health and Environmental Factors' Association with American Indian Youth Tobacco Use

The present study merged problem behavior and social ecological theories to examine how mental health and environmental factors, including culture, were associated with American Indian youth tobacco use. A stratified random sample of 205 reservation-based and 196 urban-based American Indian adolescents were interviewed in 2001. Two-thirds of the reservation youth and half of the urban youth reported lifetime tobacco use. Logistic regression showed that, when controlling for age and location, a mental health factor (substance abuse/dependence) and environmental factors (e.g., family members' mental health problems and peer misbehavior) were significant predictors of American Indian adolescent tobacco use. Cultural factors and location (reservation vs. urban) were not significant predictors of their tobacco use. Therefore, environmental and mental health factors should be assessed for and incorporated into

tobacco use intervention and prevention plans for American Indian youths in both reservation and urban areas. Yu, M., Stiffman, A.R. and Freedenthal, S. Factors Affecting American Indian Adolescent Tobacco Use. Addictive Behaviors, 30(5), pp. 889-904, 2004.

Reconciling Ideal Research Requirements with Fieldwork and Cultural Factors

The realities of doing field research with high risk, minority, or indigenous populations may be quite different than the guidelines presented in research training. There are overlapping and competing demands created by human subjects, cultural, and research imperatives. A NIDA funded study of American Indian youths illustrates competing pressures between research objectives and cultural sensitivity. This account of the problems confronted, solutions, or lack of them, fills a gap in the research literature and serves as thought-provoking examples for other researchers. In this study, cross-cultural bridges were built; the stakeholder/researcher team modified extant instruments and methods to achieve cultural appropriateness, and the researchers agreed to the communities' demands for increased service access and rights of refusal for all publications and presentations. Data indicate that these compromises did not substantially harm the data completeness, well being of the youths or later waves of the longitudinal study. To the contrary, it enhanced the ability to disseminate results to those with the most vested interests. The conflicts between ideal research requirements and cultural demands confronted by the researchers and interviewers in the American Indian community were not necessarily different from issues faced by researchers in other communities. Researchers conclude that there are no easy answers to such issues within research. Stiffman, A.R., Freedenthal S., Brown E., Ostmann E. and Hibbeler P. Addictions Field Research with Underserved Minorities: the Ideal and the Real. Journal of Urban Health, 82(2), Supplement 3, pp. iii56-iii66, 2005.

Methadone Maintenance Treatment Retention Among Street-Recruited Injection Drug Users

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). Targeted sampling methods were used to establish recruitment quotas in Denver census tracks. A total of 577 IDUs were randomly assigned to either a risk reduction intervention, focusing on safer injection and sex behaviors, or to 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 the desire for treatment, or motivation, was associated in univariate analyses with retention, there were no differences observed between the motivational interviewing and risk reduction interventions. Booth, R.E., Corsi, K.F., Mikulich-Gilbertson, S.K. Factors Associated With Methadone Maintenance Treatment Retention Among Street-recruited Injection Drug Users. Drug and Alcohol Dependence, 74, pp. 177-185, 2004.

Quality of Social Support Affects Employment Outcomes

This study examined social support and its association with employment, income, and drug use in a sample of 534 low-income women. Social support was operationalized as two distinct categories. Functional support was defined as the perceived quality of one's interactions with others, considered as either actual or perceived assistance from others. Structural support was defined as the number of individuals within a network as well as the social ties or links within the network. Such networks as social, employment, drug, and emergency are characterized by size and density. Over the two-year study period, significant increases attributable to the quality of these relationships were observed in hours-worked, income from work, income from other sources, and total income. There was also a significant decrease in welfare income. Results suggest that the perceived quality of support received is an important factor in achieving positive employment outcomes. Simply using a quantitative measure of social support was not sufficient in this analysis. For welfare populations a beneficial change in the quality of functional support could lead to improvements in work hours. Brown, V.L. and Riley, M.A. Social Support, Drug Use, and Employment Among Low-Income Women. American Journal of Drug and Alcohol Abuse, 31, pp. 203-223, 2005.

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Research Findings - Intramural Research

Development and Plasticity Section, Cellular Neurobiology Research Branch

Protective Effects of Delta9-Tetrahydrocannabinol against N-methyl-D-Aspartate-Induced AF5 Cell Death The neuroprotective effects of delta9-tetrahydrocannabinol (THC) were examined using an in vitro model in which the AF5 CNS cell line was exposed to toxic levels of N-methyl-D-aspartate (NMDA), an agonist of the NMDA glutamate receptor. NMDA toxicity was reduced by THC, but not by the more specific cannabinoid receptor agonist, WIN55,212-2. Addition of dibutyryl cAMP (dbcAMP) to the culture medium did not alter the neuroprotective effect of THC and did not unmask a neuroprotective effect of WIN55,212-2. The cannabinoid antagonist SR141716A did not inhibit the neuroprotection induced by THC or alter the response to WIN55,212-2, even in the presence of dbcAMP, indicating that the neuroprotective effect of THC was cannabinoid receptor-independent. On the other hand, both THC and WIN55,212-2 produced cellular toxicology at higher dosages, an effect which was blocked in part by SR141716A. Capsaicin, an antioxidant and vanilloid receptor agonist, also produced a protective effect against NMDA toxicology. The protective effect of capsaicin was blocked by co-application of ruthenium red, but was not blocked by the specific vanilloid receptor antagonist capsazepine, and the transient receptor potential vanilloid type 1 (TRPV1) and ANKTM1 transcripts were not detected in AF5 cells. Thus, the neuroprotective effects of THC and capsaicin did not appear to be mediated by TRP ion channel family receptors. The antioxidant alpha-tocopherol prevented neurotoxicity in a dose-dependent manner. Therefore, THC may function as an antioxidant to increase cell survival in NMDA-induced neurotoxicity in the AF5 cell model, while higher dosages produce toxicity mediated by CB1 receptor stimulation. Chen, J., Lee, C.T., Errico, S., Deng, X. Cadet, J.L., and Freed, W.J. Brain Research Molecular Brain Research, 134, pp. 215-225, 2005.

Development of a Focused Microarray to Assess Human Embryonic Stem Cell Differentiation Human embryonic stem cells (hESC) must be differentiated before clinical use. In addition, the extent of contamination of undifferentiated cells and the efficiency of differentiation must also be assessed prior to clinical application. In this manuscript, IRP investigators describe the development of a focused microarray that may be used to discriminate between hESC and their differentiated progeny. This array contains 755 genes including embryonic stem cell markers as well as markers of differentiation into neural, mesodermal, and endodermal phenotypes. In addition, authors have included candidate genes belonging to families of cytokines, chemokines, receptors, signaling pathways, and homeodomain proteins that are likely to be important in the process of differentiation. Testing and validation of the focused array was performed using RNA from hESC, human embryoid body (hEB) outgrowths, and a human embryonal carcinoma (hEC) cell line. Authors have compared gene expression with negative background, GAPDH, _-actin positive controls, and human universal RNA (hURNA), showing that such an array can rapidly distinguish between undifferentiated and differentiated hESC-derived cell populations. Authors expect that the described array will be extremely useful in evaluating the extent of differentiation and the state of the hESC-derived population utilized for therapeutic purposes. Yang, A.X., Mejido, J., Luo, Y., Zeng, X., Schwartz, C., Wu, T., Thies, R.S., Bhattacharya, B., Han, J., Freed, B., Rao, M., and Puri, R.K. Stem Cells and Development, 14, pp. 270-284, 2005.

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

The Potential Role of Sigma-1 Receptors in Lipid Transport and Lipid Raft

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Reconstitution in the Brain: Implication for Drug Abuse The brain is highly enriched in lipids. However, the molecular biological roles of lipids in the brain have been largely unexplored. Although, in the 1990s, several studies demonstrated the roles of lipids in a variety of neuronal functions and certain neurological diseases, the involvement of lipids in drug dependence, if any, is almost totally unknown. Sigma-1 receptors are brain-enriched proteins that interact with psychostimulants such as cocaine and methamphetamine. Sigma-1 receptors possess a putative sterol-binding pocket and are predominantly expressed on the endoplasmic reticulum (ER) where most lipids and their precursors are synthesized. Sigma-1 receptors are involved in drug-seeking behaviors and in psychostimulant-induced behavioral sensitization. Recent studies demonstrated that sigma-1 receptors target the lipid-storing subcompartments of the ER and are colocalized with cholesterol and neutral lipids. Sigma-1 receptors form detergent-insoluble lipid microdomains (lipid rafts) on the ER subcompartments and can translocate on the ER when stimulated. Upregulation of sigma-1 receptors affect the levels of plasma membrane lipid rafts by changing the lipid components therein. The membrane reconstitution thus induced by sigma-1 receptors in turn affects functions of proteins residing in plasma membrane lipid rafts including tropic factor receptors and tyrosine kinases. Specifically, IRP scientists recently found that sigma-1 receptors modulate MAP kinase activation induced by tropic factors, neuritegenesis and oligodendrocyte differentiation-all related to lipid raft reconstitution. Sigma-1 receptors may thus play a role in psychostimulant-induced long-lasting morphological changes in the brain via the capacity of sigma-1 receptors in regulating ER lipid transport and the resultant plasma membrane lipid raft reconstitution. Hayashi, T, and Su, T.P. Life Sciences, 77, pp. 1612-1624, 2005.

Picomolar Concentrations of Hibernation Induction Delta Opioid Peptide [D-Ala2,D-Leu5]Enkephalin Increase the Nerve Growth Factor in NG-108 Cells The delta opioid peptide [D-Ala2,D-Leu5]enkephalin (DADLE) has been shown to be a neuroprotective agent via mechanisms that are not totally understood. IRP investigators previously demonstrated that the i.p. injection of DADLE in mice causes an increase of nerve growth factor (NGF) in the brain. To further clarify the NGF-increasing action of DADLE, authors examined here the NGF-increasing effect of DADLE in vitro, using cultured NG-108 cells. DADLE dose-dependently increases the immunoreactive level of NGF in NG-108 cells in a bell-shape manner, with the effective DADLE concentrations in the picomolar range (0.01-100 pM). Also, DADLE at 1 pM selectively increases c-Jun and c-Fos, but not c-Rel. These results indicate that DADLE is one of the most potent agents in increasing the NGF in the biological system and that this action of DADLE involves selective increases of c-Jun and c-Fos, transcription factors that promote the NGF expression. Tsai, S.Y., Hayashi, T., and Su, T.P. Synapse, 57, pp. 179-181, 2005.

Electrophysiology Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Additive Effects of Endogenous Cannabinoid Anandamide and Ethanol on Alpha7-Nicotinic Acetylcholine Receptor-Mediated Responses in Xenopus Oocytes The interaction between the effects of the endogenous cannabinoid receptor agonist anandamide and ethanol on the function of homomeric alpha7-nicotinic acetylcholine (nACh) receptors expressed in Xenopus oocytes were investigated using the two-electrode voltage-clamp technique. Anandamide and ethanol reversibly inhibited currents evoked with ACh (100 iM) in a concentration-dependent manner. Coapplication of anandamide and ethanol caused a significantly greater inhibition of alpha7- nACh receptor function than anandamide or ethanol alone. The IC50 value of 238 +/- 34 nM for anandamide inhibition decreased significantly to 104 +/- 23 nM in the presence of 30 mM ethanol. The inhibition of alpha7-mediated currents by coapplication of anandamide and ethanol was not altered by phenylmethylsulfonyl fluoride, an inhibitor of anandamide hydrolyzing enzyme, or AM404, an anandamide-transport inhibitor. Analysis of oocytes by matrix-assisted laser desorption/ionization technique indicated that ethanol treatment did not alter the lipid profile of oocytes and there is negligible, if any, anandamide present in these cells. Results of studies with chimeric alpha7-nACh-5-HT3 receptors comprised of the amino-terminal domain of the alpha7-nACh receptor and the transmembrane and carboxyl-terminal domains of 5-HT3 receptors suggest that while ethanol inhibition of the alpha7-nAChR is likely to involve the N-terminal region of the receptor, the site of action for anandamide is located in the transmembrane and carboxyl-terminal domains of the receptors. These data indicate that endocannabinoids and ethanol potentiate each other's inhibitory effects on alpha7-nACh receptor function through distinct regions of the receptor. Oz, M., Jackson, S., Woods, A., Morales, M., and Zhang, L. Journal of Pharmacology Experimental Therapeutics, 313, pp. 1272-1280, 2005.

Grantee Honors

In Memoriam

Presynaptic Angiotensin II AT1 Receptors Enhance Inhibitory and Excitatory Synaptic Neurotransmission to Motoneurons and other Ventral Horn Neurons in Neonatal Rat Spinal Cord In neonatal spinal cord, IRP scientists previously reported that exogenous angiotensin II (ANG II) acts at postsynaptic AT1 receptors to depolarize neonatal rat spinal ventral horn neurons in vitro. This study evaluated an associated increase in synaptic activity. Patch clamp recordings revealed that 38/81 thoracolumbar (T7-L5) motoneurons responded to bath applied ANG II (0.3-1 microM; 30 s) with a prolonged (5-10 min) and reversible increase in spontaneous postsynaptic activity, selectively blockable with Losartan (n = 5) but not PD123319 (n = 5). ANG-II-induced events included both spontaneous inhibitory (IPSCs; n = 6) and excitatory postsynaptic currents (EPSCs; n = 5). While most ANG induced events were tetrodotoxin-sensitive, ANG induced a significant tetrodotoxin-resistant increase in frequency but not amplitude of miniature IPSCs (n = 7/13 cells) and EPSCs (n = 2/7 cells). In 35/77 unidentified neurons, ANG II also induced a tetrodotoxin-sensitive and prolonged increase in their spontaneous synaptic activity that featured both IPSCs (n = 5) and EPSCs (n = 4) when tested in the presence of selective amino acid receptor antagonists. When tested in the presence of tetrodotoxin, ANG II was noted to induce a significant increase in the frequency but not the amplitude of mIPSCs (n = 9) and mEPSCs (n = 8). ANG also increased spontaneous motor activity from isolated mouse lumbar ventral rootlets. Collectively, these observations support the existence of a wide pre- and postsynaptic distribution of ANG II AT1 receptors in neonatal ventral spinal cord that are capable of influencing both inhibitory and excitatory neurotransmission. Oz, M., Yang, K.H., O'Donovan, M.J., and Renaud, L.P. Journal of Neurophysiology, 94, pp. 1405-1412, 2005.

Endocannabinoid Release from Midbrain Dopamine Neurons: A Potential Substrate for Cannabinoid Receptor Antagonist Treatment of Addiction Substantial evidence suggests that all commonly abused drugs act upon the brain reward circuitry to ultimately increase extracellular concentrations of the neurotransmitter dopamine in the nucleus accumbens and other forebrain areas. Many drugs of abuse appear to increase dopamine levels by dramatically increasing the firing and bursting rates of dopamine neurons located in the ventral mesencephalon. Recent clinical evidence in humans and behavioral evidence in animals indicate that cannabinoid receptor antagonists such as SR141716A (Rimonabant) can reduce the self-administration of, and craving for, several commonly addictive drugs. However, the mechanism of this potentially beneficial effect has not yet been identified. IRP researchers propose, on the basis of recent studies in their laboratory and others, that these antagonists may act by blocking the effects of endogenously released cannabinoid molecules (endocannabinoids) that are released in an activity- and calcium-dependent manner from mesencephalic dopamine neurons. It is hypothesized that, through the antagonism of cannabinoid CB1 receptors located on inhibitory and excitatory axon terminals targeting the midbrain dopamine neurons, the effects of the endocannabinoids are occluded. The data from these studies therefore suggest that the endocannabinoid system and the CB1 receptors located in the ventral mesencephalon may play an important role in regulating drug reward processes, and that this substrate is recruited whenever dopamine neuron activity is increased. Lupica, C.R. and Riegel, A.C. Neuropharmacology, 48, pp. 1105-1116, 2005.

Identification of CRF Binding Protein Expression In VTA: A Link Between Reward and Stress Systems? Corticotropin releasing factor (CRF) interacts with specific receptors and a binding protein (CRF-BP). CRF-BP is produced in peripheral tissue and brain. While a role of peripheral CRF-BP in lowering free circulating CRF levels is well established, the effect of CRF-BP in brain is less clear. Ungless et al., (Neuron, 2003) showed that application of CRF-BP to in vitro preparations of midbrain slices from mice was required for CRF to potentiate N-methyl-D-aspartate receptor mediated synaptic transmission in dopamine (DA) neurons in the ventral tegmental area (VTA). Whereas these studies highlight the participation of CRF-BP on CRF and glutamatergic transmission on DA neurons in VTA, the neuronal distribution of CRF-BP in VTA is unknown. IRP investigators detected CRF-BP immunoreactivity in Western blots prepared from VTA homogenates. Consistent with this result, CRF-BP immunoreactive cells and varicose fibers were observed in VTA of rat brain sections. To determine possible origin of CRF-BP detected in VTA, authors examined whether CRF-BP mRNA was found in neurons located in VTA or in cells projecting to this region. In situ hybridization analysis demonstrated CRF-BP mRNA in VTA cells but not in those of the substantia nigra compacta or reticulata. By combining in situ hybridization (to identify cellular expression of CRF-BP mRNA) and tract tracing immunohistochemistry (to detect projecting neurons to VTA), authors found no neurons innervating VTA that expressed CRF-BP. This suggests that CRF-BP detected within the VTA is synthesized by VTA neurons. By double in situ hybridization

histochemistry authors demonstrated that in VTA, CRF-BP expression was mainly present in a subset of DAergic neurons and in some GABAergic neurons. Based on these anatomical observations and previous in vitro electrophysiological studies (Ungless et al., 2003), authors suggest that CRF-BP synthesized in VTA, mainly by DAergic neurons, is well positioned to affect the reward system in response to local release of CRF. Morales M., Roach E., and Diaz Ruiz O. Poster. Anatomy of the Soul, Ameland, The Nethetlands, May 19-25, 2005.

Proteomics Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Direct Profiling of Lipid Distribution in Brain Tissue Using MALDI-TOFMS
Recent developments in mass spectrometry have permitted direct analysis of biomolecules in tissue. However, most studies have focused on proteins with emphasis on biomarker discovery. In the present work, matrix-assisted laser desorption/ionization mass spectrometry was used for the direct analysis of lipids in rat cerebellum. The lipid bilayer role as a storage depot for small organic molecules such as therapeutic drugs and pollutants such as DDT, as well as the ability to compare lipid profiles in healthy and diseased animal models, are a few of the many reasons why the direct probing of tissue to determine the qualitative and possibly quantitative lipid content could be a very useful tool. Molecular ions corresponding to cholesterol, phosphatidylcholines, sphingomyelins, and phosphatidylethanolamines were recorded in positive ion mode, while ones corresponding to phosphatidylinositols, sulfatides, and gangliosides were recorded in negative ion mode. Overall, representatives from all major categories of brain lipids including cholesterol, 15 phospholipid species (9 phosphatidylcholines, 1 sphingomyelin, 3 phosphatidylethanol-amines, 2 phosphatidylinositols), 10 sulfatides (5 hydroxylated species and 5 nonhydroxylated species), and 7 species of gangliosides were detected. Jackson, S.N., Wang, H.Y., and Woods, A.S. Analytical Chemistry, 77, pp. 4523-4527, 2005.

Amazing Stability of the Arginine-Phosphate Electrostatic Interaction
Electrostatic interactions between a basic epitope containing adjacent arginine residues and an acidic epitope containing a phosphorylated serine are involved in receptor heteromerization. In the present study, IRP researchers demonstrate that this arginine-phosphate electrostatic interaction possesses a "covalent-like" stability. Hence, these bonds can withstand fragmentation by mass spectrometric collision-induced dissociation at energies similar to those that fragment covalent bonds and they demonstrate an extremely low dissociation constant by plasmon resonance. The present work also highlights the importance of phosphorylation-dephosphorylation events in the modulation of this electrostatic attraction. Phosphorylation of the acidic epitope, a casein kinase one consensus site, makes it available to interact with the basic epitope. On the other hand, phosphorylation of serine and/or threonine residues adjacent to the basic epitope, a protein kinase A consensus site, slows down the attraction between the epitopes. Although analyzed here in the frame of receptor heteromerization, the arginine-phosphate electrostatic interaction most likely represents a general mechanism in protein-protein interactions. Woods, A.S., and Ferre, S. Journal of Proteome Research, 4, pp. 1397-1402, 2005.

Role of Electrostatic Interaction in Receptor-Receptor Heteromerization Using pull-down and mass spectrometry experiments, IRP scientists have previously demonstrated that adenosine A2A-dopamine D2 receptor-receptor heteromerization depends on an electrostatic interaction between an Arg-rich epitope from the third intracellular loop of the D2 receptor (217RRRRKR222) and two adjacent Asp residues (DD401-402) or a phosphorylated Ser (pS374) residue in the carboxyl terminus of the A2A receptor. It has been demonstrated recently that a specific region in the carboxyl terminus of the dopamine D1 receptor (L387-L416) and a specific region in the carboxyl terminus of the NR1-1 subunit of the NMDA receptor (E834-S938) are involved in D1-NMDA receptor-receptor heteromerization. Careful perusal of these interacting regions shows the presence of a phosphorylated serine (pS397) and adjacent glutamates (EE404-405) in the D1 receptor, whereas NR1-1 contains three adjacent Arg residues (RRR893-896). These epitopes are highly conserved in all species, a sign that the epitopes are likely to be involved in a physiologically significant activity. If similar epitopes are found to be involved in the formation of receptor heteromers other than A2A-D2 and D1-NMDA, the epitope-epitope electrostatic interaction might represent an important general mechanism underlying receptor- receptor interactions. Woods, A.S., Ciruela, F., Fuxe, K., Agnati, L.F., Lluis, C., Franco, R., and Ferre, S. Journal of Molecular Neuroscience, 26, pp. 125-132, 2005.

How Proteins Come Together in the Plasma Membrane and Function in

Macromolecular Assemblies: Focus on Receptor Mosaics Some theoretical aspects on structure and function of proteins have been discussed previously. Proteins form multimeric complexes, as they have the capability of binding other proteins (Lego property) resulting in multimeric complexes capable of emergent functions. Multimeric proteins might have either a genomic or a postgenomic origin. Proteins spanning the plasma membrane have been analyzed by considering the effects of the microenvironment in which the protein is embedded. In particular, the different effects of the hydrophilic (extracellular and intracellular) versus the lipophilic (intramembrane) environment have been considered. These aspects have been discussed in the framework of membrane microdomains, in particular, the so-called rafts. In alpha-helix proteins the individual peptide dipoles align to produce a macrodipole crossing the entire membrane. This macrodipole has its positive (extracellular) pole at the N-terminal end of the helix and its negative (intracellular) pole at the C-terminal end. This arrangement has been analyzed in the framework of the counter-ion atmosphere, that is, the formation of a cloud of small ions bearing an opposite charge. Excitable cells reverse their resting potential during the all-or-none action potentials. Hence, the extracellular side of the plasma membrane becomes negative with respect to the intracellular side. This change of polarization affects also the direction and magnitude of the alpha-helix dipole in view of the fact that there is a displacement of the counter ions. The oscillation in the intensity of the dipole caused by the action potentials opens the possibility of an interaction among dipoles by electromagnetic waves. Agnati, L.F., Guidolin, D., Genedani, S., Ferre, S., Bigiani, A., Woods, A.S., and Fuxe, K. Journal of Molecular Neuroscience, 26, pp. 133-154, 2005.

Computer-Assisted Image Analysis of Caveolin-1 Involvement in the Internalization Process of Adenosine A2A-Dopamine D2 Receptor Heterodimers A functional aspect of horizontal molecular networks has been investigated experimentally, namely the heteromerization between adenosine A2A and dopamine D2 receptors and the possible role of caveolin-1 in the cotrafficking of these molecular complexes. This study has been carried out by means of computer-assisted image analysis procedure of laser images of membrane immunoreactivity of caveolin-1, A2A, D1, and D2 receptors obtained in two clones of Chinese hamster ovary cells one transfected with A2A and dopamine D1 receptors and the other one with A2A and D2 receptors. Cells were treated for 3 h with 10 microM D1 receptor agonist SKF 38393, 50 microM D2-D3 receptor agonist quinpirole, and 200 nM A2A receptor agonist CGS 21680. In A2A-D1-cotransfected cells, caveolin-1 was found to colocalize with both A2A and D1 receptors and treatment with SKF 38393 induced internalization of caveolin-1 and D1 receptors, with a preferential internalization of D1 receptors colocalized with caveolin-1. In A2A-D2-cotransfected cells, caveolin-1 was found to colocalize with both A2A and D2 receptors and either CGS 21680 or quinpirole treatment induced internalization of caveolin-1 and A2A and D2 receptors, with a preferential internalization of A2A and D2 receptors colocalized with caveolin-1. The results suggest that A2A and D2 receptors and caveolin-1 likely interact forming a macrocomplex that internalizes upon agonist treatment. These observations are discussed in the frame of receptor oligomerization and of the possible functional role of caveolin-1 in the process of co-internalization and, hence, in controlling the permanence of receptors at the plasma membrane level (prerequisite for receptor mosaic organization and plastic adjustments) and in the control of receptor desensitization. Genedani, S., Guidolin, D., Leo, G., Filaferro, M. Torvinen, M., Woods, A.S., Fuxe, K. Ferre, S., and Agnati, L.F. Journal of Molecular Neuroscience, 26, pp. 177-184, 2005.

Adenosine A2A and Dopamine D2 Heteromeric Receptor Complexes and Their Function The existence of A2A-D2 heteromeric complexes is based on coimmunoprecipitation studies and on fluorescence resonance energy transfer and bioluminescence resonance energy transfer analyses. It has now become possible to show that A2A and D2 receptors also coimmunoprecipitate in striatal tissue, giving evidence for the existence of A2A-D2 heteromeric receptor complexes also in rat striatal tissue. The analysis gives evidence that these heteromers are constitutive, as they are observed in the absence of A2A and D2 agonists. The A2A-D2 heteromers could either be A2A-D2 heterodimers and/or higher-order A2A -D2 hetero-oligomers. In striatal neurons there are probably A2A-D2 heteromeric complexes, together with A2A-D2 homomeric complexes in the neuronal surface membrane. Their stoichiometry in various microdomains will have a major role in determining A2A and D2 signaling in the striatopallidal GABA neurons. Through the use of D2/D1 chimeras, evidence has been obtained that the fifth transmembrane (TM) domain and/or the I3 of the D2 receptor are part of the A2A-D2 receptor interface, where electrostatic epitope-epitope interactions involving the N-terminal part of I3 of the D2 receptor (arginine-rich epitope) play a major role, interacting with the carboxyl terminus of the A2A receptor. Computerized modeling of A2A-D2 heteromers are in line with these

findings. It seems likely that A2A receptor-induced reduction of D2 receptor recognition, G protein coupling, and signaling, as well as the existence of A2A-D2 co-trafficking, are the consequence of the existence of an A2A-D2 receptor heteromer. The relevance of A2A-D2 heteromeric receptor complexes for Parkinson's disease and schizophrenia is emphasized as well as for the treatment of these diseases. Finally, recent evidence for the existence of antagonistic A2A-D3 heteromeric receptor complexes in cotransfected cell lines has been summarized. Fuxe, K., Ferre, S., Canals, M., Torvinen, M. Terasmaa, A., Marcellino, D., Goldberg, S.R., Staines, W., Jacobsen, K.X., Woods, A.S., Agnati, L.F., and Franco, R. Journal of Molecular Neuroscience, 26, pp. 209-220, 2005.

Heptaspanning Membrane Receptors and Cytoskeletal/Scaffolding Proteins: Focus on Adenosine, Dopamine, and Metabotropic Glutamate Receptor Function Most cellular functions are mediated by multiprotein complexes. In neurons, these complexes are directly involved in the proper neuronal transmission, which is responsible for phenomena like learning, memory, and development. In recent years studies based on two-hybrid screens and proteomic, biochemical, and cell biology approaches have shown that intracellular domains of G protein-coupled receptors (GPCRs) or heptaspanning membrane receptors (HSMRs) interact with intracellular proteins. These interactions are the basis of a protein network associated with these receptors, which includes scaffolding proteins containing one or several PDZ (postsynaptic-density-95/discs-large/zona occludens-1) domains, signaling proteins, and proteins of the cytoskeleton. The present article is focused on the emerging evidence for interactions of adenosine, dopamine, and metabotropic glutamate receptors, with scaffolding and cytoskeletal proteins that play a role in the targeting and anchoring of these receptors to the plasma membrane, thus contributing to neuronal development and plasticity. Finally, given the complexity of neurological disorders such as ischemic stroke, Alzheimer's disease, and epilepsy, exploitation of these HSMR-associated interactions might prove to be efficient in the treatment of such disorders. Ciruela, F., Canela, L., Burgueno, J., Soriguera, A., Cabello, N., Canela, E.I., Casado, V., Cortes, A., Mallol, J., Woods, A.S., Ferre, S., Lluis, C., and Franco, R. Journal of Molecular Neuroscience, 26, pp. 277-292, 2005.

Clinical Psychopharmacology Section, Medications Discovery Research Branch

Chronic Morphine Upregulates Ga12 and Cytoskeletal Proteins in CHO Cells Expressing the Cloned Mu Opioid Receptor A growing body of literature indicates that chronic morphine exposure alters the expression and function of cytoskeletal proteins in addition to the well-established interactions between mu opioid receptors and G proteins. In the present study, IRP scientists hypothesized that chronic morphine alters the expression and functional effects of G_12, a G protein that regulates downstream cytoskeletal proteins via its control of RhoA. Results showed that chronic morphine treatment decreased the expression of G_i2 (64%) and G_i3 (60%), had no effect of G_o and increased G_12 (66%) expression in CHO cells expressing the cloned human mu opioid receptors (hMOR-CHO cells), but not in cells expressing a mutant mu opioid receptor that do not develop morphine tolerance and dependence (T394A-CHO cells). Morphine treatment had no significant effect on PAR-1 thrombin receptor-activated G protein activity, as measured by thrombin-stimulated [35S]GTP-__S binding. Chronic morphine treatment significantly enhanced thrombin-stimulated RhoA activity and thrombin-stimulated expression of _-actinin, a cytoskeletal anchoring protein, in hMOR-CHO cells. Proteomic analysis of 2D spots prepared from hMOR-CHO cells showed that morphine treatment affected the expression of a number of proteins associated with morphological changes. Up-regulation of G_12 and _-actinin by chronic morphine was also observed in mouse brain. Viewed collectively, these findings indicate, for the first time, that chronic morphine enhances the G_12-associated signaling system, which is involved in regulating cellular morphology and growth, supporting other findings that chronic morphine may alter cellular morphology, in addition to cellular function. Xu H., Wang X, Zimmerman D., Boja E.S., Wang J.B., Bilsky E.J. and Rothman R.B. Journal of Pharmacology and Experimental Therapeutics June 29, 2005 [Epub ahead of print].

Medicinal Chemistry Section, Medications Discovery Research Branch

Radioiodinated Azide and Isothiocyanate Derivatives of Cocaine for Irreversible Labeling of Dopamine Transporters: Synthesis and Covalent Binding Studies Two novel N-substituted-3b-phenyl tropane alkaloids have been labeled with iodine-125 for use as irreversible probes of dopamine transporter (DAT) binding sites. One contains an iodoarylazide moiety for photolabeling, while the other bears an iodoaryl isothiocyanate for direct conjugation. Both radioligands were prepared in a one-flask procedure by electrophilic radioiodination of the corresponding

aniline under no-carrier-added conditions, followed either by diazotization and treatment with sodium azide, or by addition of thiophosgene under basic conditions. Specifically, (-)-N-[4-(3'-[125I]-iodo-4'-azidophenyl) butyl]-2b-carbomethoxy-3b-(4-chlorophenyl)tropane ([125I]-MFZ-2-24) and (-)-N-[4-(3'-[125I]-iodo-4'-isothiocyanophenyl) butyl]-2b-carbomethoxy-3b-(4-chlorophenyl) tropane ([125I]-MFZ 3-37) were synthesized. Isolation by reverse phase HPLC and solid-phase extraction gave good average yields of [125I]-MFZ-2-24 (67%, n = 5) and [125I]-MFZ-3-37 (45%, n = 3) with high radiochemical purities (96 - 99%) and specific radioactivities (> 2000 mCi / _mol). The utility of the radioligands was demonstrated by their covalent linkage to rat striatal membranes, and immunoprecipitation of a single radiolabeled band at 80 kDa corresponding to the full-length DAT. Lever, J. R., Zou, M.-F., Parnas, M. L., Duval, R. A., Wirtz, S. E., Justice, J. B., Vaughan, R. A., Newman, A. H.. Bioconjugate Chemistry, 16, pp. 644-649, 2005.

Yawning in Rats: A Dopamine D3 Receptor Mediated Behavior A specific role for the dopamine D3 receptor in behavior has not been definitively defined. IRP researchers now report that dopamine D2/D3 agonists elicit dose dependent yawning behavior in rats, resulting in an inverted U-shaped dose-response curve. A series of experiments was directed toward testing the hypothesis that this induction of yawning is a D3 receptor mediated effect, while the inhibition of the yawning seen at higher doses is due to competing D2 receptor activity. Authors compared several dopaminergic agonists with a wide range of in vitro D3 selectivity, including; PD-128,907, PD-128,908, quinelorane, pramipexole, 7-OH-DPAT, quinpirole, bromocriptine, and apomorphine with respect to their ability to induce yawning in rats. A series of D2/D3 antagonists differing in selectivity for D3 over D2 receptors were evaluated for their ability to alter the effects of the dopamine agonists. The antagonists studied were L-741,626, haloperidol, nafadotride, U99194, SB-277011A, and PG01037; they have been used to determine effects on dose-response curves for D2/D3 agonist induced yawning. In addition, the potential contribution of cholinergic and/or serotonergic mechanisms to the yawning response was investigated using selective ligands including scopolamine, mianserin, and the D3-preferring antagonists; nafadotride, U99194, SB-277011A, and PG01037 to differentially modulate yawning induced by the PD-128,907, physostigmine, and TFMPP. The results of these experiments provide convergent evidence that dopamine D2/D3 agonist-induced yawning is a D3 agonist induced behavior, with subsequent inhibition of yawning at higher doses being driven by competing D2 agonist activity. Thus, dopamine agonist-induced yawning may represent an *in vivo* method for selectively identifying D3 and D2 receptor-mediated activities. Collins, G. T., Witkin, J. M., Newman, A. H., Svensson, K. A., Grundt, P., Cao, J., Woods, J. H. Journal of Pharmacology and Experimental Therapeutics, 314, pp. 310-319, 2005.

Recognition of Benztropine by the Dopamine Transporter (DAT) Differs from that of the Classical Dopamine Uptake Inhibitors Cocaine, Methylphenidate and Mazindol as a Function of a DAT Transmembrane 1 Aspartic Acid Residue Binding of cocaine to the dopamine transporter (DAT) protein blocks synaptic dopamine clearance, triggering the psychoactive effects associated with the drug; the discrete drug-protein interactions, however, remain poorly understood. A longstanding postulate holds that cocaine inhibits DAT-mediated dopamine transport via competition with dopamine for formation of an ionic bond with the DAT transmembrane aspartic acid residue D79. In the present study, DAT mutations of this residue were generated and assayed for translocation of radiolabeled dopamine and binding of radiolabeled DAT inhibitors under identical conditions. When feasible, dopamine uptake inhibition potency and apparent binding affinity Ki values were determined for structurally diverse DAT inhibitors. The glutamic acid substitution mutant (D79E) displayed values indistinguishable from wildtype DAT in both assays for the charge-neutral cocaine analog 8-oxa-norcocaine, a finding not supportive of the D79 "salt bridge" ligand docking model. In addressing whether the D79 side chain contributes to the DAT binding sites of other portions of the cocaine pharmacophore, only inhibitors with modifications of the tropane ring C-3 substituent, i.e., benztropine and its analogs, displayed a substantially altered dopamine uptake inhibition potency as a function of the D79E mutation. A single conservative amino acid substitution thus differentiated structural requirements for benztropine function relative to those for all other classical DAT inhibitors. Distinguishing the precise mechanism of action of this DAT inhibitor with relatively low abuse liability from that of cocaine may be attainable using DAT mutagenesis and other structure-function studies, opening the door to rational design of therapeutic agents for cocaine abuse. Ukairo, O. T., Bondi, C. D., Newman, A. H., Kulkarni, S.S., Kozikowski, A. P., Pan,S., Surratt, C. K. Journal of Pharmacology and Experimental Therapeutics, 314, pp. 575-583, 2005.

fMRI Section, Neuroimaging Research Branch

Neural Correlates of Cocaine Self-administration Modern theories of drug dependence hold the hedonic effects of drugtaking central to understanding the motivation for compulsive drug use. Previous neuroimaging studies have begun to identify brain regions associated with acute drug effects after passive delivery. In this study, a more naturalistic model of cocaine self-administration (SA) was employed in order to identify those sites associated with drug-induced high and craving as measures of reward and motivation. Nontreatment seeking cocaine-dependent subjects chose both when and how often i.v. cocaine administration occurred within a medically supervised SA procedure. Both functional magnetic resonance imaging (fMRI) data and real-time behavioral ratings were acquired during the 1-h SA period. Drug-induced HIGH was found to correlate negatively with activity in limbic, paralimbic, and mesocortical regions including the nucleus accumbens (NAc), inferior frontal/orbitofrontal gyrus (OFC), and anterior cingulate (AC), while CRAVING correlated positively with activity in these regions. This study provides the first evidence in humans that changes in subjective state surrounding cocaine self-administration reflect neural activity of the endogenous reward system. Risinger, R.C., Salmeron, B.J., Ross, T.J., Amen, S.L., Sanfilipo, M., Hoffmann, R., Bloom, A.S., Garavan, H., and Stein, E.A., NeuroImage, 26, pp. 1097-1108, 2005.

Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch

Self-administration of Cannabinoids by Experimental Animals and Human Marijuana Smokers Drug self-administration behavior has been one of the most direct and productive approaches for studying the reinforcing effects of psychoactive drugs, which are critical in determining their abuse potential. Cannabinoids, which are usually abused by humans in the form of marijuana, have become the most frequently abused illicit class of drugs in the United States. The early elucidation of the structure and stereochemistry of delta-9-tetrahydrocannabinol (THC) in 1964, which is now recognized as the principal psychoactive ingredient in marijuana, activated cannabinoid research worldwide. This review examines advances in research on cannabinoid self-administration behavior by humans and laboratory animals. There have been numerous laboratory demonstrations of the reinforcing effects of cannabinoids in human subjects, but reliable self-administration of cannabinoids by laboratory animals has only recently been demonstrated. It has now been shown that strong and persistent self-administration behavior can be maintained in experimentally and drug-naive squirrel monkeys by doses of THC comparable to those in marijuana smoke inhaled by humans. Furthermore, reinforcing effects of some synthetic CB1 cannabinoid agonists have been recently reported using intravenous and intracerebroventricular self-administration procedures in rats and mice. These findings support previous conclusions that THC has a pronounced abuse liability comparable to other drugs of abuse under certain experimental conditions. Self-administration of THC by squirrel monkeys provides the most reliable animal model for human marijuana abuse available to date. This animal model now makes it possible to study the relative abuse liability of other natural and synthetic cannabinoids and to preclinically assess new therapeutic strategies for the treatment or prevention of marijuana abuse in humans. Justinova, Z., Goldberg, S.R., Heishman, S.J. and Tanda, G. Pharmacol Biochem Behav. May 30, 2005 (Epub ahead of print) PMID 15932767.

Neuropeptide Y Protects Against Methamphetamine-induced Neuronal Apoptosis in the Mouse Striatum Methamphetamine (METH) is an illicit drug that causes neuronal apoptosis in the mouse striatum, in a manner similar to the neuronal loss observed in neurodegenerative diseases. In the present study, injections of METH to mice were found to cause the death of enkephalin-positive projection neurons but not the death of neuropeptide Y (NPY)/nitric oxide synthase-positive striatal interneurons. In addition, these METH injections were associated with increased expression of neuropeptide Y mRNA and changes in the expression of the NPY receptors Y1 and Y2. Administration of NPY in the cerebral ventricles blocked METH-induced apoptosis, an effect that was mediated mainly by stimulation of NPY Y2 receptors and, to a lesser extent, of NPY Y1 receptors. Finally, authors also found that neuropeptide Y knock-out mice were more sensitive than wild-type mice to METH-induced neuronal apoptosis of both enkephalin- and nitric oxide synthase-containing neurons, suggesting that NPY plays a general neuroprotective role within the striatum. Together, these results demonstrate that neuropeptide Y belongs to the class of factors that maintain neuronal integrity during cellular stresses. Given the similarity between the cell death patterns induced by METH and by disorders such as Huntington's disease, these results suggest that NPY analogs might be useful therapeutic agents against some neurodegenerative processes. Thiriet, N., Deng, X., Solinas, M., Ladenheim, B., Curtis, W., Goldberg, S.R., Palmiter, R.D. and Cadet, J.L. J Neurosci, 25, pp. 5273-5279, 2005.

Control of the Reinforcing Effects of Nicotine by Associated Environmental Stimuli in Animals and Humans Tobacco dependence through cigarette smoking is the leading preventable cause of death in the world and kills nearly 4 million people annually. Nicotine, a psychoactive component of tobacco, is thought to have a major role in tobacco dependence by acting directly as a reinforcer of drug-seeking and drug-taking behavior. However, recent findings obtained with two procedures that are used widely to assess reinforcing effects of drugs in experimental animals, intravenous drug self-administration and conditioned place-preference procedures, demonstrate that environmental factors have a major influence on the reinforcing effects of nicotine. Under some experimental conditions, nicotine is also self-administered reliably by humans. Environmental stimuli that have been associated previously with the self-administration of nicotine can reinstate extinguished drug-seeking behavior in animals and precipitate relapse to smoking behavior in ex-smokers. Innovative medications that target cannabinoid CB(1) and dopamine D(3) receptors and might block specifically the influence of such conditioned environmental stimuli in smokers are in development. LeFoll, B. and Goldberg, S.R. Trends Pharmacol Sci, 26, pp. 287-293, 2005.

Cannabinoid Agonists but not Inhibitors of Endogenous Cannabinoid Transport or Metabolism Enhance the Reinforcing Efficacy of Heroin in Rats Accumulating evidence suggests that the endogenous cannabinoid system is involved in the reinforcing effects of heroin. In rats intravenously self-administering heroin, IRP scientists investigated effects of cannabinoid CB(1) receptor agonists and compounds that block transport or metabolism of the endogenous cannabinoid anandamide. The natural cannnabinoid CB(1) receptor agonist delta-9-tetrahydrocannabinol (THC, 0.3-3 mg/kg i.p.) did not alter self-administration of heroin under a fixed-ratio one (FR1) schedule, except at a high 3 mg/kg dose which decreased heroin self-administration. Under a progressive-ratio schedule, however, THC dose-dependently increased the number of 50 mug/kg heroin injections self-administered per session and the maximal ratio completed (break-point), with peak increases at 1 mg/kg THC. In addition, 1 mg/kg THC increased break-points and injections self-administered over a wide range of heroin injection doses (25-100 mug/kg), indicating an increase in heroin's reinforcing efficacy and not its potency. The synthetic cannabinoid CB(1) receptor agonist WIN55,212-2 (0.3-3 mg/kg i.p.) had effects similar to THC under the progressive-ratio schedule. In contrast, AM-404 (1-10 mg/kg i.p.), an inhibitor of transport of anandamide, and URB-597 (0.01-0.3 mg/kg i.p.), an inhibitor of the enzyme fatty acid amide hydrolase (FAAH) that degrades anandamide, or their combination, did not increase reinforcing efficacy of heroin at any dose tested. Thus, activation of cannabinoid CB(1) receptors facilitates the reinforcing efficacy of heroin and this appears to be mediated by interactions between cannabinoid CB(1) receptors and mu-opioid receptors and their signaling pathways, rather than by an opioid-induced release of endogenous cannabinoids. Solinas, M., Panlilio, L.V., Tanda, G., Makriyannis, A., Matthews, S.A. and Goldberg, S.R. Neuropsychopharmacology, May 4, 2005 (Epub ahead of print) PMID: 15870833.

Motivational Effects of Cannabinoids and Opioids on Food Reinforcement Depend on Simultaneous Activation of Cannabinoid and Opioid Systems Strong functional interactions exist between endogenous cannabinoid and opioid systems. Here, IRP researchers investigated whether cannabinoid-opioid interactions modulate motivational effects of food reinforcement. In rats responding for food under a progressive-ratio schedule, the maximal effort (break point) expended to obtain 45 mg pellets depended on the level of food deprivation, with free-feeding reducing break points and food-deprivation increasing break points. Delta-9-tetrahydro-cannabinol (THC; 0.3-5.6 mg/kg intrapeitoneally (i.p.)) and morphine (1-10 mg/kg i.p.) dose-dependently increased break points for food reinforcement, while the cannabinoid CB1 receptor antagonist rimonabant (SR-141716A; 0.3-3 mg/kg i.p.) and the preferential mu-opioid receptor antagonist naloxone (0.3-3 mg/kg i.p.) dose-dependently decreased break points. THC and morphine only increased break points when food was delivered during testing, suggesting that these treatments directly influenced reinforcing effects of food, rather than increasing behavior in a nonspecific manner. Effects of THC were blocked by rimonabant and effects of morphine were blocked by naloxone, demonstrating that THC's effects depended on cannabinoid CB1 receptor activation and morphine's effects depended on opioid-receptor activation. Furthermore, THC's effects were blocked by naloxone and morphine's effects were blocked by rimonabant, demonstrating that mu-opioid receptors were involved in the effects of THC and cannabinoid CB1 receptors were involved in the effects of morphine on food-reinforced behavior. Thus, activation of both endogenous cannabinoid and opioid systems appears to jointly facilitate motivational effects of food measured under progressive-ratio schedules of reinforcement and this

facilitatory modulation appears to critically depend on interactions between these two systems. These findings support the proposed therapeutic utility of cannabinoid agonists and antagonists in eating disorders. Solinas, M. and Goldberg, S.R. Neuropsychopharmacology, April 6, 2005 (Epub ahead of print) PMID: 15812567.

Nanomolar Concentrations of Kynurenic Acid Reduce Extracellular Dopamine Levels in the Striatum Precise regulation of dopaminergic activity is of obvious importance for the physiology and pathology of basal ganglia. IRP investigators report here that nanomolar concentrations of the astrocyte-derived neuroinhibitory metabolite kynurenic acid (KYNA) potently reduce the extracellular levels of striatal dopamine in unanesthetized rats *in vivo*. This effect, which is initiated by the KYNA-induced blockade of alpha7 nicotinic acetylcholine receptors, highlights the functional relevance of glia-neuron interactions in the striatum and indicates that even modest increases in the brain levels of endogenous KYNA are capable of interfering with dopaminergic neurotransmission. Rassoulpour, A., Wu, H.Q., Ferre, S. and Schwarcz, R. J Neurochem, 93, pp. 762-765, 2005.

How Receptor Mosaics Decode Transmitter Signals. Possible Relevance of Cooperativity It has been demonstrated that receptor-receptor interactions between G-protein-coupled receptors (GPCRs) occur at the plasma-membrane level. It has also been shown that clustering of GPCRs in aggregates or receptor mosaics (RMs) results in the reciprocal modulation of their binding and decoding characteristics. It is hypothesized that cooperativity plays an important part in the decoding of signals processed by RMs of GPCRs. Thus, the binding of the ligand at one receptor alters the likelihood of the same ligand binding at the next site, in the case of RMs, formed by identical receptors and/or by iso-receptors (receptors that bind the same ligand). Agnati, L.F., Fuxe, K. and Ferre, S. Trends Biochem Sci, 30, pp.188-193, 2005.

The Endogenous Cannabinoid Anandamide and Its Synthetic Analog R(+)-Methanand-amide are Intravenously Self-Administered by Squirrel Monkeys Anandamide, an endogenous ligand for brain cannabinoid CB1 receptors, produces many behavioral effects similar to those of _9-tetrahydrocannabinol (THC), the main psychoactive ingredient in marijuana. Reinforcing effects of THC have been demonstrated in experimental animals, but there is only indirect evidence that endogenous cannabinoids like anandamide participate in brain reward processes. IRP scientists now show that anandamide serves as an effective reinforcer of drug-taking behavior when self-administered intravenously by squirrel monkeys. They also show that methanandamide, a synthetic long-lasting anandamide analog, similarly serves as a reinforcer of drug-taking behavior. Finally, they show that the reinforcing effects of both anandamide and methanandamide are blocked by pretreatment with the cannabinoid CB1 receptor antagonist rimonabant (SR141716). These findings strongly suggest that release of endogenous cannabinoids is involved in brain reward processes and that activation of cannabinoid CB1 receptors by anandamide could be part of the signaling of natural rewarding events. Justinova, Z., Solinas, M., Tanda, G., Redhi, G.H. and Goldberg, S.R. J Neurosci, 25, pp. 5645-5650, 2005.

Treatment Section, Clinical Pharmacology and Therapeutics Research Branch

Cyclazocine: Comparison to Hydromorphone and Interaction with Cocaine Kappa opioid agonists produce neurobiological and behavioral effects opposite those of cocaine and may be useful for the treatment of cocaine dependence. To evaluate the kappa and mu agonist effects of cyclazocine and test whether cyclazocine pretreatment would attenuate the effects of cocaine, the acute effects of cyclazocine and the mu agonist hydromorphone were compared and the effects of repeated administration of cyclazocine on response to cocaine were evaluated in experienced opiate and cocaine users. Cocaine was given 2 hours after oral pretreatment with cyclazocine (0, 0.1, 0.2, 0.4, 0.8, and 0 mg, in that order) in sessions conducted daily Monday to Friday and the following Monday. Physiological, subjective, and behavioral measures were collected in each session. Hydromorphone produced prototypic mu agonist effects. Cyclazocine exhibited modest kappa-like effects; on most measures, its effects tended to be similar to those of hydromorphone (15 mg), but lower in magnitude. Cyclazocine also had only modest, non-dose-related effects on response to cocaine. However, cocaine effects were consistently lower on the last administration (cyclazocine 0 mg pretreatment) following 4 days of cyclazocine pretreatment compared to the first administration (0 mg pretreatment). This finding is unlikely to be fully attributable to cocaine tolerance, and is not accounted for by pharmacokinetic changes; plasma concentrations of cocaine and its major metabolites were not altered by cyclazocine. The results were consistent with preclinical studies showing that repeated administration of a kappa agonist alters responses to cocaine. Preston, K.L. Umbricht, A, Schroeder, J., Abreu, M., and Pickworth, W.B. Behavioural

Pharmacology, 5, pp. 91-102, 2004.

Effects of High-Dose Intravenous Buprenorphine in Experienced Opioid Abusers Sublingual (SL) buprenorphine, a long-acting, partial mu-opioid agonist, is as effective as methadone in the treatment of heroin dependence, with a better safety profile due to its antagonist activity. However, the safety of therapeutic doses (8 to 16 mg) that might be diverted for intravenous (IV) use had not been demonstrated. Buprenorphine was administered to 6 non-dependent opioid abusers residing on a research unit; the doses tested, in separate sessions, were 12 mg buprenorphine SL, IV/SL placebo, and escalating IV buprenorphine (2 to 16 mg). Physiological and subjective measures were collected for 72 hours post drug administration. Buprenorphine minimally but significantly increased systolic blood pressure with no other statistically significant changes in blood pressure, heart rate or oxygen (02) saturation among the 7 drug conditions. The mean maximum decrease in 02 saturation from baseline was greatest for the 8 mg IV dose. Buprenorphine produced positive mood effects, although with substantial variability among participants. Onset and peak effects occurred earlier following IV than SL administration: peak IV effects occurred between 0.25 and 3 hrs; peak SL effects occurred at 3 to 7 hrs. Duration of effects varied among the outcome measures. The dose-response curves were flat for most parameters, particularly subjective measures. Side effects were mild except in one participant who experienced severe nausea and vomiting after the 12 mg IV dose. Buprenorphine appears to have a ceiling for cardio-respiratory and subjective effects and a high safety margin even when taken by the IV route. Umbricht, A., Huestis, M.A., Cone, E.J., and Preston, K.L. Journal of Clinical Psychopharmacology, 24, pp. 479-487, 2004.

Menstrual Cycle Length during Methadone Maintenance While heroin's menstrual disruption has been demonstrated, there are few published data concerning methadone maintenance (MM) and menstrual function. This study was conducted to evaluate whether cycles were more regular during MM. Start/end dates of each menses were collected from 191 drug-using women from two clinical trials, lasting 25-29 weeks, while on 70-100 mg of methadone. Participants were classified as regular, irregular, transient amenorrhea, persistent amenorrhea, or cycle restarters. Repeated-measures regression modeling was used to determine correlates of cycle length, probability of long cycles (>40 days), and short cycles (<20 days). Bleeding episodes (days from "start" to "stop") were defined as one or more bleeding days, bound by at least two non-bleeding days. Correlates of cycle length, body mass index, drug use, methadone dose, and race were calculated. Women had a high prevalence of cycle length irregularity; 133 participants: regular 37 (27.8%); irregular 62 (46.7%); transient amenorrhea 7 (5.3%); persistent amenorrhea 11 (8.3%); cycle restarters 16 (12%). Each additional week on MM was associated with decreased risk of long (OR=0.96, p=0.001 and short (OR=0.92, p=0.001) cycles. Of 27 women with secondary amenorrhea pre-study, 16 (59%) restarted menses. Positivity for opioids or cocaine was not significantly associated with short or long cycles. Cycle length begins to normalize during MM. Menses resumption may occur. MM, despite interfering with menstrual function in an absolute sense, may interfere less than illicit heroin abuse. Schmittner, J., Schroeder, J.R., Epstein, D.H., and Preston, K.L. Addiction, 100(6), pp. 829-836, 2005.

Clinical Pharmacology Section, Clinical Pharmacology and Therapeutics Research Branch

Calorie Restriction Increases Cigarette Use In Adult Smokers Cigarette smokers weigh less than nonsmokers, and smokers often gain weight when they quit. This is a major barrier to smoking cessation, especially among women. However, strict dieting is not recommended during smoking cessation out of concern that it might promote relapse. One reason is that calorie restriction increases self-administration of drugs of abuse in animals. This relationship has never been experimentally demonstrated in humans. This study evaluated whether calorie restriction increases cigarette smoking in humans. Seventeen (9M, 8F) healthy, normal-weight smokers not attempting to quit were cycled in partially counterbalanced order, double-blind, through four diets: normal calorie (2000-2800 kcal/day), low calorie (700 kcal/day deficit), low carbohydrate (CHO)-normal calorie, and low CHO-low calorie, for six days per diet on an inpatient research ward. Smoking was assessed by cigarette counts, breath carbon monoxide (CO) levels, and cigarette craving. Compared with the normal calorie diet, while on the low calorie diet, subjects smoked 8% more cigarettes ($p<0.02$) and had 11% higher breath CO levels ($p<0.01$). The low CHO- normal calorie diet showed no significant effect on either variable, but there was a 15% increase in breath CO levels ($p<0.05$) on the low CHO-low calorie diet. There were no changes in self-reported cigarette craving or mood.

Consistent with animal studies, moderate calorie restriction was associated with a small but statistically significant increase in cigarette smoking, with no independent effect of carbohydrate deprivation. These findings suggest that dieting may increase smoking behavior, and could impede smoking cessation attempts. Cheskin, L.J., Hess, J.M., Henningfield, J., and Gorelick, D.A. Psychopharmacology 179, pp. 430-436, 2005.

Influence of Psychotherapy Attendance on Buprenorphine Treatment Outcome Buprenorphine is a partial mu-opioid receptor agonist approved for the treatment of opiate dependence. This study evaluated the influence of psychotherapy attendance on treatment outcome in 90 dually (cocaine and heroin) dependent outpatients who completed 70 days of a controlled clinical trial of sublingual buprenorphine (16 mg, 8 mg, or 2 mg daily, or 16 mg every other day) plus weekly individual standardized interpersonal cognitive psychotherapy. Treatment outcome was evaluated by quantitative urine benzoylecgonine (BZE) and morphine levels (log-transformed), performed three times per week. Repeated-measures linear regression was used to assess the effects of psychotherapy attendance (percent of visits kept), medication group, and study week on urine drug metabolite levels. Mean psychotherapy attendance was 71% of scheduled visits. Higher psychotherapy attendance was associated with lower urine BZE levels, and this association grew more pronounced as the study progressed ($p=0.04$). The inverse relationship between psychotherapy attendance and urine morphine levels varied by medication group, being most pronounced for subjects receiving 16 mg every other day ($p = 0.02$). These results suggest that psychotherapy can improve the outcome of buprenorphine maintenance treatment for patients with dual (cocaine and opioid) dependence. Montoya, I.D., Schroeder, J.R., Preston, K.L., Umbricht, A., Fudala, P., Johnson, R., Contoreggi, C., and Gorelick, D.A. Journal of Substance Abuse Treatment, 28, pp. 247-254, 2005.

Imaging Brain Mu-opioid Receptors in Abstinent Cocaine Users: Time Course and Relation to Cocaine Craving Cocaine treatment upregulates brain mu-opioid receptors (mOR) in animals. Human data regarding this phenomenon are limited. IRP scientists previously used positron emission tomography (PET) with 11C-carfentanil to show increased mOR binding in brain regions of 10 cocaine-dependent men after 1 and 28 days of abstinence. The present study, in collaboration with scientists at the Johns Hopkins PET Center, measured regional brain mOR binding potential (BP) using [11C]carfentanil PET scanning in 17 cocaine users over 12 weeks of enforced abstinence on a closed research ward and in 16 healthy control subjects. mOR BP was increased in the frontal, anterior cingulate, and lateral temporal cortex after one day of abstinence. mOR BP remained elevated in the first two regions after one week and in the anterior cingulate and anterior frontal cortex after 12 weeks of abstinence. Increased binding in some regions at one day and one week was positively correlated with self-reported cocaine craving. mOR BP was significantly correlated with percentage of days with cocaine use and amount of cocaine used per day of use during the two weeks prior to admission, and urine benzoylecgonine concentration at the first PET scan. These results suggest that chronic cocaine use influences endogenous opioid systems in the human brain, and may explain mechanisms of cocaine craving and reinforcement. Gorelick, D.A., Kim, Y.-K., Bencherif, B., Boyd, S.J., Nelson, R., Copersino, M., Endres, C.J., Dannals, R.F., and Frost, J.J. Biological Psychiatry, 57, pp. 1573-1582, 2005.

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

Pharmacological Treatment of Adolescent Tobacco Addiction To determine the safety and efficacy of the nicotine patch and gum for adolescents who want to quit smoking, IRP researchers conducted a clinical trial with nicotine patch (21 mg), nicotine gum (2 and 4 mg), or a placebo patch and gum. All participants received cognitive-behavioral group therapy and were 13-17-year-old adolescents who smoked at least 10 cigarettes per day (CPD), scored at least 5 on the Fagerstrom Test of Nicotine Dependence, and were motivated to quit smoking. Participants were treated for 12 weeks with nicotine patch or gum with cognitive-behavioral therapy, with a follow-up visit at 6 months (3 months after the end of treatment). Safety was assessed on the basis of adverse event reports for all 3 groups, prolonged abstinence, assessed through self-report and verified with exhaled carbon monoxide (CO) levels of less than 6 ppm, in intent-to-treat analyses, and smoking reduction (CPD and thiocyanate concentrations) among trial completers. A total of 120 participants were randomized (72% white, 70% female; age: 15.2 +/- 1.33 years; smoking: 18.8 +/- 8.56 CPD; Fagerstrom Test of Nicotine Dependence score: 7.04 +/- 1.29) from 1999 to 2003. Participants started smoking at 11.2 +/- 1.98 years of age and had been

smoking daily for 2.66 +/- 1.56 years; 75% had at least 1 current psychiatric diagnosis. Mean compliance across groups was higher for the patch (mean: 78.4-82.8%) than for the gum (mean: 38.5-50.7%). Both the patch and gum were well tolerated, and adverse events were similar to those reported in adult trials. Changes in mean saliva cotinine concentrations throughout treatment were not statistically significant. Intent-to-treat analyses of all randomized participants showed CO-confirmed prolonged abstinence rates of 18% for the active-patch group, 6.5% for the active-gum group, and 2.5% for the placebo group; the difference between the active-patch and placebo arms was statistically significant. There was no significant effect of patch versus gum or gum versus placebo on cessation outcomes. Abstinence rates at the 3-month follow-up assessment were sustained but were not significantly associated with treatment group. Mean smoking rates, but not CO or thiocyanate concentrations, decreased significantly in all 3 arms but not as a function of treatment group. Nicotine patch therapy combined with cognitive-behavioral intervention was effective, compared with placebo, for treatment of tobacco dependence among adolescent smokers. Decreases in the numbers of cigarettes smoked appeared to be offset by compensatory smoking. Additional study of nicotine gum, with enhanced instructional support, is needed to assess its efficacy among adolescent smokers. Moolchan, E.T., Robinson, M.L., Ernst, M., Cadet, J.L., Pickworth, W.B., Heishman, S.J. and Schroeder, J.R. Pediatrics, 115, pp. 407-414, 2005.

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

Program Activities

New NIDA PAs and RFAs

On June 9, 2005, NIDA issued a Program Announcement (PA) entitled **Drug Abuse Prevention Intervention Research (PA-05-118)**. The goals of this PA are to encourage investigations of cognitive, behavioral, and social processes as they relate to: 1) the development of novel drug abuse prevention approaches; 2) the efficacy and effectiveness of newly developed and/or modified prevention programs; 3) the processes associated with the selection, adoption, adaptation, implementation, sustainability, and financing of empirically validated interventions; and 4) methodologies appropriate for studying complex aspects of prevention science.

In July 2005, NIDA reissued the Program Announcement entitled **Science Education Drug Abuse Partnership Award (PA-05-105)**. This PA supports the development and evaluation of innovative model programs and materials for enhancing knowledge and understanding of neuroscience and the biology of drug abuse and addiction among K-12 students, the general public, health care practitioners, and other groups. The award provides support for the formation of partnerships between scientists and educators, media experts, community leaders, and other interested organizations for the development and evaluation of programs and materials that will enhance knowledge and understanding of science related to drug abuse. The program contact is Dr. Cathrine Sasek, OSPC.

On August 19, 2005, NIDA issued a new RFA entitled **Pilot Clinical Trials of Pharmacotherapies for Substance Related Disorders (RFA-DA-06-002)**. The purpose of this RFA is to support pilot clinical studies of medications for investigation as possible treatments for substance related disorders. Because the purpose of this initiative is to support pilot studies in this area, preliminary studies are not required.

PAs and RFAs Issued With Other NIH Components/Agencies

On May 18, 2005, NIDA, in collaboration with NIAAA, issued a Program Announcement (PA) entitled **Economics of Prevention and Treatment Services for Drug and Alcohol Abuse (PA-05-111)**. This PA solicits research projects on the economics of prevention and treatment services for drug and alcohol abuse. Such research projects might emphasize any of the following subjects: 1) financing, including health insurance and/or payment mechanisms; 2) alternative delivery systems and managed care; 3) cost-benefit, cost-effectiveness, or cost-utility analyses; 4) service costs and production; and 5) methodological research.

On June 3, 2005, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement (PA) entitled **Ruth L. Kirschstein National Research Service Award Short-Term Institutional Research Training Grants (T35) (PA-05-117)**. Grants awarded under this PA will enable eligible institutions to develop or enhance research training opportunities for individuals interested in careers in biomedical and behavioral research.

On June 14, 2005, NIDA, in collaboration with several other NIH components, issued a Program Announcement (PA) entitled **Development of PET and SPECT Ligands for Brain Imaging (SBIR/STTR Award) (PA-05-122)**. This initiative is intended to stimulate the commercial development of novel radioligands for positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging in human brain, and to incorporate pilot or clinical feasibility evaluation in pre-clinical studies, model development or clinical studies.

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On June 30, NIDA, in collaboration with numerous other NIH components and the FDA's Center for Biologics Evaluation and Research (CBER), issued a Program Announcement (PA) entitled **Short-Term Courses in Human Embryonic Stem Cell Culture Techniques (PAR-05-133)**. Through this PA, NIH invites applications for grants to develop and conduct short-term continuing education programs on laboratory research techniques for human embryonic stem cell (hESC) lines, and to disseminate course materials and instructional experience to the scientific community. The program should include laboratory and didactic experiences to improve the knowledge and skills of biomedical researchers, and to enable them to maintain, characterize and utilize hESC lines in basic research projects.

On July 14, 2005, NIDA, in collaboration with NIAAA, issued a Program Announcement (PA) entitled **Health Services Research on the Prevention and Treatment of Drug and Alcohol Abuse (PA-05-139)**. This PA solicits health services research on the prevention and treatment of drug and alcohol abuse. Proposed research might emphasize any of the following subjects: 1) Factors that affect the delivery of drug and alcohol abuse intervention and related services, such as social factors, personal behaviors and attributes, financing, organization, management and health technologies; 2) Dimensions of drug and alcohol abuse intervention and related services, such as accessibility, utilization, quality, effectiveness, and costs; 3) Processes of blending science-based practices into community-based provision of drug and alcohol abuse prevention services; and 4) Research tools to facilitate higher quality health services research on drug and alcohol abuse.

On July 14, 2005, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement (PA) entitled **AIDS International Training and Research Program (PAR-05-140)**. The purpose of this announcement is to invite applications from eligible institutions for innovative, collaborative training programs that would contribute to the long-term goal of building sustainable research capacity in HIV/AIDS and HIV related conditions at institutions in low- and middle- income countries. These research-training programs will strengthen scientific knowledge and skills to enhance prevention of and treatment and care for HIV/AIDS and HIV-related conditions in these countries.

On July 22, 2005, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement (PA) entitled **Mentored Patient-Oriented Research Career Development Award (K23) (PA-05-143)**. The goals of this NIH-supported career development programs are to help ensure that a diverse pool of highly trained scientists are available in adequate numbers and in appropriate research areas to address the Nation's biomedical, behavioral, and clinical research needs. The purpose of this award is to support the career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research.

On August 3, 2005, NIDA, in collaboration with NIMH and NINDS, issued a Program Announcement (PA) entitled **Collaborative Neurological Sciences (CNS) Award (PAR-05-149)**. The purpose of this award is to encourage collaborative research investigations among scientists at minority institutions and grantees from leading research laboratories that have NIH or equivalent grant support to conduct neuroscience research. The CNS award will support an investigator-initiated research project in which the applicant and collaborating neuroscientist(s) work in a clearly defined area of mutual research interest.

On August 5, 2005, NIDA, in collaboration with NIMH, issued a Program Announcement (PA) entitled **Mechanism for Time-Sensitive Research Opportunities (PAR-05-150)**. This PA is intended to support public mental health and/or substance abuse services research in rapidly evolving areas (e.g., changes in service systems, health care financing, policy, etc.) where opportunities for empirical study are, by their very natures, only available through expedited award of support.

On August 8, 2005, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement (PA) entitled **Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral MD/PhD Fellows (F30) (PA-05-151)**. Grants awarded under this PA will support individual predoctoral fellowships for combined MD/PhD training in research areas relevant to the mission of the participating Institutes.

On June 30, 2005, NIDA, in collaboration with a number of other NIH components and the Agency for Healthcare Research and Quality (AHRQ), issued an RFA entitled **Research on Research Integrity (RFA-NR-06-001)**. Through this RFA,

participating organizations invite applications to support empirical research on research integrity. Applications must have clear relevance to biomedical, behavioral health sciences, and health services research.

On August 5, 2005, NIDA, in collaboration with NIMH and the Substance Abuse and Mental Health Services Administration (SAMHSA), issued an RFA entitled **Enhancing Practice Improvement in Community-Based Care for Prevention and Treatment of Drug Abuse or Co-occurring Drug Abuse and Mental Disorders (RFA-DA-06-001)**. This initiative aims to develop research capacity in a group that historically has been the object rather than the initiator of research-to-practice investigations. Accordingly, this RFA is intended to enhance the capacity of community-based providers of drug abuse prevention/treatment services, including services for individuals with co-occurring mental disorders, to conduct practice improvement research. Such research may entail the examiniation of therapeutic and/or business practices currently in use but lacking scientific evidence of effectiveness, or it may entail examination of the adoption, implementation, and sustained use of science-based therapeutic and/or business innovations.

On August 19, 2005, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **New Ways to Image Neural Activity (RFA-EB-05-001)**. This RFA is an initiative of the NIH Blueprint for Neuroscience Research, a coordinated effort of 15 NIH Institutes and Centers to accelerate progress in neuroscience by supporting research and development of enabling tools and resources. This RFA will be administered by the NIBIB on behalf of the Neuroscience Blueprint. This initiative is intended to support research leading to new ways for high resolution imaging of the neural activity that is reflected in electrophysiological signals.

On September 8, 2005, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Completion of a Comprehensive Mouse Knockout Resource (RFA-HG-05-007)**. The ultimate aim of the Knockout Mouse Project is to generate a null-mutant mouse resource comprising a null mutation marked with a reporter of high utility for each gene in mouse strain C57BL/6. The purpose of this RFA is to make maximum progress toward this goal using gene targeting, transposon-mediated mutagenesis or gene trapping.

On April 6, 2005, a Notice was released through the NIH Guide announcing the availability of administrative supplement funding to support interdisciplinary research in the behavioral/social and biological sciences. This announcement was associated with the Interdisciplinary Research efforts of the NIH Roadmap, with set-aside funding of approximately $2.4 million. Application receipt date was June 15, 2005, with start dates for successful applications expected to be September 30, 2005. NIDA grantees represented a large proportion of those applications received in response to this call for applications, and NIDA staff actively participated in the review of the applications.

Response to NIDA RFAs

Thirty-nine applications were received in response to **RFA DA-05-007, Consequences of Drug Abuse and Alcohol Exposure on Brain and Behavioral Development.** These applications were reviewed July 26-27, 2005.

Twenty-two applications (2 competetive supplement applications) were received in response to the RFA **Neurobiology of Treatment: Recovery of Brain Structure and Function, RFA-DA-05-006**. These applications were reviewed on July 12, 2005.

On July 26, 2005, reviewers evaluated applications received in response to **RFA-DA-05-008, HIV and Drug Abuse Interventions among Pregnant Women in Drug Abuse Treatment.** In total, 15 responsive applications were received.

Other Program Activities

CTN Update

Two new contracts were awarded for: DA-5-2207 for the Data and Statistics Center to Duke Clinical Research Institute and DA-5-2208 for the Clinical Coordinating Center to The EMMES Corporation. Both contracts were awarded April 29, 2005. The Data and Statistics Center is actively involved in statistical and data management aspects of the CTN clinical trials. The Clinical Coordinating Center is supporting protocol development, training, regulatory, monitoring, and lab and pharmacy supplies.

Twelve protocols that started since 2001 have completed enrollment. These studies enrolled 3,186 patients who were randomized in 75 community treatment programs located in 17 states.

Nine additional protocols are currently recruiting and enrolling patients. These protocols plan to enroll approximately 4,000 patients across 88 Community Treatment Programs when completed. Highlights of the active protocols include:

- Protocol CTN 0003 (Bup/Nx: Comparison of Two Taper Schedules) began enrollment June 30, 2003. New enrollment has stopped - reached 108% of target enrollment. Study is in follow-up phase and data clean up. The last follow-up visit is expected in November 2005.
- Protocol CTN 0010 (Buprenorphine/Naloxone Facilitated Rehabilitation for Opioid Dependent Adolescents/Young Adults) began enrollment in July 2003. This is the first protocol in the CTN that targets adolescent substance abusers. Enrollment is at nearly 60% of the projected target.
- Protocol CTN 0013 (Motivational Enhancement Therapy to Improve Treatment Utilization and Outcome In Pregnant Substance Abusers) began enrollment in November 2003 and has enrolled nearly 70% of the projected target enrollment.
- Protocol CTN 0014, Brief Strategic Family Therapy for Adolescent Drug Abusers (BSFT), has been implemented at 6 sites. An additional 2 sites have finished the provider training and overall site preparation and will start patient enrollment in summer 2005. This intervention is the first CTN study to target adolescents and their families.
- Protocol CTN 0015 (Women's Treatment for Trauma and Substance Use Disorder: A Randomized Clinical Trial) began in March 2004. The study has reached over 90% of the targeted patient enrollment and is expected to complete enrollment in September 2005.
- Protocol CTN 0017 (HIV and HCV Intervention in Drug Treatment Settings). The study began enrollment in November 2004 and enrollment has reached nearly 50% of the target goal. This study is enrolling at 8 community treatment sites across 5 Nodes.
- CTN 0018 (Reducing HIV/STD Risk Behaviors: A Research Study for Men in Drug Abuse Treatment) began enrolling in April 2004 and has reached over 90% of the target. New enrollment is expected to be completed in fall 2005.
- CTN 0019 (Reducing HIV/STD Risk Behaviors: A Research Study for Women in Drug Abuse Treatment) began enrollment in April 2004 and has reached 90% of the target. New enrollment is expected to be completed in fall 2005.
- CTN 0020 (Job Seekers Training for Substance Abusers). The protocol began enrollment in October 2004 and has reached over 60% of the enrollment goal. This study is also being conducted in a Navajo American Indian site, the Na'nizhoozhi Center, Inc. in Gallup, New Mexico, the first CTN study to be conducted there.
- 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. The study has reached over 80% of the target. This study is expected to close to new enrollment in the fall 2005.

Two protocols have recently completed all data collection phases and are pending data lock (April/May 2005). Those include:

- Protocol CTN 0004 (Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome in Subjects Seeking Treatment for Substance Abuse).
- Protocol CTN 0009 (Smoking Cessation Treatment with Transdermal Nicotine Replacement Therapy in Substance Abuse Rehabilitation Programs)

Three protocols have recently locked their data sets and are at the analysis stage. Those include:

- Protocol CTN 0008 (Assessment of the National Drug Abuse Clinical Trials Network: A Baseline for Investigating Diffusion of Innovation).
- Protocol CTN 0012 (Characteristics of Screening, Evaluation, and Treatment of HIV/AIDS, Hepatitis C Viral Infections, and Sexually Transmitted Infections in Substance Abuse Treatment Programs).

- Protocol CTN 0016 (Patient Feedback: A Performance Improvement Study in Outpatient Addiction Treatment Settings).

Four additional Protocols are currently being developed for the Network. Highlights of those protocols include:

- Protocol CTN 0028: Randomized Controlled Trial of Osmotic-Release Methylphenidate (OROS MPH) for Attention Deficit Hyperactivity Disorder (ADHD) in Adolescents with Substance Use Disorders (SUD). The protocol implementation is planned for fall 2005.
- Protocol CTN-0029: A Pilot Study of Osmotic-Release Methylphenidate (OROS MPH) in Initiating and Maintaining Abstinence in Smokers with Attention Deficit Hyperactivity Disorder (ADHD). Implementation is planned for fall 2005.
- Protocol CTN 0030: Prescription Opioid Addiction Treatment Study (POATS) is a randomized 2-phases, open-label, multi-center study in outpatient treatment settings. The protocol was submitted for DSMB review.
- Protocol CTN 0031: Twelve Step Facilitation: Evaluation of Two Interventions to Increase 12-Step Involvement and Improve Outcomes among Substance Dependent Individuals. This activity is at the concept development stage.

In addition to the primary CTN trials, there are 12 studies supported by independent grants or as supplements that use CTN studies as a platform.

New Collaborative Study: Starting Treatment with Agonist Replacement Therapies (START) Study: The CTN will participate with the Division of Pharmacotherapies & Medical Consequences of Drug Abuse on a multi-centered trial to compare the effect of buprenorphine/naloxone (Bup/Nx) and methadone (MET) on liver function. This is a randomized, open-label, multi-center, Phase 4 study in participants entering opioid agonist treatment programs at community centers (methadone centers) throughout the country. Flair Lindsey, Program Analyst, Special Populations Office, coordinated the ninth 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 over the summer. In 2005, 84 students and 32 grantees participated in the program.

The CTN Data and Safety Monitoring Board (DSMB) met July 20-22, 2005, in Bethesda, Maryland. The DSMB group reviewed ongoing protocols CTN 015 (Women's Treatment for Trauma and Substance Abuse), CTN 0017 (HIV/HCV Intervention in Drug Treatment Settings), and CTN 0020 (Job Seekers Training for Substance Abusers).

NIDA's New and Competing Continuation Grants Awarded Since May 2005

Ahijevych, Karen L. -- Ohio State University
Menthol, Ethnicity and Nicotine Dependence

Ahmed, Mahmoud S. -- University of Texas Medical, Galveston
Medications Development for the Pregnant Opiate Addict

Akbarian, Schahram -- University of Massachusetts Medical School, Worcester
Dopaminergic Signaling Modifies Stratial Histones

Ames, Steven C. -- Mayo Clinic College of Medicine, Jacksonville
Smoking Cessation For Young Adults Who Binge Drink

Arkes, Jeremy -- RAND Corporation
Economic Determinants of Prescription Drug Abuse

Banks, William A. -- St. Louis University
Opiate Addiction and HIV-1 Induced Release of Cytokines

Barrick, Christopher -- State University of New York at Buffalo
Knowledge Exchange and Skills Training for Therapists

Bauer, Lance O. -- University of Connecticut School of Medicine/Dentistry
Genetic Versus Phenotypic Markers of Relapse Risk

Bechara, Antoine -- University of Iowa
Residual Effects of Ecstasy on Decision-Making & Driving

Belenko, Steven -- Treatment Research Institute, Inc. (TRI)
STI/HIV Risk, Services, and Drug Use for Young Arrestees

Berns, Gregory S. -- Emory University
Neurobiology of Reward and Perference In Adolescence

Bernstein, Steven L. -- Montefiore Medical Center, Bronx, NY
Strategies To Help Adult ER Patients Quit Smoking

Bickel, Warren K. -- University of Arkansas Medical Sciences, Little Rock
Improving Combined Buprenorphine-Behavioral Treatment

Bisaga, Adam M. -- New York State Psychiatric Institute
Memantine Naltrexone Treatment For Opioid Dependence

Blow, Frederic C. -- University of Michigan at Ann Arbor
Tailored Youth Drug Intervention In Primary Care

Boyer, Edward W. -- University of Massachusetts Medical School, Worcester
Adulterants, Drugs, Coingestants and Associated HIV Risk

Bruijnzeel, Adriaan W. -- University of Florida
Neuropeptide-Based Therapies For Nicotine Dependence

Burdon, William M. -- University of California, Los Angeles
Increasing Engagement In Prison-Based Drug Treatment

Carroll, Frank I. -- Research Triangle Institute
Development of Pharmacotherapies For Nicotine Addiction

Case, Patricia -- Harvard University Medical School
Assessing HIV In Hidden Populations: A Feasibility Study

Coghill, Robert C. -- Wake Forest University Health Sciences
Dynamic Mechanisms of Pain Modulation

Colon, Hector M. -- Universidad Central Del Caribe
Introducing New Drug Preparation Materials To Reduce HIV/HCV Transmission

Conger, Rand D. -- University of California, Davis
Mexican Family Culture & Substance Use Risk & Resilience

Cooley, Michele R. -- Johns Hopkins University
Community Violence & Youth: Affect, Behavior, Academics

Cornelius, Marie D. -- University of Pittsburgh at Pittsburgh
Teen Tobacco Use In A Birth Cohort & Prenatal Effects

Costello, E. Jane -- Duke University
Vulnerability To Drug Abuse: Effects of Stressors & Stress

Cravatt, Benjamin F. -- Scripps Research Institute
Enzymes That Regulate Fatty Acid Amide Function in vivo

Curran, Patrick J. -- University of North Carolina Chapel Hill
Measurement Models In Latent Curve Analysis

Dileone, Ralph J. -- Yale University
Role of the Orexin Neuropeptide In Responses To Morphine

Ehrlich, Michelle E. -- Thomas Jefferson University
Buprenorphine Treatment of Neonatal Abstinence Syndrome

Fals-Stewart, William -- Research Triangle Institute
Group-Based Couples Therapy for Drug Abuse

Fals-Stewart, William -- Research Triangle Institute
Children of Drug Abusing Fathers

Fals-Stewart, William -- Research Triangle Institute
Cognitive Rehabilitation For Substance Abusers

Farabee, David J. -- University of California, Los Angeles
Four Models of Telephone Support For Stimulant Recovery

Fiellin, David A. -- Yale University

Counseling For Primary Care Office-Based Buprenorphine

Forman, Robert F. -- University of Pennsylvania
Opioid Medications Without Prescriptions on the Internet

Forster, Gina L. -- University of South Dakota
Neural Sensitivity To Stress During Drug Withdrawal

Francesconi, Walter G. -- Scripps Research Institute
Synaptic Plasticity In the BNST and Drug Dependence

Frantz, Kyle J. -- Georgia State University
Sex Differences In Adolescent Vulnerability To Morphine

Frazier, Charles J. -- University of Florida
Endocannabinoids and Tonic GABA In The Dentate Gyrus

French, Michael T. -- University of Miami, Coral Gables
Economic Evaluation Methods: Development and Application

Friedman, Samuel R. -- National Development & Research Institutes
Staying Safe: Long-Term IDUs Who Avoided HIV & HCV

Frisman, Linda K. -- Connecticut State Dept. of Mental Health/Addiction Services
Promoting Adoption of EBPS In Addiction Treatment

Fuchs Lokensgard, Rita A. -- Medical University of South Carolina
Neural Bases of Drug Context-Induced Cocaine Seeking

Gelernter, Joel -- Yale University
Genetics of Opioid Dependence

Gil-Rivas, Virginia -- University of North Carolina, Charlotte
Treatment Outcomes, Comorbid Disorders and PTSD

Gould, Thomas J. -- Temple University
Nicotine Addiction: Learning, Neural & Genetic Process

Grant, Igor -- University of California, San Diego
NeuroAIDS: Effects of Methamphetamine and HCV

Griffiths, Roland R. -- Johns Hopkins University
Licit and Illicit Abused Stimulant Drugs

Hauser, Kurt F. -- University of Kentucky
Opiate Drug Abuse and CNS Vulnerability To HIV

Hayes, Steven C. -- University of Nevada, Reno
Stigma and Burnout In Addiction Counselors

Hoffer, Lee D. -- Washington University
Evaluating the Social Structure of a Local Heroin Market

Horsburgh, C. Robert -- Boston University Medical Campus
Natural History of Hepatitis C Infection In HIV Disease

Horwith, Gary -- Nabi Biopharmaceuticals
Efficacy of a Nicotine Vaccine for Smoking Cessation

Howell, Leonard L. -- Emory University
Cocaine Use and Monoamine Function

Hruby, Victor J. -- University of Arizona
Novel Non-Peptide Opioid Ligands for Pain

Hughes, John R. -- University of Vermont & State Agricultural College
Internal Barriers To Seeking Smoking Cessation Treatment

Inciardi, James A. -- University of Delaware
Prescription Drug Abuse Among Club Drug Users

Ingram, Susan L. -- Washington State University
Dendritic DAT Conductances In Psychostimulant Addiction

Jansson, Lauren M. -- Johns Hopkins University
Fetal and Infant Neurobehavior In Opiate Dependent Women

Johnson, Knowlton W. -- Pacific Institute for Research and Evaluation
A School-Based Program To Prevent Inhalant Use In Alaska

Kaminski, Norbert E. -- Michigan State University
Il-2 Suppression By Endocannabinoid Activation of Ppargamma

Karpatkin, Simon -- New York University School of Medicine
AIDS and Thrombocytopenia: Drug Abusers and Homosexuals

Kasinathan, Chinnaswamy -- University of Medicine/Dentistry of New Jersey, Newark
Gel Depot for Narcotic Addiction

Kellam, Sheppard G. -- American Institutes for Research
A Follow-Up of Classroom Services to Prevent Drug Use

Kemp, Jack -- Delaware State Department of Health & Social Services
Statewide Science-Based Concurrent Recovery Monitor

King, Andrea C. -- University of Chicago
Efficacy of Naltrexone In Women's Smoking Cessation

Kirby, Kimberly C. -- Treatment Research Institute, Inc. (TRI)
Behavior Therapy Development of Group CM In Methadone Tx

Knutson, Brian D. -- Stanford University
Affective Neuroscience Probes of Cigarette Craving and Consumption

Lamb, Richard J. -- University of Texas Health Science Center, San Antonio
Increasing Contingency Management Success Using Shaping

Larkby, Cynthia A. -- University of Pittsburgh at Pittsburgh
Child Abuse, Violence, and PTSD In Early Substance Use

Lejuez, Carl W. -- University of Maryland College Park Campus
Behavioral Technologies for Predicting HIV Risk

Lesage, Mark G. -- Minneapolis Medical Research Foundation, Inc.
Modeling Behavioral Treatments for Stimulant Abuse

Lewin, Anita H. -- Research Triangle Institute
Trace Amine Receptor As Medication Development Targets

Lipton, Jack W. -- University of Cincinnati
Prenatal MDMA-Induced Changes In Axonal Guidance Cues

Lynskey, Michael T. -- Washington University
Cannabis and Other Illicit Drug Use: A Twin Study

Maciver, M. Bruce -- Stanford University
Abused Inhalant Actions At GABA and Glutamate Synapses

Malcolm, Robert J. -- Medical University of South Carolina
A Controlled Trial of NAC for Cocaine Dependence

Malenka, Robert C. -- Stanford University
Drugs of Abuse & Synaptic Processes In Dopamine Systems

Martinez, Diana -- New York State Psychiatric Institute
PET Imaging of Mesolimbic Dopamine In Heroin Dependence

Mason, W. Alex -- University of Washington
Role of Psychopathology In Adolescent Problem Drug Use

Matsumoto, Rae R. -- University of Mississippi
Sigma Ligands for the Treatment of Cocaine Overdose

Mccarty, Dennis -- Oregon Health & Science University
Adoption of Buprenorphine In An HMO Setting

Mccarty, Dennis -- Oregon Health & Science University
Organizational Change to Improve Access and Retention

Mccorry, Francis A. -- New York State Office of Alcoholism/Substance Abuse
A Case Study of NY's Infrastructure To Improve Practice

Mckee, Sherry -- Yale University
Negative Affect and Smoking Behavior In Women and Men

Mcrae, Aimee L. -- Medical University of South Carolina
Atomoxetine Treatment For ADHD and Marijuana Dependence

Mendelson, John E. -- California Pacific Medical Center-Pacific Campus
MDMA Dependence and Discontinuation Syndrome

Mermelstein, Paul G. -- University of Minnesota Twin Cities
Nfat-Mediated Gene Expression and Striatal Plasticity

Messina, Nena P. -- University of California, Los Angeles
Children Exposed to Methamphetamine Use and Manufacture

Messina, Nena P. -- University of California, Los Angeles
Gender-Responsive Treatment for Women In Prison

Metsch, Lisa R. -- University of Miami-Medical
Prevention Among HIV+ Crack Users In The Hospital

Miller, Brenda A. -- Pacific Institute for Research and Evaluation
Prevention Of Young Adult Drug Use In Club Settings

Miller, Richard J. -- Northwestern University
Chemokine Receptor Function In The Nervous System

Mintzer, Miriam Z. -- Johns Hopkins University
Effects of Opioid Pharmacotherapy on Functioning

Moberg, D Paul. -- University of Wisconsin Madison
Recovery High Schools As Continuing Care For Drug Abuse

Mulvey, Edward P. -- University of Pittsburgh at Pittsburgh
Pathways To Desistance From Substance Use Problems and Crime

Nader, Michael A. -- Wake Forest University Health Sciences
Social Stress: Vulnerability To Cocaine Abuse In Monkeys

Negus, Sidney S. -- Mc Lean Hospital, Belmont, MA
Novel Delta Opioids: Analgesic Effects & Abuse Liability

Nestler, Eric J. -- University of Texas Southwest Medical Center, Dallas
Neurotrophic Factors and Drugs of Abuse

Neumeyer, John L. -- Mc Lean Hospital, Belmont, MA
Mixed Kappa-Mu Opioids: Synthesis and Evaluation

Niaura, Raymond S. -- Butler Hospital, Providence, RI
Ethnic Health/Motivating HIV+ Latinos To Quit Smoking

Nishi, Rae -- University of Vermont & State Agricultural College
Nicotinic Acetylcholine Receptors In Neural Development

Okuyemi, Kolawole S. -- University of Kansas Medical Center
Effects of Menthol on Bupropion Pharmacokinetics

O'Neill, Joseph -- University of California, Los Angeles
1h Mrsi/Response Inhibition/Methamphetamine Abusers

Owens, S. Michael -- University of Arkansas Medical Sciences, Little Rock
Immunotherapy for Drug Abuse

Page-Shafer, Kimberly -- University of California, San Francisco
Acute Hepatitis C Infection In Young Injectors

Park, Sohee -- Vanderbilt University
Neurocognitive Consequences of Cannabis Use

Parsons, Loren H. -- Scripps Research Institute
Endocannabinoids and Cue-Induced Drug-Seeking Behavior

Pasternak, Gavril W. -- Sloan-Kettering Institute For Cancer Research
Pharmacology of Opioid Receptor Subtypes

Peng, Junmin -- Emory University

Quantitative Approach To Postsynaptic Density Proteome

Phillips, Paul E. -- University of Washington
Dynamic Control of Dopamine Release In Cocaine Abuse

Piomelli, Daniele -- University of California, Irvine
Characterization of a Novel Cannabinoid Ligand

Potenza, Marc N. -- Yale University
fMRI of Craving In Addictions: Gender Differences

Potter, Philip M. -- St. Jude Children's Research Hospital
Novel Therapeutic Approaches For Narcotic Overdose

Pyne, Jeffrey M. -- University of Arkansas Medical Sciences, Little Rock
Cost-Effectiveness of Reducing Drug Treatment Barriers

Rabiner, David L. -- Duke University
College Students' Non-Medical Use & Misuse of ADHD Meds

Rauhut, Anthony S. -- Dickinson College
Bupropion and Secondary Motivational Effects of Nicotine

Rayport, Stephen G. -- New York State Psychiatric Institute
Transgenic Analysis of Glutamate In Sensitization

Rich, Josiah D. -- Miriam Hospital
Opiate Replacement Therapy at Release from Incarceration

Robinson, Gene E. -- University of Illinois Urbana-Champaign
Neuromodulation of Excessive Reward-Directed Behavior

Roffman, Roger A. -- University of Washington
Motivating Substance Abusing Batterers To Seek Treatment

Role, Lorna -- Western New York State Psychiatric Institute
in vivo Studies of Neuregulin 1 In Addiction Pathways

Rothenberg, Richard B. -- Emory University
Geography, Networks, and Risk In Disease Transmission

Rush, Craig R. -- University of Kentucky
Stimulant Abuse Pharmacotherapy: Novel Antipsychotics

Sacks, Stanley -- National Development & Research Institutes
Re-Entry MTC For Offenders With MICA Disorders

Salloum, Ihsan M. -- University of Pittsburgh at Pittsburgh
Valproate Efficacy In Cocaine-Bipolar Comorbidity

Sanders, Bill -- Children's Hospital, Los Angeles
Youth Gangs: Drug Use, Sexual Behavior, Violence & HIV Risk

Santisteban, Daniel -- University of Miami-Medical
Borderline Adolescent Family Therapy Trial

Schafer, William -- University of California, San Diego
Machine Vision Analysis Of C.Elegans Phenotypic Patterns

Schiller, Peter W. -- Clinical Research Institute of Montreal
Development of Receptor-Specific Opioid Peptide Analogs

Schinke, Steven P. -- Columbia University of New York, Morningside
Drug Abuse Prevention: Mother-Daughter Intervention

Schulteis, Gerhard -- Veterans Medical Research Foundation, San Diego
Development of Opiate Dependence--Neural Substrates

Shinnick-Gallagher, Patricia -- University of Texas Medical, Galveston
Amygdala Neurons and Cocaine

Smith, Carolyn A. -- State University of New York at Albany
Long-Term Consequences of Exposure To Family Violence

Stark, Kenneth D. -- Washington State Department of Social/Health Services
Measuring and Tracking Statewide Model Program Fidelity

Stefansson, Kari -- Decode Genetics
Genes Contributing to Nicotine Dependence In Humans

Stein, Flo A. - North Carolina State Department of Health & Human Services
Adopting Prevention & Treatment Science-Based Practices

Stevens, Stacey L. -- Treatment Comm on Alcohol and Drug Abuse
Texas Process & Practice Improvement Initiative

Stormshak, Elizabeth A. -- University of Oregon
A Family Intervention for Adolescent Problem Behavior

Stotts, Angela L. -- University of Texas Health Science Center, Houston
Acceptance Therapy During Methadone Detoxification

Strong, David R. -- Butler Hospital, Providence, RI
Mood Management Phone Counseling In Smoking Cessation

Stroud, Laura R. -- Miriam Hospital
Prenatal Smoking, Fetal Behavior, and Infant Withdrawal

Supplee, Lauren H. -- University of Pittsburgh at Pittsburgh
Early Maternal Strategy Instruction In An At-Risk Sample

Taxman, Faye S. -- Virginia Commonwealth University
Effects of Manualized Treatment In A Seamless System

Taylor, Bradley K. -- Tulane University of Louisiana
Supraspinal Modulation of Neuropathic Pain

Trujillo, Keith A. -- California State University, San Marcos
Role of Glutamate In Opiate Tolerance and Sensitization

Van Bockstaele, Elisabeth -- Thomas Jefferson University
Modulation of Norepinephrine By Cannabinoids

Verkhusha, Vladislav V. -- University of Colorado, Denver/HSC, Aurora
Development of Imaging Technique To Study Regulation

Vezina, Paul -- University of Chicago
Sensitization and Stimulant Self-Administration

Vijayaraghavan, Sukumar -- University of Colorado, Denver/HSC, Aurora
Cholinergic Signaling In The Brain

Vilim, Ferdinand S. -- Mount Sinai School of Medicine of NYU
Neural Basis of Behavior Priming: Induction and Memory

Vlahov, David -- New York Academy of Medicine
The HIV Risk Behavior and the Urban Environment

Waldrop-Valverde, Drenna -- University of Miami-Medical
HIV+ Drug Users: Neurocognitive Aspects of ARV Adherence

Weeks, Margaret R. -- Institute For Community Research
Longitudinal Study of the Rap Peer Intervention for HIV

Weingardt, Kenneth R. -- Palo Alto Institute For Research & Education
Web-Based Instruction for Counselor Training

Weinshenker, David -- Emory University
Modeling Genetically Controlled DBH Activity In Mice

Weinshenker, David -- Emory University
Disulfiram, DBH, and Cocaine-Induced Anxiety

Weinstein, Harel -- Weill Medical College of Cornell University
Structure and Function of Neurotransmitter Transporters

Weiss, Jie W. -- California State University, Fullerton
Predicting Tobacco and Alcohol Initiation

Wenzel, Suzanne L. -- RAND Corporation
Residential Status, Drug Use, Health Among Impoverished Women

Wessendorf, Martin W. -- University of Minnesota, Twin Cities

Circuits In Descending Facilitation of Nociception

Whitbeck, Leslie B. -- University of Nebraska, Lincoln
Ojibwe Pathways Through the High School Years

Wunsch, Martha J. -- Virginia College of Osteopathic Medicine
Opioid Mortality In Southwestern Virginia

Xu, Ming -- University of Cincinnati
Role of C-Fos In Cocaine Actions

Yantis, Steven G. -- Johns Hopkins University
Cortical Mechanisms of Task Switching Revealed By fMRIi

Yin, Deling -- East Tennessee State University
Role of Opioids Signaling In Immune Suppression

Zacny, James -- University of Chicago
Behavioral Effects of Opioids In Volunteers

Zarcone, Troy J. -- University of Rochester
Behavior Consequences of Amphetamine Dependence In Mice

Zvolensky, Michael J. -- University of Vermont & State Agricultural College
Smoking and Panic Vulnerability

Zvolensky, Michael J. -- University of Vermont & State Agricultural College
Anxiety Sensitivity and Smoking

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Extramural Policy and Review Activities

Receipt, Referral, and Review

NIDA received 1441 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 1122 applications.

OEA arranged and managed 22 grant review meetings in which 462 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 11 contract proposal reviews, 10 concept reviews, and reviews of 151 applications to the Loan Repayment Program.

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 18 Special Emphasis Panels for a variety of reasons:

Conflicts with the chartered committees
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)
6 Special Emphasis Panels that reviewed RFA submissions.

OEA managed the following RFA reviews:

- DA05-004: Lapse or Relapse to Drug Abuse and Other Chronic Conditions
- DA05-005: Secondary Analysis of the NESARC and NSPY Datasets
- DA05-006: Neurobiology of Behavioral Treatment: Recovery of Brain Structure and Function
- DA05-007: Consequences of Drug Abuse and Alcohol Exposure on Brain and Behavioral Development
- DA05-008: HIV and Drug Abuse Interventions Among Pregnant Women in Drug Abuse Treatment
- DA05-009: Strategic Program for Innovative Research on Drug Addiction Pharmacotherapy (SPIRDAP)

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

Contract Reviews (R&D and non-R&D)

- N01DA-5-5532: National Survey of Parents and Youth (NSPY) Data Archive, Analysis, and Management Center
- N01DA-5-7753: Neuroscience Information Framework
- N01DA-5-8845: Medications Development for Stimulant Dependence II (MDS II)

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N01DA-6-8852: Regulatory Affairs Support for IND Applications

- N01DA-5-8853: Using Drug Self-Administration in Rats to Evaluate Drugs of Abuse and Pharmacotherapies in Drug Addiction
- N01DA-5-8856: Medical Writing and Report Coordination Support
- N01DA-5-8857: Clinical Data Management - Support for Clinical Trials

SBIR Phase I and Phase II

- N44DA-5-5526: A Web and PC-based Substance Abuse Screening Program
- N44DA-5-5528: Real-time Data Collection Utilizing Automated Speech Recognition Technologies
- N44DA-5-7741: Nanoscience-based Design of Therapies for Substance Abuse Treatment
- N44DA-5-7742: Discovery of New Chemical Probes

SBIR Phase I Concept Reviews

64	N43DA-6-7756	Nanoscience-based Design of Therapies for Substance Abuse Treatment
76	N43DA-6-1127	Development of Science Literacy Materials or Programs
77	N43DA-6-4404	Development of Serious Games for Neuro-Rehabilitation of Drug-Induced Cognitive Deficiencies
78	N43DA-6-4405	E-Health Applications of Empirically Supported Therapies in English and/or Spanish
79	N43DA-6-5533	Development of State-of-the-Art Mechanisms for Epidemiological Research
80	N43DA-6-5534	Training and Infrastructure Development for Community Coalitions
81	N43DA-6-8861	Clinical Trials for Anti-Addiction Medication Development
82	N43DA-6-8862	Development of Novel Drug Delivery Systems for Treatment of Drug Addictions
83	N43DA-6-7757	Create High Quality Feeder Layer Independent C57BL/6 Mouse ES Cells and Other Inbred ES Lines for High-throughput Gene Targeting
84	N43DA-6-1128	Develop Methods for Stimulating International Collaborations

Certificates of Confidentiality

Between May 18 and August 11, 2005, 59 new certificates, 19 extensions, and 4 amendments were processed.

Extramural Outreach

Dr. Rita Liu, OEA, participate in the workshop " What's New at NIDA and NIH: How will it Affect You? " at the CPDD meeting in June 2005.

Dr. Rita Liu made a presentation at an extramural program workshop at the International Narcotics Research Conference in Annapolis, MD in July 2005.

Dr. Teresa Levitin, Director, OEA, joined colleagues from several NIH Institutes and NSF for a workshop for graduate students and new faculty on how to obtain federal funding that was presented in conjunction with the 17th annual convention of the American Psychological Society held in Los Angeles in May 2005.

Dr. Teresa Levitin participated in a CPDD workshop in June 2005 entitled " What's New at NIDA and NIH: How will it Affect You?"

Dr. Levitin served on the NIDA committee that organized a number of activities at the American Psychological Association annual meeting in Washington D.C. in August 2005. She, along with other NIDA colleagues, represented NIDA at the symposium "Meet the National Institutes of Health: Research and Training for New Investigators" and, with Drs. Minda Lynch and Larry Stanford, she co-chaired a symposium "Adolescent Brain Development: What Does It Have To Do With Cognitive Processes?"

Dr. Levitin continues to serve on a number of trans-NIH committees, including the communications workgroup that drafted recommendations about communication

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In Memoriam

between DEAS and the ICs, and the Extramural Program Management Committee's workgroup on the implementation of the OHRP Guidance on Research Involving Human Data or Specimens.

Dr. Mark Green, OEA, made a presentation at an extramural program workshop at the International Narcotics Research Conference in Annapolis, MD in July 2005.

Dr. Mark Green organized a workshop for the June 2005 CPDD meeting entitled " What's New at NIDA and NIH: How will it Affect You? " that also included Drs. Gerald McLaughlin, Teri Levitin, Mark Swieter, and Rita Liu.

Dr. Mark Swieter, OEA, made a presentation on grant application review in a Grant Writing Workshop at the CPDD meeting in June 2005.

Dr. Mark Swieter participated in at workshop "What's New at NIH and NIDA: How Will it Affect You?" at the CPDD meeting in June 2005.

Dr. Mark Swieter participated in the Training Grant Mixer at the CPDD meeting in June 2005.

Dr. Mark Swieter gave a talk entitled, "NIDA Research Mechanisms and Review Procedures", at the NIDA Mentored K Awardees Meeting at the Grand Hyatt Hotel in Bethesda in August 2005.

Staff Training and Development

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 a presentation on changes instituted by NIH dealing with coded private data and biological specimens and there are open forums where staff can bring up their own questions about grants and other extramural policy.

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

Congressional Affairs (Prepared September 12, 2005)

BUDGET FY 2006

The FY 2006 budget request for NIH is $28.510 billion, an increase of $145 million or 0.5 percent over the FY2005 funding level. The FY 2006 President's request for NIDA is $1.01 billion, 0.4 percent above the FY 2005 level.

On June 24, 2005, the House passed HR 3010, the Labor, Health and Human Services, and Education appropriations bill. NIH is funded at $28.510 billion and NIDA would receive $1.01 billion, identical to the President's request.

On July 14, the Senate Appropriations Committee reported the FY 2006 Labor, Health and Human Services and Education Appropriations bill, H.R. 3010, with $29.317 billion for NIH; this is $953 million above the FY2005 level and $808 million above the budget request. NIDA would receive $1.035 billion, a 2.9 percent increase above the FY 2005 level.

Floor action in the Senate is not yet scheduled. Plans for a conference between the House and Senate are also unclear at this time.

Other Hearings and Briefings of Interest

Methamphetamine Briefing on the Hill Sponsored by the Friends of NIDA

The Friends of NIDA, in conjunction with the Congressional Methamphetamine Caucus and the Congressional Addiction Treatment and Recovery Caucus, sponsored a June 28, 2005 briefing entitled "Methamphetamine Addiction: Cause for Concern — Hope for the Future." The event was very popular and well attended — approximately 180 members, staff, and constituent group representatives attended.

Speakers at the briefing included Representative Rick Larsen (D-WA), Co-Chair of the Congressional Methamphetamine Caucus; Dr. Charles O'Keeffe of Virginia Commonwealth University (Representing the Friends of NIDA); NIDA Director Dr. Nora Volkow, Ms. Vicki Sickels, a counselor in a Des Moines, Iowa hospital and a person in recovery from methamphetamine addiction, and Dr. Richard Rawson of the UCLA Integrated Substance Abuse Programs.

Related Links:
To access Dr. Volkow's presentation please see:
http://www2.apa.org/ppo/volkow62805.ppt

To access Dr. Rawson's presentation please see:
http://www2.apa.org/ppo/rawson62805.ppt

On May 4, 2005, the American Psychological Association's Science Policy Office sponsored a congressional briefing entitled, *"NIH Research in Action: Innovative Behavioral Treatments for Mental and Substance Use Disorders"*. Dr. Kathleen Carroll (PI — New England Node) and Dr. William Miller (PI — Southwest Node) were two of the three invited speakers. Dr. Carroll spoke on contingency management in successfully treating substance users in research (CTN 0006 and CTN 0007). Dr. Miller discussed the success of motivational interviewing as an effective treatment (CTN 0005).

Hearing on NIH Reauthorization — July 19, 2005 — "Legislation to Reauthorize the National Institutes of Health"

The House Energy and Commerce Committee held a hearing to examine issues

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surrounding the reauthorization of NIH. NIH Director Dr. Elias Zerhouni was the sole witness.

The purpose of the hearing was to discuss draft legislation that would reauthorize the National Institutes of Health. The discussion draft legislation, distributed shortly before the hearing, contained provisions that would categorize existing institutes and centers into two major categories: mission specific institutes and science enabling institutes and centers; delineate new authorities for the NIH Director; establish four specific authorization of appropriations; establish an electronic coding system and require a biennial report to Congress; and authorize grants for demonstration projects for research at the interface between biological and physical sciences.

Dr. Zerhouni described the NIH mission, key authorities, structure, and the committee's proposal for NIH, including the establishment of a Division of Program Coordination, Planning, and Strategic Initiatives which would create a priority setting process for trans-NIH initiatives such as the NIH Roadmap for Medical Research, the NIH Strategic Plan for Obesity Research, and the NIH Neuroscience Blueprint. Chairman Barton expressed his feeling that NIH reauthorization is a top priority for the House Energy and Commerce Committee. The Chairman explained that reauthorization of NIH is a means to reassert the jurisdiction of the Committee. Members of both parties expressed support for general concepts while expressing a desire to further consider particular provisions.

Subsequent to the hearing, a second version of the discussion draft was circulated by the committee. Changes were made as a result of comments from committee members and other concerned parties. Further committee action and finalization of any bill that might be introduced is not certain at this time.

PASSED BILLS OF INTEREST

H.R. 3 — This law was originally introduced by Representative Young (R-AK) as the "Transportation Equity Act: A Legacy for Users," a bill to authorize funds for federal aid for highways, highway safety programs, and transit programs. The original House version of this bill included language (Section 2013 "Drug Impaired Driving Research and Prevention Act") that would require the development of a model statute for States relating to drug impaired driving. The model would include threshold levels of impairment for a controlled substance; methods for detecting the presence of controlled substances; and penalties for drug impaired driving. It would be based on recommendations contained in a report to be developed by NIH and submitted to Congress not later than 18 months after the date of enactment. The final version of the law maintains the requirements for model statute development, and for a report to be developed on the problem of drug-impaired driving. The Secretary of Transportation will develop the report, "in cooperation with the National Institutes of Health." The President signed the bill into law (109-59) on August 10.

S. 45/H.R. 869 — Senator Carl Levin (D-MI) in the Senate and Representative Mark Souder (R-IN) in the House introduced identical bills to amend the Controlled Substances Act to lift the patient limitation on prescribing drug addiction treatments by medical practitioners in group practices, and for other purposes. Both the House and Senate passed their bills prior to their recess, and the President signed the bill into law (P.L. 109-56) on August 2. This law will impact practices that prescribe buprenorphine products for treatment of opiate addiction, making the medication available to more patients across the country.

S. 518/H.R. 1132 — Senator Sessions (R-AL) in the Senate and Representative Whitfield (R-KY) in the House introduced identical bills, the "National All Schedules Prescription Electronic Reporting Act of 2005." This law (P.L. 109-60) will provide for the establishment of a controlled substance monitoring program in each State; it was signed by the President on August 11.

BILLS OF INTEREST - SENATE

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

S. 103 — Senator Talent (R-MO) introduced on January 24, 2005 the "Combat Meth Act of 2005," a bill to respond to the illegal production, distribution, and use of methamphetamine in the United States, and for other purposes. Among many things, the bill would have SAMHSA establish a methamphetamine research, training, and technical assistance center "Éin consultation with the Director of the National Institutes of HealthÉ" The bill was passed by the Senate on September 9, in the form

of an amendment to the Commerce, Justice, Science FY 2006 appropriation bill (HR 2662). Related Bills: See H.R. 314.

S. 259 — Senator Johnson (D-SD) introduced on February 2, 2005 a bill to require that federal forfeiture funds be used, in part, to clean up methamphetamine laboratories. Committee: Judiciary.

S. 408 — Senator DeWine (R-OH) introduced on February 16, 2005 the "STOP Underage Drinking Act." In part, the bill would authorize the Director of ONDCP to award "enhancement grants" to eligible entities to design, test, evaluate and disseminate strategies to maximize the effectiveness of community-wide approaches to preventing and reducing underage drinking. Committee: Health, Education, Labor and Pensions. Related Bills: See H.R. 864.

S. 521 — Senator Hutchison (R-TX) introduced on March 3, 2005 the "Hepatitis C Epidemic Control and Prevention Act," a bill to amend the Public Health Service Act to direct the Secretary HHS to establish, promote, and support a comprehensive prevention, research, and medical management referral program for hepatitis C virus infection. Committee: Health, Education, Labor and Pensions. Related Bills: See H.R. 1290.

S. 537 — Senator Bingaman (D-NM) introduced on March 7, 2005 the "Child Healthcare Crisis Relief Act" a bill to increase the number of well-trained mental health service professionals (including those based in schools) providing clinical mental health care to children and adolescents, and for other purposes. Committee: Health, Education, Labor and Pensions. Related Bills: See H.R. 1106.

S. 538 — Senator Biden (D-DE) introduced on March 7, 2005 the "Health Professionals Substance Abuse Education Act." In introductory remarks, he explained that the bill would do three things for each of the fiscal years 2006 thru 2010: (1) authorize $9 million in grants to train medical generalists to recognize substance abuse and know properly how to refer patients and their families for treatment; (2) authorize $6 million to fund a faculty fellowship program at educational institutions to teach courses on substance abuse, incorporate substance abuse issues into required courses, and educate health professionals about matters involving non-therapeutic uses of prescription medications; and (3) authorize $6 million to establish centers of excellence at medical centers or universities to initiate and implement training, research and clinical activities related to special focal areas of substance abuse, and provide opportunities for interdisciplinary collaboration in curriculum development, clinical practice, research and policy analysis. Committee: Health, Education, Labor and Pensions.

S. 666 — Senator DeWine (R-OH) introduced on March 17, 2005 the "Family Smoking Prevention and Tobacco Control Act," a bill to protect the public health by providing the FDA with certain authority to regulate tobacco products. Committee: Health, Education, Labor and Pensions.

S. 803 — Senators Norm Coleman (R-MN) and Hillary Rodham Clinton (D-NY) introduced on April 14, 2005 the "Help Expand Access to Recovery and Treatment Act of 2005," to provide parity with respect to substance abuse treatment benefits under group health plans and health insurance coverage. Committee: Health, Education, Labor and Pensions. Related Bills, see H.R. 1258.

S. 884 — Senator Cantwell (D-WA) introduced on April 25, 2005 the "Methamphetamine and Identity Theft Study Act of 2005," instructing the Attorney General to conduct a study evaluating whether there is a connection between the commission of crimes involving methamphetamine and the commission of identity theft crimes. Committee: Judiciary.

S. 927 — Senator Corzine (D-NJ) introduced on April 27, 2005 the "Medicare Mental Health Modernization Act of 2005," which would amend Title XVIII of the Social Security Act to expand and improve coverage of mental health services under the Medicare program. Committee: Finance. Related Bills: See H.R. 1946.

S. 1317 — Senator Hatch (R-UT) introduced the "Stem Cell Therapeutic and Research Act of 2005," bill to provide for the collection and maintenance of cord blood units for the treatment of patients and research, and to amend the Public Health Service Act to authorize the Bone Marrow and Cord Blood Cell Transplantation Program to increase the number of transplants for recipients suitably matched to donors of bone marrow and cord blood. The bill was reported by the Health, Education, Labor and Pensions Committee and awaits floor action.

S. 1332 — On June 29, Senator Arlen Specter (R-PA) introduced S. 1332, the Personal Data Privacy and Security Act of 2005. Of specific interest to NIH, the measure would prohibit the display, sale or purchase of Social Security numbers (SSNs) to third parties without an individual's informed consent. Exemptions are included for public health and research conducted for the purpose of advancing public knowledge. Researchers would be required to provide adequate assurances that the SSNs will not be used inappropriately, and that there are safeguards to protect the privacy and confidentiality of any information about individuals. S. 1332, which has two cosponsors, was placed on the Senate Legislative Calendar under General Orders.

S. 1334 — On June 29, Senator Bunning (R-KY) introduced the "Professional Sports Integrity and Accountability Act," to provide for integrity and accountability in professional sports. Committees: Finance; Commerce, Science and Transportation.

S. 1436 — On July 20, Senator Mike DeWine (R-OH) introduced S. 1436, the Campus-Based Underage Alcohol Use Reduction Act. The bill would require the Secretary of Education to award grants to reduce the rate of underage alcohol use and binge drinking among students at institutions of higher education. The bill was referred to the Committee on Health, Education, Labor, and Pensions.

BILLS OF INTEREST - HOUSE

H.R. 240 — Representative Pryce (R-OH) introduced on January 4, 2005 the "Personal Responsibility, Work, and Family Promotion Act of 2005." The bill, which would extend welfare legislation, was approved by the Ways and Means Committee's Human Resources Subcommittee on March 15, 2005. The subcommittee amended the bill to cut federal welfare funding to any state that does not drug test those applying for or receiving welfare benefits. No state currently drug tests welfare recipients. In fact, a 2003 ruling by a federal appeals court that covers the states of Kentucky, Michigan, Ohio, and Tennessee ruled that states cannot drug test welfare recipients because it is unconstitutional. Those states, and many others, could lose federal funding if the drug testing provision makes it into law. Status: pending at House Financial Services.

H.R. 314 — Representative Blunt (R-MO) introduced on January 25, 2005 the "Combat Meth Act of 2005," a bill to respond to the illegal production, distribution, and use of methamphetamine in the United States, and for other purposes. In part the bill would authorize funds to provide training to State and local prosecutors and law enforcement agents for the investigation and prosecution of methamphetamine offenses. Committees: Judiciary, Subcommittee on Crime, Terrorism, and Homeland Security; Energy and Commerce, Subcommittee on Health. Related Bills: See S. 103.

H.R. 370 — Representative Bilirakis (R-FL) introduced on January 26, 2005 the "Biomedical Research Assistance Voluntary Option Act," a bill to amend the Internal Revenue Service Code to allow taxpayers to designate part or all of any income tax refund be paid for use in biomedical research conducted through the NIH. Committees: Energy and Commerce, Subcommittee on Health; Ways and Means.

H.R. 798 -- Representative Gordon (D-TN) introduced on February 16, 2005 the "Methamphetamine Remediation Research Act of 2005," a bill to provide for a research program for remediation of closed methamphetamine production laboratories, and for other purposes. Committee: Science, Subcommittee on Environment, Technology, and Standards. Status: voted out of full committee on 4/13/05, see House Report 109-42.

H.R. 812 -- Representative Cummings (D-MD) introduced on February 16, 2005 the "Dawson Family Community Protection Act," a bill to amend the Office of National Drug Control Policy Reauthorization Act of 1998 to ensure that adequate funding is provided for certain high intensity drug trafficking areas. Committees: Government Reform; Energy and Commerce.

H.R. 864 — Representative Roybal-Allard (D-CA) introduced on February 16, 2005 a bill to provide for programs and activities with respect to the prevention of underage drinking. Committee: Energy and Commerce, Subcommittee on Health. Related Bills: See S. 408.

H.R. 1020 — Representative Rogers (R-MI) introduced on March 1, 2005 a bill to declare adequate pain care research, education, and treatment as national public health priorities, and for other purposes. In part the bill would establish within NIH a center to be known as the National Center for Pain and Palliative Care Research. Committees: Energy and Commerce, Subcommittee on Health; Veterans Affairs, Subcommittee on Health; Ways and Means; Armed Services.

H.R. 1054 — Representative Green (R-WI) introduced on March 2, 2005 the "Tools for Community Initiatives Act," which would establish an Office of Faith Based and Community Initiatives in the Executive Office of the President. Committee: Government Reform.

H.R. 1055 — Representative Hooley (D-OR) introduced on March 2, 2005 the "Comprehensive Methamphetamine Response Act," a bill to provide for the designation and funding of high intensity methamphetamine abuse and trafficking areas. Committees: Energy and Commerce, Subcommittee on Health; Judiciary.

H.R. 1056 — Representative Hooley (D-OR) introduced on March 2, 2005 the "Methamphetamine Precursor Control Act of 2005," a bill to amend the Controlled Substances Act with respect to the distribution of pseudoephedrine. Section 7 of the bill would authorize funding for NIH to conduct research on medical alternatives to pseudoephedrine. Committees: Energy and Commerce, Subcommittee on Health; Judiciary.

H.R. 1106 — Representative Kennedy (D-RI) introduced on March 3, 2005 the "Veterans Medical Research Assistance Voluntary Option Act of 2005," a bill to increase the number of well-trained mental health service professionals (including those based in schools) providing clinical mental health care to children and adolescents, and for other purposes. Committees: Energy and Commerce, Subcommittee on Health; Ways and Means. Related Bills: See S.537.

H.R. 1258 — Representative Ramstad (R-MN) introduced on March 10, 2005 the "Time for Recovery and Equal Access to Treatment in America (TREAT America) Act, a bill to amend the Employee Retirement Income Security Act of 1974, PHSA and the IRS Code of 1986 to provide parity with respect to substance abuse treatment benefits under group health plans and health insurance coverage. Committees: Energy and Commerce, Subcommittee on Health; Education and Workforce, Subcommittee on Employer-Employee Relations; Ways and Means. Related Bills: See S. 803.

H.R. 1290 — Representative Wilson (R-NM) introduced on March 14, 2005 the "Hepatitis C Epidemic Control Prevention Act," to require the Secretary of Health and Human Services to establish, promote, and support a comprehensive prevention, research, and medical management referral program for hepatitis C virus infection. The bill also would require the Director of NIH to establish a Liver Disease Research Advisory Board, which would be charged with developing a Liver Disease Research Plan. Committee: Energy and Commerce, Subcommittee on Health. Related Bills: See S. 521.

H.R. 1350 — Representative Peterson (D-MN) introduced on March 16, 2005 the "Methamphetamine Blister Pack Loophole Elimination Act of 2005," a bill to eliminate the safe-harbor exception for certain packaged pseudoephedrine products used in the manufacture of methamphetamine. Committees: Energy and Commerce, Subcommittee on Health; Judiciary. Related Bills: See H.R. 1446.

H.R. 1357 — Representative Weldon (R-FL) introduced on March 17, 2005, the Human Cloning Prohibition Act of 2005, a bill to prohibit human cloning. Committee: House Judiciary, Subcommittee on Crime, Terrorism, and Homeland Security.

H.R. 1376 — Representative Davis (R-VA) introduced on March 17, 2005 the "Family Smoking Prevention and Tobacco Control Act," a bill to protect the public health by providing the FDA with certain authority to regulate tobacco products. The bill text states that the use of tobacco products by the Nation's children is a pediatric disease of considerable proportions that results in new generations of tobacco-dependent children and adults and that nicotine is an addictive drug . Committee: Energy and Commerce, Subcommittee on Health.

H.R. 1378 — Representative Emerson (R-MO) introduced on March 17, 2005 the "Ephedrine Alkaloids Regulation Act of 2005," a bill to amend the Controlled Substances Act with respect to regulation of ephedrine alkaloids, including ephedrine and pseudoephedrine. The bill states that methamphetamine is a highly addictive drug that can be readily made from products and precursors purchased from retail stores. Committee: Energy and Commerce, Subcommittee on Health.

H.R. 1402 — Representative Kennedy (D-RI) introduced on March 17, 2005 the "Paul Wellstone Mental Health Equitable Treatment Act of 2005," a bill to provide for equal coverage of mental health benefits with respect to health insurance coverage unless comparable limitations are imposed on medical and surgical benefits. Committees: Education and the Workforce, Subcommittee on Employer-Employee Relations;

Energy and Commerce, Subcommittee on Health.

H.R. 1446 — Representative Souder (R-IN) introduced on March 17, 2005 the "Methamphetamine Abuse Prevention Act of 2005," a bill to eliminate the safe-harbor exception for certain packaged pseudoephedrine products used in the manufacture of methamphetamine, Committees: Energy and Commerce, Subcommittee on Health; Judiciary. Related Bills: See H.R.1350.

H.R. 1528 — Representative James Sensenbrenner (R-WI) introduced on April 6, 2005 the "Defending America's Most Vulnerable: Safe Access to Drug Treatment and Child Protection Act of 2005," which would amend the Controlled Substances Act to protect vulnerable persons from drug trafficking, and for other purposes. Committees: Energy and Commerce, Subcommittee on Health; Judiciary, Subcommittee on Crime, Terrorism and Homeland Security.

H.R. 1639 — Representative DeLauro (D-CT) introduced on April 14, 2005 the "Military Health Services Improvement Act of 2005," which would require pre- and post-deployment mental health screenings for members of the Armed Forces, and for other purposes. Committee: Armed Services.

H.R. 1704 — Representative Portman (R-OH [now resigned from the House]) introduced on April 19, 2005 the "Second Chance Act: Community Safety Through Recidivism Prevention Act of 2005," which would reauthorize the grant program of the Department of Justice for reentry of offenders into the community, to establish a task force on Federal programs and activities relating to the reentry of offenders into the community, and for other purposes. Committees: Judiciary; Education and the Workforce.

H.R. 1758 — Representative Andrews (D-NJ) introduced on April 21, 2005 the "Open Air Drug Market Penalty Act of 2005," which would amend the Controlled Substances Act to provide penalties for open air drug markets, and for other purposes. Committees: Judiciary; Energy and Commerce.

H.R. 1789 — Representative Kennedy (D-RI) introduced on April 21, 2005 the "Health Professionals Substance Abuse Education Act," designed to educate health professionals concerning substance use disorders and addiction. Committee: Energy and Commerce. Related Bill: See S. 538.

H.R. 1862* ** — Representative Stearns (R-FL) introduced on April 26, 2005 the "Drug Free Sports Act," which would direct the Secretary of Commerce to issue regulations requiring testing for steroids and other performance-enhancing substances for certain sports associations engaged in interstate commerce. Committee: Education and Commerce; Education and the Workforce.

H.R. 1946 — Representative Stark (D-CA) introduced on April 27, 2005 the "Medicare Mental Health Modernization Act of 2005," which would amend Title XVIII of the Social Security Act to expand and improve coverage of mental health services under the Medicare program. Committees: Ways and Means; Energy and Commerce. Related Bills: See S. 927.

H.R. 2087 — Representative Frank (D-MA) introduced on May 4, 2005 the "States' Rights to Medical Marijuana Act," which would provide for the medical use of marijuana in accordance with the laws of the various States. Committee: Energy and Commerce.

H.R. 2124 — Representative Weldon (R-FL) introduced on May 5, 2005 the "Clinical Research Act of 2005," which would amend the Public Health Service Act to provide for clinical research support grants, clinical research infrastructure grants, and a demonstration program on partnerships in clinical research, and for other purposes. Committee: Energy and Commerce.

H.R. 2195 — Representative Lynch (D-MA) introduced on May 5, 2005 the "Act to Ban Oxycontin," which would provide for the withdrawal of the drug OxyContin from the commercial market. Committee: Energy and Commerce.

H.R. 2520 — Representative Smith (R-NJ) introduced the "Stem Cell Therapeutic and Research Act of 2005" to provide for the collection and maintenance of human cord blood stem cells for the treatment of patients and research, and to amend the Public Health Service Act to authorize the C.W. Bill Young Cell Transplantation Program. The bill has been passed and sent to the Senate.

H.R. 2565* ** — Representative Davis (R-VA) on May 24 introduced the "Office of National Drug Control Policy Reauthorization Act," to reauthorize the Office of National

Drug Control Policy Act and to establish minimum drug testing standards for major professional sports leagues. Committees: Government Reform, Energy and Commerce, Education and the Workforce.

H.R. 2829* — Representative Souder (R-IN) introduced on June 9 the "Office of National Drug Control Policy Reauthorization Act of 2005." The bill expands and enhances certain authorities of the Office. Committees: Government Reform, Judiciary, Energy and Commerce, Select Intelligence.

H.R. 3084* — On June 28, Representative Cliff Stearns (R-FL) introduced H.R. 3084, the Drug Free Sports Act of 2005. The bill would direct the Secretary of Commerce to issue regulations requiring testing for steroids and other performance enhancing substances for certain sports associations engaged in interstate commerce. The bill would also require the Secretary of Health and Human Services, in consultation with the NIDA Director, to prescribe the substances for which professional athletes are tested, establish criteria by which professional sports associations may provide substances to athletes prior to or after any drug test, and establish criteria for test administration. The measure also calls for penalties for a positive test, and criteria under which the names of athletes testing positive may be disclosed. H.R. 3084, which has eight cosponsors, was referred to the House Committees on Energy and Commerce, and Education and the Workforce.

H.R. 3196 — On June 30, Representative Henry Waxman (D-CA) introduced H.R. 3196, the Fair Access to Clinical Trials Act (FACT). The measure would require sponsors of privately and publicly funded studies of drugs, biologics, or medical devices to register using a database that builds on the National Library of Medicine's www.clinicaltrials.gov. It would provide public access to basic information on studies before they begin, such as the disease or condition with which the trial is concerned, the hypothesis being tested, the sponsor and principal investigator, and the sources of funding. Public access to the results of clinical studies, including primary and secondary outcomes and significant adverse events, would also be permitted under the legislation. H.R. 3196 also would authorize the Secretary of HHS to impose penalties for noncompliance, including revoking a sponsor's eligibility for further Federal funding and imposing civil money penalties. The bill was referred to the House Committee on Energy and Commerce.

***** - Note: House Leadership and Committee chairs are currently working to resolve the differences in these bills regarding steroids, and intend to have one bill that they will then push through the legislative process to focus on steroids issues.**

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International Activities

International Program Supports Distance Learning Efforts
The International Program has expanded its efforts to develop Internet-based applications that could provide relatively low-cost training, education, and communication in the research arena by supporting planning efforts for an international Master's Degree in Addiction Studies and issuing two Small Business Innovation Research (SBIR) contracts. NIDA participated in and provided travel support for participants in a June 14-16, 2005, meeting held at Virginia Commonwealth University (VCU) to discuss the international Master's Degree program. The program will be a collaborative effort between VCU, Kings College at the University of London, and The University of Adelaide in Australia. During the meeting, representatives from the three educational institutions explored the need for a cross-cultural degree program; described their institutions' existing campus-based and distance learning programs; discussed the kind of curriculum that would most benefit the communities, participants, and the addiction field; and identified next steps. NIDA-supported participants included Drs. Jason White and Olga Lopatko, University of Adelaide; and Drs. John Strang and Kim Wolff, King's College London. Drs. Charles O'Keefe and Robert Balster led the VCU contingent. Dr. Vladimir Poznyak, World Health Organization, and Ms. Dale Weiss, NIDA IP, discussed their respective organizations' educational plans. Ms. Weiss described how the International Program is developing a set of distance learning products and web-based research resources tailored to NIDA's international constituencies; NIDA has since issued two Phase 1 SBIR awards:

Drug Abuse Research Training for International Investigators was awarded July 15, 2005, to Danya International, Inc., to develop an interactive and user-friendly Web site for the international drug abuse research community that will include training modules and links to other resources, including funding opportunities, a partnering database, and a roadmap to NIDA resources tailored for an international audience.

International Drug Abuse Researcher E-Learning Program was awarded July 18, 2005, to Medical Directions, Inc., to develop effective, science-based, drug abuse training modules that meet the linguistic, cultural, and technological needs of NIDA's international research collaborators and to provide a versatile and robust E-Learning delivery technology.

NIDA International Forum Draws an Accomplished Crowd
More than 300 registrants from 51 nations participated in the NIDA International Forum June 17-20, 2005, before the College on Problems of Drug Dependence (CPDD) meeting in Orlando, Florida. Nearly half of those registered presented their research findings at a joint NIDA International Forum poster session and CPDD workshop that has allowed attendees from both meetings to learn about drug abuse research conducted outside the United States. Participants were enthusiastic about the Forum symposium, workshops, and the joint poster session. The one-day symposium, Linking Drug Abuse and HIV/AIDS Research, featured a presentation by NIDA Deputy Director Dr. Timothy P. Condon, who summarized the Institute's current research priorities and funding constraints, and a discussion of emerging issues, responses, and research priorities to address the intertwined epidemics of drug addiction and HIV/AIDS by NIDA AIDS Research Director Dr. Jacques Normand and Dr. Paul Griffiths, European Monitoring Centre for Drugs and Drug Addictions. NIDA staff members who discussed the Institute's international drug abuse research activities included Dr. Steven W. Gust, IP; Dr. David Shurtleff, DBNBR; Dr. Yonette Thomas, DESPR; Dr. Frank Vocci, DPMCDA; Dr. Betty Tai, CCTN; and Dr. Steven Goldberg, IRP.

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Participants in international research collaborations discussed how to create and conduct collaborative research programs by using varied support mechanisms. Dr. Joseph E. Schumacher, University of Alabama at Birmingham, described collaborative research with Ukrainian researchers that grew out of a Fogarty International Center (FIC) ICOHRTA award. Dr. Jan M. van Ree, Rudolf Magnus Institute for Neurosciences, described collaborative research fostered by the U.S.-Netherlands Binational Agreement. A panel of Middle Eastern scientists coordinated by Dr. Rick Rawson, University of California, Los Angeles, described how they use funding from the U.S. Department of State to supplement research awards supporting a cooperative network that operates in Egypt, Israel, and the Palestinian Territory. Representatives from organizations that support international drug abuse research and training who discussed their activities and funding mechanisms included Dr. Vladimir Poznyak, World Health Organization; Dr. Robert W. Eisinger, NIH Office of AIDS Research; Ms. Flora Katz, FIC; and Ms. Daria Tuetonico, Hubert H. Humphrey Fellowship Program. Workshops featured interactive discussions about writing journal articles, adapting the Addiction Severity Index across cultures, and prioritizing HIV/AIDS research needs in drug abuse treatment settings.

U.S. - Netherlands Binational Meeting Reviews Research Proposals and Results

As the first joint research teams are publishing their results and the second group of scientists are completing their projects, representatives from NIDA and the Dutch Addiction Program (DAP) met May 19-20, 2005, in Baltimore, Maryland, to consider applications for new funding and assess the status of the unique binational agreement between NIDA, The Netherlands Health Research and Development Council (ZONMw), and The Netherlands Organization for Scientific Research (NWO). The meeting was co-chaired by IP Director Dr. Steven Gust and Drs. Jan van Ree and Nick Ramsey, University of Utrecht. During the meeting, participants toured the NIDA Intramural Research Program and met with scientists at Johns Hopkins University. In addition, Dr. Dirk Ruwaard, Counselor for Health, Welfare and Sport, Royal Netherlands Embassy, briefed participants on agreements between the U.S. Department of State, the U.S. Office of National Drug Control Policy, and the Netherlands Ministry of Health to collaborate on drug abuse issues, including supply- and demand-reduction.

The joint scientific reviews conducted by the separate U.S. and Dutch funding agencies ensure that each binational research project meets the individual nations' research criteria and priorities; the joint funding permits NIDA, ZONMw, and NWO to expand the impact of their scarce financial resources. The newly proposed collaborations include research on neuroimaging to assess the effects of marijuana use on adolescent brain development, the connection between ADHD and substance abuse, the effectiveness of community-based versus institutionalized introductions of a system to evaluate and select empirically proven prevention interventions, improving decision-making skills to prevent drug abuse, and comparative studies of training activities.

One of the first binational projects funded under NIDA-DAP agreement has helped narrow the search for specific genes linked to nicotine dependence (*Pharmacogenomics Journal*, 2004, 4, 345-346). Dr. Geoffrey Hunt, Institute for Scientific Analysis, described how research teams examining the international youth dance club scene in Rotterdam, San Francisco and Hong Kong adopted a global perspective in their research, integrating qualitative and quantitative methods to adapt to differing customs and developing culturally appropriate prevention and intervention strategies. Research teams at the University of Southern California (USC) and the University of Maastricht are comparing the power of independently developed measures of implicit cognition to predict substance abuse in high-risk adolescents. Dr. Susan Ames, USC, outlined the research results and their impact on scientific understanding of assessment, theory, and intervention feasibility. Leading researchers from each country conduct productive collaborative research by sharing data available in only one of the two countries, assembling teams with complimentary skills, and investigating new research topics.

U.S., Spanish Scientists Build Collaborative Research

Building on their introduction at the 2003 U.S.-Spain Binational Workshop, Dr. Flavio Francisco Marsiglia, Arizona State University, and Dr. Maria Angeles Luengo, University of Santiago de Compostela, have exchanged research visits and completed a pilot study on drug abuse prevention among 917 Spanish students. The researchers are preparing an R01 application, and their respective universities have agreed to support further cooperative activities.

NIDA, State Department Select Humphrey Drug Abuse Research Fellows

NIDA and the U.S. Department of State have selected six international drug abuse professionals as 2005-2006 Hubert H. Humphrey Drug Abuse Research Fellows. The two agencies cosponsor competitive, 10-month awards that provide academic training at Johns Hopkins University and six-week professional affiliations with NIDA-supported researchers. The new Humphrey Fellows include: Dr. Fadi Hammal, Syrian Center for Tobacco Studies; Ms. Alexandra Hill, Anti-Drug Foundation of El Salvador; Dr. Danesh Kumar, Indian Institute of Human Behaviour and Allied Sciences; Dr. Stephen Nsimba, Muhimbili University College of Health Sciences, Tanzania; Dr. Anna Tkachenko, Far East Center of Mental Health, Khabarovsk, Russia; and Ms. Nataliya Yuirievna Vlasova, STEPS Treatment Center, Ukraine.

International Meetings/Conferences

Drs. Eve Reider and Beverly A. Pringle, DESPR, co-chaired a symposium August 20, 2005, during the American Psychiatric Association Annual Convention that focused on research being conducted under the U.S.-Netherlands Binational Agreement. Dr. John Lochman, University of Alabama, presented research he conducted with Dr. Walter Matthys, University of Utrecht, on the impact of early intervention for aggressive behavior on future substance abuse; Dr. Geoffrey Hunt, Institute for Scientific Analysis, described research he is conducting with Dr. Dike van de Mheen, Rotterdam Addiction Research Institute, examining the international youth dance club scene in Rotterdam, San Francisco and Hong Kong; and Dr. Susan Ames, University of Southern California, discussed research conducted with Dr. Reinout W. Weirs, University of Maastricht, on the value of implicit cognition to predict substance abuse in high-risk adolescents. Ms. Dale Weiss, IP, was the discussant.

NIDA cosponsored a conference, **Delivery Systems for Substance Abuse Treatment: Integration with Primary Care, Mental Health and Social Services**, held September 5-8, 2005, in Istanbul, Turkey, and organized by the Integrated Substance Abuse Programs at the University of California, Los Angeles (UCLA). In addition to NIDA and UCLA, the conference was cosponsored by the United States Institute of Peace, the World Health Organization, the United Nations Office on Drugs and Crime, the International Society of Addiction Medicine, and the International Association of Addiction Journal Editors. Dr. Jack Stein, DESPR, served on the conference steering committee, co-chaired a session on research and training opportunities, and presented about NIDA-supported research and training programs. NIDA also supported the participation of four grantees at the conference: Drs. Christine Grella and Walter Ling, UCLA; Dr. Jeffery Samet, Boston University; and Dr. Constance Weisner, University of California, San Francisco.

NIDA provided travel support to Dr. Nancy Jainchill, National Development and Research Institutes, for participation in the **International Therapeutic Communities Conference**, held May 10, 2005, in Madrid, Spain.

NIDA supported three researchers who participated in the scientific meeting, **Alcohol, Drugs, and Violence: Youth Risk Taking Behaviors and Prevention**, held May 27 to June 3, 2005, at the University of California, Riverside, by the Kettil Bruun Society for Social and Epidemiological Research. Dr. Katarzyna Okulics-Kozaryn, Warsaw Institute of Psychiatry and Neurology, Poland, discussed research on the validity of screening tests for problematic cannabis and other drug use among adolescents. Dr. Ifeta Licanin, University of Sarajevo, Bosnia and Herzegovina, reviewed drug-induced risk behaviors among adolescents; and Dr. Adriana Tucci, UNIFESP/EPM, Brazil, presented research on the effectiveness of the Childhood Trauma Questionnaire to evaluate childhood neglect and abuse in alcohol- and drug-dependent patients and in patients with depression.

NIDA supported the participation of three international researchers at the **Transportation Research Board Summer Workshop on Drugs in Traffic**, held June 20-21, 2005, Woods Hole, Massachusetts. Dr. Johannes G. Ramaekers, University of Maastricht, the Netherlands, reviewed the effects of drugs on drivers; Dr. Alain Versraet, University of Ghent, Belgium, described the legal framework for dealing with drugs in traffic; and Dr. Phillip Swann, VicRoads, Australia, outlined enforcement issues with regard to drug-impaired drivers.

NIDA supported the July 10-13, 2005, visit by former INVEST Drug Abuse Research Fellow Dr. Marco Bortolato to the NIDA IRP in Baltimore to work on an on-going multidisciplinary collaborative study between the University of Cagliari, Italy; the University of California, Irvine; and the NIDA IRP on levels of the endogenous cannabinoid anandamide and levels of FAAH enzyme activity in selected brain areas of squirrel monkeys.

NIDA supported the participation of three international researchers at the **International Association of Forensic Toxicologists (TIAFT)** meeting, held August 29 to September 2, 2005, in Seoul, Korea. Dr. Serap Annette Akgur, Ege University of Medicine, Izmir, Turkey, discussed her research on drugged driving; Dr. Tasduq Abdullah, Sagar University, Jammu, India, presented his research on the health benefits of Indian natural drugs that protect against tissue toxicity with excessive free radicals; and Mr. Juan Manuel Triszcz, University of La Plata, Argentina, described his study of the kinetics of ethanol degradation in forensic blood samples.

NIDA provided travel support to Dr. Deni Carise, Treatment Research Institute, University of Pennsylvania, to conduct Addiction Severity Index training at the **Brazilian Conference on Drug and Alcohol Abuse (ABEAD)**, held August 31 to September 3, 2005, in Ouro Preto, Brazil.

NIDA provided conference support for the **27th Annual Substance Abuse Librarians and Information Specialists Conference**, held May 3-7, 2005, in Chicago, Illinois.

International Visitors

Dr. Nathan Appel, DPMCDA, attended the 10th Annual CyberTherapy Conference/1st International Conference on Applied Technologies in Medicine and Neuroscience in Basel, Switzerland organized by the Interactive Media Institute. He chaired the Addictions session on June 8, 2005. Speakers, including a NIDA SBIR award recipient, reported on how they have applied or plan to apply virtual reality technology to treat cocaine and nicotine craving and to reduce risky behaviors.

At the invitation of the School of Medicine, International American University, St. Lucia, West Indies, Dr. Jag Khalsa, DPMCDA, presented a symposium on HIV/AIDS and Drug Abuse. NIDA/NIH-supported researchers including Drs. Royal, Kumar, Nair, and Sopori presented current research on various aspects of drug abuse and HIV/AIDS. Dr. Khalsa discussed medical/clinical consequences of drug abuse and co-occurring infections, funding opportunities and possible collaborations at NIDA/NIH.

Dr. Frank Vocci, Director, DPMCDA, attended the International Association of Law and Mental Health meeting in Paris, France from July 1-4, 2005. He presented on The Treatment Efficacy for Addictive Disorders: the Policy Implications of Expectations and Realities on July 2, 2005.

Dr. Wilson Compton, Director, DESPR, presented a paper on the epidemiology of drug abuse at the NIDA-sponsored pre-conference on drug abuse at the International Academy of Law and Mental Health, Paris, France, July 2-3, 2005.

Dr. Meyer Glantz, DESPR, represented NIDA at the 2005 World Mental Health Consortium annual meeting in Amsterdam. The Consortium is a collaboration of the World Health Organization, NIMH and NIDA, and other mental health institutions. The Consortium members sponsor and conduct the World Mental Health Survey, a multi-site investigation of the prevalence and concomitants of mental and substance use disorders in 28 countries. The United States component of the survey, the National Comorbidity Survey-Replication, has completed data collection and is currently analyzing and publishing its findings.

Drs. Eve Reider, PRB, DESPR, and Bev Pringle, SRB, DESPR, collaborated with Dr. Steven Gust, International Office in organizing a symposium for the annual meeting of the American Psychological Association, August 20, 2005, Washington D.C. Drs. Reider and Pringle chaired and Dr. Gust led the discussion for the symposium "The United States-Netherlands Bi-national Collaboration on Drug Abuse." Presenters included: 1) John E. Lochman (University of Alabama) and Walter Matthys (University of Utrecht, The Netherlands), 2) Geoffrey Hunt, (Institute for Scientific Analysis, Alameda, California), and 3) Susan Ames (University of Southern California).

Drs. Elizabeth Robertson and Wilson Compton, DESPR, met with Davide Antognazza and Alberto Terzi of Italy to discuss strategic planning for prevention programming in Italy. Italy has recently translated the NIDA publication Preventing Drug Abuse among Child and Adolescents into Italian and is basing their programming plans on the Principles of Prevention presented in the publication.

On June 8, 2005, Dr. David Thomas, DBNBR, gave a presentation at the Cybertherapy 2005 meeting, in Basel Switzerland, entitled NIDA's Virtual Reality Pain Research Program as part of the Pain and Pathological Grief Symposium. Dr. Thomas also served as chair of this session.

Dr. Melissa Racioppo, DCNDBT, participated in a meeting of Dutch-American research collaborations sponsored by NIDA's program on international research held in Baltimore, Maryland on April 19-20, 2005.

Dr. Jag Khalsa, DPMCDA, presented a mini-symposium on Metabolic and Endocrine Disorders and Interventions in Drug Abusers Co-infected with HIV and HCV at the XIII World Psychiatry Congress, in Cairo, Egypt, September 10-15, 2005. Speakers (Dr. Adrian Dobs of JHU, Dr. Tim Flanigan of Brown University, Dr. Charles Hinkin of UCLA, and Christine Wanke of Tufts) presented current research findings on the subject. A brief summary of the symposium will be placed on NIDA's website.

Dr. Frank Vocci, Director, DPMCDA, presented on international research funded by the Division of Pharmacotherapies and Medical Consequences of Drug Abuse at the NIDA International Satellite Symposium in Orlando, June 18, 2005.

Dr. Betty Tai, Director, CCTN, presented an update of the CTN research at the NIDA international Forum in Orlando Florida on June 17th, 2005.

Dr. Yonette Thomas, DESPR, presented at the International Forum at the CPDD Annual Meeting in Orlando, Florida in June 2005.

Dr. Peter Hartsock, DESPR, served on the conference committee of the Fourteenth International Conference on AIDS and Public Health, St. Petersburg, Russia, May 23-27, 2005.

Dr. Peter Hartsock organized and chaired a special symposium titled "Multi-Disciplinary Research on the Epidemiology of HIV/AIDS and Evaluation of the Public Health Impact and Cost Effectiveness of HIV/AIDS Interventions." The symposium was part of the Fourteenth International Conference on AIDS and Public Health, St. Petersburg, Russia, May 23-27, 2005.

Dr. Peter Hartsock participated a special meeting held by the Council on Foreign Relations titled, "HIV and National Security: Where Are the Links." The meeting took place in Washington, D.C., July 18, 2005 and was co-chaired by Dr. Peter Piot, Executive Director, UNAIDS; Richard C. Holbrooke, Former U.S. Representative to the United Nations; and Laurie Garrett, Senior Fellow for Global Health, Council on Foreign Relations and Pulitzer Prize-winning journalist.

Dr. Peter Hartsock participated in a meeting held by the Kaiser Family Foundation, the Center for Strategic and International Studies, and the Council on Foreign Relations title "Post G8 Briefing on Future HIV/AIDS Financing," Washington D.C., July 21, 2005. The meeting was held to discuss the key outcomes of the G8 Summit as they related to HIV/AIDS.

Dr. Amina Woods, Cellular Neurophysiology Section, IRP presented data on the instrumentation and technical development of their MALDI Ion Mobility orthogonal time of flight instrument at the "3rd Conference on Mass Spectrometry Applied to Chemical and Biological Warfare Agents" in Noordwijkerhout, Netherlands on April 18, 2005.

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Meetings/Conferences

The National Institute on Drug Abuse (NIDA) held a research track at the **American Psychiatric Association's 158th Annual Meeting**, May 21-26, 2005, in Atlanta, GA with some 22,000 conference attendees. The NIDA program included sessions on increases in opioid analgesic abuse, scientific advances in the neurobiology of behavior, cannabis dependence treatment and the neurobiology of compulsive reward-seeking. This year's program built on the major research track NIDA held at APA's conference in 2004 to raise awareness of new and emerging issues in addiction and psychiatry and provide important information related to best practices and treatment strategies. A number of NIDA staff, including NIDA's Director, Dr. Nora Volkow, participated in the 2005 meeting.

The National Institute on Drug Abuse (NIDA), in collaboration with the Center for Substance Abuse Treatment (CSAT), and the National Association of State Alcohol and Drug Abuse Directors (NASADAD) held a meeting **"Forging Federal-State Collaborations to Blend Research and Practice,"** on June 5, 2005 at the Sheraton Bal Harbour Hotel in Miami, Florida in conjunction with the 2005 Annual NASADAD Conference. This meeting built on a series of meetings held over the past year to examine collaborative strategies to enhance the adoption of evidence-based practices in State drug abuse prevention and treatment systems.

NIDA hosted a two-day Blending Conference at the Sheraton Bal Harbour Hotel, Miami Beach, Florida on June 6 - 7, 2005, titled **"Smart Practice, Practical Science: Blending Clinical Treatment and Research."** This successful event brought together clinicians and researchers to present and discuss scientific findings related to empirically supported treatments for drug abuse research. A hallmark of this meeting was that Spanish translation was available. The Conference was dedicated in memoriam to Mr. Glen Fischer. The NIDA planning committee of this meeting included Drs. Timothy P. Condon, Cindy Miner, Suman King and Denise Pintello, as well as Jane Smither, OSPC.

NIDA convened a **Grant Writing Workshop** on June 21, 2005, at the 2005 **College on Problems of Drug Dependence (CPDD)** Conference in Orlando, Florida. Approximately 60 early-career scientists attended and were provided information about the grant process at NIDA and how to apply for NIH grants. The presenters included: Drs. Cindy Miner, David Shurtleff, Mark Swieter from NIDA; Dr. Scott Lukas, McLean Hospital, Harvard Medical School and Dr. Jeffery Hoffman, Danya International Inc. The Workshop was chaired and coordinated by Dr. Denise Pintello, OSPC.

A NIDA **Grant Writing Workshop** was held in Annapolis, Maryland at the 2005 International Narcotics Research Conference (INRC) on July 13, 2005. Presenters from NIDA were: Drs. Cindy Miner, Rita Liu and Mark Greene, and Dr. Ellen Unterwald from Temple University. Workshop attendees included approximately 75 early-career researchers.

On August 3 - 4, 2005, NIDA hosted its first **"Mentored K Awardees Meeting: Making the Transition to Independent Scientist"** in Bethesda, MD. The meeting offered a forum for successful K grantees from various areas within drug abuse to present their experiences, provide a grant-writing workshop for R applications, learn about the NIDA and NIH review process, meet with NIDA Program Officials as well as other K colleagues, and for showcasing research posters by current K awardees. The meeting was a success with over 70 awardees attendance as well as program staff representation from all Divisions and Centers of NIDA. The NIDA planning committee

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In Memoriam

included: Drs. Susan Weiss, Suman King, Allison Chausmer, and Aria Crump.

The National Institute on Drug Abuse (NIDA) organized a major program of events at this year's **American Psychological Association's (APA) Annual Meeting** in Washington, D.C. August 18-21, 2005. A number of NIDA staff were involved in organizing and/or presenting on a wide range of session topics such as, "Behavior Genetics of Drug Abuse in the Molecular Genetics Era," "Adolescent Brain Development - What Does It have to do with Cognitive Processes?," "Drugs, African Americans, HIV, and Criminalization: Breaking the Cycle," and the "Neurobiological Aspects of Drug Addiction: Implications for Treatment." In addition, NIDA Director, Dr. Nora Volkow, presented in an invited symposium on "Are Alcohol and Drug Dependence Developmental Disorders?" NIDA also sponsored an Early Career Investigator Poster Session with APA's Divisions 28 and 50 and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as part of the two Divisions' Social Hour. NIDA sponsored 54 poster participants, giving them an opportunity to present their research to clinicians and researchers who attended this session. A highlight of this event was the presentation of APA's Presidential Citation Award to Dr. Volkow to recognize her contributions in support of psychological and behavioral science.

On June 17, 2005, just prior to the CPDD meeting in Orlando, NIDA DPMCDA and DBNBR held a consultants meeting entitled **Review and Evaluation of NIDA Targets for Potential NIH Roadmap Library Screening Efforts**. A series of 30 minute presentations were given by NIDA-funded researchers whose findings suggest specific targets for potential library screening efforts within the NIH Roadmap-supported Molecular Libraries High Throughput Screening Centers. The potential targets under discussion ranged from traditional receptors (such as the D-1 dopamine receptor) that are highly validated as targets for medications discovery to less traditional targets (such as G protein-coupled receptor kinases) that may yield useful research tools. A group of five consultants with pharmaceutical and biotechnology company experience in target identification/validation and high-throughput screening assay development participated in the meeting. They are in the process of providing written recommendations to NIDA regarding the perceived merits and readiness of each potential target for high-throughput screening and additional target validation and/or assay development efforts that may be desirable. The consultant recommendations will help NIDA to prepare NIDA-relevant targets for incorporation into the NIH Roadmap library screening effort. The meeting organizers were Dr. Dr. David McCann, DPMCDA, Dr. Jane B. Acri, DPMCDA, Dr. Frank Vocci, DPMCDA, Dr. David Shurtleff, DBNBR, Dr. Paul Schnur, DBNBR and Dr. Christine Colvis, DBNBR.

On May 4-5, 2005, at the Embassy Suites Hotel, Chevy Chase, MD. Drs. Christine Colvis and Joni Rutter, DBNBR, convened a meeting of experts to discuss "Epigenetics of Drug Addiction."

On June 23, 2005, the Prevention Research Branch, DESPR, hosted a briefing by Drs. David Hawkins, Richard Catalano, and Michael Arthur for the co-funding agencies of the Science-based Prevention: Testing Communities that Care. Representatives from NCI, NIMH, NICHD, CSAP and SAMHSA were in attendance.

NIDA's National Hispanic Science Network Summer Research Training Institute was held in June 2005 at the University of Houston, Houston TX. A number of NIDA staff gave presentations on a variety of topics.

NIDA's Special Populations Office supported the Health Disparities grantees meeting on July 20-21, 2005 in Rockville, Maryland.

NIDA's Special Populations Office convened a meeting of the African American Researchers and Scholars Work Group on July 19, 2005 at the Marriott Pooks Hill in Bethesda, Maryland. Workgroup members continued to work on development of the objectives previously outlined in their strategic plan. Members received an update on activities within the Special Populations Office from Dr. Lula Beatty, Ph.D. Work group members also provided updates on their current research and activities.

A workshop entitled **Telling Your Story: The Art of Professional Authorship** was held on June 5, 2005, in Miami, FL, preceding the NIDA Blending Meeting. This was a 3 1/2 hour workshop for clinicians and researchers to receive "authorship coaching" from CTN presenters who spoke about successful strategies for CTP/Researcher collaboration in the authorship of CTN findings.

CTN National Steering Committee (SC) Meetings were held June 8-10, 2005 in Miami, Florida. Dr. Nora Volkow, NIDA Director, outlined goals for the CTN over the next five years, identified steps the CTN might take to meet increasing resource challenges, and identified additional opportunities for the CTN. The SC discussed a

modified governance structure for the CTN and the status of ongoing efforts. Representatives from community treatment providers from all 17 Nodes attended.

NIDA's Translationally Oriented Approaches and Devices (TOADS) Workgroup co-sponsored **The Critical Issues In E-Health Conference** in Bethesda, MD, June 9-10, 2005.

NIDA co-sponsored the **First Annual Interdisciplinary Conference on Clinical Supervision** June 16-18, 2005 in Buffalo, NY.

Dr. Timothy P. Condon, Deputy Director, NIDA, gave a plenary presentation entitled "Addiction as a Brain Disease: New Implications for Research and Practice" and presented a workshop on "Methamphetamine: The Science of Addiction," at the 39th Annual Wisconsin Association on Alcohol and Other Drug Abuse (WAAODA) conference, on May 9, 2005 in Madison, Wisconsin.

Dr. Timothy P. Condon was the plenary speaker on "Addiction as a Brain Disease and the Implications for Treatment and HIV/AIDS," at the 14th Annual Canadian Conference on HIV/AIDS Research (CAHR) on May 14, 2005 in Vancouver, British Columbia.

Dr. Timothy P. Condon presented the keynote address entitled, "Advances in Drug Abuse and Addiction Research: Implications for Prevention," at the 4th Annual Substance Abuse Prevention Regional Conference on May 23, 2005 in Ft. Myers, Florida.

Dr. Timothy P. Condon presented an "Update on the Blending Initiative: The Partnership Between the National Institute on Drug Abuse (NIDA) and The Substance Abuse and Mental Health Services Administration (SAMHSA)," at the Forging Federal-State Partnerships to Enhance Service Quality on June 5, 2005 in Miami Beach, Florida.

Dr. Timothy P. Condon presented an "Update on the Blending Initiative," at the Clinical Trials Network (CTN) External Affairs Coordinating Committee on June 8, 2005 in Miami, Florida.

Dr. Timothy P. Condon welcomed participants and presented "The National Institute on Drug Abuse (NIDA) Institute Update," at the Community Epidemiology Work Group Meeting on June 14, 2005 in Denver, Colorado.

Dr. Timothy P. Condon presented "Blending Science and Services: The Work of the National Institute on Drug Abuse (NIDA) and Substance Abuse and Mental Health Services Administration (SAMHSA)" at the Center for Substance Abuse Treatment (CSAT) Satellite session and participated in the 2005 NIDA International Forum, "Linking Drug Abuse and HIV/AIDS Research" at the Sixty-Seventh Scientific Meeting of the College on Problems of Drug Dependence (CPDD) on June 18, 2005 in Orlando, Florida.

Dr. Timothy P. Condon supported the NIDA Director in organizing and convening the second meeting of the Medications Development Work Group on July 26-27, 2005, in North Bethesda, Maryland. The purpose of this Work Group (composed of members from the National Advisory Council on Drug Abuse and distinguished leaders from the drug abuse and addiction fields) was to help NIDA's medications development program engage in creative visioning for the future with a focus on preclinical grants.

Dr. Timothy P. Condon presented the closing keynote address - "Addiction as a Brain Disease: Blending Research and Practice to Enhance Prevention and Treatment in Your Community" at the Arizona Summer Institute: Life in the Community, Preventing and Treating Substance Use through Evidence-Based Practices on July 29, 2005 in Sedona, Arizona.

Dr. Timothy P. Condon presented "Methamphetamine: The Science of Addiction" at the National Conference of State Legislators (NCSL) on methamphetamine on August 18, 2005 in Seattle, Washington.

Dr. Cindy Miner, Deputy Director, OSPC, presented the Keynote Address - "Addiction as a Brain Disease: Implications for Treatment" at the Chief Resident Immersion Training Program (CRIT) on May 19, 2005 in Cape Cod Massachusetts.

Dr. Cindy Miner participated in a session entitled "Workers Compensation - Rising Medical Costs and Reinsurance" at the Reinsurance Association of America's 2005 Current Issues Forum on May 24, 2005 in Philadelphia, PA.

Dr. Cindy Miner participated in a Grantwriting Workshop at the 67th Annual College on Problems of Drug Dependence on June 21, 2005 in Orlando, Florida.

Dr. Cindy Miner presented "Addiction as a Brain Disease: Blending Research and Practice at the NAADAC/TAPP 2005 Annual Conference in Corpus Christi, Texas on July 7, 2005.

Dr. Cindy Miner participated in a workshop entitled "NIDA Update and Grantwriting Workshop for Young Investigators" at the International Narcotics Research Conference, July 13, 2005 in Annapolis, Maryland.

Dr. Suman King, OSPC, presented at the Tenth Annual Research Colloquium for Junior Investigators at Emory University School of Medicine on May 22, 2005 in Atlanta, GA. She presented information about research training and funding opportunities available at NIDA.

Dr. Suman King hosted the NIDA Tutorials Workshop at the 2005 College on Problems of Drug Dependence Conference (CPDD) on June 18, 2005. Approximately 30 pre-doctoral fellows received NIDA Directors' Travel Awards to attend this event that showcased cutting-edge areas within the drug abuse field presented by four current NIDA T32 Directors.

Dr. Suman King coordinated the NIDA Training Mixer at the 2005 College on Problems of Drug Dependence Conference (CPDD) on June 20, 2005 in Orlando, Florida. Seven NIDA T32s co-sponsored this successful networking event for trainees to meet with each other and T32 Program Directors.

Dr. Donald R. Vereen, Jr., Special Assistant to the Director, NIDA, gave the keynote address at the 1st Annual Dug Conference at the McMillen Center at the Torrance Memorial Medical Center on May 17, 2005 in Torrance, CA.

Dr. Donald R. Vereen, Jr. presented in a panel to the Society for Academic Emergency Medicine (SAEM) on May 24, 2005 in New York City.

Dr. Donald R. Vereen, Jr. was the morning session plenary presenter for the Maryland State Attorney Training Day at the Maryland Public Defenders Conference on June 3, 2005 in Ocean City, MD.

Dr. Donald R. Vereen, Jr. presented at the Summer Expert Panel Meeting on Adolescent Trauma and Substance Abuse, organized by the National Child Traumatic Stress Network, which is funded by SAMHSA on June 20-21, 2005 in Boston, MA.

Dr. Donald R. Vereen, Jr. presented at the National Youth Leadership Forum held at Georgetown University on July 19, 2005 in Washington, DC.

Dr. Donald R. Vereen, Jr. presented updates on drug abuse research to the Pediatrics, Psychiatry, and Public Health Sections of the National Medical Association at the Annual Convention and Scientific Assembly July 23-26, 2005 in New York City.

Dr. Donald R. Vereen, Jr. presented on a panel entitled, "African Americans, Drugs, HIV, and Criminalization: Research, Training and Service Needs" with NIDA colleagues Dr. Lula Beatty and Dr. Dionne Jones at the Annual Convention of the Association of Black Psychologists on August 11, 2005 in Miami, FL.

Dr. Donald R. Vereen, Jr. was a plenary presenter at the annual meeting of the Department of Education's Safe and Drug Free Schools Program on August 16, 2005 in Washington, DC.

Dr. Donald R. Vereen, Jr. was the keynote presenter at the annual meeting of the Louisiana Association of State Substance Abuse Counselors on August 18, 2005 in Lafayette, LA.

Dr. Donald R. Vereen, Jr. was the opening plenary speaker and ran a workshop on drug abuse treatment and prevention research at the Merrill Scott Symposium, an annual event in the state of Washington for drug treatment and prevention professionals, on August 25, 2005 in Yakima, WA.

Dr. Donald R. Vereen, Jr. was the dinner speaker for the NIH funded Minority Trainee Research Forum on September 8, 2005 in Aventura, FL.

Dr. Donald R. Vereen, Jr. was the guest speaker at the 3rd Annual ASAM Region VII Symposium on September 10, 2005 in San Antonio, TX.

Dr. Lula Beatty, Chief Special Populations Office, NIDA, participated in the following

sessions at the American Psychological Convention, August 18 - 21, 2005 in Washington, D.C.: (1) Drugs, African Americans, HIV, (2) Criminalization: Breaking the Cycle, Drug Use in Communities of Color: Inside Perspectives and Needs, (3) Funding Opportunities at NIH, CDC and SAHMSA as a moderator and presenter.

Dr. Lula Beatty chaired and presented with Drs. Dionne Jones and Donald Vereen a symposium entitled African Americans, Drugs, HIV, and Criminalization: Research, Training, and Service Needs at the convention of the Association of Black Psychologists on August 11, 2005 in Miami, FL.

Dr. Lula Beatty presented a session entitled Addressing AAPI Concerns at the National Institute on Drug Abuse at NAPAFASA on May 12, 2005 in Los Angeles, CA.

Dr. Lula Beatty presented a session entitled Improving Health in the Black Population through Psychological Research: Responsibilities, Opportunities, and Challenges for Black Psychologists and Universities at Graduate School's Psychology Symposium on May 13, 2005 at Howard University in Washington, DC.

Dr. Lula Beatty presented a session entitled Unlocking the Doors to the National Institute on Drug Abuse: Keys to Success for HBCUs at the annual meeting of the National Sponsored Programs Administrators Alliance of Historically Black Colleges and Universities, Inc. on June 9, 2005 in Norfolk, VA.

Dr. Lula Beatty presented a session on funding opportunities at NIDA for the NIH Extramural Associates Program on June 30, 2005 in Bethesda, MD.

Dr. Lula Beatty hosted a roundtable at NIDA's mentored K meeting on August 4, 2005 in Bethesda, Maryland.

Ana Anders, Senior Advisor on Special Populations, SPO, participated in the "Blending" conference held June 7- 9, 2005 in Miami Beach, Florida.

Ana Anders participated in the CPDD conference on June 17-19, 2005, in Orlando, Florida.

Ana Anders presented information on NIDA's National Hispanic Science Network to the Hispanic Association of Colleges and Universities faculty at a meeting hosted by NIMH on July 20, 2005.

Dr. Betty Tai, Director, CCTN, updated participants on the CTN program at the State Director's meeting in Miami, June 5, 2005.

Paul Wakim, Ph.D., CCTN senior statistician, chaired an invited symposium on special design challenges in multi-site trials involving behavioral interventions, May 24, 2005, as part of the annual meeting of the Society for Clinical Trials in Portland, Oregon. Speakers included : Daniel Feaster, University of Miami School of Medicine; Paula Schnurr, VA National Center for PTSD and Dartmouth Medical School; Rickey Carter, Medical University of South Carolina; and Ellen Hodnett, University of Toronto Faculty of Nursing.

Janet Levy, Ph.D. and Paul Wakim, Ph.D., CCTN, presented a poster, titled: "The selection of population-average versus subject-specific models for analyzing longitudinal data from clinical trials of treatments for drug addiction" at the Society for Clinical Trials in Portland, Oregon, May 2005.

On June 18, 2005, Dr. David Shurtleff presented "Basic Research in HIV/AIDS and Drug Abuse" at NIDA's International Forum in Orlando, FL.

On June 20, 2005 at the College on Drug Dependence meeting in Orlando, FL. Dr. Christine Colvis chaired and organized a symposium entitled, "Proteomics and Its Application to Drug Abuse Research".

On June 20, 2005 at the College on Drug Dependence meeting in Orlando, FL, Dr. Jonathan D. Pollock, chaired and organized, the symposium, entitled: "Using Molecular Genetics to Understand Addiction".

On June 22, 2005 at the College on Drug Dependence meeting in Orlando, FL, Drs. Rutter and Shurtleff chaired and organized the symposium entitled "Pharmacogenetics and Drug Abuse." Dr. Rutter also served as the symposium discussant.

On June 21, 2005 at the College on Drug Dependence meeting in Orlando, FL Dr. David Shurtleff participated in the NIDA Grant-writing workshop and presented on "Defining the Role of NIDA Program Staff and Navigating the Research Funding Process".

In July of 2005 Dr. Jonathan Pollock presented Molecular Genetics of Addiction at the INRC Meeting in Annapolis, MD.

On August 10, 2005, Dr. Jonathan D. Pollock spoke about the funding process in the "Cellular Biology of Addiction" course, CSHL, Cold Spring Harbor Laboratory.

Dr. Jerry Frankenheim, FNRB, DBNBR, presented the seminar "Inhalant Abuse," Science and Technology, Gerber Adult Seminars, Jewish Community Center, Rockville MD in April 2005.

Dr. Jerry Frankenheim, DBNBR, presented the seminar "Methamphetamine Effects," 2005 National Conference, U.S. Department of Education Office of Safe and Drug-Free Schools, Washington DC in August 2005.

Dr. Rao S. Rapaka, DBNBR, organized a Lipidomics symposium at the 2005 National Biotechnology Conference (NBC) of the American Association of Pharmaceutical Scientists (AAPS), June 2005, San Francisco. This symposium was selected as a HOT TOPIC for this meeting. Dr. Rapaka served as the Chair. The proceedings of this symposium will be published.

Dr. Rao S. Rapaka, along with Dr. Allyn Howlett, presented a talk on grant writing and funding mechanisms for young scientists at the International Cannabinoid Research Society's Annual meeting at Clearwater, FL.

Dr. Cora Lee Wetherington, DBNBR and NIDA's Women & Gender Research Coordinator, gave a presentation, Show Us the Money: Opportunities for Women's Health at NIDA, at the conference, "Show Us the Money: Unlocking Doors to Funding for Women's Health," Virginia Commonwealth University, May 16, 2005, Richmond, VA.

Dr. Joseph Frascella, Director, DCNDBT, together with Dr. Michael Sesma of NIMH conducted a workshop on the NIH Grant-Writing Process at the National Hispanic Science Network Summer Research Training Institute on Hispanic Drug Abuse in Houston, Texas, June 10, 2005.

Dr. Joseph Frascella co-chaired with Dr. Nora Volkow an all-day satellite symposium to the annual meeting of the College on Problems of Drug Dependence entitled "Food, Drugs, Obesity and Addiction: Common Neurobiologic Processes?" The meeting was held in Orlando, Florida on June 18, 2005.

Dr. Nicolette Borek, DCNDBT, attended the Pediatric Academic Society's 2005 Annual meeting, May 14-17th in Washington, DC.

Dr. Vincent Smeriglio, DCNDBT, collaborated with the Center for Substance Abuse Treatment (CSAT), SAMHSA, in the planning of a session on child and adolescent research for the CSAT Women and Children's Treatment meeting held August 1-3, 2005 in Washington, DC. He also made a presentation on NIDA research. Drs. Nicolette Borek and Melissa Racioppo also participated in the meeting.

Dr. Laurence Stanford, DCNDBT, co-organized and co-chaired a symposium entitled New Advance in Pediatric Neuroimaging at the 11th Annual Meeting of the Organization for Human Brain Mapping, June 13-16, 2005 in Toronto, Canada.

Dr. Cecelia McNamara, DCNDBT, chaired a panel on the Critical Issues In E-Health Conference in Bethesda MD, June 10, 2005 entitled Health Behaviors in eHealth Research-The Good, The Bad, and Their Methodological Challenges (The Ugly).

On June 17 & 18, 2005 Dr. Cecelia McNamara presented several talks on NIH funding opportunities for research on clinical supervision at the First Annual Interdisciplinary Conference on Clinical Supervision in Buffalo New York.

In August 2005, Judy Cole, M.A., and Dr. Melissa W. Racioppo, DCNDBT, presented a workshop on deciphering the NIH Roadmap and a poster on marriage and family treatments for substance abuse at the annual meeting of the American Psychological Association in Washington, D.C.

Dr. Ro Nemeth-Coslett, DCNDBT, represented NIDA at the NIH SBIR Conference, Natcher Auditorium, July 29, 2005.

Dr. Ro Nemeth-Coslett was a co-organizer for NIDA's SBIR Showcase, NIDA NSC, August 25, 2005.

Dr. Ro Nemeth-Coslett presented at a mini-symposium on Substance Abuse Treatment with Game Technologies at the Games For Health Conference, September

22, 2005 in Baltimore, MD.

Dr. Steven Grant, DCNDBT, co-chaired a breakout group on Neuroimaging and participated in the Program Discussion at the NIDA Mentored K-Awardee Training Meeting, held on August 3-4, 2005 in Bethesda, MD.

Dr. Steven Grant represented NIDA at the annual meeting of the Society for Neuroeconomics on September 15-18, 2005 in Charleston, NC.

Dr. Steven Grant was an organizer and chair of the NIDA workshop on "Cognitive Approaches to Drug Addiction" September 11-12, 2005 in Bethesda, MD.

Dr. Melissa W. Racioppo, DCNDBT, collaborated with Program staff from the Division of Epidemiology, Services, and Prevention Research, in organizing several symposia and a grants workshop at the Joint Meeting on Adolescent Treatment Effectiveness. The NIDA-, CSAT-, and SASATE-sponsored meeting was held in Washington, D.C. on March 21 - 23, 2005. Symposia on the use of contingency management in the treatment of adolescent drug abuse, and on the treatment of adolescent smoking were presented, with several NIDA-funded adolescent researchers contributing their perspectives on these problems.

Dr. Racioppo presented a talk on treatments for drug and alcohol abuse at the NIMH-sponsored Outreach Partnership Program Meeting in Omaha, Nebraska, April 1, 2005. The meeting brought together "outreach partners" from across the country whose role is to advocate for treatment programs with community, state, and federal partners who have a stake in mental health service delivery.

Dr. Racioppo participated in an orientation meeting of newly-recruited trainees for the continuation of an institutional K12 awarded to the American Academy for Child and Adolescent Psychiatry in Miami, Florida on June 14-17, 2005.

Dr. Lisa Onken hosted an OBSSR-sponsored symposium featuring Dr. Mark Bouton on May 16, 2005. Dr. Bouton spoke about "Learning and Extinction: The Place of Basic Behavioral Science in a Translational Research Agenda."

Dr. Frank Vocci, Director, DPMCDA, was a discussant at the Marijuana Therapy symposium at the CPDD meeting in Orlando, June 23, 2005. Dr. Robert Stevens and Dr. Alan Budney spoke about the behavioral treatments for marijuana dependence. Dr. Margaret Haney spoke about developing pharmacotherapies and Dr. Alan Green spoke about pharmacotherapies in marijuana-abusing schizophrenic patients that may alter both the psychosis and marijuana abuse.

Dr. Frank Vocci presented on Opiate Abuse Patterns in the United States: A Changing Scene at the INRC meeting in Annapolis, MD on July 12, 2005.

Dr. Ivan Montoya, DPMCDA, co-chaired the symposium entitled Smoking Cessation and Psychiatric Comorbidity: Treatment Implications, during CPDD in Orlando, on Sunday June 19th, 2005. The sessions covered: 1) Biological determinants of nicotine dependence in severe mental disorders: Cognitive deficits and genetic polymorphisms as targets for therapeutics development. 2) Treatment of nicotine dependence in individuals with schizophrenia, 3) Treatment of comorbid ADHD and nicotine dependence, and 4) Current research and future directions for treating nicotine dependence among illicit drug users. The speakers were Tony P. George (Yale University), Douglas M. Ziedonis (Robert Wood Johnson Medical School), Himanshu P. Upadhyaya (Medical University of South Carolina), and Kimber P. Richter (University of Kansas Medical Center). The discussant was Dr. Lirio S. Covey from Columbia University and the New York State Psychiatric Institute.

Dr. Ivan Montoya was the discussant of a workshop entitled Data and Safety Monitoring for Clinical Trials in Health Services Research, during CPDD in Orlando. The workshop was organized by NIDA-DESPR and co-chaired by Wilson M. Compton (NIDA) and Michael L. Dennis (Chestnut Health Systems). The topics discussed included: 1) NIH and NIDA policies regarding Data Safety Monitoring Boards for Multi-site and phase III clinical trails (Redonna K. Chandler, NIDA), 2) The Practical and Effective use of DSMB in Health Services Research (Michael Dennis), 3) HIV community interventions for drug-involved women: Risks of partner abuse, self-empowerment and safety planning (Nabila El-Bassel, Columbia University), 4) DSMB Issues in Conducting Research in Criminal Justice Settings (Gary Field) and 5) Medical Adverse Events and DSMBs (Robert P. Schwartz, Friends Research Institute).

Dr. Ivan Montoya presented a poster during CPDD in Orlando entitled Exploratory Evaluation of the Effect of Buprenorphine on Marijuana Use. The co-authors were

Jennifer R. Schroeder (NIDA), Carlo Contoreggi (NIDA), Kenzie Preston (NIDA), Rolley E. Johnson (Reckitt Benckiser Pharmaceuticals), Paul J. Fudala (University of Pennsylvania).

Dr. Wilson Compton, Director, DESPR, presented three papers at the annual meeting of the American Psychiatric Association, May 21-26, 2005, Atlanta, Georgia on: 1) Prevention of secondary disorders, 2) An update on preparations for revisions to the DSM system of diagnosis, and 3) Prescription drug abuse. Dr. Compton co-chaired the symposium on Prescription Drug Abuse.

Dr. Wilson Compton presented at the State of Missouri Spring Training Institute, May 19, 2005.

Dr. Wilson Compton presented at the joint NIDA-NASADAD meeting, Miami, FL, June 5, 2005.

Dr. Wilson Compton co-chaired a workshop on data safety monitoring boards for services and intervention research at the annual meeting of the College on Problems of Drug Dependence, June 21, 2005, Orlando, Florida.

Dr. Wilson Compton participated in a round-table discussion at the annual meeting of Research Society on Alcoholism, Santa Barbara, California, June 28, 2005.

Dr. Kevin Conway, ERB, DESPR, chaired a symposium entitled Translational Research on Drug Abuse: Linkages between Genetics and Prevention at the Society for Prevention Research, May 26, 2005.

Dr. Kevin Conway co-chaired a symposium entitled Behavior Genetics of Drug Abuse in the Molecular Genetics Era at the American Psychological Association, August 18, 2005.

Dr. Naimah Weinberg, ERB, DESPR, served as discussant at a symposium entitled Longitudinal Relationships between Psychopathology and Substance Use Disorders, at the meeting of the International Society for Research in Child and Adolescent Psychopathology, in June, 2005, in New York City.

Dr. Naimah Weinberg organized and chaired a symposium on Using Mental Health Intervention Outcomes to Inform Substance Abuse Etiology and Prevention, at the annual meeting of the Society of Prevention Research in Washington, DC, in May 2005.

Drs. Wilson Compton and Elizabeth Robertson, DESPR, presented a workshop at the National Prevention Network meeting in New York City August 30, 2005. The topic of the workshop was recent findings in epidemiologic, etiologic and prevention research sponsored by NIDA.

Dr. Elizabeth Robertson made a presentation titled: The Role of Attitudes and Beliefs in Predicting Drug Use Behaviors at ONDCP on July 13, 2005.

Dr Elizabeth Robertson participated in the Strategic Prevention Framework - State Incentive Grants Technical Assistance workshop on May 27 and 28, 2005 in Boston, MA.

On May 26, 2005, Dr. Elizabeth Robertson was the discussant for a symposium at the Society for Prevention Research titled Issues in a Population-Level Approach to Strengthening Parenting. Presenters were Drs. Denis Embry, Matt Sanders and Ron Prinz. Each presenter discussed their experiences implementing the Triple-P program in different environmental contexts.

Dr. Aria Crump, DESPR, co-chaired a panel for Junior Investigators entitled "NIH New Investigator's Workshop" at the 13th Annual Meeting of the Society for Prevention Research in Washington, DC on May 26, 2005.

Dr. Eve Reider, DESPR, moderated a session at the 2005 National HIV Prevention Conference on June 14, 2005, in Atlanta, Georgia. The title of the session was "Integrating Substance Abuse and HIV Prevention." Presenters included: Sheila Harmison (SAMHSA), Mary Allen (Maryland AIDS Administration), and Ron Stall (University of Pittsburgh).

Drs. Eve Reider and Elizabeth Robertson chaired a Scientific Dialogue/Roundtable Discussion at the Society for Prevention Research Conference in Washington D.C. on May 25, 2005. The title of the Roundtable Discussion was "Foster Care and Substance Abuse: Understanding and Ending the Cycle." The panel of discussants included: Richard Barth (University of North Carolina, Chapel Hill), Patricia Chamberlain

(Oregon Social Learning Center), John Landsverk (San Diego State University), John Reid (Oregon Social Learning Center), Steve Hornberger, and Mary Bruce Webb (Administration for Children and Families, DHHS).

Drs. Eve Reider and Elizabeth Robertson chaired a Scientific Dialogue/Roundtable Discussion at the Society for Prevention Research Conference in Washington D.C. on May 25, 2005. The title of the Roundtable Discussion was "Youth with Multiple Problem Behaviors: What Have We Learned about Them, How Successful Have We Been in Intervening with Them, and Where to Go from Here?" The panel of discussants included: Anthony Biglan (Oregon Research Institute), Deborah Capaldi (Oregon Social Learning Center), Thomas Dishion (University of Oregon), David Olds (University of Colorado), and Mary Jane Rotheram Borus (University of California Los Angeles).

Dr. Elizabeth Ginexi, PRB, DESPR, chaired a Paper Symposium at the annual meeting for the Society for Prevention Research in Washington, DC on May 25, 2005. The title of her Symposium was "The Developmental Plasticity of Neural Systems: Implications for Prevention Science." Ronald Dahl, M.D. of University of Pittsburgh, Philip A. Fisher, Ph.D. of the Oregon Social Learning Center, and Diana H. Fishbein, Ph.D. of RTI International, presented papers. Daniel Shaw, Ph.D. of University of Pittsburgh, led discussion.

Dr. Elizabeth Ginexi co-authored a paper presentation with Drs. Booil Jo of Stanford University and George W. Howe, of the George Washington University titled "Randomized Trials with Non-participation and Non-response: Model Choices in Intention-to-treat Analysis" at the annual meeting for the Society for Prevention Research in Washington, DC on May 25, 2005. The paper was presented as part of a Symposium on Advances in Latent Variable Modeling chaired by Daniel Feaster of University of Miami, Bengt Muthen of University of Southern Florida and Karen Nylund of University of California Los Angeles.

Drs. Elizabeth Ginexi, DESPR and Minda Lynch, DBNBR, along with Drs. Michael Bardo, University of Kentucky and Steve Sussman, University of Southern California, organized a satellite workshop at the CPDD meeting in June 2005, Orlando, FL. This interactive full-day workshop titled "Translating Basic Research from Neural, Behavioral and Social Sciences to Prevention: Challenges and Opportunities," was co-sponsored by NIDA and the Center for Drug Abuse Research Translation (CDART) at the University of Kentucky. Expert panel members from both basic and prevention science presented examples of translation research in action, and discussed strategies, challenges and barriers to the translational process in prevention with a focus on cross-disciplinary models, tools, and technologies. Travel awards were offered to Early Career investigators to attend the meeting and present posters on a variety of basic science and prevention research topics.

Dr. William S. Cartwright, DESPR, participated in the Conference Planning Meeting on Alcohol: Impact on the Health of Women, Children, and Families, June 19-20, 2005 at the Centers for Disease Control, Atlanta, GA.

Dr. Beverly Pringle, DESPR, participated in several symposia at the Annual Meeting of the American Psychological Association, Washington, DC, August 18-21, 2005. Dr. Pringle chaired a symposium entitled Translational Research on Smoking Cessation: Types I and II; co-chaired a symposium entitled, The United States-Netherlands Binational Collaboration on Drug Abuse; and served as discussant on a symposium entitled Rural Substance Abuse Research: New Methods, New Findings, New Funding.

Dr. Beverly Pringle, DESPR, presented on a panel entitled "Is the Cup Half Full or Half Empty?" Tobacco Control and Systems Change Research Funding at the capstone meeting of Addressing Tobacco in Managed Care, a program of the Robert Wood Johnson Foundation, Chicago, IL, May 3, 2005.

Dr. Redonna Chandler, DESPR, presented on a panel entitled, Data Safety Monitoring for Clinical Trials in Health Services Research, at the annual meeting of The College On Problems of Drug Dependence, Orlando, FL, June 18-23, 2005.

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Media and Education Activities

Press Releases

June 22, 2005 - **Adult Antisocial Syndromes Common among Substance Abusers.**
Data from a recent epidemiologic survey of more than 43,000 U.S. adults show that antisocial syndromes - marked by little concern for the rights of others and violations of age-appropriate societal rules - are more common among people with substance abuse disorders than those without these disorders. The study by researchers from the National Institute on Drug Abuse (NIDA) and National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institutes of Health, was published in the June 2005 issue of *The Journal of Clinical Psychiatry*.

June 2, 2005 - **NIDA NewsScan #36 - Special Blending Issue**
NIDA's June 2005 Blending Conference Brings Clinicians & Researchers Together in Florida
Drug Abuse and Depression Often Co-Occur
Mothers More Likely Than Fathers to Allow Family Interventions
Nicotine Patch Therapy Effective for Adolescents Trying to Quit Smoking
Tobacco Smoking Linked to Cognitive Impairments in Adolescents
Follow-up Care Shows Promise for Alcohol, Cocaine Addiction
Medication in Combination with Behavioral Therapy May Reduce Cocaine Abuse
Childhood Sexual Abuse, PTSD, Depression Increase High-Risk Sexual Behavior in Men
Patients Who Attend Psychotherapy Sessions Have Better Success with Buprenorphine Treatment

Articles of Interest

June 20, 2005, Washington Post-"What's the Lure of the Edge? The Answer is all in Their Heads"-Interview with Nora D. Volkow M.D.

July 23, 2005, The New Scientist-"Demon Healer, Doctors are Doling out Amphetamines to Children as Well as Adults"-Interview with Nora D. Volkow M.D.

August 2005, Ladies Home Journal-"The Deadliest Drug You've Never Heard Of"-Interview with Joseph Frascella, Ph. D.

Dr. Frank Vocci, Director, DPMCDA, was interviewed by Malini Guha on June 15, 2005, on the effect of an activator of G protein signaling 3 (AGS3) on heroin-seeking behavior in a rodent study (Yao et al., PNAS 102, p. 8746, 2005).

Dr. Frank Vocci was interviewed by Jennifer Holman on July 13, 2005, regarding the development of the nicotine vaccine.

Dr. Frank Vocci was interviewed by Amanda James on August 4, 2005, regarding the current prescribing of buprenorphine.

An interview with Dr. David Gorelick, IRP, on "Smoking and Dieting," appears in the August, 2005 issue of Allure magazine, p. 124. Dr. Gorelick was interviewed about his recently published research study "Calorie Restriction Increases Cigarette Use In Adult Smokers" (Cheskin, L.J., Hess, J.M., Henningfield, J., and Gorelick, D.A. Psychopharmacology 179, pp. 430-436, 2005).

Educational Activities

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In Memoriam

New SEDAPA Web Site. NIDA has added a new component on the Science Education Drug Abuse Partnership (SEDAPA) program to its web site. The SEDAPA program funds innovative grants for improving science education and knowledge among school children, the general public, and others. This site provides information on the program as well as a brief synopsis of some of the grants that have been funded since the program's inception in 1992. The site can be accessed at http://www.nida.nih.gov/SEDAPA/index.html.

Anabolic Steroids. Recent reports of steroid abuse by professional athletes, many of whom are role models to young people, have increased the need to raise awareness on the dangers that steroids cause. In response to this damaging trend NIDA has re-issued the "Game Plan" Public Service Announcement campaign. "Game Plan" seeks to encourage young men and women to work with what nature has provided and not "cheat" by using steroids and thereby exposing themselves to the negative side-effects associated with these drugs. The announcements, available in English and Spanish, have been distributed to TV stations and other information dissemination outlets nationwide.

Heads Up: Real News About Drugs and Your Body. Through a contract and partnership with SCHOLASTIC INC, in October NIDA begins Year 4 (2005/6 school year) of an aggressive outreach to middle school and early high school students and teachers with the Heads Up article inserts for use in the classroom. Magazines such as Junior Scholastic, Science World, and Up Front (a collaboration with The New York Times) have carried these articles, written in collaboration with NIDA program staff and researchers, since 2003. Each Heads Up insert is distributed to nearly 2 million students nationwide, with a reach of nearly 7 million-and this occurs 4-5 times per school year.

NIDA Free Post Card Program. From May 15 through June 15 a mix of our latest HIV/AIDS and methamphetamine awareness post cards were distributed to the general public in free venues nationwide. More than 677,000 cards went to 1,840 venues in the 12 cities with the highest recent HIV increases: Washington DC, Atlanta, Miami, Los Angeles, San Francisco, New York City, Chicago, Philadelphia, Baltimore, Houston, Charlotte, and Newark. Most distribution sites included clubs, restaurants, coffee shops, and book shops. In the smaller cities of Baltimore, Houston, Charlotte, and Newark, they were also distributed in health clubs and beauty salons.

Brain Power! Science Ed for Grade School Students. The Brain Power! series of science education products for grade schoolers was completed with production of the final module, a video designed to introduce 4-5th grade students to the brain and the effects of abused drugs on the brain. This video is summarized in our Publications section.

NIDA's Brain Power Materials Win a Gold National Health Information Award Brain Power! The NIDA Junior Scientists Program for kindergarten and first grade has been selected as a winner in the 2005 National Health Information Awards honoring the Nation's best consumer health information programs and materials. The materials were evaluated for health information content, creativity, and overall excellence. NIDA's materials received a gold award, the highest award possible. The program is organized by the Health Information Resource Center, a national professional clearinghouse for consumer health information.

Conferences/Exhibits

National Association of State Alcohol and Drug Abuse Directors/National Prevention Network Annual Meeting -- June 2-5, 2005

NIDA Blending Clinical Practice and Research -- June 6-7, 2005

National Association of County and City Health Officials and Association of State and Territorial Health Officials Joint Meeting -- July 12-16, 2005

Association of Black Psychologists -- August 9-14, 2005

American Psychological Association -- August 18-21, 2005

Latino Behavioral Health Institute 11th Annual Meeting -- September 20-22, 2005

American Academy of Pediatrics National Conference and Exhibition -- October 8-11, 2005

Employee Assistance Professionals Association Annual Conference -- October 15-17,

2005

American Academy of Child and Adolescent Psychiatry -- October 18-23, 2005

American School Health Association Annual Conference -- October 19-23, 2005

Bridging Science & Culture to Improve Drug Abuse Research in Minority Communities -- October 24-26, 2005

American Public Health Association Annual Meeting and Exposition -- November 5-9, 2005

National Association for the Education of Young Children -- December 7-10, 2005

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Planned Meetings

NIDA will hold a **Frontiers in Addiction Meeting** in conjunction with the Society for Neuroscience Meeting, November 11, 2005 in Washington, D.C. The meeting will include sessions on: Addiction and Obesity-Brain System Commonalities; Keynote Speech: Jacob P. Waletzky Memorial Award Presentation; Neurobiological Basis for Co-Occurring Substance Abuse and Mental Illness; mGluR: A Substrate in the Neurobiology of Addiction; Reconsolidation of Memory: A New Approach to Treat Drug Addiction?; and Adolescent Drug Abuse: Brain Development, Cognition, and Vulnerability. In addition, there will be a poster session that will include young and international investigators.

Drs. Eve Reider and Elizabeth Robertson, DESPR, have planned a meeting titled **Bidirectional Influences of Drug Abuse and Child Abuse and Neglect**. This meeting is sponsored by NIDA's Office of Science Policy and Communication in conjunction with the Child Welfare League of America. It will be held October 27, 2005 at the Holiday Inn Select in Bethesda, Maryland.

Dr. Jag Khalsa, Dr. Jacques Normand, Director, Office on AIDS, Dr. Pat Needle, and the NIH OAR Staff will present an **Indo-US Workshop on AIDS and Drug Abuse**, New Delhi, India, October 27-30, 2005. NIDA/NIH supported researchers including Drs. Strathdee, Wanke, Flanigan and many others will exchange current research with the Indian counterparts, foster collaborations, and discuss ways to facilitate approval of research protocols by the respective approval authorities.

National CTN Steering Committee Meetings are planned for the following dates and locations: October 24-28, 2005, Bethesda, MD, and March 21-22, 2006, in Dallas, Texas.

A NIDA meeting entitled **The NIH Roadmap: Inviting Drug Abuse and Addiction Researchers to Contribute to the Clinical Research Enterprise** will be held preceding the CTN Steering Committee Meeting, October 24, 2005, in Bethesda, Maryland. The one-day symposium will provide clinical researchers with a better understanding of the NIH Roadmap and opportunities available under *Re-Engineering the Clinical Research Enterprise*.

The CTN Data and Safety Monitoring Board will meet November 16-18, 2005, in Bethesda, Maryland. The group will review the continuing progress of the active CTN's protocols.

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

Publications

NIDA Publications

Progress Report: NIDA-Spain Cooperation
Dr. M. Patricia Needle, former IP Senior Adviser, has published an article about collaborative drug abuse research supported by NIDA and the Spanish National Plan on Drugs (PNSD). The article appeared in the January 2005 issue of the Spanish-language journal, Trastornosadictivos. Dr. Needle summarizes the history of cooperation between NIDA and PNSD; describes NIDA-supported postdoctoral fellowships, research exchange programs for senior scientists, online resources, and funding mechanisms; and invites Spanish drug abuse researchers to join NIDA grantees in cooperative activities to advance scientific understanding of drug abuse and addiction.

Epidemiologic Trends on Drug Abuse - Community Epidemiology Work Group - Volume II - Meeting Proceedings January 2005
NIH Pub. No. 05-5281
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.

National Survey Results from the Monitoring the Future 2004, Volume I: Secondary Students
NIH Pub. No. 05-5727
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 2004, Volume II: College
Students and Adults Ages 19-40
NIH Pub. No. 05-5728
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.

Community Drug Alert Bulletin - Prescription Drugs
NIH Pub. No. 05-5580
This publication summarizes current information about the consequences that can result from the abuse of some prescription and over-the-counter (OTC) medications. Classes of drugs to be discussed include benzodiazepines, opiates, sedative/hypnotics, and stimulants. The medicinal value, as well as some of the potential health problems that can result from abuse of these drugs are addressed. Some data will be presented from what we currently know about who is abusing and how they are accessing these medications. There is information on what can be done to reduce prescription/OTC drug abuse, and how to diagnose and treat individuals who have become addicted to these drugs.

Research Report Series: Prescription Drugs (Rev.)
NIH Pub. 05-4881
Describes the dangers of prescription drug abuse and reviews recent research in this area. Offers approaches for patients and providers to help them avoid the misuse of prescription drugs. Reviews most commonly abused prescription drugs.

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Brain Power Video (Gr. 4-5)
NIH Pub. No: 05-4945A
Brain Power! Is designed to introduce 4-5th grade students to the brain and the effects of abused drugs on the brain. The final module in the Brain Power series explores how different regions of the brain work, how information travels to and from the brain, and techniques for studying brain function. In addition, it explores how various drugs, including nicotine, Ritalin, amphetamine, cocaine, alcohol, marijuana and inhalants affect the brain. This last module introduces students to addiction and the drug abuse problem in the U.S. Students have the opportunity to explore the impact of drug use on society, and to explore the difference between legal and illegal drugs.

NIDA Notes

NIDA Notes Volume 19 Issue No. 6
NCADI #NN0074
The Director's Column addresses health disparities in minority populations compared with the White population, and introduces NIDA's Health Disparities Initiative, which is a three-pronged approach to understanding and researching these differences. The Initiative will expand support of training and career development programs for minority scientists, focus the research agenda to help researchers reach underrepresented populations and study responses to drugs and the consequences of drug abuse in these populations, and disseminate research results to the widest possible audience.

The lead article highlights a pilot study on the use of topiramate to help cocaine-addicted outpatients remain abstinent from the drug. Currently used to treat seizure disorders, topiramate helped study participants stay off cocaine longer than control subjects; 60% of patients taking topiramate attained three or more weeks of continuous abstinence compared with 26% of those taking placebo. The researchers found that topiramate seems to change the brain's response to cocaine by indirectly influencing dopamine through two other neurotransmitter systems-GABA and glutamate. Additional studies are planned to further evaluate the efficacy of topiramate as a treatment for addiction.

Other research findings include:

Contrary to previous assumptions, NIDA-funded scientists have found that it takes very little experience with cocaine to establish environmental associations that become powerful cues for cocaine relapse. After exposure to a two-hour session of access to cocaine, rats continued seeking the drug when cued for up to a year after access had been extinguished. A similar experiment using sweetened condensed milk, a highly palatable food to rats, failed to produce similar long-term cravings.

A review of the 2000 and 2001 National Household Surveys on Drug Abuse revealed that adolescent inhalant abuse was more likely in the presence of specific behaviors, such as stealing, fighting, or carrying a handgun. Based on the traits the researchers identified, they concluded that adolescents with inhalant abuse or dependence disorders comprise a subgroup of highly troubled youths with multiple vulnerabilities. Girls were just as likely to abuse inhalants as boys, a finding that contradicts most conventional patterns of drug abuse.

A study of 182 adolescents for a year after substance abuse treatment showed that those with co-occurring externalizing disorders recovered more slowly than those without psychiatric disorders. The researchers concluded from the study that drug abuse treatment in adolescents must address these co-occurring disorders to increase the chances for success.

The Bulletin Board focuses on two researchers who received awards at the 2004 Society for Neuroscience conference. Dr. Antonello Bonci received the second annual Waletzky Memorial Award for Innovative research in Drug Abuse and Alcoholism for his work on the long-term changes in brain cells that underlie addictive behaviors. Dr. Rochelle Schwartz-Bloom received the annual Science Educator Award for her curriculum models that help high school students learn the biology and chemistry underlying drug addiction. The Tearoff presents results of the most recent Monitoring the Future survey.

NIDA Notes Volume 20, Issue No. 1
NCADI #NN0075
The Director's Column discusses NIDA's efforts to not only understand the effects of marijuana abuse at the formative stages of human development, but to develop

better treatments for marijuana abuse. The damaging effects of marijuana abuse fall most heavily on adolescents and young adults; half of all patients admitted to treatment for marijuana abuse are younger than 21. NIDA's research initiative will produce a fuller understanding of normative brain development and will illuminate the importance of family and social contexts in adolescence as well as the differing biological and environmental factors that precede marijuana use or nonuse. The Institute is also expanding efforts to develop medications that treat marijuana-associated disorders such as intoxication, delirium, psychosis, and anxiety.

The lead research story shows that cocaine-related environmental cues, which generate strong drug-seeking urges in people trying to recover from drug abuse, produce physiological stress responses in addicted men and women. Dr. Rajita Sinha and colleagues had cocaine-addicted patients listen to tapes recounting a personalized drug-related scenario, a stressful scenario, and a relaxing scenario. After undergoing baseline measures of stress responses-blood pressure, pulse, and stress hormones, patients listened to the various tapes and researchers measured their stress levels. Stressful and drug-related tapes not only increased levels of stress hormones, they also increased participants' subjective responses-craving and anxiety-compared with the relaxing tapes. These findings will help researchers identify treatment approaches for cocaine-addicted people.

Other research findings include:

Researchers report that high school girl athletes who participated in ATHENA, a NIDA-supported nutritional and behavioral guidance program, were less likely than non-participating peers to engage in substance abuse and other high-risk behaviors. In post-season surveys, girls on teams that participated in the peer-led ATHENA program reported significantly less use of diet pills, amphetamines, anabolic steroids, and muscle-building supplements during the season. They also reported being less likely to engage in risky behaviors such as riding in a car without using a seatbelt.

Researchers from two laboratories have conducted research on rats to determine the causes and symptoms of cocaine "abstinence syndrome," marked by low energy, irritability, restlessness, an inability to feel pleasure, and problems with concentration. By exposing rats to a clonidine challenge, Dr. Baumann discovered that cocaine desensitizes the adrenergic system. Dr. Spealman found that giving adrenergic blockers to cocaine-"abstinent" monkeys produced anxiety-related effects similar to abstinence syndrome. These findings will help researchers develop better medication to treat stimulant abuse and withdrawal.

First-graders who receive help learning to concentrate and control their behavior are less likely to begin smoking in middle-school years than children who receive no intervention. About a third of children who participated in one of two different interventions had begun smoking by age 13, compared with 47 percent of the control group.

The Bulletin Board highlights the Institute of Medicine's new publication: *New Treatments for Addiction: Behavioral, Ethical, Legal, and Social Questions*. NIDA funded the report, which identifies issues that must be considered in the development and application of active and passive immunotherapies and sustained-release medication to treat or prevent drug abuse and addiction. The Tearoff highlights the *Brain Power!* program, a Web-based curriculum for elementary-school children that fosters knowledge of the brain and scientific methods.

NIDA NOTES CD-ROM

This CD-ROM contains PDF files of the nine popular Collections of NIDA NOTES Articles, in addition to direct links to NIDA's Web site for current NIDA NOTES articles, NIDA publications, science summary reports, and information on drugs of abuse. The Collections include Articles That Address Research on Drug Abuse Prevention, Drug Abuse Treatment, Drugs and AIDS, Cocaine, Heroin, Marijuana, Methamphetamine, Nicotine, and Women and Gender Differences

A Collection of NIDA Notes Articles That Address Research on Nicotine - Revised 2005

This edition covers articles and research findings on nicotine originally published in NIDA NOTES from 1995 through 2004. Articles include topics such as smoking exposure in utero and the effects of early nicotine initiation.

A Collection of NIDA NOTES Articles That Address Research on Heroin - Revised 2005

This updated collection includes 18 articles about heroin research published in NIDA NOTES from 1998 to 2004. Article topics range from buprenorphine treatment to HIV

risk prevention programs for IV drug users.

During the months May - August 2005, seven editions of the CTN Bulletin Board were distributed. The Bulletin Board is an electronic report on the progress of the protocols, committees, and node activity in the CTN.

Other Publications

Beatty, L.A., Wetherington, C.L, Jones, D.J. and Roman, A.B. Substance Abuse in Girls and Women. In J. Worrell and C. D.Goodheart, Handbook of Girls' and Women's Psychological Health. Oxford University Press, 2005.

p>Lever, J.R., Zou, M-F., Parnas, M.L., Duval, R.A., Wirtz, S.E., Justice, J.B., Vaughan, R.A. and Newman, A.H. Radioiodinated Azide and Isothiocyanate Derivatives of Cocaine for Irreversible Labeling of Dopamine Transporters: Synthesis and Covalent Binding Studies. Bioconjugate Chem. 16, pp. 644-649, 2005.

Tanda, G., Ebbs, A., Newman, A.H. and Katz, J.L. Effects of 4-Cl-BZT on Mesostriatal, Mesocortical and Mesolimbic Dopamine Transmission: Comparison with Effects of Cocaine. J. Pharm. Exp. Ther. 313, pp. 613-620, 2005.

Gilbert, J., Newman, A.H., Gardner, E.L., Ashby, C.R., Heidbreder, C.A., Pak, A.C. and Xi, Z-X. Acute Administration of SB-277011A, NGB 2904 or BP 897 Inhibits Cue-induced Reinstatement of Drug-seeking Behavior in Rats: Role of Dopamine D3 Receptors. Synapse, 57, pp. 17-28, 2005.

Raje, S., Cornish, J., Newman, A.H., Cao, J., Katz, J.L. and Eddington, N.D. Pharmacodynamic Assessment of the Benztropine Analogues AHN 1-055 and AHN 2-005 Using Intracerebral Microdialysis to Evaluate Brain Dopamine Levels and Pharmacokinetic/Pharmocodynamic Modeling. Pharm. Res. 22, pp. 603-612, 2005.

Newman, A.H., Grundt, P. and Nader, M.A. Dopamine D3 Receptor Partial Agonists and Antagonists as Potential Drug Abuse Therapeutic Agents. J. Med. Chem. 11, pp. 3663-3679, 2005. Invited Perspective.

Li, S-M., Newman, A.H. and Katz, J.L. Place Conditioning and Locomotor Effects of N-Substituted, 4',4"-Difluorobenztropine Analogues in Rats. J. Pharmacol. Exp. Ther. 313, pp. 1223-1230, 2005.

Collins, G.T., Witkin, J.M., Newman, A.H., Svensson, K.A., Grundt, P., Cao, J., Woods, J.H. Yawning in Rats: A Dopamine D3 Receptor Mediated Behavior. J. Pharmacol. Exp. Ther. 314, pp. 310-319, 205.

Ukairo, O.T., Bondi, C.D., Newman, A.H., Kulkarni, S.S., Kozikowski, A.P., Pan, S. and Surratt, C.K. Recognition of Benztropine by the Dopamine Transporter (DAT) Differs from that of the Classical Dopamine Uptake Inhibitors Cocaine, Methylphenidate and Mazindol as a Function of a DAT Transmembrane 1 Aspartic Acid Residue. J. Pharmacol. Exp. Ther. 314, pp. 575-583, 2005.

Yang, S, Ross, TJ., Zhang, Y-Q, Stein, E.A. and Yang, Y. Head-motion Suppression Using Real-time Feedback of Motion Information and its Effects on Task Performance in fMRI. NeuroImage. 27, pp. 153-162, 2005.

Risinger, R.C., Salmeron, B.J., Ross, T.J., Amen, S.L., Sanfilipo, M., Hoffmann, R., Bloom, A.S., Garavan, H., and Stein, E.A. Neural Correlates of High and Craving During Cocaine Self-administration Using BOLD fMRI. NeuroImage, 26, pp. 1097-1108, 2005.

Woods, A.S. and Ferre, S. The Amazing Stability of the Arginine-Phosphate Electrostatic Interaction. J. Proteome Res. 4, pp. 1397-1402, 2005.

Wang, H.Y.J., Taggi, A.E., Meinwald, J., Wise, R.A. and Woods, A.S. A Study of the Interaction of Chlorisondamine and Chlorisondamine Analogs with An Epitope of the _-2 Neuronal Acetylcholine Nicotinic Receptor Subunit J. Proteome Res. 4, pp. 532-539, 2005.

Novikov, A., Caroff, M., Della-Negra, S., Depauw, J., Fallavier, M., Lebeyec, Y., Pautrat, M. , Schultz, J.A., Tempez, A. and Woods, A.S. The Au(n) Cluster Probe in Secondary Ion Mass Spectrometry: Influence of the Projectile Size and Energy on the Desorption/ionization Rate from Biomolecular Solids. RCM 19, pp. 1851-1857, 2005.

Oz, M., Jackson, S.N., Woods, A.S., Morales, M. and Zhang, L. Additive Effects of Endogenous Cannabinoids Anandamide and Ethanol on _7-nicotinic Acetylcholine Receptor-mediated Responses in Xenopus Oocytes J Pharmacol Exp Ther, 313, pp.

1272-1280, 2005.

Jackson, S.N., Wang, H.Y.J. and Woods, A.S. Direct Profiling of Lipid Distribution in Brain Tissue Using MALDI-TOF MS, Anal. Chem 77, pp. 4523-4527, 2005.

Woods, A.S., Ciruela, F., Fuxe, K., Agnati, L.F., Lluis, C., Franco, R. and FerrŽ, S. The Role of Electrostatic Interaction in Receptor-receptor Heteromerization, J. of Mol Neurosci 26, pp. 125-132, 2005.

Ciruela, F., Canela, L., Burgue–o, J., Soriguera, A., Cabello, N., Canela, E.I., Casad—, V., CortŽs, A., Mallol, J., Woods, A., FerrŽ, S., Lluis, C. and Franco, R.. Heptaspanning Membrane Receptors and cytoskeletal/Scaffolding Proteins: Focus on Adenosine, Dopamine and metabotropic glutamate receptors Function. J. of Mol Neurosci 26, pp. 277-292, 2005.

Fuxe, K., FerrŽ, S., Canals, M., Torvinen, M., Terasmaa, A., Marcellino, D., Staines, W., Jacobsen, K., Lluis, C., Woods, A.S., Agnati, L.F. and Franco, R. Adenosine A2A and Dopamine D2 Heteromeric Receptor Complexes and their Function. J Mol Neurosci 26, pp. 209-220, 2005.

Genedani, S., Guidolin, D., Leo, G., Filaferro, M., Torvinen, M., Woods, A.S., Fuxe, K., FerrŽ, S. and Agnati, L.F. Computer Assisted Image Analysis of Caveolin-1 Involvement in the Internalization Process of Adenosine A2A-dopamine D2 Receptor Hetero-dimers. J Mol Neurosci 26, pp. 177-184, 2005.

Agnati, L.F., Guidolin, D., Genedani, S., Ferre, S., Bigiani, A., Woods, A. and Fuxe, K. How Proteins Come Together in the Plasma Membrane and Function in Macromolecular Assemblies: Focus on Receptor Mosaics. J Mol Neurosci 26, pp. 133-154, 2005.

Agnati, L.F., Ferre, S., Burioni, R., Woods, A., Genedani, S., Franco, R. and Fuxe, K. Existence and Theoretical Aspects of Homomeric and Heteromeric Dopamine Receptor Complexes and Their Relevance for Neurological Diseases. Neuromolecular Med. 7, pp. 61-78, 2005.

Compton, W.M., Conway, K.P., Stinson, F.S., Colliver, J.D. and Grant, B.F. Prevalence and Comorbidity of DSM-IV Antisocial Personality Syndromes and Specific Substance Use Disorders in the United States: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. Journal of Clinical Psychiatry, 66, pp. 677-685, 2005.

Compton, W.M., Thomas, Y., Conway, K.P. and Colliver, J.D. Developments in the Epidemiology of Drug Use and Drug Use Disorders. American Journal of Psychiatry, 162(8), pp. 1494-1502, 2005.

Compton, W.M. and Volkow, N.D. Major Increases in Opioid Analgesic Abuse: Concerns and Strategies. Drug and Alcohol Dependence [Epub ahead of print] July 12, 2005. PMID: 16023304.

Glantz, M.D., Conway, K.P. and Colliver, J.D. Drug Abuse Heterogeneity and the Search for Subtypes. In Z. Sloboda (Ed.). Epidemiology of Drug Abuse. New York: Springer; pp. 15-28, 2005. This chapter discusses the importance of determining drug abuse subtypes in order to further understand and effectively treat drug abuse.

Simons-Morton, B., Haynie, D., Saylor, K, Crump, A.D. and Chen, R. Impact Analysis and Mediation of Outcomes: The Going Places Program. Health Education and Behavior, 32(2), pp. 227-241, 2005.

Flanzer, J. The Status of Health Services Research on Adjudicated Drug-abusing Juveniles: Selected Findings and Remaining Questions. Substance Use and Misuse, 40, pp. 887-911, 2005.

Herbeck, D.M., Fitek, D.J., Svikis, D.S., Montoya, I.D., Marcus, S.C. and West, J.C. Treatment Compliance in Patients with Comorbid Psychiatric and Substance Use Disorders. Am. J. Addict., 14, pp. 195-207, 2005.

Levav, I., Kohn, R., Montoya, I., Palacio, C., Rozic, P., Solano, I. et al. Training Latin American Primary Care Physicians in the WPA Module on Depression: Results of a Multicenter Trial. Psychol. Med., 35, pp. 35-45, 2005.

Montoya, I.D., Schroeder, J.R., Preston, K.L., Covi, L., Umbricht, A., Contoreggi, C. et al. Influence of Psychotherapy Attendance on Buprenorphine Treatment Outcome. J. Subst. Abuse Treat., 28, pp. 247-254, 2005.

Khalsa, J., Kresina, T.F., Sherman, K. and Vocci, F. Medical Management of HIV-Hepatitis C Virus Co-infection in Injection Drug Users. Clin Infect Dis. 41 Suppl 1:S1-66, 2005.

Kresina, T.F., Khalsa, J., Cesari, H. and Francis, H. Hepatitis C Virus Infection and Substance Abuse: Medical Management and Developing Models of Integrated Care--An Introduction. Clin Infect Dis. 40 Suppl 5:S259-62, 2005.

Purohit, V., Khalsa, J. and Serrano, J. Mechanisms of Alcohol-associated Cancers: Introduction and Summary of the Symposium. Alcohol. 35(3), pp. 155-160, 2005.

Vocci, F.J. and Elkashef, A.E. Pharmacotherapy and Other Treatments for Cocaine Abuse and Dependence. Current Opinion in Psychiatry 18, pp. 265-270, 2005.

Vocci, F.J., Acri, J.B. and Elkashef, A.E. Medications Development for Addictive Disorders: State of the Science. Am J Psychiatry 162, pp. 1432-1440, 2005.

Herman, B.H., Elkashef, A.E. and Vocci, F.J. Medications for the Treatment of Cocaine Addiction: Emerging Candidates. Drug Discovery Today: Therapeutic Strategies 2, pp. 87-92, 2005.

Drs. Dionne Jones and Aria Crump, DESPR, guest edited a special issue of the Journal of Urban Health (volume 82 number 2, June 2005/supplement 3) entitled "Methodological Challenges in Conducting Health Disparities Research."

Dr. Steven Grant, DCNDBT, was a co-author on the publication "Risky Decision Making and the Anterior Cingulate Cortex in Abstinent Drug Abusers and Nonusers". Fishbein, D.H., Eldreth, D.L., Hyde, C., Matochik, J.A. London, E.D., Contoreggi, C., Kurian, V., Kimes, A.S., Breeden, A. and Grant, S. Cognitive Brain Research. 23, pp. 119-136, 2005.

Walter Ling, Leslie Amass, Steve Shoptaw, Jeffrey J. Annon, Maureen Hillhouse, Dean Babcock, Greg Brigham, Judy Harrer, Malcolm Reid, Joan Muir, Betty Buchan, Debbie Orr, George Woody, Jonathan Krejci, and the Buprenorphine Study Protocol Group have published a paper entitled "A Multi Center Randomized Trial Of Buprenorphine-Naloxone versus Clonidine for Opioid Detoxification: Findings from the National Institute On Drug Abuse Clinical Trials Network," in Addiction electronically June 22, 2005 and in the August 2005 print edition. This paper highlights the primary outcomes from CTN Protocol 0001 and CTN Protocol 0002.

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Staff Highlights

Staff Honors and Awards

Dr. Teresa Levitin, Director, OEA, has been selected to receive the NIH Merit Award for her work on the trans-NIH committee on Council Operations. This workgroup award was presented on August 18, 2005.

Dr. Rao S. Rapaka, DBNBR, was the recipient of the "American Peptide Society 2005 Achievement Award for Scientific and Administrative Excellence". This was "in recognition of his many contributions to the promotion and advancement of research to peptide science and for scientific and administrative foresight which has advanced public health". The award was presented at the 19th Peptide Symposium June 18-23, 2005 in San Diego, CA.

CAPT Steve Oversby, US PHS, a Health Scientist Administrator with DPMCDA, completed the two year graduate course series of the U.S. Naval War College on July 15, 2005. The U.S. Naval War College provides government and military education in the political, organizational, and behavioral influences on national security decision making and implementation, as well as, education in the alternatives to war, as an instrument of policy. The graduation ceremony will be held at the U.S. Naval War College, Newport, Rhode Island.

Dr. Ro Nemeth-Coslett, DCNDBT, was elected President of Executive Toastmasters, 2005-2006.

Dr. Vincent Smeriglio, DCNDBT, received an NIH Mentoring Award "For exemplary performance while demonstrating significant leadership, skill and ability in serving as a mentor."

Dr. Laurence Stanford, DCNDBT, received an NIH Director's Award "In recognition of outstanding contributions in clinical developmental neurobiology with NIDA and across the NIH."

Dr. Laurence Stanford served as the co-chair of the Training Subcommittee of the NIH Neuroscience Blueprint.

Dr. Marisela Morales, Staff Scientist, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch, is the recipient of the 2005 Presidential Early Career Awards for Scientists and Engineers (PECASE), the highest honor bestowed by the United States government on outstanding scientists and engineers beginning their independent careers.

Dr. Santosh Kulkarni, Medicinal Chemistry Section, IRP, was invited to give a seminar at the Department of Medicinal Chemistry, School of Pharmacy, University of Georgia.

Dr. Amy Newman, Chief, Medicinal Chemistry Section, IRP, filed a patent on June 10, 2005: Newman, A. H.; Grundt, P.; Katz, J. L. N-8-Substituted Benztropinamines as Therapeutic Agents for CNS Disorders.

Staff Changes

Ms. Susan Cook joined NIDA on July 25, 2005 as the Institute's Deputy Executive Officer. Susan has a broad range of both education and experience that will serve NIDA well. She has a Masters in Business Administration as well as a Masters of Science, and has worked in the intramural, extramural, and OD components of

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Institutes. She began her career at NIH in 1987 as a chemist in the NCI intramural program. She then moved into the NCI administrative arena, serving as a Grants Management Specialist, Administrative Officer, and Program Analyst. In 2000, Susan joined NIAID as Chief of the Management Services Branch, providing support to the NIAID OD as well as management analysis activities NIAID-wide. For the past 6 months, she has also served as Acting Director of the Office of Administrative Services, an umbrella organization providing services Institute-wide.

OEA is pleased to announce that **Dr. Meena Hiremath** has joined our office. Meena was previously at NINDS, where she served as a Scientific Program Analyst. At NINDS, she had a wide variety of responsibilities, including providing detailed scientific analyses of grant portfolios and scientific codes for them. In addition, she co-organized an annual Junior Investigator Special Interest Group at the American Epilepsy Society meeting to foster a network of junior investigators and to provide a forum for discussion of issues specific to this group. She is currently participating as a mentee in the HHS Career Mentoring Program through which she is learning more about adapting to the rapidly changing work environment. Meena is particularly interested in training, mentoring, and fostering the next generation of scientists. Meena received her PhD in Microbiology and Immunology from the University of North Carolina at Chapel Hill. For her dissertation project, she developed neurotoxin-induced murine model for demyelination and applied that model to assess the role of lymphocytes and antigen presentation molecules in this model. She then trained in cellular and molecular immunology at NCI as a postdoctoral fellow. Her postdoctoral training focused primarily on the role that Csk homologous kinase (CHK) has in differentiation of human monocytes. Her areas of expertise include glial cell biology, neuroimmunology, autoimmunity, pathogenesis, and inflammation.

Dr. Belinda Sims recently joined DESPR's Prevention Research Branch as a Health Scientist Administrator for the prevention services and early childhood programs. Dr. Sims is a developmental psychologist, and came to NIDA from NIMH where she was the chief of the child and adolescent preventive intervention program. Prior to joining NIH, Dr. Sims was a faculty research associate at the Johns Hopkins Bloomberg School of Public Health, Department of Mental Hygiene (now Mental Health), where she conducted children's mental health services research.

Dr. Richard Denisco joined DESPR on September 6, 2005, as a member of the Services Research Branch staff. Dr. Denisco comes to us from the Johns Hopkins University, where he just completed a MPH in epidemiology, biostatistics, and policy. His Medical Degree is from the University of Florida, Gainesville. Dr. Denisco has served as the Medical Director of two chronic pain management and rehabilitative centers. He also has expertise in medical practice management, clinical research, medical affairs, and policy analysis.

Dr. Karin Johnson has joined DCNDBT in a part-time capacity for the 2005-2006 academic year as an IPA appointment. Dr. Johnson, who is a Professor at Salisbury University, was previously at NIDA as an AAAS/SRCD (American Association for the Advancement of Science/Society for Research in Child Development) fellow in 2000-2001.

Erin Iturriaga, R.N., CCRC, has joined NIDA's DPMCDA as a Clinical Trials Nurse Specialist. Erin brings a strong background in multiple aspects of clinical research, including clinical trials management, education, and regulatory responsibilities. Prior to moving to the Washington, D.C., area, Erin managed neuromuscular clinical trials at University of Texas Southwest Medical Center in Dallas and the University of Texas Health Science Center at San Antonio. Most recently, Erin worked at the National Cancer Institute as the Acting Head of the Protocol Information Office. Erin is a registered nurse as well as a certified clinical research coordinator.

Jennifer Wong, Ph.D. is leaving the Regulatory Affairs Branch, in the Division of Pharmacotherapies and Medical Consequences of Drug Abuse, to join the National Cancer Institute. Dr. Wong joined NIDA on July 27, 2003 as a Health Scientist Administrator. Before coming to NIDA, Dr. Wong was a Regulatory Compliance Specialist at Technical Resources International in Bethesda, Maryland.

Dr. Laurence Stanford was appointed Deputy Director of the Division of Clinical Neuroscience, Development and Behavioral Treatment in June 2005.

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Dr. Thomas Babor, University of Connecticut, School of Medicine received the Jellinek Memorial Prize for "Social, Cultural and Policy Studies" on alcohol.

Dr. Andrew Barrett of McLean Hospital received the 2005 American Psychological Association Division 28, Outstanding Dissertation Award.

Dr. Marsha Bates of Rutgers University was elected President of Division 50 (Addictions) of the American Psychological Association. She took over as President at the APA convention in August 2005.

Dr. Ricky N. Bluthenthal received the following two awards: President's Award, RAND Corporation, 2004; Junior Scholar Award, Drinking and Drugs Division of the Society for the Study of Social Problems, 2004.

Dr. Richard Clayton, Professor, School of Public Health, University of Kentucky and Scientific Director in the University of Kentucky, Center for Prevention Research received a Presidential Award from the Society for Prevention Research at the annual meeting in Washington, DC, May 2005. The Presidential Award is given to those who have made a major lifetime contribution to prevention science research.

Dr. Cynthia Conklin of the University of Pittsburgh Medical Center received the 2005 American Psychological Association Division 28, Young Psychopharmacologist Award.

Dr. Philip R. Costanzo, Professor, Department of Psychology: Social and Health Sciences at Duke University and Co-PI of the Duke/NIDA Transdisciplinary Prevention Research Center, received the Duke University Scholar/Teacher of the Year Award for 2005. The University Scholar/Teacher of the Year Award, established in 1981 by the Division of Higher Education and Ministry of the United Methodist Church, recognizes outstanding faculty members for their dedication and contributions to the learning arts and to their institutions.

Dr. Linda B. Cottler of Washington University received the Outstanding Faculty Mentor Award from the Washington University Postdoctoral Society in February 2005.

Dr. Ben Cravatt of the Scripps Research Institute was the recipient of the Young Investigator Award that was presented at the 2005 International Cannabinoid Research Society Meeting in Clearwater, FL. This is in recognition of his creativity and high quality of research.

Dr. Linda A. Dykstra of the University of North Caroliona at Chapel Hill received the 2005 College on Problems of Drug Dependence Mentorship Award.

Dr. Thomas E. Eissenberg of Virginia Commonwealth University received the 2005 College on Problems of Drug Dependence Joseph Cochin Young Investigator Award.

Dr. Phyllis Ellickson of RAND Corporation has been listed in the 2005 Who's Who in America.

Dr. Richard Houghten of the Torrey Pines Institute for Molecular Studies was the recipient of the 2005 "R. Bruce Merrifield Award". The American Peptide Society sponsors this award, which was presented at the 19th American Peptide symposium 2005 Biannual meeting, San Diego, CA. Dr. Richard Houghten is a NIDA grantee and the principal investigator on the contract that synthesizes peptides for NIDA's Drug Supply Program.

Dr. Conan Kornetsky of Boston University School of Medicine received the 2005

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College on Problems of Drug Dependence Nathan B. Eddy Award.

Dr. Mary Jeanne Kreek of The Rockefellar University received the 2005 College on Problems of Drug Dependence Marian W. Fischman Lectureship Award.

Dr. John Lochman received the 2005 Blackmon-Moody Outstanding Professor Award from the University of Alabama in recognition of his research program on understanding, treating and preventing aggression and violence in children and youth.

Dr. John Lochman was elected Fellow of the American Psychological Association, Division of Clinical Psychology.

Dr. John E. Lochman, University of Alabama, was appointed as Editor-in-Chief, Journal of Abnormal Child Psychology (term 2006-2010).

Dr. Dennis McCarty (PI for the CTN Oregon/Hawaii Node) received a "Distinguished Faculty Award in Recognition of Outstanding Research" on May 18, 2005 at the Oregon Health and Science University Faculty Senate Awards Luncheon.

Dr. Nancy K. Mello of McLean Hospital received the 2005 American Psychological Association Division 28 Brady-Schuster Award.

Dr. Rosalie Pacula has been selected as Co-Director of the Drug Policy Research Center, RAND, Santa Monica, CA.

Dr. Cheryl Perry of the University of Minnesota was recognized as one of the 100 Most-cited Researchers in Tobacco-related Research in 2005. Also, the Institute for Scientific Information recognized her as the Most Cited Researcher in Social Science for 1983-2002.

Dr. Angela Robertson, of the Social Science Research Center at Mississippi State University, was promoted to Associate Research Professor, effective July 1, 2005.

Dr. Melisa D. Rowland has been promoted from assistant to associate professor in the Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina.

Dr. James K. Rowlett of Harvard Medical School received the 2005 College on Problems of Drug Dependence Joseph Cochin Young Investigator Award.

Dr. Ian P. Stolerman of the Institute of Psychiatry Kings College London received the 2005 College on Problems of Drug Dependence Meritorious Service Award.

Dr. Shiela Strauss of NDRI was awarded a Fulbright Senior Specialist grant in May 2005 to conduct a series of workshops and seminars in Israel regarding the institutional response to the hepatitis C virus (HCV) among drug users.

NIDA awarded 30 **Women & Gender Junior Investigator Travel Awards** for the annual meeting of the College on Problems of Drug Dependence (CPDD), June 18-23, 2005, Orlando, FL. These $750 awards, which have been made annually beginning in 2000, are designed to promote entry of junior investigators into drug abuse research on women and sex/gender differences. To further promote research in this field, NIDA published a mini-program book, Focus on Women & Sex/Gender Differences, for the CPDD meeting. Excerpted from the CPPD program book, it contains only those program listings related to women and sex/gender differences. It also contains the CPDD abstracts on women and sex/gender differences, information about the Women & Gender Junior Investigator Travel Awardees, announcement of the travel award program for CPDD 2006, and information on current NIDA program announcements in this area.