Director's Report to the National Advisory Council on Drug Abuse - May, 2007

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Director's Report to the National Advisory Council on Drug Abuse - May, 2007

Research Findings - Basic Neuroscience Research

Multimodal Fast Optical Interrogation of Neural Circuitry

Karl Deisseroth, M.D., Ph.D., a NIDA grantee and an awardee for PECASE (Presidential Earlier Career Award for Scientists and Engineers) as well as NIH Director's Pioneer Award, and his research team at Stanford University and collaborators at Max-Plank Institute have published a groundbreaking photogenetic technology work in the April 5, 2007 issue of Nature, describing how genetically engineered proteins can be used to activate or silence very precise groups of neurons at a flick of a light switch (ms time scale), allowing real time, direct control and interrogation of neural circuits dynamics in the brain, a dream that has long been sought by neuroscientists but has been impossible until now. The technology involves a pair of light-activated membrane proteins present in nature, that is, the ChR2 (Channelrhodopsin-2)-NpHR (Natronomonas pharaonis halorhodopsin) system. The ChR2 is a light-activated ion-channel protein present in the green alga Chlamydomonas reinhardtii. When neurons were genetically engineered to express ChR2, blue light activates ChR2 and rapidly and selectively depolarizes the cell and triggered action potentials, giving a genetically encodable, remote-control "on" switch for neurons. NpHR, on the other hand, is a chloride ion pump present in the archaeum Natronomonas pharaonis. When it is expressed in neurons, yellow light activates NpHR and causes rapid and reversible hyperpolarization, thus preventing spikes, allowing a genetically encodable, remote-control "off" switch for neurons. The ChR2- NpHR system, although like all opsins, requires a vitamine-A-based chromophore cofactor in order to be activated by light, needs no addition of such cofactor because mammalian neural tissue normally contains enough of this cofactor. In addition, when combined with fluorescent-based methods for monitoring activity, the ChR2- NpHR system allows simultaneous real-time control and tracking of neuronal activity on both ends. The authors demonstrated that, when genetically targeted to specific types of neuron in the worm C. elegans, ChR2-NpHR system is able to rapidly and reversibly activate or silence a particular neuronal subtype with light, and simultaneously observe the effect on behavior, in this particular case, swimming behavior. The spectacular beauty of the technology is that the ChR2 and the NpHR are totally compatible with and complementary to each other in all measures examined, including temporal resolution (m sc), spatial specificity, and separation of absorption spectrum. That is, the spectral bandwidths for activation of ChR2 and NpHR is such that coexpression of both proteins in the same neuron allows different wavelengths of light - blue and yellow, respectively, to be used to selectively activate or inactivate the same cell. In essence, the ChR2- NpHR system provides a two-knob remote control for increasing or decreasing the activity of specific neurons using different colors of light. Also, there is an additional advantage; the spectral bandwidth remaining is sufficient enough to be used for monitoring neural activity optically using a

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fluorescent indicator of intracellular calcium. In conclusion, the technology is a stunning technical breakthrough. It allows targeting genes in specific neurons, is safe (nontoxic), fully reversible, has rapid onset and offset, allows bidirectional control, and offers experimenters remote control. The technology is unprecedented, immensely powerful and offers, for the first time, neuroscientists the opportunity to directly interrogate neural circuits dynamics and observe their effects on behavior in real time. The impact of the technical breakthrough is obvious, and will be far reaching beyond neurological and psychiatric disorders and the technology promises to revolutionize neuroscience research. The work has been featured in the same issue of Nature, Web Focus, Technical Breakthroughs in Neuroscience. Zhang, F., Wang, L.-P., Brauner, M., Liewald, J.F., Kay, K., Watzke, N., Wood, P.G., Bamber, E., Nagel, G., Gottschalk, A., and Deisseroth, K. Multimodal Fast Optical Interrogation of Neural Circuitry. Nature, 446(7136), pp. 633-639, 2007.

Dicarba Analogues of the Cyclic Enkephalin Peptides H-Tyr-c[D-Cys-Gly-Phe-D(or L)-Cys]NH2 Retain High Opioid Activity

Dicarba analogues of the cyclic opioid peptides might have potential as lead compounds for analgesic drug discovery. Dicarba analogues of the cyclic opioid peptides H-Tyr-c[D-Cys-Gly-Phe-D(or L)-Cys]NH2 were synthesized on solid phase by substituting allylglycines for the cysteines and cyclization by ring-closing metathesis between the side chains of the allylglycine residues. Mixtures of cis and trans isomers of the resulting olefinic peptides were obtained, and catalytic hydrogenation yielded the saturated -CH2-CH2- bridged peptides. The dicarba analogues retained high mu- and delta-agonist potencies. Remarkably, the trans isomer of H-Tyr-c[D-Allylgly-Gly-Phe-L-Allylgly]NH2 was a mu-agonist/delta-agonist with subnanomolar potency at both receptors. These chimeric peptides may potentially serve as lead compounds for analgesic drug discovery. Berezowska, I., Chung, N.N., Lemieux, C., Wilkes, B.C., and Schiller, P.W. Dicarba Analogues of the Cyclic Enkephalin Peptides H-Tyr-c[D-Cys-Gly-Phe-D(or L)-Cys]NH2 Retain High Opioid Activity. Journal of Medicinal Chemistry, 50, pp. 1414-1417, 2007.

Role of Endocannabinoids in Alcohol Consumption and Intoxication: Studies of Mice Lacking Fatty Acid Amide Hydrolase

Dr. Cravatt and colleagues have recently reported that endocannabinoid signaling plays an important role not only in the regulation of drug intake, but also in regulation of ethanol intake. Fatty acid amide hydrolase (FAAH) is a key membrane protein for metabolism of endocannabinoids, including anandamide, and blockade of FAAH increases the level of anandamide in the brain. To determine if FAAH regulates ethanol consumption, the PI studied mutant mice with deletion of the FAAH gene. Null mutant mice showed higher preference for alcohol and voluntarily consumed more alcohol than wild-type littermates. There was no significant difference in consumption of sweet or bitter solutions. To determine the specificity of FAAH for ethanol intake, the PI studied additional ethanol-related behaviors. There were no differences between null mutant and wild-type mice in severity of ethanol-induced acute withdrawal, conditioned taste aversion to alcohol, conditioned place preference, or sensitivity to the hypnotic effect of ethanol. However, null mutant mice showed shorter duration of loss of righting reflex induced by low doses of ethanol (3.2 and 3.4 g/kg) and faster recovery from motor in-coordination induced by ethanol. All three behavioral phenotypes (increased preference for ethanol, decreased sensitivity to ethanol-induced sedation, and faster recovery from ethanol-induced motor incoordination) seen in mutant mice were reproduced in wild-type mice by injection of a specific inhibitor of FAAH activity--URB597. These data suggest that increased endocannabinoid signaling increased ethanol consumption owing to decreased acute ethanol intoxication. Blednov, Y.A.,

Cravatt, B.F., Boehm II, S.L., Walker, D., and Harris, R.A. Role of Endocannabinoids in Alcohol Consumption and Intoxication: Studies of Mice Lacking Fatty Acid Amide Hydrolase. Neuropsychopharmacology, pp. 1-13, 2006, epub ahead of print.

Solubilized Neurotransmitter Assay

Membrane transporters such as the dopamine, serotonin, and norepinephrine transporters facilitate the uptake or reuptake of the corresponding neurotransmitters dopamine, serotonin, and norepinephrine across neuronal membranes in a process involving co-transport of sodium and chloride ions. Mammalian versions of these particular transporters are of interest to NIDA because of their affinity for cocaine and amphetamine. Because the limited expression of mammalian transporter quantities suitable for structural studies is a concern, researchers are also interested in over-expressing bacterial transporter homologs in hosts such as E. coli, for biophysical study of structure and function, and possible crystallization, which would yield a three dimensional picture of the transporter. Drs. Javitch and Quick have recently reported on the application of an existing assay technique, the scintillation proximity assay (SPA), to measure the tritiated tyrosine binding affinity and binding rate of bacterial tyrosine transporter Tyt1 solubilized in detergent. Using the SPA system, it was possible to show that Tyt1 has a high and specific affinity for tyrosine binding at pH 6.5-7.5, and operates with a stoichiometry of two sodium ions to one of tyrosine, with no dependence on chloride ion. The practical advantages of this system include obtaining binding affinity constants for tyrosine and sodium, comparison of results in different E. coli host expression systems and in different detergents, and optimization of purification techniques by comparison of results from different chromatographic fractions. In the case of newly isolated bacterial orphan transporters, this technique can be used to determine relative affinity toward a battery of commercially available tritiated amino acids. Quick, M. and Javitch, J.A., Monitoring the Function of Membrane Transport Proteins in Detergent-Solubilized Form. Proceedings of the National Academy of Sciences, 104(9), pp. 3603-3608, 2007.

Adolescent Anabolic-Androgen Steroids Exposure and its Consequences

Earlier work in hamsters has demonstrated that adolescent anabolic-androgen steroids (AAS) exposure facilitates offensive aggression, in part by altering the development and activity of anterior hypothalamic arginine vasopressin (AH-AVP). In a recent study Dr. Richard Melloni and his group first determined whether adolescent AAS exposure had lasting behavioral effects on aggression following suspension of AAS administration. Adolescent hamsters administered AAS were tested as adults for offensive aggression at 1, 4, 11, 18, or 25 days following AAS withdrawal. Data from this study showed that AAS-exposed hamsters were significantly more aggressive than age-matched controls through Day 12 of AAS withdrawal, however, these behavioral differences were no longer observable by Day 19 indicating the behavioral effects are not permanent. This study also examined whether the effects of AAS withdrawal on AH-AVP neural system were long-lasting or short-term. Using immuno-histochemical techniques, they measured AH-AVP afferent innervation. As seen with aggression, AH-AVP innervation was significantly higher in AAS-treated hamsters compared to controls through Day 12 of AAS withdrawal; however, these differences were no longer observable by Day 19 of withdrawal, at which point the neurobiology of AAS-treated hamsters reverted to that observed in controls, again as seen with the behavioral study. These findings suggest that adolescent AAS exposure has short-term, reversible effects on both aggression and AH-AVP, correlating AH-AVP with the aggressive/ non-aggressive behavioral phenotype during AAS withdrawal. Grimes, J.M., Ricci, L.A., and

Melloni Jr, R.H. Plasticity in Anterior Hypothalamic Vasopressin Correlates with Aggression during Anabolic-androgenic Steroid Withdrawal in Hamsters. Behavioral Neuroscience, 120(1), pp. 115-124, 2006.

Chronic Morphine Exposure Causes Pronounced and Altered Virus Replication

Two recent reports delineate some important results following exposure to a "trivirulent" SIV in combination with morphine dependence. This combination results in increased mortality and increased neurologic disorders were more prevalent with opiate-dependence. In a corresponding paper, increased genetic evolution of the SIV was associated with morphine-dependence. This may indicate that opiates could exacerbate viral strain evolution in humans and provide an understanding of some of the bases for different HIV viruses being present in drug abusers. Kumar, R., Orsoni, S., Norman, L., Verma, A.S., Tirado, G., Giavedoni, L.D., Staprans, S., Miller, G.M., Buch, S.J. and Kumar, A. Chronic Morphine Exposure Causes Pronounced Virus Replication in Cerebral Compartment and Accelerated Onset of AIDS in SIV/SHIV-infection, Virology, 354, pp. 192-206, 2006.

Synthesis of Salvinorin A Analogues as Opioid Receptor Probes

The main active constituent isolated from the leaves of Salvia divinorin is salvinorin A, a neoclerodane diterpene. This compound was found to be a potent and selective kappa opioid receptor agonist. Interestingly the pharmacology of Salvinorin A appeared to be different from other kappa agonists. Research has shown that salvinorin A decreases dopamine levels in the caudate putamen of mice and that this effect is blocked by the kappa opioid antagonist nor-binaltorphimine. Another study has shown that salvinorin A dose dependently increases immobility in the forced swim test, indicating that this compound has depressive like effects. Recently authors have described the synthesis of several analogues of salvinorin A that were found to be opioid receptor ligands. In this paper they have reported the semi-synthesis of neoclerdane diterpenes and the structure-affinity relationships at opioid receptors. This work will allow the further development of novel opioid receptor ligands that may be important for the treatment of substance abuse. Tidgewll, K., Harding, W.W., Lozama, A., Cobb, H., Shah, K., Kannan, P., Dersch, C.M., Parrish, D., Deschamps, J.R., Rothman, R.B., and Prisinzano, T.E. Synthesis of Salvinorin A Analogues as Opioid Receptor Probes. Journal of Natural Products, 69, pp. 914-918, 2006.

Novel Non-Opioid Analgesics Developed

Improgan has been found to have analgesic properties in animal models. Improgan is chemically related to histamine, yet does not produce analgesia via an action at the histamine receptor, or by a direct action at any other receptors known to be involved with pain modulation (e.g. opioid receptors). NIDA grantee Lindsay Hough (Albany Medical College, Albany, NY) and his colleagues have now produced a series of improgan congeners, where five compounds showed analgesic activity with potencies greater than that of improgan. One compound, VUF5420, produced maximal analgesia in rats after doses that produced no motor impairment or other obvious toxicity. VUF5420 analgesia was unaffected by the administration of the opioid antagonist naltrexone, but was inhibited by the CB1 cannabinoid antagonist SR141716A. However, VUF5420 had a very low affinity for the CB1-receptor in vitro, indicating that its analgesic action in vivo was not the result of a direct action on the CB1 receptor. Thus, VUF5420 may have clinical use as a non-opioid analgesic, which may indirectly activate cannabinoid pain-relieving mechanisms. Hough, L.B., de Esch, I.J.P., Janssen, E., Phillips, J., Svokos, K.,

Kern, B., Trachler, J., Abood, M.E., Leurs, R., and Nalwalk, J.W. Neuropharmacology, 51, pp. 447-456, 2006.

Inhibition of Cdk5 in the Nucleus Accumbens Enhances the Locomotor-Activating and Incentive-Motivational Effects of Cocaine

Genes provide instructions for carrying out cellular processes by telling the cell whether a protein or enzymes that carries out cellular processes is to be made. The instructions are carried out by first "transcribing" the DNA sequence in the gene into a messenger RNA transcript (mRNA) in the cell nucleus. The mRNA is then transported to the ribosomes in the cytoplasm where the mRNA is translated into proteins consisting of strings of amino acids. The process of transcription is regulated by proteins called transcriptional factors. One transcriptional factor called delta FOSB is upregulated in the nucleus accumbens by addictive drugs when administered chronically. The accumbens is a subcortical region involved in reward. One of the genes turned on by delta FOSB is cyclin dependent kinase-5 (cdk-5). Dr. Bibb and his colleagues examined the role of cdk-5 in the nucleus accumbens on cocaine-induced locomotor sensitization, responding for reward-associated stimuli (conditioned reinforcement), and cocaine self-administration. Injections of cdk-5 blockers into the nucleus accumbens augmented the increased sensitivity of rats to the locomotor effects of cocaine following repeated administration of cocaine. In addition, responding to a conditioned reward, in which a stimulus such as light is paired with cocaine injection, is greatly enhanced when rats received intra-accumbens injections of cdk-5 blockers. Dr. Bibb and his colleagues also show that rats will work harder to self-administer cocaine following injections in the nucleus accumbens of cdk-5 blockers. These results suggest that cdk-5 acts as negative feedback regulator to dampen the psychomotor and incentive-motivational effects of cocaine. Taylor, J.R., Lynch, W.J., Sanchez, H., Olausson, P., Nestler, E.J., and Bibb, J.A. Inhibition of Cdk5 in the Nucleus Accumbens Enhances the Locomotor-Activating and Incentive-Motivational Effects of Cocaine. Proceedings of the National Academy of Sciences 104, pp. 4147-4152, 2007.

IRS2-Akt Pathway in Midbrain Dopamine Neurons Regulates Behavioral and Cellular Responses to Opiates

Chronic administration of morphine is associated with tolerance or decrease in the ability to produce euphoria. During long term abstinence this process is reversed. Eric Nestler and his colleague show in a recent issue of Nature Neuroscience that the development of tolerance to the rewarding properties parallels the decreased size of Ventral Tegmental Area (VTA) dopamine neurons. The size of the VTA dopamine neurons returns to normal after tolerance to the euphoric properties of morphine is reversed by abstinence. Because knockouts of brain derived neurotrophic factor (BDNF) abolishes the rewarding effects of morphine and infusions of BDNF into the VTA block the decrease in size, Dr. Nestler and his colleagues hypothesized that one of the intracellular messengers activated by BDNF mediates the reduction in size. The BDNF uses three intracellular messengers to convey the BDNF signal from the cell surface to inside the cell. These are ras-erk pathway; the phopholipase C-gamma pathway, and the IRS2-Akt. Dr. Nestler and his colleagues report that the IRS-Akt pathway is downregulated following chronic morphine and is responsible for the decreased size of VTA dopamine neurons and the development of tolerance to morphine reward. The decrease in the amount of IRS parallels the decrease in size of the VTA neurons and the development of tolerance. The size of the VTA dopamine neurons and morphine reward as measured by conditioned place preference were decreased when infected with a virus expressing a mutant IRS protein that blocks the activation of the IRS-Akt pathway. The effect on size of the dopamine neurons was not due to the

viral infection because normal viruses not expressing the mutant IRS protein did not have any effect on size. Furthermore, the decrease in size of the VTA dopamine neurons following chronic morphine could be reversed by infecting VTA dopamine neurons with a virus that expresses the normal IRS protein. The effect of the mutant IRS protein on cell size was selective because ERK and PLC-gamma mutants had no effect on cell size. Increased expression of the normal IRS protein in dopamine neurons is also associated with increased locomotor activity and reward in response to morphine. These results suggest that activation of the IRS protein is necessary and sufficient for regulating dopamine cell morphology and morphine reward. An understanding of the role of the IRS-Akt pathway may help in the development of therapeutics that can delay or reverse the transition to opiate addiction. Russo, S.J., Bolanos, C.A., Theobald, D.E., DeCarolis, N.A., Renthal, W., Kumar, A., Winstanley, C.A., Renthal, N.E., Wiley, M.D., Self, D.W., Russell, D.S., Neve, R.L., Eisch, A.J., and Nestler, E.J. IRS2-Akt Pthway in Midbrain Dopamine Neurons Regulates Behavioral and Cellular Responses to Opiates. Nature Neuroscience, 10, pp. 93-99, 2007.

Disruption of the Circadian Regulator, CLOCK, Induces Mania-like Behavior in Mice

Individuals with bipolar disorder often have disturbances in their circadian rhythms (sleep, wake and activity cycles). Furthermore, a specific genetic polymorphism in the human circadian regulator Clock is associated with a propensity for manic episodes. To functionally test the relationship between Clock and mania, Dr. McClung and coworkers characterized the behaviors of mice with a mutation in the Clock gene. They found that compared to wild type mice, Clock mutant mice had an enhanced preference for rewarding stimuli such as cocaine or sucrose, reduced levels of anxiety, and reduced levels of depression-like behavior. In fact the behaviors exhibited by the Clock mutant mice were very similar to the behaviors exhibited by bipolar patients in a manic state. Furthermore, the mania-like behavior of the Clock mutant mice could be reduced by lithium, a common treatment for human mania. This further argues that the suite of behaviors exhibited by the Clock mutant animals models the manic phase of human bipolar disorder. Clock is expressed in a number of brain regions, but where is it required to regulate mania-like behaviors? Several lines of evidence link mania with the ventral tegmental area (VTA). Dr. McClung and colleagues used a viral gene transfer method to restore Clock function specifically to the VTA. The animals with restored Clock function in the VTA had levels of anxiety and activity similar to "normal" wild type animals, indicating that these behaviors are regulated by Clock function in the VTA. Dr. McClung's work has led to the development of a robust mouse genetic model for the manic phase of bipolar disorder. This mouse model will be extremely useful for future genetic and therapeutic investigations into this psychiatric disorder as well as the links between this disorder and drug addiction. Roybal, K., Theobold, D., Graham, A., DiNieri, J.A., Russo, S.J., Krishnan, V., Chakravarty, S., Peevey, J., Oehrlein, N., Birnbaum, S., Vitaterna, M.H., Orsulak, P., Takahashi, J.S., Nestler, E.J., Carlezon, W.A. Jr, and McClung, C.A. Proceedings of the National Academy of Sciences, 104, pp. 6406-6411, 2007.

Aberrant GABA Neuronal Migration Caused by Imbalance of Dopamine Receptors in Embryonic Brain

During brain development newly generated neurons migrate to the cortical walls to form layers, as well as to the limbic areas to form nuclei. GABA neurons, generated in the basal forebrain migrate into the neocortical areas during development and play a role in modulating neuronal proliferation and migration, thereby generating functional neural circuits. A team led by Pradeep Bhide at Harvard University and Massachusetts General Hospital reports that since GABA neurons express dopamine receptors D1 and D2, and since the

embryonic basal forebrain is enriched in dopamine, GABA neuron migration is heavily influenced by the activation of dopamine receptors. Specifically, using ex vivo live cortical slices and in vivo tracing, the researchers show that increased dopamine concentration and activation of the D1 receptor promotes GABA neuron migration from the medial and caudal ganglionic eminences to the cerebral cortex, but increased dopamine concentration and activation of D2 receptor decreases this migration. This finding is then confirmed using slice preparations from D1 or D2 receptor knock-out mouse embryos. They show that D1 receptor electroporation into cells of the basal forebrain and pharmacological activation of these receptors promotes the migration of the electroporated cells to the cerebral cortex. Finally, to identify the cellular mechanisms involved, the team shows that dopamine receptor activation mobilizes striatal neuronal cytoskeleton in a manner consistent with the effects on neuronal migration. These data suggest that impairing the physiological balance between D1 and D2 receptors can alter GABA neuron migration from the basal forebrain to the cerebral cortex, with resulting consequences in widely distributed abnormalities in the embryonic brain. This observation provides insights into how the exposure of developing brains to certain drugs of abuse, such as cocaine and amphetamine that activate dopamine receptors, results in the malformation of the brain. Crandall, J.E., McCarthy, D.M., Araki, K.Y., Sims, J.R., Ren, J.-Q., and Bhide, P.G. Dopamine Receptor Activation Modulates GABA Neuron Migration from the Basal Forebrain to the Cerebral Cortex. Journal of Neuroscience, 27, pp. 3813-3822, 2007.

Activation of the cAMP/PKA/DARPP-32 Signaling Pathway is Required for Morphine Psychomotor Stimulation but not for Morphine Reward

In this study, using a mouse model the researchers show that, in key brain regions, acute administration of morphine resulted in an increase in the state of phosphorylation of the dopamine- and cAMP-regulated phosphoprotein of 32 kDa (DARPP-32) at one site of phosphorylation, Thr34, without affecting phosphorylation at Thr75. In the striatum, activation of dopamine D1 receptors leading to phosphorylation of Thr34 leads to a cascade of molecular events ultimately potentiating responses produced by activation of the cAMP cascade. These researchers examined the possible involvement of DARPP-32 in the acute motor stimulant effect of morphine, and in morphine behavioral sensitization. The study shows that morphine's psychomotor effects are mediated through DARPP-32 and specifically through the phosphorylation of Thr34, but not Thr75, which are known to have opposing effects on DARPP-32 activity. To address the question of the possible role of DARPP-32 in the rewarding properties of morphine, they used the conditioned place preference (CPP) paradigm. The data clearly show that morphine-induced place preference is present in mice lacking the DARPP-32 gene, providing strong evidence that DARPP-32 is not involved in morphine reward. This is in contrast to similar studies conducted with cocaine, suggesting a different mechanism for morphine reward. These results demonstrate that dopamine D1 receptor-mediated activation of the cAMP/DARPP-32 cascade in striatal neurons is involved in the psychomotor action, but not in the rewarding properties, of morphine. Borgkvist, A., Usiello, A., Greengard, P., and Fisone, G. Activation of the cAMP/PKA/DARPP-32 Signaling Pathway is Required for Morphine Psychomotor Stimulation but not for Morphine Reward. Neuropsychopharmacology, pp. 1-9, 2007.

Association of the Neuronal Nicotinic Receptor B2 Subunit Gene (CHRNB2) with Subjective Responses to Alcohol and Nicotine

Nicotine and alcohol dependence are highly co-morbid disorders and may share overlapping genetic components. Dr. Ehringer and her colleagues examined two neuronal nicotinic receptor subunit genes (CHRNA4 and CHRNB2) that code

for the alpha4 and beta2 subunits. The alpha4 beta2 subunits are the most frequently encountered nicotinic receptor subtype in the brain, and are promising candidates for genetic studies with nicotine and alcohol dependence. So far, strong evidence supports a role for alpha4 in dependence, but there is no evidence for involvement of beta2. In this report, six single nucleotide polymorphisms (SNPs) in the alpha4 gene and two SNPs in the beta 2 gene were examined individually and by haplotype analysis for association with nicotine and alcohol phenotypes (use), including subjective measures of response to each drug in the period shortly after initiation to capture critical steps in early development of addictive behaviors. The results provided stronger support for the beta 2 subunit in early subjective (negative physical responses to tobacco) responses to alcohol and nicotine with the SNP rs2072658. This SNP is located 42 bp upstream of the transcription initiation site, and may be important for regulating expression of the gene. This study highlights the potential importance of careful definition of phenotypes when studying complex disorders such as addiction. This study also provides the first evidence for association between the CHRNB2 gene and nicotine- and alcohol-related phenotypes, and suggests that polymorphisms in the CHRNB2 gene may be important in mediating early responses to nicotine and alcohol. Ehringer, M.A., Clegg, H.V., Collins, A.C., Corley, R.P., Crowley, T., Hewitt, J.K., Hopfer, C.J., Krauter, K., Lessem, J., Rhee, S.H., Schlaepfer, I., Smolen, A., Stallings, M.C., Young, S.E., and Zeiger, J.S. Association of the Neuronal Nicotinic Receptor _2 Subunit Gene (CHRNB2) with Subjective Responses to Alcohol and Nicotine. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 2007. (epub ahead of print).

Multiple ADH Genes Modulate Risk for Drug Dependence in both African- and European-Americans

Cocaine dependence (CD) and opioid dependence (OD) are commonly co-morbid with alcohol dependence, and studies indicate that there are common genetic risk factors for these addictive disorders. Dr. Gelernter and his colleagues recently studied the relationship among seven alcohol dehydrogenase (ADH) genes in CD and OD. ADH genes have been shown to be important risk factors for alcohol dependence, and since CD and OD are commonly co-morbid with alcohol dependence, the hypothesis was that ADH genes might also contribute to CD and OD. Sixteen markers within the ADH gene cluster and 38 ancestry-informative markers were genotyped in a sample of 718 individuals. Analysis showed that the ADH5 and ADH6 genotypes, and diplotypes (pairs of haplotypes that comprise genetic data from an individual) from ADH1A, ADH1B, ADH1C and ADH7 were associated with CD and OD in both African- and European Americans. This is the first report to link alcohol risk loci with CD and OD, and provides new insights into explaining the high rate of co-morbidity between these addictive disorders. Luo, X., Kranzler, H.R., Zuo, L., Wang, S., Schork, N.J., and Gelernter, J. Multiple ADH Genes Modulate Risk for Drug Dependence in both African- and European-Americans. Human Molecular Genetics, 16, pp. 380-390, 2007.

DAT-Ubiquitin Conjugates are Required for Protein Kinase C-Induced Internalization of DAT

The amount of DAT at the cell surface is determined by its relative rates of internalization and recycling. Activation of protein kinase C (PKC) increases the rate of endocytosis of DAT. PKC activation also results in the ubiquitination of DAT. Dr. Sorkin's group investigated whether ubiquitination of DAT and DAT endocytosis were linked and by mutating the ubiquitination sites of the DAT, found that three sites in the amino terminus of the DAT were critical for internalization. They also conducted an RNA interference screen and discovered that ubiquitin ligase, Nedd4-2 (neural precursor cell expressed, developmentally downregulated 2-4) was essential for the internalization of

DAT. These data proved the first evidence for a new model of DAT regulation, showing that DAT-ubiquitin conjugates may be the molecular interface of transporter interaction with endocytic machinery. Miranda, M., Dionne, K.R., Sorkina, T., and Sorkin, A. Three Ubiquitin Conjugation Sites in the Amino Terminus of the Dopamine Transporter Mediate Protein Kinase C-dependent Endocytosis of the Transporter. Molecular Biology of the Cell, 18, pp. 313-323, 2007. Sorkina, T. Miranda, M., Dionne, K.R., Hoover, B.R., Zahniser, N.R., and Sorkin, A. RNA Interference Screen Reveals an Essential Role of Nedd4-2 in Dopamine Transporter Ubiquitination and Endocytosis. The Journal of Neuroscience, 26, pp. 8195-8205, 2006.

Mechanisms Governing Secretory Granule Biogenesis and Exocytosis: Proteins of the Regulated Pathway Are Sequestered in Secretory Granules Differently from Proteins of the Constitutive Pathway

Secretory granules carrying fluorescent cargo proteins are widely used to study granule biogenesis, maturation, and regulated exocytosis. The investigators fused the soluble secretory protein peptidylglycine _-hydroxylating monooxygenase (PHM) to green fluorescent protein (GFP) to study granule formation. When expressed in AtT-20 or GH3 cells, the PHM-GFP fusion protein partitioned from endogenous hormone (adrenocorticotropic hormone, growth hormone) into separate secretory granule pools. Both exogenous and endogenous granule proteins were stored and released in response to secretagogue. Neither luminal acidification nor cholesterol-rich membrane microdomains play essential roles in soluble content protein segregation. Their data suggest that intrinsic biophysical properties of cargo proteins govern their differential sorting, with segregation occurring during the process of granule maturation. Proteins that can self-aggregate are likely to partition into separate granules, which can accommodate only a few thousand copies of any content protein; proteins that lack tertiary structure are more likely to distribute homogeneously into secretory granules. Therefore, a simple "self-aggregation default" theory may explain the little acknowledged, but commonly observed, tendency for both naturally occurring and exogenous content proteins to segregate from each other into distinct secretory granules. Sobota, J.A., Ferraro, F., Baeck, N., Eipper, B.A., and Mains, R.E. Not All Secretory Granules Are Created Equal: Partitioning of Soluble Content Proteins. Molecular Biology of the Cell, 17, pp. 5038-5052, 2006.

D1-D2 Dopamine Receptor Heterooligomers with Unique Pharmacology Are Coupled to Rapid Activation of Gq/11 in the Striatum

Dr. Susan George and her research team at the University of Toronto discovered a heteromeric D1-D2 dopamine receptor signaling complex in brain that is coupled to Gq/11 and requires agonist binding to both receptors for G protein activation and intracellular calcium release. The D1 agonist SKF83959 was identified as a specific agonist for the heteromer that activated Gq/11 by functioning as a full agonist for the D1 receptor and a high-affinity partial agonist for a pertussis toxin-resistant D2 receptor within the complex. They provide evidence that the D1-D2 signaling complex can be more readily detected in mice at 8 months of age compared to 3 months of age, suggesting that calcium signaling through the D1-D2 dopamine receptor complex is relevant for function in the post-adolescent brain. Activation of Gq/11 through the heteromer increases levels of calcium/calmodulin-dependent protein kinase II_ (CAMKII_) in the nucleus accumbens, indicating a mechanism by which D1-D2 dopamine receptor complexes may contribute to synaptic plasticity. The formation of a distinct dopaminergic signaling unit by two receptors that signal through separate pathways is highly significant in that it provides a greater

repertoire of signaling pathways by which dopamine can modulate neuronal function than would be possible by each of the five different dopamine receptor subtypes acting solely as separate units. Characterization of changes in this signaling unit with age and the functional consequences of signaling through the complex will increase our understanding of how D1-D2 heteromers contribute to neuronal function as well as the role this pathway may play in the etiology or pathophysiology of disorders in which altered dopamine signaling is implicated, such as schizophrenia and drug addiction. Rashid, A.J., So, C.H, Kong. M.M.C., Furtak, T., El-Ghundi, M., Cheng, R., O'Dowd, B.F., and George, S.R. D1-D2 Dopamine Receptor Heterooligomers with Unique Pharmacology Are Coupled to Rapid Activation of Gq/11 in the Striatum. Proceedings of the National Academy of Sciences, 104, pp. 654-659, 2007.

Neuronal Oxidative Stress Induced By HIV-1 and Alcohol Blocked By Cholesterol-Depleting Statin Drugs

In the brain, both HIV-1 and alcohol induce oxidative stress, which is considered a precursor for cytotoxic responses. Several reports have suggested that statins exert antioxidant as well as anti-inflammatory pleiotropic effects, besides their inherent cholesterol-depleting potentials. In this study, post-mitotically differentiated neurons were co-cultured with uninfected or HIV-1-infected monocytes, T cells, or their cellular supernatants in the presence or absence of physiological concentrations of alcohol. In neurons cultured with HIV-infected monocytes or T cells, or with supernatants from those cells, neuronal oxidative stress responses (8-isoprostane-F2-alpha, NOS activity, and Hsp70) were significantly increased compared to co-cultures using uninfected cells. Exposure to ethanol further elevated Hsp70 in both infected and uninfected cultures. The amount of total nitrates was significantly elevated in the co-culture system when both infected cells and alcohol were present. Surprisingly, pretreatment of postmitotic neurons with clinically available inhibitors of HMG-coenzyme A reductase (statins) inhibited HIV-1-induced release of stress/toxicity-associated parameters (i.e., Hsp70, isoprostanes, and total nitrates) from HIV-1-infected cells. The statins also blocked the enhanced oxidative stress due to HIV-1-infected cells and ethanol. The results of this study provide new insights into HIV-1 neuropathogenesis aimed at the development of future HIV-1 therapeutics to eradicate viral reservoirs from the brain. Acheampong, E., Parveen, Z., Mengistu, A., Ngoubilly, N., Wigdahl, B., Lossinsky, A.S., Pomerantz, R.J., and Mukhtar, M. Cholesterol-Depleting Statin Drugs Protect Postmitotically Differentiated Human Neurons against Ethanol- and Human Immunodeficiency Virus Type 1-Induced Oxidative Stress In Vitro. Journal of Virology, 81, pp. 1492-1501, 2007.

Director's Report to the National Advisory Council on Drug Abuse - May, 2007

Research Findings - Basic Behavioral Research

Nornicotine Enantiomers Decrease Nicotine Self-Administration in Rats

Dr. Michael Bardo and colleagues compared R(+) and S(-) enantiomers of nornicotine (a naturally occurring metabolite of nicotine) for their potency to decrease intravenous nicotine self-administration and sucrose-maintained responding. They also measured bioavailability in brain, effects on blood pressure and heart rate, and the development of tolerance. Given subcutaneously, both enantiomers dose-dependently decreased nicotine self-administration at the highest doses (5.6 and 10 mg/kg), however R(+)-nornicotine was more effective. In an intermediate dose (3 mg/kg), only R(+)-nornicotine reduced nicotine self-administration. Both enantiomers showed a similar magnitude of effect in decreasing nicotine self-administration; an effect that lasted up to 240 minutes. Repeated doses of R(+)- or S(-)-nornicotine did not change the number of nicotine infusions, indicating a lack of tolerance to this effect. Sucrose pellet-maintained behavior was also dose-dependently reduced by both enantiomers, however unlike their effects on nicotine self-administration, there were no significant differences between the enantiomers. Assessment of brain levels 60 min after systemic nornicotine enantiomer treatment revealed no difference in brain levels between R(+) and S(-)-nornicotine. Cardiovascular effects were assessed over a course of 9 treatment days. Both enantiomers increased heart rates and mean arterial pressure when given acutely, however tolerance to these effects only developed in the rats given chronic R(+)-nornicotine. These data suggest that, although both of these enantiomers of nornicotine might be useful in developing a pharmacotherapy for nicotine addiction, the R(+) enantiomer may hold more promise. Stairs, D.J., Neugebauer, N.M., Wei, X., Boustany, C., Hajahmat, M., Cassis, L.A., Crooks, P.A., Dwoskin, L.P. and Bardo, M.T. Effects of Nornicotine Enantiomers on Intravenous S(-)-Nicotine Self-Administration and Cardiovascular Function in Rats. Psychopharmacology, 190, pp. 145-155, 2007.

Chlordiazepoxide and Dizocilpine Selectively Impair Acquisition Learning in Rats

Dr. Joseph Galizio and colleagues tested the effects of the NMDA-antagonist dizocilpine (DZP), the opiate-agonist morphine (MOR), and the benzodiazepine chlordiazepoxide (CDP) using a novel repeated-acquisition and performance (RAP) task. This within-session procedure measures a rat's food-reinforced nose-poke response to one of six target locations on a computer touch screen. One location (target) is designated the correct location in the performance component of the task. Pretreatment with DZP, MOR or CDP increased the number of errors on this task. MOR increased the errors for both the acquisition and performance target locations. But interestingly, CDP, and some

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doses of DZP, increased errors only in the acquisition component, with little effect on the performance component. These data suggest that benzodiazepines and NMDA antagonists can selectively interfere with acquisition (learning) processes. The procedures used in the current task more closely resemble the RAP used in primates than those used in rodents. These results therefore shed some light on the controversy over whether or not species differences, or different RAP tasks, are responsible for different results on repeated-acquisition testing. Pitts, R.C., Buda, D.R., Keith, J.R., Cerutti, D.T. and Galizio, M. Chlordiazepoxide and Dizocilpine, but not Morphine, Selectively Impairs Acquisition under a Novel Repeated-Acquisition and Performance Task in Rats. Psychopharmacology, 189, pp. 135-143, 2006.

Mecamylamine Attenuates Responding for Nicotine and Cue-Induced Reinstatement

Drs. Xiu Liu, Anthony Cagguila, and colleagues tested the impact of noncompetitive nicotinic acetylcholine blockade (using mecamylamine) on cue-induced reinstatement of nicotine seeking. Rats were trained to self-administer intravenous nicotine, with a stimulus light accompanying the nicotine infusion. A second group was trained to respond on a lever for food reinforcement. The behavior was then extinguished, with lever pressing resulting in no food/light or drug/light consequences. Following extinction, rats were pretreated with either saline or mecamylamine prior to a test session in which pressing the drug or food- associated lever resulted in the light cue only. Mecamylamine dose-dependently attenuated cue-induced reinstatement for the nicotine-associated light cue, but not for the food-associated light cue. After the reinstatement test session, rats were again trained to self-administer nicotine or food, and behavior was re-established after 5-7 sessions. After retraining, mecamylamine was given as a challenge prior to a test session, when levers remained active. It significantly reduced nicotine self-administration. These data indicate that nicotine receptor blockade selectively attenuates both responding for nicotine and cue-induced reinstatement. Moreover, this is a specific effect, as reinstatement to the food-associated cue was unaffected. These findings suggest that mecamylamine might be clinically useful in promoting smoking cessation and for preventing relapse. Liu, X., Caggiula, A.R., Yee, S.K., Nobuta, H., Sved, A.F., Pechnick, R.N. and Poland, R.E. Mecamylamine Attenuates Cue-Induced Reinstatement of Nicotine Seeking Behavior in Rats. Neuropsychopharmacology, 21, pp. 710-718, 2007.

Adolescent Rats Show Reduced Nicotine Withdrawal

Dr. Athina Markou and colleagues compared the motivational and somatic signs of nicotine withdrawal in adolescent versus adult male rats. Motivational signs of nicotine withdrawal was measured using intracranial self-stimulation (ICSS) threshold measures. Results indicate that adolescent rats displayed less motivational and somatic effects of nicotine withdrawal, with no significant difference in ICSS threshold compared to baseline, and fewer total observed somatic signs during precipitated withdrawal. Adults, on the other hand, displayed a significant increase in the ICSS threshold (indicating withdrawal) and a dose-dependent increase in somatic signs. Thus, it appears that the negative effects of nicotine withdrawal are less severe in adolescent rats as compared to their adult counterparts. As adolescence is known to be a period of increased vulnerability to nicotine addiction, the current data suggest that adolescents may be not only more sensitive to the positive reinforcing effects of nicotine, but also less sensitive to the negative effects of withdrawal, and that both may underlie this enhanced vulnerability as well. O'Dell, L.E., Bruijnzeel, A.S., Smith, R.T., Parsons, L.H., Merves, M.L., Goldberger, B.A., Richardson, H.N., Koob, G.F. and Markou, A. Diminished Nicotine Withdrawal in Adolescent Rats: Implications for Vulnerability to Addiction. Psychopharmacology, 186, pp. 612-618, 2006.

Planned Meetings

Publications

Staff Highlights

Grantee Honors

MDMA ("Ecstasy") Self-Administration Is Abolished in Serotonin Transporter Knockout Mice

The rewarding properties of MDMA have been established in monkeys, rats, and mice, but the neurobiological mechanisms underlying MDMA's reinforcing effects remain unclear. MDMA increases the synaptic concentration of serotonin (5-HT), dopamine (DA) and norepinephrine as well as other neurotransmitters. Although some pharmacological studies have implicated DA in the reinforcing properties of MDMA, other data support a role for 5-HT in MDMA's rewarding effects, and in agreement with this MDMA binds with higher affinity to the 5-HT transporter (SERT) than to the DA transporter. The goal of this study was to evaluate the role of SERT in the reinforcing properties of MDMA using intravenous self-administration in SERT knockout (KO) and wild-type mice. The investigators used microdialysis to measure MDMA-evoked DA and 5-HT release in the nucleus accumbens (NAc) and prefrontal cortex (PFC), respectively. DA release in the NAc did not differ between KO and WT mice, whereas 5-HT release in the PFC was greatly reduced in the KO mice compared to WT. These results provide evidence for a key role for serotonin in MDMA's rewarding effects, and suggest that the SERT might be a fruitful target for the development of effective treatments for MDMA abuse, as has also been suggested for methamphetamine dependence in humans. Trigo, J.M., Renoir, T., Lanfumey, L., Hamon, M., Lesch, K.P., Robledo, P., and Maldonado, R. 3,4-Methylenedioxymethamphetamine Self-Administration is Abolished in Serotonin Transporter Knockout Mice. Biological Psychiatry [Epub ahead of print], 2007.

Methamphetamine Exposure Increases Synapse Formation in Striatal Regions Important for Habit Learning

Dr. Terry Robinson and his colleagues have been using anatomical methods to investigate structural changes in neuron morphology after treatment with a variety of drugs of abuse, mostly focused on brain regions that mediate the psychomotor activating and incentive motivational effects of drugs. However, repeated exposure to psychostimulant drugs also facilitates a transition in control of behavior guided by action-outcome associations, to behavior controlled by "automatized" stimulus-response habits. This transition is thought to be due to increasing engagement and control over behavior by the dorsolateral (but not dorsomedial) striatum. In this study, the PI hypothesized that repeated exposure to methamphetamine would differentially alter the density of dendritic spines on medium spiny neurons (MSNs) in the dorsolateral vs. dorsomedial striatum. Rats were treated with repeated injections of methamphetamine, and 3 months later dendrites were visualized using a technique in which green fluorescent protein can be expressed in vivo. Prior exposure to methamphetamine produced a significant increase in mushroom and thin spines on MSNs in the dorsolateral striatum and a significant decrease in mushroom spines in the dorsomedial striatum. These changes in spine densities may reflect differential alterations in glutamatergic innervation of these two subregions in dorsal striatum and indicate that, after drug exposure, the dorsolateral subregion receives more excitatory drive. The authors speculate that exposure to psychostimulant drugs may facilitate the development of stimulus-response habits by reorganizing patterns of synaptic connectivity in the dorsal striatum such that the dorsolateral subdivision has increased control over behavior. Behavior then would become more automatic and habitual, consistent with patterns of drug consumption behavior that have been observed in human addicts. Jedynak, J.P., Uslaner, J.M., Esteban, J.A., Robinson, T.E. Methamphetamine-Induced Structural Plasticity in the Dorsal Striatum. European Journal of Neuroscience, 25, pp. 847-853, 2007.

The Subthalamic Nucleus (STN) and Control of Impulsive Behavior

in the Rat

Recent evidence suggests that the STN is involved in mediating the effects of drugs of abuse and in impulse control. In animal models, lesions of the STN alter the behavioral and reinforcing effects of cocaine and either increase or decrease impulsive responding, depending on the exact nature of the behavioral task. The goals of the current study were (a) to determine the effects of STN lesions on behaviors indicative of "impulsive action" (or behavioral disinhibition) and "impulsive choice" (or impulsive decision making); and (b) to examine the effects of amphetamine and food restriction on these behaviors in animals with STN lesions. To test for impulsive action, the investigators used differential reinforcement of low rates of responding (DRL). In the DRL task, the rat is rewarded only if it restrains from pressing the reward lever for a specified time period (30 s in these experiments). Impulsive choice was measured by performance on a delay discounting task in which the rat has a choice between a lever that delivers one banana-flavored pellet immediately vs. another lever that delivers four pellets, but only after a delay (delay times varied from 3 to 24 s). Food restriction and acute amphetamine exposure, which are known to affect impulsivity, were tested in both tasks after STN lesions to determine if they augmented the lesions' effects. The investigators found that STN lesions increased impulsive action in the DRL task but decreased impulsive choice in the delay discounting task. Amphetamine and food restriction each increased impulsive action and decreased impulsive choice to a greater extent in STN-lesioned animals than in sham-lesioned controls. The authors speculate that these apparently discrepant effects may be because STN lesions enhance the incentive salience assigned to rewards, rather than having a more general effect on impulsivity or ability to measure time. In the DRL task, enhanced incentive salience could produce premature responding because the subjects are overly eager to receive the reward; in the delay discounting task, such enhancement could favor willingness to wait for the larger reward. The results of these experiments, and the authors' thoughtful discussion of the underlying psychological processes, provide a theoretical framework for understanding the role of STN and its viability as a potential target for treating disorders characterized by deficits of behavioral control, such as drug addiction and attention deficit hyperactivity disorder. Uslaner, J.M. and Robinson, T.E. Subthalamic Nucleus Lesions Increase Impulsive Action and Decrease Impulsive Choice--Mediation by Enhanced Incentive Motivation? European Journal of Neuroscience, 24, pp. 2345-2354, 2006.

Orbitofrontal Neurons of Rats Treated with Chronic Cocaine Fail to Efficiently Encode Cues Associated with Negative Outcomes

Recent evidence has linked exposure to addictive drugs to an inability to use information about adverse consequences, or outcomes, to control behavior. For example, drug-experienced animals often fail to adapt their behavior to avoid adverse outcomes in reversal tasks or after changes in the value of expected rewards. These deficits are similar to those caused by damage to the orbitofrontal cortex (OFC), suggesting that addictive drugs may cause long-lasting changes in the representation of outcome associations in a circuit that includes the OFC. In the present study, the investigators tested this hypothesis by recording from OFC neurons during a discrimination task in rats previously treated with cocaine (30 mg / kg i.p. for 14 days) and in saline treated controls. Rats were trained to associate one odor with sucrose reward and a second odor with a bitter quinine solution. Activity of neurons in OFC was recorded while animals were learning the discrimination. All rats learned the odor discrimination, but the behavior of the two groups during learning differed. Even before reaching criterion, control rats made fast responses towards the fluid well when they anticipated sucrose, but when they made incorrect approaches after sniffing quinine-associated odors, they approached

slowly. By contrast, cocaine-treated rats, failed to appropriately slow responses made towards the quinine well during learning. OFC activity was analyzed first during this learning phase, when animals were still making some incorrect responses. Firing rate was quantified in the interval between odor cue presentation and fluid delivery, during which time OFC responses would indicate neural encoding of expected outcomes (i.e., not a response to odor or taste per se). In both groups of rats, the investigators found that different subsets of neurons fired selectively in anticipation of the sucrose vs. quinine in this delay interval. Therefore, OFC neurons in both groups were capable of signaling the expected outcome after the animal had made a behavioral response towards the fluid well. They then saw that as the animals learned the task to criterion, neurons began responding to the odor cues themselves (i.e., began firing earlier in the trial). In control animals, sucrose-expectant neurons (i.e. those that had fired more during the delay interval on a sucrose trial) also fired more intensely to the sucrose-associated odor, and quinine-expectant neurons fired more to the other odor. That is, in control animals, OFC neurons developed selective responsivity to conditioned stimulus associated with appetitive or aversive events. In the cocaine-treated rats sucrose-expectant neurons also developed a preference for the CS associated with sucrose, but these animals also showed impaired encoding of aversive outcomes: quinine-expectant neurons did not develop selective responses to the odor that signaled quinine in this group. Therefore, these neurons would be ineffective in guiding appropriate behavioral responses to stimuli that signal an aversive event, as was also evident by the inability of cocaine-treated animals to slow their approach to the quinine well. These results provide direct neurophysiological evidence that exposure to cocaine can cause behaviorally relevant changes in the processing of associative information in a circuit that includes the OFC, and that encoding of adverse outcomes is particularly vulnerable. Stalnaker, T.A., Roesch, M.R., Franz, T.M., Burke, K.A. and Schoenbaum, G. Abnormal Associative Encoding in Orbitofrontal Neurons in Cocaine-Experienced Rats During Decision-Making. European Journal of Neuroscience, 24, pp. 2643-2653, 2006.

Animal Study Indicates that the ADHD Medication, Atomoxetine, May Help Alleviate Nicotine Withdrawal

Nicotine withdrawal symptoms are an important target for medications development because they are a major indicator of smoking relapse following cessation. The cognitive symptoms of nicotine withdrawal and attention deficit hyperactivity disorder (ADHD) are similar and may share neural correlates. Thus, therapeutics that ameliorate ADHD symptoms may also ameliorate nicotine-withdrawal symptoms. The present research tested this hypothesis in an animal model of nicotine withdrawal-associated cognitive deficits using atomoxetine, a norepinephrine reuptake inhibitor that is approved to treat the symptoms of ADHD. Mice were administered nicotine (or saline in control animals) for 12 days. Twenty-four hours after nicotine administration ceased, the animals were trained in fear conditioning by pairing two presentations of an auditory conditioned stimulus (CS) with a footshock in a specific training environment (context) to examine the effects of nicotine withdrawal on learning. One day after training, the animals were tested for freezing behavior in response to either the context or the tone CS. Fear conditioning is useful because it can be rapidly acquired and it involves two types of learning that engage different brain areas. Associations between context and shock require the hippocampus, while associations between tone and shock do not. Consistent with previous research, mice withdrawn from chronic nicotine had lower levels of contextual fear conditioning than mice that were not withdrawn from chronic nicotine, but showed no differences in response to the CS. Atomoxetine dose-dependently reversed this deficit, suggesting that nicotine withdrawal may be associated with changes in noradrenergic function, acetycholinergic function, and/or with changes in cell signaling cascades in the

hippocampus or its associated circuits that are activated by both nicotine and norepinephrine. These data suggest that atomoxetine may be efficacious for treating nicotine withdrawal-associated cognitive deficits that promote relapse in abstinent smokers. Davis, J.A. and Gould, T.J. Atomoxetine Reverses Nicotine Withdrawal Associated Deficits in Contextual Fear Conditioning. Neuropsychopharmacology, 2007 [Epub ahead of print].

Combined Inhibition of Dopamine and Serotonin Transporters Reduces Cocaine Self-Administration

The dopamine transporter (DAT) is now acknowledged as a critical recognition site for cocaine and is a major factor in cocaine's significant abuse liability. Dr. Leonard Howell and his associates at Yerkes National Primate Research Center are studying DAT inhibitors because this class of compounds show promise in effectively treating cocaine abuse. They studied effects of a selective DAT inhibitor, RTI-336, in rhesus monkeys self-administering the drug, and examined the ability of the RTI-336 to substitute for cocaine in this paradigm. In addition, Dr. Howell used PET imaging to quantify the DAT occupancy of RTI-336 in the range of doses tested in the other studies. He reports that RTI-336 produces a dose-related decrease in cocaine self-administration, with approximately 90% DAT occupancy. RTI-336 did substitute for cocaine, i.e. the compound was self-administered, though with lower rates of responding that those associated with cocaine. Interestingly, when RTI-336 was given along with an inhibitor of the serotonin transporter, cocaine self-administration was completely eliminated. Dr. Howell and his colleagues propose that inhibiting both dopamine and serotonin transporters may represent a new approach to treating cocaine abuse in humans. Howell, L.L., Carroll, F.I., Votaw, J.R., Goodman, M.M., and Kimmel, H.L. Effects of Combined Dopamine and Serotonin Transporter Inhibitors on Cocaine Self-Administration in Rhesus Monkeys. Journal of Pharmacology and Experimental Therapeutics, 320, pp. 757-765, 2007.

MDMA, MDA, and Methamphetamine Produce Hyperthermia in Nonhuman Primates

Dr. Michael Taffe and his colleagues at the Scripps Research Institute have been studying the thermoregulatory effects of several structurally distinct amphetamine compounds in rhesus monkeys. A better understanding of these effects is important because severe and malignant hyperthermia is an often reported effect in MDMA abusers when seen by emergency medical personnel. Dr. Taffe compared the body temperature and locomotor effects of MDMA, MDA, and methamphetamine in monkeys outfitted with radiotelemetric devices that allowed continuous and unobtrusive monitoring. All three compounds were found to elevate temperature significantly, though the time course and duration of these effects varied and did not depend on increased activity. These studies are important in extending our knowledge of the hyperthermia-inducing effects of these compounds in that all three are commonly found in samples of the abused street drug ecstasy. Crean, R.D., Davis, S.A., Von Huben, S.N., Lay, C.C., Katner, S.N., and Taffe, M.A. Effects of (+/-)3,4-Methylenedioxymethamphetamine, (+/-)3,4-Methylenedioxyamphetamine and Methamphetamine on Temperature and Activity in Rhesus Macaques. Neuroscience, 142, pp. 515-525, 2006.

Acquistion of i.v. Cocaine Self-Administration in Adolescent and Adult Male Rats Selectively Bred for High and Low Saccharin Intake

Animal studies have explored numerous variables that confer vulnerability to the reinforcing effects of drugs of abuse. A growing number of studies are

pointing to greater vulnerability to the reinforcing effects of abused drugs in adolescents compared to adults. Another factor shown to confer vulnerability to the reinforcing effects of drugs is the propensity for high saccharin consumption. Recent work by Dr. Marilyn Carroll and her colleagues revealed heightened vulnerability to the reinforcing effects of cocaine in female rats selectively bred for high (HiS) versus low saccharin intake (LoS). HiS rats exhibited faster escalation of cocaine intake, self-administered more cocaine, and exhibited more cocaine-associated lever pressing during maintenance, extinction, and cocaine-primed reinstatement than LoS rats (Perry, J.L., Morgan, A.D., Anker, J.J., Dess, N.K., and Carroll, M.E. Escalation of I.V. Cocaine Self-administration and Reinstatement of Cocaine-Seeking Behavior in Rats Bred for High and Low Saccharin Intake. Psychopharmacology, 186, pp. 235-245, 2006). Given the growing body of animal research demonstrating greater adolescent vulnerability to the reinforcing effects of drugs (e.g., nicotine, alcohol, and morphine), Dr. Carroll and her colleagues compared the role of HiS versus LoS in cocaine self-administration in adult and adolescent male rats. In each of the four groups, faster acquisition of cocaine self-administration was correlated with higher cocaine intake during the last five days of acquisition. Acquisition was faster and in a greater percentage of rats in the LoS adolescents than LoS adults, but not HiS adolescents versus HiS adults, possibly indicating an age-independent ceiling effect among HiS rats. These results extend those from other rodent studies indicating greater vulnerability to the reinforcing effects of drugs (e.g., nicotine, alcohol, and morphine) in adolescent versus adult rats, and suggest that genetic background (saccharin avidity) modulates this effect. Perry, J.L., Anderson, M.M., Nelson, S.E, and Carrroll, M.E. Acquistion of I.V. Cocaine Self-Administration in Adolescent and Adult Male Rats Selectively Bred for High and Low Saccharin Intake. Physiology and Behavior, [epub ahead of print], 2007.

Nicotine Withdrawal Effects Differ in Adolescent and Adult Male Rats

Most smokers initiate smoking during adolescence. Adolescent initiation is associated with faster development of symptoms of dependence, greater severity of dependence, and greater difficulty quitting. Studies employing animal models of nicotine use suggest that adolescents are more sensitive than adults to the reinforcing effects of nicotine. Drs. Carrie Wilmouth and Linda Spear recently reported differences in adolescent and adult withdrawal effects. After seven days of chronic exposure to nicotine via implanted osmotic minipumps, nicotine withdrawal was induced via the nicotine antagonist mecamylamine, and anxiety-producing effects of withdrawal were assessed via behavior in open versus closed arms of the elevated plus maze (EPM). Following removal of the minipumps, spontaneous withdrawal was assessed by prepulse inhibition (PPI, i.e., inhibition of the acoustic startle response by presentation of a lesser intensity acoustic stimulus immediately prior to the startle stimulus), as a measure of withdrawal-related cognitive effects. Evaluation of behavior in the EPM indicated that withdrawal from chronic nicotine produced anxiety-like behavior in adults, but not in adolescents. Withdrawal from chronic nicotine had no effect on PPI in adults, but disrupted PPI in adolescents. These differences in adult versus adolescent withdrawal effects may contribute to understanding the enhanced vulnerability to nicotine during adolescence. Wilmouth, C.E. and Spear, L.P. Withdrawal From Chronic Nicotine in Adolescent and Adult Rats. Pharmacology, Biochemistry and Behavior, 85, pp. 648-657, 2006.

Nociceptive Threshold and Analgesic Response to Morphine in Aged and Young Adult Rats

Dr. Conan Kornetsky and colleagues conducted experiments to determine whether there are differences between young (5 mos) and aged (24 mos) rats

in their sensitivity to pain (nociception) and in their analgesic response to morphine. When nociception was assessed peripherally using a standard tail-flick response to nociceptive stimulation, aged rats exhibited a higher nociceptive threshold than young rats (i.e., less sensitivity to pain); however, when nociception was assessed by delivering nociceptive stimulation directly to a pain pathway in the brain (the mesencephalic reticular formation), there were no differences in pain sensitivity between the two age groups. These outcomes suggest that registration of peripheral nociceptive stimulation (as measured in the tail-flick procedure, which is commonly used to assess nociception in rodents), may be compromised in the aged rat. Assessment of morphine's analgesic effects revealed that at the higher two of the three morphine doses tested, both the young and the aged rats exhibited morphine analgesia; however, at the lowest dose, only the young rats exhibited analgesia. To the extent to which these data can be extrapolated to humans, the authors conclude these data suggest that "...the belief that the aged patient feels less pain and requires less analgesic medication than the young patient needs to be re-examined." Crosby, S.J., Knapp, C.M., and Kornetsky, C. Nociceptive Threshold and Analgesic Response to Morphine in Aged and Young Adult Rats as Determined by Thermal Radiation and Intracerebral Electrical Stimulation. Pharmacology Biochemistry and Behavior, 84, pp. 148-157, 2006.

Racial Discrimination, Conduct Disorder and Subsequent Drug Use: A Critical Period Hypothesis

The present study provided a test of a critical period hypothesis that links early experiences with both racial discrimination and conduct disorder (CD) to subsequent drug use. The hypothesis was examined in a longitudinal study of 889 African American adolescents selected from the Family and Community Health Study (FACHS), which is a study of environmental factors associated with health (mental and physical) in African American families. The first phase, time 1 (T1), conducted in 2004 when the children were on average, 10.5 years of age, examined both the children and their parents through self-report measures that included substance use, conduct disorder and a host of other factors. A second wave, T2, examined the same relationships when the children were 12.5 years of age. The current study of 606 families (average age of adolescents 15.5 years), at T3, continued the examination of the relation between CD, discrimination and substance use. Results examined to date have revealed a number of interesting relationships: For example, early onset CD was associated with earlier use of marijuana and more drug use 5 years later. The amount of use was higher by those who manifested behavioral problems early on as opposed to at age 12.5. Also interesting was the finding that almost every child (77%) manifesting diagnosable CD symptoms was above the median in discriminatory experience, and 54% of the T1 CD cases were in the top 20% of self-reported discrimination. Early discrimination was also related to earlier use of marijuana, and it predicted drug use 5 years later, through its relation with friends who were using. Moreover, the combination of discrimination and conduct problems was particularly influential, as those CD-diagnosed adolescents who were in the top quarter of the discrimination distribution were more likely to report using than was any other group. In short, it appears that early discriminatory experiences can have an aversive effect on Black children that can last for a while and, for some, may precipitate behaviors that are harmful to their health. Finally, the impact of discrimination was not limited to the adolescents: the relation between the parents' T1 reports of discrimination and their T1 use was also very strong. These results suggest that identification of behavioral problems as well as distress associated with discriminatory experience at an early age among African Americans is very important. Preventive interventions aimed at helping Black parents prepare their children for the difficulties they are likely to face as a result of discrimination from others, may be particularly effective, especially if presented to children under the age of 12 or 13. Gibbons, F.X., Yeh, H-C, Gerrard, M.,

Cleveland, M.J., Cutrona Carolyn, Simons, R.L., and Brody, G.H. Early Experience with Racial Discrimination and Conduct Disorder as Predictors of Subsequent Drug Use: A Critical Period Hypothesis. Alcohol and Drug Dependence, 88S, S27-S87, 2007.

Effects of 1 Receptor Blockade on Cocaine Seeking

Sigma1 (_1) receptors have been implicated in cognitive function, anxiety, depression, and regulation of stress responses. In addition, _1 receptors have been found to modulate several neurobehavioral effects of cocaine, including the drug's subjective, psychomotor stimulant, rewarding, and toxic actions. Moreover, pharmacological blockade of this receptor attenuates expression of cocaine-conditioned place preference (CPP), suggesting that _1 receptors participate in mediating the conditioned incentive effects of cocaine-related environmental stimuli. The present study was designed to investigate the role of _1 receptors in cocaine-seeking by testing the effects of a potent, selective _1 receptor antagonist, BD1047, on conditioned stimulus elicited reinstatement of cocaine self-administration. To establish whether BD1047 preferentially modifies drug-directed behavior or exerts general suppressant effects on motivated behavior, BD1047 effects were tested also on responding induced by stimuli conditioned to a potent conventional reinforcer, sweetened condensed milk (SCM). Because _1 receptors have been implicated not only in the expression but also acquisition of cocaine CPP, tests of BD1047 effects on self-administration of cocaine and SCM were conducted as well. BD1047 (1-30 mg/kg) reversed response reinstatement induced by the cocaine SD at 20 and 30 mg/kg but only modified SCM SD-induced responding at the highest (30 mg) dose, when responding was reversed to extinction levels. BD1047 did not modify responding reinforced directly by SCM or cocaine. The findings support a role for _1 receptors in regulating conditioned responses to cocaine-related contextual stimuli and identify this receptor as a potential treatment target for the prevention of craving and relapse. Martin-Fardon, R., Maurice, T., Aujla, H., Bowen, W.D., and Weiss, F. Differential Effects of 1 Receptor Blockade on Self-Administration and Conditioned Reinstatement Motivated by Cocaine vs Natural Reward. Neuropsychopharmacology advance online publication 31 January 2007.

Behavioral Regulation in Individuals Co-morbid for both Cocaine and Alcohol Abuse

Neuronal integrity of frontal cortical regions may be compromised in chronic psychostimulant abusers. These frontal regions show a hypoactivity that persists after drug use is discontinued and long-term abusers show functional deficits on cognitive tasks that involve evaluating outcomes and taking risks. Human subjects with lesions to these frontal regions have similar difficulty with risk taking tasks and it appears that these deficits are due to an inability to inhibit prepotent responses, especially those that are environmentally triggered. Animal studies have mimicked these deficits in rats and monkeys with lesions of the orbitofrontal cortex (OFC). OFC lesions produce a behavioral inflexibility that manifests as a deficit in reversal learning. Recently, Drs. Fillmore and Rush at the University of Kentucky have been studying cognitive flexibility in cocaine abusers who are also moderate or heavy drinkers of alcohol. Previous investigations from this laboratory had revealed that subjects with a history of cocaine + alcohol abuse have difficulty inhibiting responses on a go/no-go task to measure control of behavioral activation and inhibition. The present study was conducted to determine if this drug abuse history can be associated with more general deficits of stimulus-response learning, which also depends on a complex neurocircuitry involving the OFC, amygdala and striatal regions. In this study authors used a cued go/no-go task where cocaine abusers or controls who were only light drinkers were tested for their speed of learning to respond to a "go" cue and withhold responding in the presence of a

"no go" cue. Subjects earned monetary rewards for correct responses. Results indicate that individuals who abuse both cocaine and alcohol may have deficits of behavioral control that can be linked to perturbations of this circuit. Fillmore, M.T. and Rush, C. R. Polydrug Abusers Display Impaired Discrimination-Reversal Learning in a Model of Behavioural Control. Journal of Psychopharmacology, 20, pp. 24-32, 2006.

Accuracy of the Expectancy Valence Model for Predicting Drug Induced Impairments in Risky Decision Making

It is important to understand how drugs of abuse might alter decision making under conditions of variable risk. For example, in evaluating situations that expose drug abusers to risk of acquiring or transmitting HIV and other STDs, drugs may affect various components of a decision making process - from reward evaluation, to sensitivity for aversive consequences, expectations, or use of prior learned information, etc. NIDA-funded investigators have been applying formal mathematical models to data from acute drug tests in the laboratory, in an attempt to deconstruct the processes influenced under conditions of risk and uncertainty. Recently Dr. Scott Lane and colleagues evaluated the ability of the expectancy valence model (EVM) to predict changes in risk taking while volunteers are under the influence of marijuana, alcohol or the benzodiazepine alprazolam. The model includes three parameters that relate to putatively independent factors in a decision making process: (a) valence (affective reaction to the outcome of each trial, weighted as an index of salience); (b) learning/memory (updating or the influence of recent outcomes on expectancies); and (c) consistency (sensitivity of the decision maker's choices to the expectancies). Learning from the consequences of each decision should increase this last, consistency parameter, whereas effects on concentration, motivation and attention might be expected to decrease this value. Theoretically, these three constructs represent motivational, learning/memory, and sensitivity components of decision making. When all drug data were collapsed, investigators noted that the learning/memory parameter was the only one that was statistically different from placebo. The authors suggest that perhaps this component of decision making is the most sensitive to influence by drugs of abuse, but additional drugs should be examined. They also suggest that the EVM might be applied to assess populations with known deficits in decision making and evaluate these components as possible targets for intervention. Lane, S.D., Yechiam, E. and Busemeyer, J.R. Application of a Computational Decision Model to Examine Acute Drug Effects on Human Risk Taking. Experimental and Clinical Psychopharmacology, 14, pp. 254-264, 2006.

Rat Prenatal or Adolescent THC Exposure is Associated with Greater Heroin Intake in Adulthood

Brain cannabinoid and opioid systems are intimately connected. Cannabinoids stimulate release of enkephalin in the nucleus accumbens (NAS).They also stimulate PENK - the precursor gene for this endogenous opioid. Cannabinoid and opioid mu receptors are found on the same VTA neurons. Dr. Yasmin Hurd and colleagues have been conducting NIDA-supported studies to model (1) prenatal effects of clinically relevant gestational THC exposure and (2) adolescent marijuana abuse, to determine effects on the vulnerability for opiate self-administration in adulthood. In the prenatal study, rats were implanted for i.v. THC administration and then bred. THC was administered (.15 mg/kg) from gestational day 5 to postnatal day (PND) two (corresponding to mid-gestation in the human). Results showed that THC rats administered more drug and emitted more responses after stress, and had more drug-seeking behavior during extinction, but resembled controls on reinstatement tests with a heroin "prime" (return to bar-pressing on the drug-associated lever). Other groups were used to measure opioid peptide mRNA expression. The authors report

that PENK mRNA in the NAS core and medial shell, and in the amygdala, was significantly increased in THC exposed animals at PND 62, suggesting a hyperactivity of the mesocorticolimbic enkaphalinergic system that may mediate greater sensitivity for heroin reinforcement seen on some measures of these behavioral paradigms. Spano, M.S, Allgren, M., Wang, X. and Hurd, Y.L. Prenatal Cannabis Exposure Increases Heroin Seeking with Allostatic Changes in Limbic Enkephalin Systems in Adulthood. Biological Psychiatry, 61, pp. 554-563, 2007. In the adolescent study, THC exposed adolescents took significantly more opiate (greater number of infusions on the active lever, with no differences on an inactive lever) than adults. During dose response testing, they also self-administered significantly more heroin at this dose, and at 60 _g/kg/inf. Interestingly, THC treated animals did not exhibit more drug-seeking behavior during extinction. In a separate group sacrificed at PND 57, THC treatment was associated with significant increases of PENK mRNA expression in the NAC shell. There was also a significant positive correlation between the heroin self-administration and DAMGO-stimulated [35S]GTP_S binding in the shell suggesting that THC increases opiate _ receptors in this region, and a significant correlation between heroin self-administration and CB-1 (cannabinoid receptor) binding in the substantia nigra. Ellgren, M., Spano, S.M. and Hurd, Y.L. Adolescent Cannabis Exposure Alters Opiate Intake and Opioid Limbic Neuronal Populations in Adult Rats. Neuropsychopharmacology, (Epub ahead of print) May 22, 2006, pp. 1-9. Findings from these studies suggest that developmental exposure to the active pharmacological ingredient in marijuana, THC, may enhance subsequent vulnerability for opiate abuse, and shed light on potential neurobiological mechanisms responsible for this effect.

Director's Report to the National Advisory Council on Drug Abuse - May, 2007

Research Findings - Behavioral and Brain Development Research

Effects of Alcohol and Combined Marijuana and Alcohol Use During Adolescence on Hippocampal Volume and Asymmetry

During the period of adolescence, the hippocampus may be particularly vulnerable to the effects of alcohol and marijuana use. This study was designed to examine hippocampal volume and asymmetry in three groups of adolescents aged 15 - 18. An additional aim of the study was to examine the relationships between verbal memory functioning and hippocampal morphometry. The groups consisted of: 1) alcohol users, 2) alcohol + marijuana users and 3) non-substance-using controls. Differential effects on hippocampal morphometry were found for those adolescents abusing alcohol compared to those abusing both alcohol and marijuana. Alcohol abuse/dependence was associated with smaller left hippocampal volumes and increased right > left asymmetry compared to the alcohol + marijuana using teens and the non-substance-using controls. While a functional relationship was shown between verbal learning and hippocampal asymmetry in the healthy controls; this relationship was not found in adolescent substance abusers. Further research is needed to examine the potential interaction of marijuana and alcohol use on neurocognitive functioning among adolescent populations. Medina, K., Schweinsburg, A., Cohen-Zion, M., Nagel, B., and Tapert, S. Effects of Alcohol and Combined Marijuana and Alcohol Use During Adolescence on Hippocampal Volume and Asymmetry, Neurotoxicology and Teratology, 29(1), pp. 141-152, 2007.

Prenatal Marijuana Exposure and Marijuana Use at Age 14

In this longitudinal study conducted at the University of Pittsburgh, a cohort was recruited during the fourth prenatal month, and the mothers and their offspring were assessed at multiple ages from that time on. The assessments involved maternal psychological, social, and environmental factors, demographic status and substance use, and offspring cognitive, behavioral, psychological, and physical development. This report focuses on the association between prenatal marijuana exposure and marijuana use by the offspring at age 14 years. The analyses in this report are based on 563 offspring-mother pairs (74% of the original sample). The sample was half African American, half Caucasian, and mostly of lower socioeconomic status. Overall, at age 14 years, 30% of the adolescents reported using marijuana in the past year, and 7.5% reported using marijuana regularly (i.e., at least three to four times per week). Thirteen additional adolescents had initiated marijuana use but did not report use in the past year. Based on multivariate models of analysis, the authors conclude that prenatal marijuana exposure (i.e., average daily joints), in addition to other factors, predicts marijuana use at age 14 years. Specifically, they report a marginally significant association between prenatal marijuana

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exposure and age of onset of marijuana use, and a significant association between prenatal marijuana exposure and frequency of marijuana use at age 14 years. Variables controlled in these analyses include child's current alcohol and tobacco use, pubertal stage, delinquency, peer drug use, family history of drug use, and parental depression, current drug use, and strictness/supervision. Prenatal marijuana use did not predict age of onset or frequency of use for either alcohol or tobacco. The investigators discuss possible mechanisms by which prenatal marijuana exposure may predict marijuana use at age 14, and also discuss limitations on generalizability of the findings. Day, N.L., Goldschmidt, L., and Thomas, C.A. Prenatal Marijuana Exposure Contributes to the Prediction of Marijuana Use at Age 14. Addiction, 101, pp. 1313-1322, 2006.

Prenatal Cocaine Exposure and Child Behavior Outcomes Through Age 7 Years

Investigators from the Maternal Lifestyle Study, a multi-site longitudinal cohort study of development following prenatal exposure to cocaine and other substances, have reported on child behavior problems at ages 3, 5, and 7 years. The Child Behavior Checklist (CBCL) was administered to caregivers at all three ages, and data were reported for internalizing (e.g., social withdrawal, somatic complaints, anxiety), externalizing (e.g., delinquent and aggressive behaviors), and total behavior problems. Between 752 and 917 children were included in data analyses depending on the score category and the assessment age. Longitudinal hierarchical linear models were utilized to investigate relationships between prenatal cocaine exposure and behavior problem trajectories from 3 to 7 years. Statistical analyses included adjusting for a number of other prenatal exposures, and for time-varying covariates such as ongoing caregiver use of substances, demographic factors, family violence, and caregiver psychological distress. The authors report that high prenatal cocaine exposure was associated with trajectories of behavior problems (high exposure was defined as use > 3 times per week in the first trimester), independent of, and less than the significant combined effect of prenatal and postnatal tobacco and alcohol exposures. Caregiver depression and family violence were found to have independent negative association with all behavior outcomes. The investigators note that although the analyses are an important step in examining relationships between prenatal cocaine exposure and behavior outcomes, causality is far from being established. In addition, they point out that the findings highlight a need not only for continued prevention and treatment programs directed toward illegal drug use, but also for increased effort toward prevention and treatment of tobacco and alcohol use. Bada, H.M., Das, A., Bauer, C.R. et al. Impact of Prenatal Cocaine Exposure on Child Behavior Problems Through School Age. Pediatrics, 119, pp. e348-e359, 2007.

Maternal Depression, Prenatal Cocaine Use, and Infant Neurobehavior

Infant neurobehavior was assessed for 1053 infants at 1 month of age, and was studied in relation to prenatal cocaine use and postpartum maternal depression. The NICU Network Neurobehavioral Scale (NNNS) was used to measure infant neurobehavior, and the Addiction Severity Index (ASI) was used to assess present and past psychiatric history. These analyses were carried out within the context of the Maternal Lifestyle Study, a multi-site longitudinal cohort study of development following prenatal exposure to cocaine and other substances. Four groups were derived based on combinations of prenatal cocaine exposure/no prenatal cocaine exposure and current postpartum depression/no current postpartum depression. Analysis of covariance (with covariates birthweight, maternal age, SES, research site, and prenatal nicotine, marijuana, and alcohol) was utilized to examine infant neurobehavior in the four groups. Prenatal cocaine exposure by postpartum

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depression interactions were significant. A postpartum depression association was found for the non-cocaine-exposed infants (poorer self-regulation and more stress signs, excitability, and arousal than infants in the other groups). The combined prenatal cocaine exposure/current postpartum depression group did not differ on any of the neurobehavioral measures from the no-prenatal cocaine exposure/no current postpartum depression group. The investigators suggest that prenatal cocaine exposure may buffer or alter the relationship between postpartum depression and infant neurobehavior, with one possible explanation being prenatal cocaine exposure influences on developing monoamine systems. While cautioning that these analyses cannot determine if the observed depression effects are related solely to postpartum depression or if prenatal depression contributes to this relationship, the authors note that the findings do suggest the importance of considering maternal mood in studies of prenatal substance exposure. Salisbury, A.L., Lester, B.M., Seifer, R. et al. Prenatal Cocaine Use and Maternal Depression: Effects on Infant Neurobehavior. Neurotoxicology and Teratology, epub ahead of print, December 2006.

Prenatal Cocaine Exposure and Infant Regulation at 7 Months of Age

Using heart rate (HR) and respiratory sinus arrhythmia (RSA) as indices of reactivity and regulation during infancy, Drs. Schuetze, Eiden, and Coles report on assessments at 7 months of age in a sample of 154 infants (79 prenatally-exposed to cocaine and 75 not prenatally-exposed to cocaine). Data were collected during baseline and during tasks designed to elicit positive and negative affect. Analyses of covariance were carried out to examine group differences in change scores, with maternal alcohol and cigarette use during pregnancy, maternal age, measures of fetal growth, and gestational age as covariates. The investigators report that there was a significant suppression of RSA during the negative affect task for the non-exposed group but not for the exposed group. The response pattern of RSA suppression from baseline to environmental challenge is noted by the authors as being associated with more optimal state regulation in infancy, decreased behavior problems in preschool aged children, and more adaptive behavior during attention and affect eliciting tasks in preschool and school aged children. Based on their RSA suppression finding and other results, the authors conclude that their findings provide additional support for an association between prenatal cocaine exposure and dysregulation during infancy. Schuetze, P., Eiden, R.D., and Coles, C.D. Prenatal Cocaine and Other Substance Exposure: Effects on Infant Autonomic Regulation at 7 Months of Age. Developmental Psychobiology, 49, pp. 276-289, 2007.

Types of Violence, Protective Factors, Psychopathology, and Behaviors in Drug-Exposed Youth at 11 Years of Age

In this examination of violence and resilience among youth exposed to cocaine and other substances during pregnancy, four types of violence (community, domestic, violent friends, history of child abuse) were studied relative to the occurrence of several outcomes (delinquency, early drug use, symptoms of depression, diagnosis of conduct disorder or oppositional defiant disorder, diagnosis of ADHD) for 517 children at 11 years of age. Measurement of protective factors involved seven indicators of positive relationships and prosocial behavior to teachers, parents, friends, and peers, as well as indicators of effortful control (inhibitory control and attentional focusing). This work was conducted in the context of the Maternal Lifestyle Study, a multi-site longitudinal study of the development of children prenatally-exposed to cocaine and other substances. Mixed model regression analysis was used for each outcome, and all models were adjusted for research site effects. The results show various patterns of associations between specific types of violence and

specific outcomes. For example, all forms of delinquency were associated with having violent friends, symptoms of depression were related to history of abuse, CD/ODD was more likely if exposed to domestic violence, and ADHD was not associated with any type of violence. Associations with protective factors also showed variation by outcome. For example, reduced occurrence of CD/ODD was associated with positive relatedness to others and with effortful control, while reduced school delinquency and reduced depression were related to positive relatedness. The authors conclude that the study provides new evidence on violence and protective factors relative to disruptive forms of psychopathology and behavior, and they comment on implications of the findings for interventions. Lagasse, L.L., Hammond, J., Liu, J., et al. Violence and Delinquency, Early Onset Drug Use, and Psychopathology in Drug-Exposed Youth at 11 Years. Annals of the New York Academy of Science, 1094, pp. 313-318, 2006.

Reliability and Validity of the Youth Version of the Balloon Analogue Risk Task (BART-Y) in the Assessment of Risk-Taking Behavior

Dr. Carl Lejuez and his colleagues examined the reliability and validity of the youth version of the Balloon Analogue Risk Task (BART-Y), a computer-based measure for assessing adolescent risk-taking propensity. In this sample of 98 inner-city African American adolescents (52% male, M age = 14.8, SD = 1.5), BART-Y demonstrated a significant relation with sensation seeking as well as a composite measure of risk behaviors across substance use, sexual behavior, delinquency, and health domains. BART-Y responding also explained unique variance in a composite of these risk behaviors above and beyond demographic variables and risk-related personality constructs, including sensation seeking and impulsivity. Lejuez, C.W., Aklin, W., Daughters, S., Zvolensky, M., Kayler, C., and Gwadz, M. Reliability and Validity of the Youth Version of the Balloon Analogue Risk Task (BART-Y) in the Assessment of Risk-Taking Behavior Among Inner-city Adolescents. Journal of Clinical Child and Adolescent Psychology, 36(1), pp. 106-111, 2007.

Improving Comprehension for HIV Vaccine Trial Information among Adolescents

Researchers from the Adolescent Trials Network for HIV/AIDS Interventions (ATN) developed and tested a simplified version of the HIV vaccine trial information provided to adults during the informed consent process by the HIV Network for Prevention Trials (HIVNET). The prototype was adapted for adolescents at risk for HIV/AIDS by: (1) reducing reading level; (2) reorganizing; (3) adding illustrations; and (4) obtaining focus group feedback. Adolescent participants (N = 187) at clinical sites in New York, Fort Lauderdale, and Los Angeles were randomly assigned to the standard or simplified version. Adolescents receiving the simplified version had significantly higher comprehension scores (80% correct vs. 72% correct), with 37% of items significantly more likely to be answered correctly and were also significantly more likely to recall study benefits and procedures. Overall, adolescents were less willing to participate in a potential HIV vaccine trial after presentation of information about the study than prior to presentation. The present study indicates the feasibility of adolescent participation in a vaccine trial, as simplification of vaccine information, combined with illustrations to depict key concepts, resulted in improved scores for adolescents on the comprehension and recall test. Murphy, D.A., Hoffman, D., Seage, G.R. 3rd, Belzer, M., Xu, J., Durako, S.J., and Geiger, M. Adolescent Trials Network for HIV/AIDS Interventions. Improving Comprehension for HIV Vaccine Trial Information Among Adolescents at Risk of HIV. AIDS Care, 19(1), pp. 42-51, 2007.

Unifying the Analyses of Anatomical and Diffusion Tensor Images Using Volume-Preserved Warping

Dr. Bradley Peterson and his colleagues at Columbia University Medical Center developed and tested an automated image analysis protocol that automatically identifies regions of anatomical abnormalities in anatomical magnetic resonance images and uses those regions as starting points for fiber tracking using diffusion tensor imaging. Their results showed that their methods could automatically identify regions of volumetric differences across groups of brains and, using those regions as seed points, identify differences in fiber tracts emanating from regions of known anatomical abnormalities. Xu, D., Hao, X., Bansal, R., Plessen, K.J., Geng, W., Hugdahi, K., and Peterson, B.S. Journal of Magnetic Resonance Imaging, 25, pp. 612-624, 2007.

Director's Report to the National Advisory Council on Drug Abuse - May, 2007

Research Findings - Clinical Neuroscience Research

Is Decreased Prefrontal Cortical Sensitivity to Monetary Reward Associated with Impaired Motivation and Self-Control in Cocaine Addiction?

Dr. Rita Goldstein and colleagues at Brookhaven National Laboratory used fMRI to investigate alterations in the brain's sensitivity to monetary rewards of different magnitudes in cocaine abusers and to study its association with motivation and self-control. Sixteen cocaine abusers and 13 matched healthy comparison subjects performed a forced-choice task under three monetary value conditions while brain activation was measured with functional magnetic resonance imaging. Objective measures of state motivation were assessed by reaction time and accuracy, and subjective measures were assessed by self-reports of task engagement. Measures of trait motivation and self-control were assessed with the Multidimensional Personality Questionnaire. The cocaine abusers demonstrated an overall reduced regional brain responsivity to differences between the monetary value conditions. Also, in comparison subjects but not in cocaine abusers, reward-induced improvements in performance were associated with self-reports of task engagement, and money-induced activations in the lateral prefrontal cortex were associated with parallel activations in the orbitofrontal cortex. For cocaine abusers, prefrontal cortex sensitivity to money was instead associated with motivation and self-control. These findings suggest that in cocaine addiction 1) activation of the corticolimbic reward circuit to gradations of money is altered; 2) the lack of a correlation between objective and subjective measures of state motivation may be indicative of disrupted perception of motivational drive, which could contribute to impairments in self-control; and 3) the lateral prefrontal cortex modulates trait motivation and deficits in self-control, and a possible underlying mechanism may encompass a breakdown in prefrontal-orbitofrontal cortical communication. Goldstein, R.Z., Alia-Klein, N., Tomasi, D., Zhang, L., Cottone, L.A., Maloney, T., Telang, F., Caparelli, E.C., Chang, L., Ernst, T., Samaras, D., Squires, N.K., and Volkow, N.D. American Journal of Psychiatry, 164(1), pp. 43-51, 2007.

Smoking Modulation of Mu-opioid and Dopamine D2 Receptor-Mediated Neurotransmission in Humans

Dr. Edward Domino and colleagues at University of Michigan used PET ligand imaging to test the hypothesis that some of the effects of smoking cigarettes in humans are mediated through nicotine activation of opioid and dopamine (DA) neurotransmission. Neuroimaging was performed using positron emission tomography and the radiotracers [C-11] carfentanil and [C-11] raclopride, labeling mu-opioid and DA D2 receptors, respectively. Six healthy male smokers were abstinent overnight. After radiotracer administration, subjects

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smoked two denicotinized cigarettes, followed 45 min later by two average nicotine cigarettes. Dynamic data were acquired over 90 min, and transformed into parametric maps of receptor availability in vivo (binding potential, BP), corresponding to low and high nicotine smoking periods and analyzed on a voxel-by-voxel basis using SPM'99 and correction for multiple comparisons. Significant activation of m-opioid receptor-mediated neurotransmission from denicotinized to average nicotine conditions was observed in the right anterior cingulate cortex. DA D2 neurotransmission was activated in the ventral basal ganglia, correlating with Fagerstrom scale nicotine dependence scores. Lower m-opioid receptor BP was also detected during the denicotinized smoking condition in the smoker group, compared to baseline scans in non-smokers, in the cingulate cortex, thalamus, ventral basal ganglia, and amygdala. These reductions were reversed during the average nicotine condition in the thalamus, ventral basal ganglia and amygdala. These data point to both the feasibility of simultaneously examining opioid and DA neurotransmission responses to smoking in humans, as well as to the need to examine non-nicotine aspects of smoking to more fully understand the behavioral effects of this drug. Scott, D.J., Domino, E.F., Heitzeg, M.M., Koeppe, R.A., Ni, L.S., Guthrie, S., and Zubieta, J.K. Neuropsychopharmacology, 32(2), pp. 450-457, 2007.

Role of the Anterior Cingulate and Medial Orbitofrontal Cortex in Processing Drug Cues in Cocaine Addiction

Dr. Rita Goldstein and colleagues at Brookhaven National Laboratory used fMRI to probe the role of the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) in processing of salient symptom-related cues during the simultaneous performance of an unrelated task in drug-addicted persons. They used a novel fMRI color-word drug Stroop task in 14 individuals with cocaine use disorders; subjects had to press for color of drug vs. matched neutral words. Although there were no accuracy or speed differences between the drug and neutral conditions in the current sample of subjects, drug words were more negatively valenced than the matched neutral words. Further, consistent with prior reports in individuals with other psychopathologies using different Stroop fMRI paradigms, this more classical color-word Stroop design revealed bilateral activations in the caudal-dorsal anterior cingulate cortex (cdACC) and hypoactivations in the rostro- ventral anterior cingulate cortex/medial orbitofrontal cortex (rACC/mOFC). A trend for larger rACC/mOFC hypoactivations to the drug than neutral words did not survive whole-brain corrections. Nevertheless, correlation analyses indicated that (1) the more the cdACC drug-related activation, the more negative the valence attributed to the drug words ($r=-0.86$, $P < 0.0001$) but not neutral words; and (2) the more the rACC/mOFC hypoactivation to drug minus neutral words, the more the errors committed specifically to the drug minus neutral words ($r=0.85$, $P < 0.0001$). Taken together, results suggest that this newly developed drug Stroop fMRI task may be a sensitive biobehavioral assay of the functions recruited for the regulation of responses to salient symptom-related stimuli in drug-addicted individuals. Goldstein, R.Z., Tomasi, D., Rajaram, S., Cottone, L.A., Zhang, L., Maloney, T., Telang, F., Alia-Klein, N., and Volkow, N.D. Neuroscience, 144(4), pp. 1153-1159, 2007.

Reinforcement Learning Signals Predict Future Decisions

Dr. Michael Cohen and colleagues at University of California, Davis used event-related brain potentials (ERPs) to investigate how flexibility to adapt decision strategies based on recent outcomes emerges through a reinforcement learning process, in which reward prediction errors are used dynamically to adjust representations of decision options. Authors recorded event-related brain potentials (ERPs) while subjects played a strategic economic game against a computer opponent to evaluate how neural responses to outcomes related to

subsequent decision-making. Analyses of ERP data focused on the feedback-related negativity (FRN), an outcome-locked potential thought to reflect a neural prediction error signal. Consistent with predictions of a computational reinforcement learning model, the authors found that the magnitude of ERPs after losing to the computer opponent predicted whether subjects would change decision behavior on the subsequent trial. Furthermore, FRNs to decision outcomes were disproportionately larger over the motor cortex contralateral to the response hand that was used to make the decision. These findings provide novel evidence that humans engage a reinforcement learning process to adjust representations of competing decision options. These findings form a foundation for understanding how drugs of abuse that act on reinforcement learning sytems could lead to dysfunctional decision-making. Cohen, M.X., and Ranganath, C. Journal of Neuroscience, 27(2), pp. 371-378, 2007.

Impaired Decision-making in Psychopathic Heroin Addicts

Dr. Jasmin Vassileva at University of Illinois, Chicago, investigated neurocognitive deficits in decision-making in a sample of pure heroin users to avoid two significant methodological challenges present in previous studies: polysubstance dependence and comorbid conditions, which are independently associated with neurocognitive impairments. Heroin addiction is highly prevalent in Bulgaria but polysubstance dependence is rare. The goal of the current study was to evaluate the potential contribution of psychopathogy to decision-making processes among this group of Bulgarian heroin addicts. They tested 78 male currently abstaining heroin addicts, classified as psychopathic or non-psychopathic using the Hare Psychopathy Checklist, Revised (PCL-R). Psychopathic heroin addicts showed notable deficits in decision-making in that they made significantly more disadvantageous decisions relative to non-psychopathic heroin addicts. Results indicate that the presence of psychopathy may exacerbate decision-making deficits in heroin addicts. Vassileva, J., Petkova, P., Georgiev, S., Martin, E.M., Tersiyski, R., Raycheva, M., Velinov, V., and Marinov, P. Drug and Alcohol Dependence, 86(2-3), pp. 287-289, 2007.

Early Sign of Cognitive Declination in Asymptomatic HIV+ individuals - Detectable upon Additional Stresses that Uncover Diminished Brain Reserve Network Capacity

Dr. Linda Chang and colleagues used fMRI to investigate how AIDS-associated dementia impairs cognitive systems, particularly working memory. Their results indicate that at the late stage of disease progression where neurodegeneration and related cognitive impairment had already developed, no therapeutic approaches can effectively intervene with the complication. Their findings suggest that new strategies are needed, such as aiming at the early stages of the disease prior to the emergence of clinical signs and symptoms of dementia become apparent, to prevent the recoverable subtle dysfunction from irreversible permanent neurodegeneration and to prevent development of risk-taking behavior due to cognitive impairment. Several recent fMRI studies carried out by Dr. Linda Chang and colleagues reveal that HIV-induced subtle brain dysfunction was detectable at early onset of the disease, which preceded clinical signs or deficits on cognitive tests, and which suggests BOLD fMRI to be more sensitive than clinical and neuropsychological evaluations in detecting early HIV-associated brain injury. Their work detected increased brain activation (elevated signal intensity of blood oxygenation) during working memory tasks in HIV patients with mild dementia, presumably because the brain injury required additional activation of the frontal lobes, greater modulation of the neural circuits, and increased usage of brain reserve to maintain normal cognitive function. The increased brain activation was also demonstrated in asymptomatic HIV+ individuals to challenges of more difficult

cognitive tasks that required heavier load of attention for working memory. Compared with control subjects, the asymptomatic HIV+ individuals showed greater magnitude of brain activation in the lateral prefrontal cortex during fMRI, yet normal on a battery of neuropsychological tests until the degree of difficulty in the task was increased. The patients with HIV also showed increased brain volume in the lateral prefrontal cortex but not in other activated regions, including the posterior parietal cortex, supplementary motor area, thalamus, caudate, and occipital cortex. The increase in activated brain volume was independent of task difficulty. Authors also observed abnormal fMRI activation and lower neuronal marker N-acetylaspartate in prefrontal and parietal cortices in another study where acoustic noise was the additional stressor, which presumably exhausted the already impaired network for more demanding working memory tasks. These studies demonstrate that fMRI can detect changes due to HIV brain injury even during the asymptomatic stage of the disease and suggest an increased usage of brain reserve to maintain cognitive performance as a compensatory response. Understanding how can brain function be strengthened to enhance compensation for HIV-associated, early stage perturbation and to preserve normal function may inform interventions to ameliorate cognitive impairment, such as facilitate neuronal processes of neuroresiliance and neuroplasticity. Tomasi, D., Chang, L., de Castro Caparelli, E., Telang, F., and Ernst, T., The Human Immunodeficiency Virus Reduces Network Capacity: Acoustic Noise Effect. Ann Neurol, 59(2), pp. 419-23, 2006.; Chang, L., Speck, O., Miller, E.N., Braun, J., Jovicich, J., Koch, C., Itti, L., and Ernst, T. Neural Correlates of Attention and Working Memory Deficits in HIV Patients. Neurology, 57(6), pp.1001-7, 2001; Ernst, T., Chang, L., Jovicich, J., Ames, N., and Arnold, S. Abnormal Brain Activation on Functional MRI in Cognitively Asymptomatic HIV Patients. Neurology, 59(9), pp. 1343-1349, 2002; Chang, L., Tomasi, D., Yakupov, R., et al. Adaptation of the Attention Network in Human Immunodeficiency Virus Brain Injury. Ann Neurol, 56, pp. 259 -272, 2004.

Altered Regional Blood Volume in Chronic Cannabis Smokers

Dr. Yurgelun-Todd and colleagues at McLean Hospital used dynamic susceptibility contrast MRI to study cerebral blood volume (CBV) alterations in long-term daily cannabis users. The objective of the present study was to examine differences in relative regional blood volume in focal regions of interest-including the frontal lobe, the temporal lobe, and the cerebellum-during a period of supervised abstinence from cannabis. Resting state CBV images were collected following a bolus of gadolinium contrast agent on 12 current, long-term daily cannabis users between 6 and 36 hr after the subjects' last reported cannabis use and 17 healthy comparison subjects. Cannabis users had significantly increased blood volumes in the right frontal area, in the left temporal area, and in the cerebellum relative to comparison subjects. Among the cannabis users, there were no significant correlations between regional blood volumes and either total lifetime episodes of smoking or urinary tetrahydrocannabinol concentrations. These findings have important implications for understanding the effects of chronic heavy cannabis use on brain function. It would be of interest to extend the investigation beyond 6-36 hr of abstinence from cannabis to determine whether increased CBV values persist for several weeks or eventually normalize. Sneider, J.T., Pope, H.G., Silveri, M.M., Simpson, N.S., Gruber, S.A., and Yurgelun-Todd, D.A. Experimental and Clinical Psychopharmacology,14(4), pp. 422-428, 2006.

Using Functional Magnetic Resonance Imaging to Pinpoint Brain Differences Relevant to Stimulant Use

Dr. Martin Paulus at University of California, San Diego, reviewed the neural substrate dysfunctions and disrupted cognitive, affective and experiential processes observed in methamphetamine and cocaine- dependent individuals.

They reviewed all publications in PubMed that conducted comparison studies between healthy volunteers and cocaine-, amphetamine- or methamphetamine- dependent individuals using functional magnetic resonance imaging. They found that stimulant dependence was characterized by a distributed alteration of functional activation to a number of experimental paradigms. Attenuated anterior and posterior cingulate activation, reduced inferior frontal and dorsolateral prefrontal cortex activation and altered posterior parietal activation point towards an inadequate demand-specific processing of information. Processes reported most consistently to be deficient in these functional neuroimaging studies include inhibitory control, executive functioning and decision-making. One emerging theme arising from this research is that stimulant-dependent individuals show specific, rather than generic, brain activation differences, i.e. instead of showing more or less brain activation regardless of task, they exhibit process-related brain activation differences that are consistent with a shift from context-specific, effortful processing to more stereotyped, habitual response generation. Aron, J.L., and Paulus, M.P. Addiction 102, pp. 33-43 Suppl. 1, 2007.

Linking Nucleus Accumbens Dopamine and Blood Oxygenation

Dr. Brian Knutson at Stanford University reviewed the literature concerning the physiological relationship between dopamine release and BOLD signal increases in the Nucleus Accumbens (NAcc). Animal research suggests that anticipation of reward can elicit dopamine release in the NAcc. Human functional magnetic resonance imaging (fMRI) research further suggests that reward anticipation can increase local blood oxygen level dependent (BOLD) signal in the NAcc. However, it is not clear whether pharmacological MRI (phMRI) evidence exists for a directional relationship between NAcc dopamine release and BOLD signal. Accumulating phMRI evidence supports a simple model in which NAcc dopamine release activates postsynaptic D1 receptors, which changes postsynaptic membrane potential, eventually increasing local BOLD signal. This continuing influence can change on a second-to-second basis. Dopamine release in the NAcc appears to increase local BOLD signal via agonism of postsynaptic D1 receptors. Such a physiological mechanism implies that fMRI may be used to track symptoms related to NAcc dopaminergic dysregulation in substance abuse and other disorders. Knutson, B., and Gibbs, S.E.B. Psychopharmacology, 191(3), pp. 813-822, 2007.

Mood Alters Amygdala Activation to Sad Distractors During an Attentional Task

Dr. Kevin Labar and colleagues at Duke University used fMRI in healthy subjects to determine whether the amygdala's response to sad sensory stimuli is functionally modulated by mood state. Healthy adults underwent functional magnetic resonance imaging during task runs that were preceded by sad or happy movie clips. Amygdala activation was subsequently evoked by sad and neutral pictures presented as distractors during an attentional oddball task. Happy and sad mood induction was conducted within-subjects on consecutive days in counterbalanced order. Amygdala activation to sad distractors was enhanced after viewing sad movies relative to happy ones and was correlated with reaction time costs to detect attentional targets. The anterior cingulate, ventromedial and orbital prefrontal conex, insula, and other posterior regions also showed enhanced responses to sad distractors during sad mood. The activation was higher in female subjects in the right hemisphere. These findings reveal brain mechanisms that integrate emotional input and current mood state, with implications for understanding cognitive distractibility in mood alterations in substance abusers. Wang, L.H., Labar, K.S., and McCarthy, G. Biological Psychiatry, 60(10), pp. 1139-1146, 2006.

The Neural Effect of Stimulus-response Modality Compatibility on Dual-task Performance: an fMRI Study

Dr. Mark D'Esposito and colleagues at University of California Berkeley used fMRI to investigate whether inferior frontal sulcus (IFS) is involved in the coordination of interfering processes in dual-task situations in healthy subjects. The present study was specifically concerned with whether the compatibility between stimulus and response modalities modulates dual-task-related activity along the IFS. It has been shown behaviorally that the degree of interference, as measured by dual-task costs, increases in modality-incompatible conditions (e.g. visual-vocal tasks combined with auditory-manual tasks) as compared to modality-compatible conditions (e.g. visual-manual tasks combined with auditory-vocal tasks). Using fMRI, authors measured IFS activity when participants performed modality-compatible and modality-incompatible single and dual tasks. Behaviorally, authors replicated the finding of higher dual-task costs for modality-incompatible tasks compared to modality-compatible tasks. The fMRI data revealed higher activity along the IFS in modality-incompatible dual tasks compared with modality-compatible dual tasks when inter-individual variability in functional brain organization is taken into account. These data suggest that the IFS is involved in the coordination of cognitive processes associated with the concurrent mapping of sensory information onto corresponding motor responses in dual-task situations. Stelzel, C., Schumacher, E.H., Schubert, T., and D'Esposito, M. Psychological Research, 70(6), pp. 514-525, 2006.

Reward-Aversion Circuitry in Analgesia and Pain: Implications for Psychiatric Disorders

Drs. Perry Renshaw, Igor Elman and colleagues at McLean Hospital reviewed how interaction between sensory and emotional systems are altered in chronic pain patients. Pain and analgesia are interpreted by the nervous system as aversive and rewarding processes that trigger specific behavioral responses. Under normal physiological conditions these processes are adaptive. However, under chronic pain conditions, functional alterations of the central nervous system frequently result in maladaptive behaviors. In this review the authors examine (a) the interactions between sensory and emotional systems involved in processing pain and analgesia in the physiological state; (b) the role of reward/aversion circuitry in pain and analgesia; and (c) the role of alterations in reward/aversion circuitry in the development of chronic pain and co-morbid psychiatric disorders. These underlying features have implications for understanding the neurobiology of substance abuse in chronic pain patients and for the development and evaluation of novel therapeutic interventions. Borsook, D., Becerra, L., Carlezon, W.A., Show, M., Renshaw, P., Elman, I., and Levine, J. European Journal of Pain, 11(1), pp. 7-20, 2007.

The Role of Emotion in Decision Making: A Cognitive Neuroscience Perspective

Dr. Antoine Bechara and colleagues reviewed how decision making is altered in the face of uncertainty about whether one's choices will lead to benefit or harm. The somatic-marker hypothesis is a neurobiological theory of how decisions are made in the face of uncertain outcome. This theory holds that such decisions are aided by emotions, in the form of bodily states, that are elicited during the deliberation of future consequences and that mark different options for behavior as being advantageous or disadvantageous. This process involves an interplay between neural systems that elicit emotional/bodily states and neural systems that map these emotional/bodily states. Naqvi, N., Shiv, B., and Bechara, A. Current Direction in Psychological Science, 15(5), pp. 260-264, 2006.

Effects of Acute Smoking on Brain Activity Vary with Abstinence in Smokers Performing the N-Back Task: A Preliminary Study

Dr. Edythe London and colleagues at University of California, Los Angeles used fMRI to determine whether recent smoking (overnight abstinence vs. smoking ad libitum) influenced the effect of smoking a cigarette on brain activity related to a working memory challenge. Six smokers performed the N-Back working memory task during functional magnetic resonance imaging (fMRI) both before and after smoking a cigarette in each of two test sessions: one following overnight abstinence from smoking (similar to 13 h) and the other following ad libitum smoking. Task-related activity in L-DLPFC showed a significant interaction between the effects of acute smoking, test session, and task load. After overnight abstinence, post-smoking brain activity in L-DLPFC was lower than before smoking at low task load and higher at high task load; corresponding activity on a day of ad libitum smoking was higher at low load and lower at high task load after smoking during the session. These data suggest that the effect of acute smoking on working memory processing depends on recent prior smoking and task load. In particular, they provide preliminary evidence that functional efficiency of working memory is improved by smoking a cigarette during abstinence, while the effect of a cigarette in a non-deprived state varies with the nature and difficulty of the working memory challenge. This interaction merits further examination in larger studies specifically designed to consider this issue. Xu, J.S., Mendrek, A., Cohen, M.S., Monterosso, J., Simon, S., Brody, A.L., Jarvik, M., Rodriguez, P., Ernst, M., and London, E.D. Psychiatry Research-Neuroimaging, 148(2-3), pp. 103-109, 2006.

Spatially Selective Representations of Voluntary and Stimulus-driven Attentional Priority in Human Occipital, Parietal, and Frontal Cortex

Dr. Steven Yantis and colleagues at Johns Hopkins University used fMRI in healthy subjects to determine the neuronal systems engaged in mediating attentional priority when competing factors are present. When multiple objects are present in a visual scene, they compete for cortical processing in the visual system; selective attention biases this competition so that representations of behaviorally relevant objects enter awareness and irrelevant objects do not. Deployments of selective attention can be voluntary (e.g., shift or attention to a target's expected spatial location) or stimulus driven (e.g., capture of attention by a target-defining feature such as color). Here authors used functional magnetic resonance imaging to show that both of these factors induce spatially selective attentional modulations within regions of human occipital, parietal, and frontal cortex. In addition, the voluntary attentional modulations are temporally sustained, indicating that activity in these regions dynamically tracks the locus of attention. These data show that a convolution of factors, including prior knowledge of location and target-defining features, determines the relative competitive advantage of visual stimuli within multiple stages of the visual system. Serences, J.T., and Yantis, S., Cerebral Cortex, 17(2). pp, 284-293, 2007.

Neuroimaging Research in Human MDMA Users: A Review

Dr. Ronald Cowan of Vanderbilt University reviewed the literature to determine under what circumstances, and to what extent 3,4-methylenedioxymethamphetamine (MDMA) exposure produces chronic changes in human brain function is a critical public health issue. MDMA is a widely used recreational drug commonly sold as "Ecstasy". Because findings from the animal literature have indicated that specific dosage regimens of MDMA can produce long-lasting alterations in serotonergic function, existing studies of MDMA effects in humans have examined brain serotonin (5-HT) transporters

(5-HTT) and receptors or have examined brain structures or functions potentially affected by MDMA. The objectives of this review were to provide a background for interpreting human MDMA neuroimaging research; to examine existing neuroimaging data regarding the rationale for and limitations to human MDMA research; and to provide suggestions for improving the design and interpretation of future neuroimaging approaches. Results showed that of the existing neuroimaging studies in human MDMA users, few experimental designs have been replicated across different research groups. Only investigations employing nuclear imaging methods to assay brain 5-HTT levels have been replicated across methods and research laboratories. These studies have found reduced levels of the 5-HTT in recently abstinent MDMA users with some evidence for normalization of 5-HTT levels with prolonged abstinence. However, the sensitivity of these methods is unknown. The current state of neuroimaging in human MDMA users does not permit conclusions regarding the long-term effects of MDMA exposure. Future study designs might benefit from improved sample homogeneity, increased length of MDMA abstinence, longitudinal study design, test-retest measures, serotonergic specificity, and multimodal approaches. Cowan, R.L. Psychopharmacology, 189(4), pp. 539-556, 2007.

The Vulnerability to Alcohol and Substance Abuse in Individuals Diagnosed with Schizophrenia

Dr. Cyril D'Souza and colleagues at Yale University reviewed the literature on how individuals with schizophrenia are at increased risk for developing substance abuse disorders. The authors considered several factors that might elevate their risk for substance abuse. The tendency among schizophrenic individuals to overvalue drug-like rewards and to devalue the potential negative consequences of substance abuse may be a contributing factor to their substance abuse risk. This bias, which may partly reflect the convergence of glutamatergic and dopaminergic input to the limbic striatum, also may contribute to disadvantageous decision-making and other impulsive behavior. This propensity to seek drug-like rewards is augmented by alterations in nicotinic cholinergic, GABAergic, glutamatergic, and cannabinnoid receptor function associated with schizophrenia that increase the abuse liability of low doses of nicotine, ethanol, and perhaps cannabis, and augment the dysphoric effects of higher doses of ethanol and cannabis. The distortions in reward processing and altered response to substances of abuse also increase the likelihood that individuals with schizophrenia will self-medicate their subjective distress with abused substances. The focus on distinctions between motivation and reward with respect to substance abuse risk by schizophrenic patients suggests a need for a reconsideration of the construct of "negative symptoms" for this dually-diagnosed patient group. Krystal, J.H., D'Souza, D.C., Gallinat, J., Driesen, N., Abi-Dargham, A., Petrakis, I., Heinz, A., and Pearlson, G. Neurotoxicity Research, 10(3-4), pp. 235-252, 2006.

Altruism is Associated with an Increased Neural Response to Agency

Dr. Scott Huettel and colleagues at Duke University used fMRI to investigate the neural mechanisms underlying altruism in healthy subjects. Empathy and its component abilities, such as the perception of the actions and intentions of others have been proposed as key contributors. Tasks requiring the perception of agency activate the posterior superior temporal cortex (pSTC), particularly in the right hemisphere. Here, the authors demonstrate that differential activation of the human pSTC during action perception versus action performance predicts self-reported altruism. These studies form the foundation for understanding how substance abuse may lead to dysfunctional social abilities. Tankersley, D., Stowe, C.J., and Huettel, S.A. Nature Neuroscience, 10(2), pp. 150-151, 2007.

Neuroimaging Attentional Impairment

Dr. David Gilbert and colleagues at Southern Illinois University used evoked response potential (ERP) to investigate how aversive and smoking-related stimuli during abstinence are related to smoking urges and relapse, and whether such stimuli can be potent distractors of selective attention. It has been suggested that the beneficial effect of nicotine replacement therapy (NRT) may be mediated partly by the ability of nicotine to reduce distraction by such stimuli and thereby to facilitate attention to task-relevant stimuli. The present study tested the hypothesis that nicotine reduces distraction by aversive and smoking-related stimuli as indexed by the parietal P3b brain response to a task-relevant target digit. The effect of nicotine on distraction by emotionally negative, positive, neutral, and smoking-related pictures immediately preceding target digits during a rapid visual information processing task in smokers was assessed. Nicotine enhanced P3b responses associated with target digits immediately subsequent to negative emotional pictures bilaterally and subsequent to smoking-related pictures only in the right hemisphere. No effects of nicotine were observed for P3bs subsequent to positive and neutral distractor pictures. Another measure of attention, contingent negative variation amplitude in anticipation of the target digits also was increased by nicotine, especially in the left hemisphere and at posterior sites. Together, these findings suggest that nicotine reduces the distraction by emotionally negative and smoking-related stimuli and promotes attention to task-related stimuli by modulating somewhat lateralized and task specific neural networks. Gilbert, D.G., Sugai, C., Zuo, Y., Rabinovich, N.E., McClernon, F.J., and Froeliger, B. Brain Indices of Nicotine's Effects on Attentional Bias to Smoking and Emotional Pictures and to Task-Relevant Targets Nicotine Tob Res. 9(3), pp. 351-363, 2007.

Several Genes are Associated with Nicotine Dependence

Dr. Li and associates continue to report discoveries from their first round of funding of genes associated with nicotine dependence. European- (EA) and African-American (AA) smokers and families were recruited over five years from regions of the mid-South. Nicotine dependence was ascertained by three commonly-used, highly-correlated measures. In linkage, association and fine-mapping methodologies the following have been reported: 1) Following replication of linkage of chromosome 9q22-q23, haplotypes of the gene encoding src homology 2 domain-containing transforming protein Cs (SHC3) within this region were found to be negatively-correlated, suggesting a protective factor in both EA and AA subjects. Li, M.D., Sun, D., Lou, X-Y., Beuten, J., and Ma, J.Z., Molecular Psychiatry 2006; 2) Neurotrophic tyrosine kinase receptor 2 gene also found in this region was also investigated with the result that some SNPs and haplotypes were significantly associated in EA and one haplotype was associated in AA. Beuten, J., Ma, J.Z., Payne, T.J., Dupont, R.T., Lou, X-Y., Crews, K.M., Elson, R.C., and Li, M.D., Biological Psychiatry 61, pp. 48-55, 2007; 3) fine-mapping of a linkage region on chromosome 17p13 (from a previous study) demonstrated associations of both the GABARAP and DLG4 genes within this region to be associated only in the EA with marginal, if any, association in AA. Lou, X.Y., Ma, J.Z., Sun, D., Payne, T.J., and Li, M.D. Human Molecular Genetics, 16(2), pp. 142-153, 2006.

Resting Motor Threshold (RMT) Was Elevated in Cocaine-Dependent Patients as Assessed by Transcranial Magnetic Stimulation (TMC)

Boutros and colleagues sought to explore differences in cortical excitability in abstinent cocaine patients compared to non-drug users. First, they replicated a

previous finding of elevated RMT using a single pulse applied to an area above the left parietal cortex in right-handers. They then investigated facilitation (or inhibition) of cortical responses with a two-pulse methodology at various interstimulus intervals (ISI) believed to indicate exaggerated motor cortical excitability. At an ISI, they found a three-fold increase (and no effect on inhibitory systems) which they hypothesized was due to enhanced glutamatergic excitability through NMDA and/or non-NMDA receptors in cocaine dependent individuals. They also suggested that the elevated resting potential might be a protective mechanism. Sundaresan, K., Ziemann, U., Stanley, J., and Boutros, N. Neuro Report, 18(3), pp. 289-292, 2007.

Increased Risk of Infection in Cocaine Patients due to Decreased Cytokine Expression

Irwin and colleagues assessed the expression of monocytes expression of tumor necrosis factor-alpha and interleukin-6 in cocaine patients a) following acute abstinence, b) in response to single-dose cocaine administration, and c) in response to bacterial ligand lipopolysaccharide. In all cases, there was decreased cytokine expression either at "rest" or in response to the bacterial ligand. Moreover, the effect persisted over a two-day period, long after cocaine had cleared metabolically from the blood. These data imply there is an increased risk of bacterial infectious diseases both in subjects with sustained use and among those who use a single dose of cocaine. Irwin, M.R., Olmos, L., Wang, M., Valladares, E.M., Motivala, S.J., Fong, T., Newton, T., Butch, A., Olmstead, R. and Cole, S.W. Journal of Pharmacology and Experimental Therapies, 320, pp. 507-515, 2007.

Alcohol Dehydrogenase Gene Variants Modulate Risk for Drug Dependence Together with or Separate from Risk Conferred to Patients with Alcohol Dependence

Following up on a previous finding that certain gene variants conferred risk in individuals with alcohol dependence, Gelernter and colleagues assessed the effect of gene variants among the ADH genotypes on drug dependence (either opioid or cocaine dependence). Using diplotype trend regression analyses, it was found that some variants of ADH5 and ADH6 were observed both in both European- and African-American drug dependent populations while others were associated in one population but not another or had opposite effects. Part of this observation is explained by differential frequencies of the rare allele in one or the other population. These data suggest that a common etiology, in part, underlies both alcohol dependence and drug dependence thereby explaining the high rate of comorbidity. Luo, X., Kranzler, H.R., Zuo, L., Wang, S., Schork, N.J., and Gelernter, J. Human Molecular Genetics, 16(4), pp. 380-390, 2007.

Prefrontal Cortex Activity is Reduced in Gambling and Non-Gambling Substance Users During Decision-Making

Poor decision-making is a hallmark of addiction, whether to substances or activities. Performance on a widely used test of decision-making, the Iowa Gambling Task (IGT), can discriminate controls from persons with ventral medial frontal lesions, substance-dependence, and pathological gambling. Positron emission tomography (PET) studies indicate that substance-dependent individuals show altered prefrontal activity on the task. Here authors adapted the IGT to an fMRI setting to test the hypothesis that defects in ventral medial and prefrontal processing are associated with impaired decisions that involve risk but may differ depending on whether substance dependence is comorbid with gambling problems. Eighteen controls, 14 substance-dependent individuals (SD), and 16 SD with gambling problems (SDPG) underwent fMRI while performing a modified version of the IGT. Group differences were

observed in ventral medial frontal, right frontopolar, and superior frontal cortex during decision-making. Controls showed the greatest activity, followed by SDPG, followed by SD. Results of this work support a hypothesis that defects in ventral medial frontal processing lead to impaired decisions that involve risk. Reductions in right prefrontal activity during decision-making appear to be modulated by the presence of gambling problems and may reflect impaired working memory, stimulus reward valuation, or cue reactivity in substance-dependent individuals. Tanabe, J., Thompson, L., Claus, E., Dalwani, M., Hutchison, K., and Banich, M.T. Hum Brain Mapp, February 1, 2007 [Epub ahead of print].

Director's Report to the National Advisory Council on Drug Abuse - May, 2007

Research Findings - Epidemiology and Etiology Research

Genetic and Environmental Influences on Initiation and Progression of Substance Use

This study sought to examine the genetic and environmental contributions to the initiation of use and progression to more serious use of alcohol, cigarettes and marijuana during adolescence, and to examine the relationship between initiation and progression of substance use, using a twin-based design and a new theoretical model, the causal-common-contingent (CCC) model, which allows modeling of the relationship between initiation of use and progression to heavier use as a two-stage model and the examination of genetic and environmental influences on both stages, while taking into account their relationship. The participants consisted of 1214 twin pairs aged 11-19 years sampled from the UK population-based Cardiff Study of All Wales and North-west of England Twins. Data on adolescent initiation and progression to more serious use of alcohol, cigarettes and marijuana were obtained using self-report questionnaires. The investigators found that initiation of alcohol and progression to heavier alcohol use had separate but related underlying etiologies. For cigarette and marijuana use the relation between initiation and progression to heavier use was stronger, suggesting greater overlap in etiology. For all three substances, environmental influences that make twins more similar (common environment) tended to be greater for initiation, while genetic influences were stronger for heavier use. The authors conclude that their findings have implications for prevention: that it may be more efficacious to focus alcohol interventions on risk factors for the development of heavier use rather than initiation of use while interventions aimed at reducing the initiation of cigarettes and marijuana use may be more appropriate. Fowler, T., Lifford, K., Shelton, K., Rice, F., Thapar, A., Neale, M., McBride, A., and Van den Bree, M. Exploring the Relationship Between Genetic and Environmental Influences on Initiation and Progression of Substance Use. Addiction, 102(3), pp. 413-422, 2007.

Increasing Trend in DXM Abuse

The investigators analyzed indicator data on dextromethorphan (DXM) abuse in California and compared findings with national trends. The investigators conducted a review of data from 1999 through 2004 on DXM abuse cases from the California Poison Control System (CPCS), American Association of Poison Control Centers (AAPCC), and Drug Abuse Warning Network (DAWN). All DXM abuse cases reported to the CPCS, AAPCC, and DAWN were included in the analyses. The data on DXM abuse cases included date of exposure, age, acute vs. long-term use, coingestants, product formulation, and clinical outcome. The main outcome examined was the annual proportion of DXM abuse cases among all exposures reported to the CPCS, AAPCC, and DAWN databases. A total of

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1382 CPCS cases were included in the study. A 10-fold increase in CPCS DXM abuse cases from 1999 (0.23 cases per 1000 calls) to 2004 (2.15 cases per 1000 calls) (odds ratio, 1.48; 95% confidence interval, 1.43-1.54) was identified. Of all CPCS DXM abuse cases, 74.5% were aged 9 to 17 years; the frequency of cases among this age group increased more than 15-fold during the study (from 0.11 to 1.68 cases per 1000 calls). Similar trends were seen in the AAPCC and DAWN databases. The highest frequency of DXM abuse occurred among adolescents aged 15 and 16 years. The most commonly abused product was Coricidin HBP Cough & Cold Tablets. This study revealed an increasing trend of dextromethorphan abuse cases reported to the CPCS that is paralleled nationally as reported to the AAPCC and DAWN. This increase was most evident in the adolescent population. Bryner, J., Wang, U., Hui, J., Bedodo, M., MacDougall, C., and Anderson, I. Dextromethorphan Abuse in Adolescence: An Increasing Trend: 1999-2004. Arch Pediatr Adolesc Med, 160(12), pp. 1217-1222, 2006.

Diagnosing Substance Use Disorders: Examination of DSM-IV and ICD-10

Two major nomenclatures, Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) and International Classification of Diseases, tenth edition (ICD-10), currently define substance use disorders for broad audiences of users with different training, experience and interests. A comparison of these definitions and their implications for DSM-V and ICD-11, not previously available, was provided by these authors in a special issue of Addiction. The authors found reliability and psychometric validity evidence for substance dependence was consistently strong, but more mixed for abuse and harmful use. Findings on the genetics of alcohol disorders supported the validity of the dependence concept, while animal studies underscored the centrality of continued use despite negative consequences to the concept of dependence. While few studies on substance-induced disorders have been conducted, those published show good reliability and validity when elements of DSM-IV and ICD-10 are combined. The authors concluded that dependence in DSM-V and ICD-11 should be retained, standardizing both criteria sets and adding a severity measure. They included several recommendations; consequences of heavy use should be measured independently of dependence; add cannabis withdrawal if further research supports existing evidence; conduct further studies of the substance-induced psychiatric categories; standardize their criteria across DSM-V and ICD-11; develop a theoretical basis for better remission criteria; consider changing substance ''abuse'' to substance ''dysfunction disorder''; and conduct clinician education on the value of the diagnostic criteria. Hasin, D., Hatzenbuehler, M., Keyes, K., and Ogburn, E. Substance Use Disorders: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and International Classification of Diseases, Tenth Edition (ICD-10). Addiction, 101 Suppl 1, pp. 59-75, 2006.

Latent Class Analysis of Drug Abuse/Dependence: Results from NESARC

This study used data from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) to examine the co-occurrence of abuse/dependence across different illicit drugs and test associations between these classes and major psychiatric disorders. Latent class analyses were used to characterize polysubstance abuse/dependence (AB/D) in 43,093 individuals who participated in the NESARC. Multinomial logistic regression was performed to examine the association between the classes of life-time illicit drug AB/D and gender, age and race, as well as life-time Diagnostic and Statistical Manual version IV (DSM-IV) alcohol abuse/dependence, nicotine dependence, major depressive disorder, generalized anxiety disorder, panic disorder, social phobia and antisocial personality disorder. The investigators found five latent classes:

Planned Meetings

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no AB/D (class 1: 92.5%), cannabis AB/D only (class 2: 5.8%), stimulants + hallucinogen AB/D (class 3: 0.6%), prescription drug AB/D (class 4: 0.6%) and polysubstance AB/D (class 5: 0.5%). Major depressive disorder and nicotine dependence were associated most strongly with class 5. Anxiety disorders were associated strongly with the prescription drug AB/D class while alcohol AB/D and ASPD were associated with classes 2, 3, 4 and 5 when compared to the reference class (class 1). The authors conclude that significant heterogeneity exists in this US population for polysubstance AB/D patterns, with evidence for a subgroup with high rates of sedative, tranquilizer and opiate AB/D and a history of anxiety disorders; a stimulant/hallucinogens group; a high-risk group with elevated rates of all psychiatric disorders; and a milder cannabis AB/D only group. Replication of such classes across other samples is recommended, which may help in characterizing risk groups that may be etiologically diverse and therefore requiring different preventive and treatment interventions. Agrawal, A., Lynskey, M., Madden, P., Bucholz, K., and Heath, A. A Latent Class Analysis of Illicit Drug Abuse/Dependence: Results from the National Epidemiological Survey on Alcohol and Related Conditions. Addiction, 102(1), pp. 94-104, 2006.

Marker or Mediator? The Effects of Adolescent Substance Use on Young Adult Educational Attainment

The purpose of this study was to test the effects of adolescent substance use on college attendance and completion by young adulthood in the context of the behavioral and familial risk factors that influence substance use. Longitudinal data were collected from a community sample of children of alcoholics (248) and matched controls (206) at three adolescent assessments (micro(age) = 13-15) and a long-term follow-up in young adulthood (micro(age) = 25). College attendance and degree completion by age 25 were self-reported in young adulthood. During adolescence, self-reports of alcohol and drug use were assessed with log-transformed quantity/frequency measures; substance use risk factors [e.g. parental monitoring, externalizing and internalizing symptoms and Diagnostic and Statistical Manual version III (DSM-III) diagnosis of parental alcoholism] were assessed by both self- and parent-report, and adolescent reading achievement was assessed using a standardized assessment of reading achievement (Wide Range Achievement Test). Growth curve modeling results suggest that mean levels and growth in adolescent substance use mark, or identify those adolescents who are at risk for reduced odds of attending and completing college. Moreover, adolescent substance use was not merely a marker of risk, in that growth in drug use (but not alcohol use) significantly mediated the effects of parental alcoholism and early externalizing behavior on later college completion, partially explaining the effects of these risk factors on college completion. The authors concluded that the current study provides evidence for both the marker and the mediator hypotheses, and identifies multiple pathways to higher educational attainment. Furthermore, the findings point to the importance of studying the effects of adolescent substance use in a broader developmental context of its correlated risk factors to specify more effectively the key pathways to later developmental outcomes. King, K., Meehan, B., Trim, R., and Chassin, L. Marker or Mediator? The Effects of Adolescent Substance Use on Young Adult Educational Attainment. Addiction, 101(12), pp. 1730-1740, 2006.

Adolescents' Motivations to Abuse Prescription Drugs

This study examines (1) adolescents' reasons for engaging in the nonmedical (illicit) use of 4 classes of prescription medications and (2) whether motivations were associated with a higher risk for substance abuse problems. Students in 7th - 12th grades (N=1086) from one ethnically diverse school district in southeastern Michigan were surveyed in 2005 using a self-administered, Web-based questionnaire. Risk of substance abuse was assessed with a modified

version of the Drug Abuse Screening Test (DAST), a self-report instrument that can be used in nonclinical settings to screen for potential abuse and dependence to various drugs. Twelve percent of the respondents reported nonmedical use of opioid pain medications in the past year: 3% for sleeping, 2% as a sedative and/or for anxiety, and 2% as stimulants. The reasons for engaging in the nonmedical use of prescription medications varied by drug classification. For opioid analgesics, when the number of motives increased, so too did the likelihood of a positive DAST score. For every additional motive endorsed, the DAST increased by a factor of 1.8. Two groups of students were compared (at-risk versus self-treatment); those who endorsed multiple motivations for nonmedical use of opioids (at-risk group) were significantly more likely to have elevated DAST scores when compared with those who were in the self-treatment group. Those in the at-risk group also were significantly more likely to engage in marijuana and alcohol use. The findings indicate that multiple motivations for the nonmedical use of prescription medications seem associated with a greater likelihood of substance abuse problems. Boyd, C., McCabe, S., Cranford, J., and Young, A. Adolescents' Motivations to Abuse Prescription Medications. Pediatrics, 118(6), pp. 2472-2480, 2006.

Medical and Nonmedical Prescription Drug Use among Secondary Student

The objectives of this study were to: (1) assess the prevalence of medical and nonmedical use of four categories of prescription drugs (opioid, stimulant, sleeping, and sedative/anxiety medication) in a racially diverse sample of secondary public school students, and (2) examine the association between the use of four categories of prescription medications and illicit drug use and probable drug abuse. Students in 7th - 12th grades (N=1086) one school district in southeastern Michigan were surveyed in 2005 using a self-administered, Web-based questionnaire. The Drug Abuse Screening Test (DAST-10), a self-report instrument that can be used in nonclinical settings, was used to screen for probable drug abuse and dependence. The sample consisted of 54% female, 52% White, 45% African American, and 3% from other racial categories. Forty-eight percent of the sample reported no lifetime use of four categories of prescription drugs (nonusers), 31.5% reported medically prescribed use only (medical users), 17.5% reported both medical and nonmedical use (medical/nonmedical users) and 3.3% reported nonmedical use only (nonmedical users). Multivariate analyses indicated that medical/nonmedical users and nonmedical users were significantly more likely than nonusers to report illicit drug use and probable drug abuse. Medical users generally reported similar or increased odds of illicit drug use and probable drug abuse than non-users. These findings provide evidence that nonmedical use of prescription drugs represents a problem behavior among secondary school students. McCabe, S., Boyd, C., and Young, A. Medical and Nonmedical use of Prescription Drugs among Secondary School Students. J Adolesc Health, 40(1), pp. 76-83, 2007.

Residential Segregation and Injection Drug Use Prevalence Among Black Adults in US Metropolitan Areas

Researchers analyzed the relationship between two 1990 dimensions of racial residential segregation (isolation and concentration) and 1998 injection drug use prevalence among Black adult residents of 93 large US metropolitan statistical areas (MSAs). The authors estimated injection drug use prevalence among Black adults in each MSA from three databases documenting IDU encounters with the health care system. Multiple linear regression methods were used to investigate the relationship of isolation and concentration to the natural logarithm of Black adult injection drug use prevalence, controlling for possible confounders. The findings indicate that median injection drug use prevalence was 1,983 per 100,000 Black adults (interquartile range: 1,422 to

2,759 per 100,000). The median isolation index was 0.48 (range: 0.05 to 0.84): in half the MSAs studied, the average Black resident inhabited a census tract where 48% or more of the residents were Black. The multiple regression model indicates that an increase of 0.50 in the isolation index was associated with a 23% increase in injection drug use prevalence among Black adults. Concentration was unrelated to the outcome. These findings show that residential isolation is positively related to injection drug use prevalence among Blacks in U.S. MSAs. The pathways that link isolation to injection drug use remain as yet poorly understood, however, indicating the need for further research. Cooper, H., Friedman, S., Tempalski, B., and Friedman, R. Residential Segregation and Injection Drug Use Prevalence among Black Adults in US Metropolitan Areas. Am J Public Health, 97(2), pp. 344-352, 2007.

Diagnostic Criteria for Substance Abuse in Adolescents

This study used Item Response Theory to characterize the psychometric properties of Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) alcohol and cannabis use disorder symptoms among 472 clinical adolescents. Item response theory has advantages over classical test theory in evaluating diagnostic criteria. For both substances, DSM-IV symptoms fit a model specifying a unidimensional latent trait of problem severity. Threshold (severity) parameters did not distinguish abuse and dependence symptoms. Abuse symptoms of legal problems and hazardous use, and dependence symptoms of tolerance, unsuccessful attempts to quit, and physical-psychological problems, showed relatively poor discrimination of problem severity. There were gender differences in thresholds for hazardous use, legal problems, and physical-psychological problems. The results illustrate limitations of DSM-IV criteria for alcohol and cannabis use disorders when applied to adolescents. The authors recommend that the development process for the fifth edition (DSM-V) should be informed by statistical models such as those used in this study. Martin, C., Chung, T., Kirisci, L., and Langenbucher, J. Item Response Theory Analysis of Diagnostic Criteria for Alcohol and Cannabis Use Disorders in Adolescents: Implications for DSM-V. J Abnorm Psychol, 115(4), pp. 807-814, 2006.

Models of Genetic Co-morbidity for Cannabis and Other Illicit Drugs

The authors investigated the co-morbidity between cannabis use (experimentation, early and repeated use, and problems) and experimentation and problems with other illicit drugs (OID) using genetic models proposed by Neale and Kendler. Using data from a sample of 4152 same-sex male and female adult Australian twins, they fit 13 genetically informative models of co-morbidity to data on experimentation, early use, repeated use of cannabis and co-morbid OID experimentation, and to abuse/dependence (A/D) problems with cannabis and OIDs. Model-fitting results suggest that common genetic, shared and unique environmental factors are responsible for the association between cannabis experimentation, early use, repeated use and A/D problems and OID experimentation or problems. The liability causation model, which is a reduced form of the correlated vulnerabilities model, also fit very well. In women, authors found evidence for high-risk cannabis experimenters and repeated users to be at increased risk for OID experimentation, despite being below the risk threshold on the liability distribution for OID experimentation. The authors conclude that co-morbid cannabis and OID use and misuse are due partly to a common predisposition to substance use disorders, but causal effects could not be ruled out. These models warrant further research, so that features of the correlated vulnerabilities model and the gateway models can be studied jointly. Agrawal, A., Lynskey, M., Bucholz, K., Martin, N., Madden, P., and Heath, A. Contrasting Models of Genetic Co-morbidity for Cannabis and Other Illicit Drugs in Adult Australian Twins. Psychol Med, 37(1), pp. 49-60,

2007.

Convergence of HIV Seroprevalence Among Injecting and Non-injecting Drug Users in New York City

HIV infection has historically been higher among injecting drug users because the virus is efficiently transmitted through the sharing of drug-injecting equipment. In this study, researchers sought to compare HIV prevalence among injecting and non-injecting heroin and cocaine users in New York City by analyzing data from 2 separate cross-sectional surveys, both with HIV counseling and testing and drug use and HIV risk behavior questionnaires. Participants included injecting and non-injecting heroin and cocaine users recruited at detoxification and methadone maintenance treatment from 2001-2004 (n = 2121) and through respondent-driven sampling from a research storefront in 2004 (n = 448). In both studies, HIV prevalence was nearly identical among current injectors (injected in the last 6 months) and heroin and cocaine users who had never injected: 13% [95% confidence interval (CI), 12-15%] among current injectors and 12% (95% CI, 9-16%) among never-injectors in the drug treatment program study, and 15% (95% CI, 11-19%) among current injectors and 17% (95% CI, 12-21%) among never injectors in the respondent driven sampling storefront study. The 95% CIs overlapped in all gender and race/ethnicity subgroup comparisons of HIV prevalence in both studies. These findings indicate that the very large HIV epidemic among drug users in New York City may be entering a new phase, in which sexual transmission is increasingly important. Additional prevention programs are needed to address this transition. Des Jarlais, D., Arasteh, K., Perlis, T., Hagan, H., Abdul-Quader, A., Heckathorn, D., McKnight, C., Bramson, H., Nemeth, C., Torian, L., and Friedman, S. Convergence of HIV Seroprevalence Among Injecting and Non-injecting Drug Users in New York City. AIDS, 21(2), pp. 231-235, 2007.

Grandmother and Parent Influences on Child Self-Esteem

This study tests a model of intergenerational influences on childhood self-esteem that proposes paths from grandmothers' drug problems to grandchildren's self-esteem via parents' drug problems and parental adaptive child rearing and from grandmothers' maternal acceptance to grandchildren's self-esteem via parents' unconventionality and adaptive child rearing. This longitudinal study uses data obtained from interviews with a New York City sample of black and Puerto Rican children (N = 149) and 1 of their parents and from mailed questionnaires or comparable interviews with those parents' mothers. Structural equation modeling was used to test the proposed model. The LISREL analysis found that, with 3 exceptions, all of the hypothesized paths were significant. The total effects analysis indicated that parents' adaptive child rearing was the strongest latent construct, a finding that was consistent with this construct's proximal position in the model. This study suggests that mothers' drug problems are not just near-term risks for their children, but also pose long-term risks for their children's future functioning as parents and thereby for their grandchildren. The authors conclude that the relative strength of parents' adaptive child rearing in this intergenerational model indicates that this area should be the focus of therapeutic intervention efforts, but addressing future grandmothers' drug problems may have positive effects on multiple generations. Brook, J., Ning, Y., Balka, E., Brook, D., Lubliner, E., and Rosenberg, G. Grandmother and Parent Influences on Child Self-Esteem. Pediatrics, 119(2), pp. 444-451, 2007.

Women Who Gave Birth as Unmarried Adolescents: Trends in Substance Use from Adolescence to Adulthood

The purpose of this study was to determine whether adolescent childbearing mothers "mature out" of substance use as they transition into adulthood; how their substance use compares to that of typical young women of the same ages; and whether there are different patterns of substance use evident in this vulnerable population. The data come from an ongoing longitudinal study of 240 young women who were unmarried, pregnant, and under age 18 at enrollment. They have been interviewed regularly from pregnancy through 11.5 years postpartum. The data are based on self-reported substance use verified by random urinalysis for drug metabolites. Substance use did not decline during the transition to adulthood nor into early adulthood. With the exception of alcohol, the prevalence of substance use was higher than that of a nationally representative sample of same-aged women. Three distinct patterns of substance use were identified: licit users (cigarettes and/or alcohol), marijuana users, and "hard" drug users. Based on these findings, the authors suggest that clinicians should routinely assess substance use among young mothers who bore children as teenagers, and make referrals for appropriate treatment. Cigarette smoking is especially a cause for concern, given its widespread use and harmful effects for both mothers and their children. Although only a small proportion (about 5%) of young mothers used hard drugs consistently over time, this group will likely require comprehensive interventions that address multiple issues such as mental health and contextual factors to be effective. Future research should address reasons for continued substance use in this population. Gillmore, M., Gilchrist, L., Lee, J., and Oxford, M. Women who Gave Birth as Unmarried Adolescents: Trends in Substance Use from Adolescence to Adulthood. J Adolesc Health, 39(2), pp. 237-243, 2006.

Predictors of Non-fatal Overdose among a Cohort of Polysubstance-Using Injection Drug Users

Non-fatal overdose is a major determinant of morbidity among injection drug users (IDU). Researchers sought to evaluate factors associated with non-fatal overdose among IDU participating in the Vancouver Injection Drug Users Study. Correlates of non-fatal overdose occurring between 1996 and 2004 were identified using generalized estimating equations (GEE). There were 1,587 participants included in the analysis, including 576 (36%) women. At baseline, 750 (47%) reported a history of non-fatal overdose. In total, 985 reports of non-fatal overdose were made during follow-up by 519 (32.7%) participants. In multivariate GEE analyses, factors independently associated with non-fatal overdose included: heroin injection (AOR=2.67), cocaine injection (AOR=2.01), benzodiazepine use (AOR=2.00), requiring help injecting (AOR=1.58), binge drug use (AOR=1.52), homelessness (AOR=1.38), alcohol use (AOR=1.32), street injecting (AOR=1.22), non-injectable opiate use (AOR=1.16), speedball use (AOR=1.15), and recent incarceration (AOR=1.14). Younger age (AOR=0.99) and methadone use (AOR=0.51) were protective. Non-fatal overdose was common among local IDU in the study, and was associated with several factors that may be amenable to intervention, including opiate and stimulant use, and the characteristic of requiring help with injecting. These findings indicate the need for the ongoing development of structural interventions to address this common cause of morbidity among IDU. Kerr, T., Fairbairn, N., Tyndall, M., Marsh, D., Li, K., Montaner, J., and Wood, E. Predictors of Non-Fatal Overdose among a Cohort of Polysubstance-Using Injection Drug Users. Drug Alcohol Depend, 87(1), pp. 39-45, 2007.

Maternal Cigarette Smoking During Pregnancy and Child Aggressive Behavior

This study's objective was to examine the association between maternal smoking during pregnancy and childhood aggressive behavior in African-American and Puerto Rican children, as well as the relationship between maternal unconventional behavior, low maternal affection, and offspring

aggression. Participants consisted of African-American and Puerto Rican children (N = 203; mean age = 8.6, SD = 0.87) and their mothers living in an inner city community. An interview consisting of a structured questionnaire was administered to the mothers and their children. Scales with adequate psychometric properties were adapted from previous validated measures. They included maternal smoking during pregnancy, maternal education, unconventionality, and warmth. Controlling for demographic factors, maternal unconventional behavior, and low maternal warmth, maternal smoking during pregnancy was associated with having offspring who were aggressive. Maternal unconventionality and warmth were independently related to childhood aggression. The authors suggest that although causal limitations are noted, it may be that a decrease in smoking during pregnancy is associated with a reduction in aggression in the offspring. Brook, D., Zhang, C., Rosenberg, G., and Brook, J. Maternal Cigarette Smoking during Pregnancy and Child Aggressive Behavior. Am J Addict, 15(6), pp. 450-456, 2006.

Personality Risk Factors Associated with Trajectories of Tobacco Use

The purpose of this longitudinal, prospective study was to evaluate trajectories of smoking in a cohort of African-American and Puerto Rican young adults and describe personality and behavioral factors associated with specific smoking trajectory group membership. Participants consisted of African-American and Puerto Rican male and female young adults (N = 451, mean age 26) from an inner-city community. Data were collected at four time points over a period of 13 years using structured interviews. Interviews took place within the schools and the participants' homes. Scales with adequate psychometric properties were adapted from previously validated measures. Variables that were examined for this study came from the domains of internalizing behaviors, externalizing behaviors, drug use, and demographic information. Data were analyzed using latent growth mixture modeling to explore discrete smoking trajectories. Logistic regression analyses were then used to examine the risk factors associated with the various smoking trajectory groups. Four trajectory groups were determined to best fit the data: nonsmokers, maturing-out smokers, late-starting smokers, and early-starting continuous smokers. Subjects who were unconventional, experienced intrapersonal distress, and used alcohol and illegal drugs were more likely to belong to one of the smoking trajectory groups than to the nonsmoking group. The early-starting continuous group scored highest on these personal risk attributes. The long-term impact of unconventional behavior, intrapersonal distress, and drug use on developmental trajectories of smoking support the importance of early intervention and prevention. Brook, J., Ning, Y., and Brook, D. Personality Risk Factors Associated with Trajectories of Tobacco Use. Am J Addict, 15(6), pp. 426-433, 2006.

Severe Anxiety Symptomatology and HIV Risk Behavior among Hispanic Injection Drug Users in Puerto Rico

Despite an overall decrease in AIDS incidence in Puerto Rico, research continues to show high prevalence of HIV risk behaviors among injection drug users (IDUs). This study seeks to evaluate whether the occurrence of injection-related and sex-related HIV risk behaviors among IDUs in Puerto Rico varies with the presence of anxiety symptomatology. Subjects included 557 IDUs, recruited from street settings in poor neighborhoods in Puerto Rico. Symptoms of severe anxiety were reported by 37.1% of the study sample. Participants with severe anxiety symptoms were more likely to share needles, cotton, and rinse water; to pool money to buy drugs; and to engage in back loading, than those without severe anxiety symptoms. Participants with severe anxiety symptomatology were also more likely to practice unprotected vaginal or oral sex. The findings from this study alert HIV prevention and treatment programs

to the need to address anxiety disorders within their programs. Reyes, J., Robles, R., Colon, H., Marrero, C., Matos, T., Calderon, J., and Shepard, E. Severe Anxiety Symptomatology and HIV Risk Behavior among Hispanic Injection Drug Users in Puerto Rico. AIDS Behav, 11(1), pp. 145-150, 2007.

A Multiwave Multi-informant Study of the Specificity of the Association Between Parental and Offspring Psychiatric Disorders

The present study was conducted to investigate the specificity of the association between parental and offspring psychiatric disorders using epidemiological data from a series of parent and offspring interviews. A community-based sample of 593 mothers and their offspring from upstate New York were interviewed during the adolescence and early adulthood of the offspring. The children of parents with generalized anxiety disorder were at specifically elevated risk for anxiety disorders when co-occurring psychiatric disorders were controlled. The associations between parental and offspring antisocial, conduct, depressive, and substance use disorders were characterized by modest specificity. Children of parents with externalizing disorders were nearly as likely to develop internalizing disorders as they were to develop externalizing disorders. Children of parents with internalizing disorders were somewhat, but not significantly, more likely to develop internalizing disorders. These findings support the inference that children of parents with generalized anxiety disorder may be more likely to develop anxiety disorders than they are to develop other psychiatric disorders. However, when co-occurring psychiatric disorders are accounted for, the children of parents with depressive, disruptive, and substance use disorders may be as likely to develop other disorders as they are to develop the same type of disorder that their parents have had. Johnson, J., Cohen, P., Kasen, S., and Brook, J. A Multiwave Multi-Informant Study of the Specificity of the Association between Parental and Offspring Psychiatric Disorders. Compr Psychiatry, 47(3), pp. 169-177, 2006.

Prescription Drug Abuse and Diversion among Adolescents

The aims of this study were to determine the prevalence of medical use of 4 classes of prescription medications relative to nonmedical use (illicit use) and to assess whether gender differences exist in the trading, selling, loaning, or giving away of medications. A Web-based survey was administered to 7th- to 12th-grade students residing in 1 ethnically diverse school district in 2005. There were 1086 secondary students, including 586 girls, 498 boys, 484 black students, and 565 white students. Students were asked about their medical and nonmedical use of sleeping, sedative or anxiety, stimulant, and pain medications. Diversion of prescription medication was assessed by determining who asked the student to divert his or her prescription and who received it. Thirty-six percent of students reported having a recent prescription for 1 of the 4 drug classes. A higher percentage of girls reported giving away their medications than boys (27.5% vs. 17.4%, respectively; chi(2)(1) = 6.7; P = .01); girls were significantly more likely than boys to divert to female friends (64.0% vs. 21.2%, respectively; chi(2)(1) = 17.5; P<.001) whereas boys were more likely than girls to divert to male friends (45.5% vs. 25.6%, respectively; chi(2)(1) = 4.4; P = .04). Ten percent diverted their drugs to parents. These findings provide evidence of the need for physicians to discuss the proper use of prescription medications with their patients and their patients' families. Boyd, C., McCabe, S., Cranford, J., and Young, A. Prescription Drug Abuse and Diversion among Adolescents in a Southeast Michigan School District. Arch Pediatr Adolesc Med, 161(3), pp. 276-281, 2007.

Predictors of Unprotected Sex with Non-cohabitating Primary Partners among Sheltered and Low-income Housed Women in Los

Angeles County

This study investigated cross-sectional associations of substance use, relationship abuse and HIV self-protective behavior with unprotected sex among 290 impoverished women with a non-cohabitating primary partner. Unprotected sex was associated with having a physically or psychologically abusive partner among low-income housed women, and having an abusive partner who also drank to intoxication among women living in shelters. Indicators of HIV self-protective behavior were associated with less frequent unprotected sex among sheltered women, even after accounting for abuse and substance use within the relationship. Results suggest the need for HIV-prevention interventions to address the problems of partner substance use and relationship abuse. Tucker, J., Wenzel, S., Elliott, M., and Hambarsoomian, K. Predictors of Unprotected Sex with Non-Cohabitating Primary Partners among Sheltered and Low-Income Housed Women in Los Angeles County. J Health Psychol, 11(5), pp. 697-710, 2006.

Psychological Correlates of Trading Sex for Money among African American Crack Cocaine Smokers

This article compares demographic characteristics, sexual practices, and psychosocial status among 193 African American female crack cocaine users who currently, previously, or never traded sex for money. Current traders were less likely to have a main sexual partner, more likely to have a casual sexual partner, and more likely to smoke larger quantities of crack. There was a significant trend towards current traders reporting lower self-esteem, greater depression and anxiety, poorer decision-making confidence, more hostility, less social conformity, greater risk taking behaviors, and more problems growing up, compared to previous and never traders. These differences suggest that interventions should address self-esteem, risk-taking practices, depression and anxiety as well as other psychosocial factors. Risser, J., Timpson, S., McCurdy, S., Ross, M., and Williams, M. Psychological Correlates of Trading Sex for Money among African American Crack Cocaine Smokers. Am J Drug Alcohol Abuse, 32(4), pp. 645-653, 2006.

Prescription Opioid Abuse among Drug-Involved Street-Based Sex Workers

National population surveys and individual studies over the past decade have documented the escalating abuse of a variety of prescription medications, particularly prescription opioids. Although surveillance data provide important information for estimating the prevalence of prescription opioid abuse in the general population, studies documenting the patterns of prescription drug abuse among chronic street-drug-using populations are extremely rare. This paper examines the abuse of prescription opioids among drug-involved street-based sex workers in Miami, Florida. The data for this study were drawn from an ongoing HIV intervention trial initiated in 2001, designed to test the relative effectiveness of two alternative HIV prevention protocols for this population. Participants in the study were recruited through traditional targeted sampling strategies, and complete data are available on 588 street-based sex workers. In terms of prescription drug abuse, 12.2 percent of the sample reported using at least one opioid analgesic in the past 90 days without having a legitimate prescription. Logistic regression analyses were conducted to examine the associations between prescription opioid abuse and its predictors. In the multivariate model, factors positively associated with prescription opioid abuse included: Caucasian race (OR = 2.53; 95 percent CI 1.30 to 4.91), current powder cocaine use (OR = 2.28; 95 percent CI 1.28 to 4.08), current heroin use (OR = 2.08; 95 percent CI 1.10 to 3.92), 90-day physical abuse/victimization (OR = 2.07; 95 percent CI 1.18 to 3.61), and shorter sex-

work involvement (OR = 1.98; 95 percent CI 1.13 to 3.48). In contrast, daily crack smoking was negatively associated with prescription opioid abuse (OR = 0.61; 95 percent CI 0.33 to 1.10). This study provides some of the first empirical evidence to indicate that prescription opioid abuse is emerging in a heretofore unstudied community of marginalized drug-using sex workers. In addition, data on this population's mechanisms of access to prescription opioids clearly suggest that there is an active black market for these drugs. These findings warrant further study to determine the relative contribution of each mechanism of diversion to the illicit market. Surratt, H., Inciardi, J., and Kurtz, S. Prescription Opioid Abuse among Drug-Involved Street-Based Sex Workers. J Opioid Manag, 2(5), pp. 283-289, 2007.

Mechanisms of Prescription Drug Diversion Among Drug-Involved Club- and Street-Based Populations

Prescription drug diversion involves the unlawful channeling of regulated pharmaceuticals from legal sources to the illicit marketplace, and can occur along all points in the drug delivery process, from the original manufacturing site to the wholesale distributor, the physician's office, the retail pharmacy, or the patient. However, empirical data on diversion are limited. In an attempt to develop a better understanding of how specific drug-using populations are diverting prescription opioids and other medications, or obtaining controlled drugs that have already been diverted, qualitative interviews and focus group data were collected on four separate populations of prescription drug abusers in Miami, Florida-club drug users, street-based illicit drug users, methadone maintenance patients, and HIV positive individuals who abuse and/or divert drugs. Sources of abused prescription drugs cited by focus group participants were extremely diverse, including their physicians and pharmacists; parents and relatives; "doctor shopping"; leftover supplies following an illness or injury; personal visits to Mexico, South America and the Caribbean; prescriptions intended for the treatment of mental illness; direct sales on the street and in nightclubs; pharmacy and hospital theft; through friends or acquaintances; under-the-door apartment flyers advertising telephone numbers to call; and "stealing from grandma's medicine cabinet." While doctor shoppers, physicians and the Internet receive much of the attention regarding diversion, the data reported in this paper suggest that there are numerous active street markets involving patients, Medicaid recipients and pharmacies as well. In addition, there are other data which suggest that the contributions of residential burglaries, pharmacy robberies and thefts, and "sneak thefts" to the diversion problem may be understated. Inciardi, J., Surratt, H., Kurtz, S., and Cicero, T. Mechanisms of Prescription Drug Diversion Among Drug-Involved Club- and Street-Based Populations. Pain Med, 8(2), pp. 171-183, 2007.

The Importance of Clearly Defining Terms When Surveying Adolescents About Smoking

Although adolescent smoking cessation has received increased research attention, little information exists as to how adolescents define change efforts for smoking behaviors. This issue is of particular importance because surveys routinely incorporate items assessing smoking cessation, yet how adolescents interpret such items is unclear. To examine how adolescents define the terms "quit," "stop," and "cut down" when describing their smoking behavior change efforts, this research team surveyed a total of 94 adolescent smokers [average age 16.7 years (SD = 1.0), 56% female, and 71% white]. Definitions of quit and stop were categorized as (a) stop permanently, (b) stop temporarily, (c) stop except in certain situations, and (d) reduce smoking (for quit only). Definitions of cut down were categorized as (a) reduce the number of cigarettes, (b) smoke less in a time frame, (c) reduce smoking occasions, and (d) smoke less. Three trained raters sorted responses into each of the categories. Definitions of quit and stop were most frequently categorized in the

stop permanently category (86% and 75%, respectively). Definitions of cut down were distributed across categories, with 51% categorized as smoke less, 25% smoking less in a time frame, and 25% reducing number of cigarettes. Different definitions of stop were related to smoking history and motivation to quit, although the other two terms were not related to adolescent individual characteristics. These findings highlight the importance of using clearly defined questionnaire items when assessing adolescent smoking change efforts. MacPherson, L., Myers, M., and Johnson, M. Adolescent Definitions of Change in Smoking Behavior: An Investigation. Nicotine Tob Res, 8(5), pp. 683-687, 2006.

A Multivariate Analysis of Neuroanatomic Relationships in a Genetically Informative Pediatric Sample

An important component of brain mapping is an understanding of the relationships between neuroanatomic structures, as well as the nature of shared causal factors. Prior twin studies have demonstrated that much of individual differences in human anatomy are caused by genetic differences, but information is limited on whether different structures share common genetic factors. Researchers performed a multivariate statistical genetic analysis on volumetric MRI measures (cerebrum, cerebellum, lateral ventricles, corpus callosum, thalamus, and basal ganglia) from a pediatric sample of 326 twins and 158 singletons. The results suggest that the great majority of variability in cerebrum, cerebellum, thalamus and basal ganglia is determined by a single genetic factor. Though most (75%) of the variability in corpus callosum was explained by additive genetic effects these were largely independent of other structures. Relatively small but significant environmental effects were observed to be common to multiple neuroanatomic regions, particularly between thalamus, basal ganglia, and lateral ventricles. These findings are concordant with prior volumetric twin studies and support radial models of brain evolution. Schmitt, J., Wallace, G., Rosenthal, M., Molloy, E., Ordaz, S., Lenroot, R., Clasen, L., Blumenthal, J., Kendler, K., Neale, M., and Giedd, J. A Multivariate Analysis of Neuroanatomic Relationships in a Genetically Informative Pediatric Sample. Neuroimage, 35(1), pp. 70-82, 2007.

Assortative Mating Explains Spousal Similarity in Cigarette and Alcohol Use and Dependence

Non-random mating affects population variation for substance use and dependence. Developmentally, mate selection leading to positive spousal correlations for genetic similarity may result in increased risk for substance use and misuse in offspring. Mate selection varies by cohort and thus, assortative mating in one generation may produce marked changes in rates of substance use in the next. This team of researchers used data from female twins and their male spouses to clarify the mechanisms contributing to spousal similarity for cigarette smoking and alcohol consumption. They found that assortative mating significantly influenced regular smoking, regular alcohol use, nicotine dependence and alcohol dependence. The bivariate models for cigarette smoking and alcohol consumption also highlighted the importance of primary assortative mating on all stages of cigarette smoking and alcohol consumption, with additional evidence for assortative mating across the two stages of alcohol consumption. They concluded that women who regularly used, and subsequently were dependent on cigarettes or alcohol were more likely to marry men with similar behaviors. After mate selection had occurred, one partner's cigarette or alcohol involvement did not significantly modify the other partner's involvement with these psychoactive substances. Agrawal, A., Heath, A., Grant, J., Pergadia, M., Statham, D., Bucholz, K., Martin, N., and Madden, P. Assortative Mating for Cigarette Smoking and for Alcohol Consumption in Female Australian Twins and their Spouses. Behav Genet, 36(4), pp. 553-566, 2006.

Heroin and Cocaine Dependence and the Risk of Accidental Non-fatal Drug Overdose

The relation between illicit drug dependence and the likelihood of drug overdose is unclear. For this analysis, researchers recruited 1,066 habitual drug users through street-based outreach in New York City, of which 99.3% used heroin in the past year and 87.1% used cocaine. They found that 819 (77.5%) heroin users and 735 (79.2%) cocaine users were severely dependent on either drug respectively. In multivariable models, among heroin users, persons who were severely heroin dependent were less likely (OR = 0.6; 95% CI = 0.4-0.9) to have overdosed on any drug in the past year; among cocaine users, those who were severely cocaine dependent were more likely (OR = 1.6; 95% CI = 1.0-2.6) to have overdosed in the past year. These findings indicate that the relationship between illicit drug dependence and risk of overdose varies for different patterns of drug dependence. These observations suggest that overdose prevention interventions, perhaps even those specifically targeting opiate overdose, may be more efficiently directed at individuals exhibiting cocaine dependence. Galea, S., Nandi, A., Coffin, P., Tracy, M., Markham Piper, T., Ompad, D., and Vlahov, D. Heroin and Cocaine Dependence and the Risk of Accidental Non-fatal Drug Overdose. J Addict Dis, 25(3), pp. 79-87, 2006.

Barriers and Facilitators to Methadone Maintenance Therapy Use among Illicit Opiate Injection Drug Users in Vancouver

Methadone maintenance therapy (MMT) has been increasingly implemented as the treatment of choice for opiate-addicted individuals and has been associated with reduced harm related to opiate addiction. Barriers to MMT uptake still exist, however, and many opiate-addicted individuals do not access this form of treatment. Researchers examined barriers to and facilitators of MMT access among opiate users enrolled in a prospective cohort study of injection drug users (IDUs). They identified individuals who had initiated MMT during follow-up interviews and used generalized estimating equations to identify sociodemographic and drug-related variables associated with MMT access. Of the 1,587 participants recruited into the Vancouver Injection Drug User Study, 1,463 were eligible for the present analysis. Factors negatively associated with MMT use included male gender (odds ratio [OR] = 0.41; 95 percent confidence interval [CI], 0.32 to 0.52), Aboriginal ethnicity (OR = 0.37; 95 percent CI, 0.29 to 0.48), recent incarceration (OR = 0.82; 95 percent CI, 0.72 to 0.93), Downtown Eastside residence (OR = 0.86; 95 percent CI, 0.75 to 0.97), sex-trade involvement (OR = 0.80; 95 percent CI, 0.67 to 0.95), syringe lending (OR = 0.76; 95 percent CI, 0.66 to 0.89), denied addiction treatment (OR = 0.81; 95 percent CI, 0.68 to 0.96), heroin injection (OR = 0.51; 95 percent CI, 0.44 to 0.59), nonfatal overdose (OR = 0.59; 95 percent CI, 0.51 to 0.68), and injecting in public (OR = 0.75; 95 percent CI, 0.63 to 0.89). Older age (OR = 1.03; 95 percent CI, 1.01 to 1.04), HIV positivity (OR = 1.89; 95 percent CI, 1.52 to 2.2.3), and crack cocaine smoking (OR = 1.41; 95 percent CI, 1.22 to 1.62) were positively associated with MMT use. The study identified a large number of barriers to and facilitators of MMT use among IDUs. While some populations such as HIV-positive individuals are frequently accessing MMT, identified barriers among men and Aboriginal IDUs are of great concern. These findings indicate the need for additional interventions aimed at maximizing coverage of MMT and other treatments for opiate-addicted individuals. Callon, C., Wood, E., Marsh, D., Li, K., Montaner, J., and Kerr, T. Barriers and Facilitators to Methadone Maintenance Therapy Use among Illicit Opiate Injection Drug Users in Vancouver. J Opioid Manag, 2(1), pp. 35-41, 2007.

Multilevel Community-Based Intervention to Increase Access to

Sterile Syringes among Injection Drug Users through Pharmacy Sales in New York City

Research has shown that there is minimal use of pharmacies among injection drug users (IDUs) in specific neighborhoods and among Black and Hispanic IDUs. This study developed a community-based participatory research partnership to determine whether a multilevel intervention would increase sterile syringe access through nonprescription syringe sales in pharmacies. Researchers targeted Harlem, NY (using the South Bronx for comparison), and disseminated informational material at community forums, pharmacist training programs, and counseling or outreach programs for IDUs. They compared cross-sectional samples in 3 target populations (pre- and post intervention): community members (attitudes and opinions), pharmacists (opinions and practices), and IDUs (risk behaviors). Among community members (N = 1496) and pharmacists (N = 131), negative opinions of IDU syringe sales decreased in Harlem whereas there was either no change or an increase in negative opinions in the comparison community. Although pharmacy use by IDUs (N=728) increased in both communities, pharmacy use increased significantly among Black IDUs in Harlem, but not in the comparison community; syringe reuse significantly decreased in Harlem, but not in the comparison community. These findings show that targeting the individual and the social environment through a multilevel community-based intervention reduced high-risk behavior, particularly among Black IDUs. Fuller, C., Galea, S., Caceres, W., Blaney, S., Sisco, S., and Vlahov, D. Multilevel Community-Based Intervention to Increase Access to Sterile Syringes among Injection Drug Users through Pharmacy Sales in New York City. Am J Public Health, 97(1), pp. 117-124, 2007.

Are Gay, Lesbian, and Bisexual Youth More Likely to Be Victims of Sexual and Physical Abuse?

This study was designed to examine the association between adolescent sexual orientation and risk for physical and sexual victimization. The authors conducted secondary data analyses from seven population-based high school health surveys in the US and Canada. Results suggest that sexual minority teens in nearly all surveys were significantly more likely to report sexual and physical abuse than their same-age heterosexual counterparts, with differences markedly stronger for boys. Data also suggest the disparities are worsening, particularly for bisexual teens. Case studies are provided and implications for interventions are discussed. Saewyc, E., Skay, C., Pettingell, S., Reis, E., Bearinger, L., Resnick, M., Murphy, A., and Combs, L. Hazards of Stigma: The Sexual and Physical Abuse of Gay, Lesbian, and Bisexual Adolescents in the United States and Canada. Child Welfare, 85(2), pp. 195-213, 2006.

Distribution of Influenza Vaccine to High-Risk Groups

Vaccine distribution programs have historically targeted individuals at high risk of complications due to influenza. Despite recommendations from the Advisory Committee on Immunization Practices, vaccination coverage among high-risk populations has been generally low. This review systematically summarizes the recent literature evaluating programs in different settings, from within medical settings to venue-based and community-based approaches, in an effort to identify successful program components. The published literature was identified by using the MEDLINE database from 1990 to 2006 covering studies that reported on interventions or programs aimed at vaccinating high-risk populations. The authors reviewed 56 studies. In the United States, the Healthy People 2010 goals included 90% vaccination coverage for adults aged >= 65 years and 60% for high-risk adults aged 18-64 years. Only a handful of the studies reviewed managed to meet those goals. Interventions that increased vaccination coverage to Healthy People 2010 goals included

advertising, provider and patient mailings, registry-based telephone calls, patient and staff education, standing orders coupled with standardized forms, targeting of syringe exchange customers, and visiting nurses. Few studies evaluated the impact of vaccination programs by race/ethnicity and socioeconomic status. Few studies targeted individuals outside of the health-care and social services sectors. Given the growing disparities in health and health-care access, understanding the way in which interventions can remedy disparities is crucial. Danielle, O.C., and Sandro, G. Distribution of Influenza Vaccine to High-Risk Groups. Epidemiol Rev, 28(1), pp. 54-70, 2006.

Director's Report to the National Advisory Council on Drug Abuse - May, 2007

Research Findings - Prevention Research

Can Universal Prevention Reduce Substance Use Among Adolescent Substance Users?

Efforts to address youth substance use have focused on prevention among non-users and treatment among severe users with less attention given to youth occupying the middle ground who have used substances but not yet progressed to serious abuse or addiction. Using a sample from 35 middle schools of 1,364 youth who reported using substances, this study examined the effectiveness of a universal youth substance use prevention program, "Keepin' it REAL", in promoting reduced or recently discontinued alcohol, cigarette, and marijuana use. Discrete-time event history methods modeled the rates of reduced and recently discontinued use across four waves of data. Each substance (alcohol, cigarettes, and marijuana) was modeled separately. Beginning at the second wave, participants who reported use at wave 1 were considered in need of reducing or discontinuing use. Since the data sampled students in schools, multi-level models accounted for the nesting of data at the school level. Results indicated that prevention program participation influenced the rates of reduced and recently discontinued use only for alcohol, controlling for baseline use severity, age, grades, socioeconomic status, ethnicity and gender. Among youth who reported use of alcohol in wave 1 (N=1,028), the rate of reducing use for program participants was 72% higher than the rate for control students. The rate of discontinuing use was 66% higher than the rate for control students. Among youth who reported use of one or more of the three substances in wave 1 (N=1,364), the rate of discontinuing all use was 61% higher for program participants than for control students. Limitations and implications of these findings and plans for further research are discussed. Kulis, S., Nieri, T., Yabiku, S., Stromwall, L., and Marsiglia, F. Promoting Reduced and Discontinued Substance Use among Adolescent Substance Users: Effectiveness of a Universal Prevention Program. Prev Sci, 8(1), pp. 35-49, 2007.

Sexual and Drug Behavior Patterns and HIV and STD Racial Disparities: The Need for New Directions

Authors used nationally representative data to examine whether individuals' sexual and drug behavior patterns account for racial disparities in sexually transmitted disease (STD) and HIV prevalence. Data were derived from wave III of the National Longitudinal Study of Adolescent Health. Participants were aged 18 to 26 years old; analyses were limited to non-Hispanic Blacks and Whites. Theory and cluster analyses yielded 16 unique behavior patterns. Bivariate analyses compared STD and HIV prevalence for each behavior pattern, by race. Logistic regression analyses examined within-pattern race effects before and after control for covariates. Unadjusted odds of STD and HIV

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infection were significantly higher among Blacks than among Whites for 11 of the risk behavior patterns assessed. Across behavior patterns, covariates had little effect on reducing race odds ratios. White young adults in the United States are at elevated STD and HIV risk when they engage in high-risk behaviors. Black young adults, however, are at high risk even when their behaviors are normative. Factors other than individual risk behaviors and covariates appear to account for racial disparities, indicating the need for population-level interventions. Hallfors, D., Iritani, B., Miller, W., and Bauer, D. Sexual and Drug Behavior Patterns and HIV and STD Racial Disparities: The Need for New Directions. Am J Public Health, 97(1), pp. 125-132, 2007.

Preventive Effects Of Treatment Of Disruptive Behavior Disorder In Middle Childhood On Substance Abuse and Delinquent Behavior

Disruptive behavior disorder (DBD) is a well-known risk factor for substance abuse and delinquent behavior in adolescence. Therefore, the long-term preventive effects of treatment of DBD in middle childhood on beginning substance use and delinquency in early adolescence were investigated. Children with DBD (8-13 years old) had been randomly assigned to manualized behavior therapy (Utrecht Coping Power Program; UCPP) or to care as usual (CU) in the Netherlands. Five years (2003-2005) after the start of treatment (1996-1999), substance use and delinquency were monitored in 61 of the initial 77 adolescents and compared with a matched healthy control group by means of self-report questionnaires. One-factor analyses of variance and Pearson's chi2 analyses were performed. Differences in substance use were revealed in favor of the UCPP, with more adolescents in the CU group smoking cigarettes in the last month (UCPP 17%, CU 42%; chi2 = 4.7; $p < .03$) and more adolescents in the CU group having ever used marijuana (UCPP 13%, CU 35%; chi2 = 4.0; $p < .045$). Moreover, in this respect, the UCPP fit in the range of the matched healthy control group. Both treatment groups were comparable to the matched healthy control group in delinquent behavior. Manualized behavior therapy for DBD in middle childhood seems to be more powerful than CU in reducing substance use in early adolescence. Both treatment conditions show a beneficial long-term preventive effect on delinquency. Zonnevylle-Bender, M., Matthys, W., Van de Wiel, N., and Lochman, J. Preventive Effects of Treatment of Disruptive Behavior Disorder in Middle Childhood on Substance Use and Delinquent Behavior. J Am Acad Child Adolesc Psychiatry, 46(1), pp. 33-39, 2007.

Implementation Fidelity and Effectiveness of the Reconnecting Youth Program

This paper reports the results of an implementation fidelity study of the Reconnecting Youth (RY) prevention program. The research questions were (i) was the program implemented with fidelity? and (ii) did better fidelity predict better outcomes? RY is an indicated drug abuse prevention program for high school students that seeks to 'reconnect' high risk youth to school before they drop out. The results reported here were part of a randomized controlled effectiveness trial of the RY prevention program conducted in two urban school districts in which 15 teachers taught 41 RY classes. Overall, implementation fidelity was high with an average 90% of core lessons being taught. In a previous study (Cho et al., 2005) researchers reported unexpected negative outcomes of the intervention condition compared to the control condition. In the current study, aspects of implementation quality--program fidelity, adherence to the curriculum and exposure to the program also predicted negative outcomes (e.g., increased alcohol use and anger, bonding to high risk peers). Thus, the negative outcomes were predicted by high implementation fidelity. Results were discussed in terms of group contagion, and several research limitations were discussed. The authors conclude by reiterating the need to study programs within real world contexts to assess whether positive

program effects are replicated, and to assess the potential for unintended consequences to occur when programs are adopted. Sanchez, V., Steckler, A., Nitirat, P., Hallfors, D., Cho, H., and Brodish, P. Fidelity of Implementation in a Treatment Effectiveness Trial of Reconnecting Youth. Health Education and Research, 22 (1), pp. 95-107, 2007.

Implementation Fidelity Impacts Prevention Program Outcomes

Implementation fidelity is increasingly recognized as a key component of effective prevention programming. The present study examined the association between implementation fidelity and youth substance use outcomes among students in 11 New York City middle schools receiving a drug abuse prevention program. Trained observers monitored the implementation of a research-based prevention program by classroom teachers (N = 38), and participating students (N = 1,857) completed surveys assessing smoking and alcohol use over a 15-month period. Findings indicated that teachers who relied more on lecturing when teaching the program were less likely to use discussion and demonstration as teaching methods. Teachers who relied on lecturing were rated by observers as being less ready to teach and having poorer classroom management skills. Findings indicated that factors related to the quality of implementation significantly predicted change in student substance use outcomes. Students who were taught by the most skilled providers reported significantly lower increases in smoking and drinking at the follow-up assessments compared to students taught by other providers. Griffin, K.W., Mahadeo, M., Weinstein, J., and Botvin, G.J. Program Implementation Fidelity and Substance Use Outcomes among Middle School Students in a Drug Abuse Prevention Program. Saludy Drogas, 6(1), pp. 9-28, 2006.

The Fast Track Prevention Program is Cost-Effective for Highest Risk Children

This study examined the cost-effectiveness of the Fast Track intervention, a multi-year, multi-component intervention designed to reduce violence among at-risk children. A previous report documented the favorable effect of intervention on the highest-risk group of ninth-graders diagnosed with conduct disorder, as well as self-reported delinquency. The current report addressed the cost-effectiveness of the intervention for these measures of program impact. Costs of the intervention were estimated using program budgets. Incremental cost-effectiveness ratios were computed to determine the cost per unit of improvement in the 3 outcomes measured in the 10th year of the study. Examination of the total sample showed that the intervention was not cost-effective at likely levels of policymakers "willingness to pay" for the key outcomes. Subsequent analysis of those most at risk, however, showed that the intervention likely was cost-effective given specified willingness-to-pay criteria. Results indicate that the intervention is cost-effective for the children at highest risk. From a policy standpoint, this finding is encouraging because such children are likely to generate higher costs for society over their lifetimes. However, substantial barriers to cost-effectiveness remain, such as the ability to effectively identify and recruit such higher-risk children in future implementations. Foster, E., and Jones, D. Can a Costly Intervention Be Cost-Effective? An Analysis of Violence Prevention. Arch Gen Psychiatry, 63(11), pp. 1284-1291, 2006.

The Gap Between Self-Reported STIs and Test-Identified STIs

Many studies rely on respondent reports of prior diagnosed sexually transmissible infections (STIs), but these self reports are likely to under-estimate infection prevalence. The extent of bias from using self-reported STI data, and whether bias varies by sex and race, is largely unknown. This gap is

addressed through a cross-sectional analysis of Wave III of the National Longitudinal Study of Adolescent Health. Participants were 18-26 years old (n = 12,359). Estimates of the prevalence of Chlamydia infection based on self-reported diagnoses in the past year were compared with actual prevalence based on nucleic acid amplification testing (NAAT) at the time of data collection. Ratios of test-identified prevalence to self-reported diagnosis prevalence were calculated by sex and race/ethnicity groups. Larger ratios indicate greater extent of self reports under-estimating infection prevalence. About 4.2% of the sample had a current NAAT-identified Chlamydia infection, but only 3.0% reported having been diagnosed with Chlamydia in the past year, yielding a ratio of 1.43. The ratio of test-identified infection prevalence to prevalence identified from self-reported diagnoses was larger among men than women (2.07 versus 1.14, $P < 0.05$). Among men, the ratio was larger among non-Hispanic blacks (2.40) compared with non-Hispanic whites (1.07, $P < 0.05$). The authors conclude that the use of self-reported diagnoses underestimates Chlamydia infection prevalence, particularly among men, and among non-Hispanic black men. Reliance on self-reported STIs may consequently lead to biased conclusions, particularly for these groups. Use of biological testing for STIs in research studies is recommended. Iritani, B., Ford, C., Miller, W., Hallfors, D., and Halpern, C. Comparison of Self-Reported and Test-Identified Chlamydia Infections Among Young Adults in The United States of America. Sex Health, 3(4), pp. 245-251, 2006.

Developmental Trajectories and the Analysis of Adolescent Substance Use Data

This study of 498 adolescents examined the covariates of early onset substance use from Grade 6 through Grade 9. The youth were randomly assigned to a family-centered Adolescent Transitions Program condition or a control condition. Variable-centered (i.e., zero-inflated Poisson growth model) and person-centered (latent growth mixture model) approaches were taken to examine treatment effects on patterns of substance use development across early adolescence. Variable-centered analysis revealed treatment effects of the intervention both on decreasing the likelihood of initiating substance use and on the rate of growth of substance use among those who initiated use. Person-centered analyses revealed the following five trajectories of early substance use (1) no use, (2) low/rare use, (3) early accelerating use, (4) late accelerating use, and (5) early high but decreasing use. Of note, random assignment to the ATP intervention was strongly predictive of following the decreasing-use trajectory. In addition, the early high but decreasing group was most likely to engage in the Family Check-Up and linked intervention services. These findings suggest that covariates of early adolescent substance use, as well as the effectiveness of prevention strategies, vary as a function of the developmental pattern underlying early adolescent risk. Connell, A.M., Dishion, T.J., and Deater-Deckard, K. Variable- and Person- Centered Approaches to the Analysis of Early Adolescent Substance Use: Linking Peer, Family, and Intervention Effects with Developmental Trajectories. Merrill-Palmer Quarterly, 52(3), pp. 421-448, 2006.

Planned Missing Data Designs in Psychological Research

The authors describe 2 efficiency (planned missing data) designs for measurement: the 3-form design and the 2-method measurement design. The 3-form design, a kind of matrix sampling, allows researchers to leverage limited resources to collect data for 33% more survey questions than can be answered by any 1 respondent. Power tables for estimating correlation effects illustrate the benefit of this design. The 2-method measurement design involves a relatively cheap, less valid measure of a construct and an expensive, more valid measure of the same construct. The cost effectiveness of this design stems from the fact that few cases have both measures, and many cases have

just the cheap measure. With 3 brief simulations involving structural equation models, the authors show that compared with the same-cost complete cases design, a 2-method measurement design yields lower standard errors and a higher effective sample size for testing important study parameters. With a large cost differential between cheap and expensive measures and small effect sizes, the benefits of the design can be enormous. Strategies for using these 2 designs are suggested. Graham, J., Taylor, B., Olchowski, A., and Cumsille, P. Planned Missing Data Designs in Psychological Research. Psychol Methods, 11(4), pp. 323-343, 2006.

Multidimensional Treatment Foster Care For Girls in the Juvenile Justice System: Two Year Follow-Up of a Randomized Clinical Trial

This study is a 2-year follow-up of girls with serious and chronic delinquency who were enrolled in a randomized clinical trial conducted from 1997 to 2002 comparing multidimensional treatment foster care (MTFC) and group care (N = 81). Girls were referred by juvenile court judges and had an average of over 11 criminal referrals when they entered the study. A latent variable analysis of covariance model controlling for initial status demonstrated maintenance of effects for MTFC in preventing delinquency at the 2-year assessment, as measured by days in locked settings, number of criminal referrals, and self-reported delinquency. A latent variable growth model focusing on variance in individual trajectories across the course of the study also demonstrated the efficacy of MTFC. Older girls exhibited less delinquency over time relative to younger girls in both conditions. Implications for gender-sensitive programming for youths referred from juvenile justice are discussed. Chamberlain, P., Leve, L., and Degarmo, D. Multidimensional Treatment Foster Care for Girls in the Juvenile Justice System: 2-Year Follow-up of a Randomized Clinical Trial. J Consult Clin Psychol, 75(1), pp. 187-193, 2007.

Feasibility of Motivational Interviewing for Addressing Drug Use Among High-Risk Teens

Prevention of substance abuse among adolescents may require multiple strategies. Universal prevention programs administered in school classrooms are effective for many students, but those adolescents who use moderate to heavy amount of drugs may benefit from other approaches. Heavy and problem drinkers, for example, have been shown to be less interested in traditional school-based programs and many appear to have limited motivation to change their behavior. A brief, one-to-one intervention based upon motivational interviewing may provide an additional intervention tool that could be used to address the needs of such high-risk students. The aim of the current study was to evaluate the feasibility and preliminary effects of an MI approach at continuation high school sites. Participants were recruited from three morning classes at two continuation high schools in the greater Los Angeles area. Continuation high schools enroll students who are unable to attend regular high schools for various reasons including conduct problems and drug use. A total of 18 students (6 female; 12 males) participated in this pilot study. Eleven students were randomly assigned to the intervention group and 7 were randomly assigned to the control group. Those assigned to the intervention group met with one of two motivational interviewers. All participants assigned to the treatment group were willing to discuss their personal drug use. Five participants chose to discuss marijuana, four chose alcohol, one chose ecstasy, and one chose methamphetamine. This pilot study demonstrated that it is feasible to administer brief individualized interventions on alternative high school campuses to students who are at risk of substance abuse. Students actively participated in brief motivational interviews and showed some improvement in five of nine outcomes at three-month follow-ups. Grenard, J., Ames, S., Wiers, R., Thush, C., Stacy, A., and Sussman, S. Brief Intervention for Substance use Among At-Risk Adolescents: A Pilot Study. J Adolesc Health,

40(2), pp. 188-191, 2007.

Neighborhood Effects on Prevention Program Efficacy

This study examines how neighborhood characteristics affect program efficacy through an analysis of data from a randomized prevention trial. The prevention program, called "Keepin' it REAL", was administered to a predominantly Mexican American sample of 4,622 middle school students in Phoenix, Arizona, beginning in 1998. The program was designed to extend evidence-based resistance and life-skills prevention approaches to incorporate ethnically appropriate traditional values and practices that promote protection against drug use. Thirty-five middle schools were randomized to one of two culturally grounded prevention conditions or a control condition. Prior research supports the overall efficacy of the prevention program. However, among less linguistically accultured Latinos, living in poorer neighborhoods and in single-mother families decreased program effectiveness in reducing alcohol use. High neighborhood immigrant composition increased program effectiveness. Unexpectedly, the program was also more effective in neighborhoods with higher rates of crime. Yabiku, S., Kulis, S., Marsiglia, F.F., Lewin, B., Nieri, T., and Hussaini, S. Neighborhood Effects on the Efficacy of a Program to Prevent Youth Alcohol Use. Subst Use Misuse, 42 pp. 65-87, 2007.

Training Active Drug Users as Peer Health Advocates

Efforts have expanded to create AIDS prevention programs for drug users that consider the social context and interpersonal relationships within which risky practices take place. The Risk Avoidance Partnership (RAP) project is designed to train active drug users as peer/public health advocates (PHAs) to bring a structured, peer-led intervention into the sites where they and their drug-using social networks use illicit drugs. The RAP peer health advocacy training curriculum and peer-led intervention promote harm reduction among drug users and support drug-user organization to reduce infectious disease and other harm in the context of injection drug use, crack cocaine use, and sexual activity. Initial findings suggest that RAP PHAs perceive a significant positive role change in themselves while conducting health advocacy work and willingly and successfully carry the peer-led intervention into locations of high-risk drug activity to deliver it to their peers even in the absence of project staff support. Weeks, M.R., Dickson-Gomez, J., Mosack, K.E., Convey, M., and Martinez, M. The Risk Avoidance Partnership: Training Active Drug Users as Peer Health Advocates. Journal of Drug Issues, Summer, pp. 541-554, 2006.

Suicidality, School Dropout, and Reading Problems Among Adolescents

The purpose of this study was to examine the risk of suicidal ideation and suicide attempts and school dropout among youth with poor reading in comparison to youth with typical reading (n = 188) recruited from public schools at the age of 15. In a prospective naturalistic study, youth and parents participated in repeated research assessments to obtain information about suicide ideation and attempts, psychiatric and sociodemographic variables, and school dropout. Youth with poor reading ability were more likely to experience suicidal ideation or attempts and more likely to drop out of school than youth with typical reading, even after controlling for sociodemographic and psychiatric variables. Suicidality and school dropout were strongly associated with each other. Prevention efforts should focus on better understanding the relationship between these outcomes, as well as on the developmental paths leading up to these behaviors among youth with reading difficulties. Daniel, S., Walsh, A., Goldston, D., Arnold, E., Reboussin, B., and Wood, F. Suicidality, School Dropout, and Reading Problems Among Adolescents Journal of Learning

Disabilities, 39(6), pp. 507-514, 2006.

Adolescent Predictors of Emerging Adult Sexual Patterns

This study estimates the percentages of young adults who fall into three groups based on the context of sexual transition: (1) those who had vaginal intercourse before marriage (Premaritals), (2) those who postponed sex until after marriage (Postponers), and (3) those who have never had vaginal intercourse (Virgins). The second purpose was to determine adolescent biopsychosocial factors that predict membership in these adult groups. Analyses are based on 11,407 respondents ages 18-27 years who participated in Waves I and III of the National Longitudinal Study of Adolescent Health. Adolescent indicators reflecting sociodemographic, biosocial, experiential, and contextual factors were used to predict young adult sexual status using multinomial logistic regression models. About 8% of the sample were virgins and 2% were virgins until marriage. Almost 90% had sex before marriage (Premaritals--referent group). Most predictors of status were similar for males and females. Compared with Premaritals, Virgins were younger, non-Black, not advanced in physical maturity relative to peers in adolescence, had higher body mass indexes, were more religious, and perceived parental disapproval of sex during adolescence. Postponers were also more religious than Premaritals but were older. Female Postponers were non-Black and perceived parental disapproval of sex during adolescence. Male Postponers were less likely to have same-gender attractions or no sexual attractions. Findings document premarital sexual activity as the almost universal sexual trajectory into young adulthood for these cohorts and underscore the roles of biosocial factors and conventional institutions in emerging sexual patterns. Halpern, C., Waller, M., Spriggs, A., and Hallfors, D. Adolescent Predictors of Emerging Adult Sexual Patterns. J Adolesc Health, 39(6), pp. e1-e10, 2006.

Drug Abuse Risk and Protective Factors among Black Urban Adolescent Girls: A Group-randomized Trial of Computer-delivered Mother-daughter Intervention

A group-randomized design tested a mother-daughter intervention in which researchers aimed to increase protective factors in a community sample of Black urban adolescent girls. Girls and their mothers at 2 community agencies were pretested and, by agency, were randomized to either an intervention arm or a control arm. Intervention arm girls and their mothers received a program for improving mother- daughter rapport. Posttest data collected 3 weeks after program delivery revealed that intervention arm mothers and daughters improved more than did control arm mothers and daughters on measures of communication and closeness. At 3-month follow-up, intervention arm mothers, relative to control arm mothers, continued to report better communication with and closeness to their daughters. Girls and mothers in the intervention arm rated the computer program favorably on parameters of enjoyment, comfort, relevance, usefulness of information, improvements to their relationship with one another, and whether they would recommend the computer program to friends. Schinke, S., Di Noia, J., Schwinn, T., and Cole, K. Drug Abuse Risk and Protective Factors among Black Urban Adolescent Girls: A Group-Randomized Trial of Computer-Delivered Mother-Daughter Intervention. Psychol Addict Behav, 20(4), pp. 496-500, 2006.

Deviant Peer Affiliation Predicts Depressive Symptoms in High-risk Adolescents

This study examined peer predictors of variation and growth in depressed mood among high-risk adolescents, using child and parent reports of monthly symptoms. One hundred seventy-six parents and their 10- to 14-year-old

children separately took part in a series of up to nine monthly interviews. Multilevel growth models examined both time-varying peer predictors of parent and child reports of the child's depressive symptoms, controlling for age, gender, and treatment status. Deviant peer affiliation significantly predicted elevated depressive symptoms in the monthly child-report of depressed mood, especially for younger adolescents. Children's level of delinquency was significantly related to parent-reported depressive symptoms, and to child-reported symptoms in older adolescents only. As expected, depressed mood was higher for girls and more prevalent among older adolescents. The results suggest that peer processes may be linked in time to the development of depression, especially among high-risk adolescents. Connell, A., and Dishion, T. The Contribution of Peers to Monthly Variation in Adolescent Depressed Mood: A Short-term Longitudinal Study with Time-varying Predictors. Dev Psychopathol, 18(1), pp. 139-154, 2006.

Relationship Between Substance Use and Sexual Risk in South African Students

Authors examined the co-variation of substance use and various sexual behaviors in students from one area of South Africa. Data were collected from 2204 eighth grade students from nine schools in a low-income, predominantly colored township as a part of baseline data collection for a randomized trial of a drug abuse and HIV prevention program. Twelve percent of the sample had ever had sexual intercourse. There was an association between lifetime substance use and lifetime sexual activity. Sexually active youth who had used alcohol and/or marijuana in their lifetimes were more likely to report sporadic condom use and more likely to report having had multiple sexual partners in the preceding six months. Youth who used alcohol or marijuana during their last sexual encounter were more likely to have just met their partner, but they were as likely to use condoms as youth who had not used these substances. Palen, L., Smith, E., Flisher, A., Caldwell, L., and Mpofu, E. Substance Use and Sexual Risk Behavior among South African Eighth Grade Students. J Adolesc Health, 39(5), pp. 761-763, 2006.

Immigration Status, Sexual Behavior and Drug Use

This paper contributes new evidence on the association between immigrant status and health by describing and attempting to explain patterns of co-occurring sex and drug use behaviors among Asian and Latino adolescents in the United States. Nine patterns of sex and drug use behaviors were identified from a cluster analysis of data from 3,924 Asian and Latino youth (grades 7-12) who participated in the National Longitudinal Study of Adolescent Health (Add Health). The relationship between immigrant status and risk cluster membership was evaluated with multinomial logistic regression. Compared to foreign-born youth, U.S. born Asian and Latino adolescents were more likely to engage in sex and drug risk behaviors. Family and residential characteristics associated with immigrant status partly accounted for this finding. The results indicate that among Asian and Latino adolescents, assimilation to U.S. risk behavior norms occurs rapidly and is evident by the second generation. Implications for screening, prevention and intervention are discussed. Hussey, J., Hallfors, D., Waller, M., Iritani, B., Halpern, C., and Bauer, D. Sexual Behavior and Drug Use Among Asian and Latino Adolescents: Association with Immigrant Status. J Immigr Minor Health, 9(2), pp. 85-94, 2007.

The Cost of ADHD

Using a cost of illness (COI) framework, this article examines the economic impact of attention-deficit/hyperactivity disorder (ADHD) in childhood and adolescence. This review of published literature identified 13 studies, most

conducted on existing databases by using diagnostic and medical procedure codes and focused on health care costs. Two were longitudinal studies of identified children with ADHD followed into adolescence. Costs were examined for ADHD treatment-related and other health care costs (all but 1 study addressed some aspect of health care), education (special education, 2 studies; disciplinary costs: 1 study), parental work loss (2 studies), and juvenile justice (2 studies). Based on this small and as yet incomplete evidence base, authors estimated annual COI of ADHD in children and adolescents at $14,576 per individual (2005 dollars). Given the variability of estimates across studies on which that number is based, a reasonable range is between $12,005 and $17,458 per individual. Using a prevalence rate of 5%, a conservative estimate of the annual societal COI for ADHD in childhood and adolescence is $42.5 billion, with a range between $36 billion and $52.4 billion. Estimates are preliminary because the literature is incomplete; many potential costs have not been assessed in extant studies. Limitations of the review and suggestions for future research on COI of ADHD are provided. Pelham, W., Foster, E., and Robb, J. The Economic Impact of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Ambul Pediatr, 7(1 Suppl), pp. 121-131, 2007.

Perceived Smoking Environment and Smoking Initiation Among Multi-ethnic Urban Girls

The purpose of this study was to examine associations between the perceived smoking environment and smoking initiation among urban multi-ethnic adolescent girls in New York City. Self-report surveys completed in grades 7, 8, and 9 assessed girls '' (n = 858) smoking initiation, and perceived smoking environment (family smoking, friends' smoking, smoking norms, and cigarette availability). Carbon monoxide breath samples were collected from girls using a variation of the bogus pipeline procedure. Differences were found in smoking prevalence with white girls reporting the highest prevalence of smoking at baseline and greatest increase in smoking prevalence from seventh to eighth grade. Black girls reported an initial increase in smoking prevalence from seventh to eighth grade followed by a decrease from eighth to ninth grade. Family smoking, friends' smoking, smoking norms, and cigarette availability were all associated with smoking initiation at eighth grade but only friends' smoking was associated with smoking initiation at ninth grade. Few ethnic differences were found in risk factors at baseline and racial/ethnic group did not modify associations between risk and smoking initiation. Urban adolescent girls of different racial/ethnic backgrounds had similar perceptions of the smoking environment. Despite the similarity of risk factors across racial/ethnic groups, urban white girls are at increased risk to initiate smoking. Preventive interventions that target girls' perceived smoking environment during early adolescence should be effective across ethnic groups. Nichols, T., Birnbaum, A., Birnel, S., and Botvin, G. Perceived Smoking Environment and Smoking Initiation among Multi-Ethnic Urban Girls. J Adolesc Health, 38(4), pp. 369-375, 2006.

Perceived Physical Maturity, Age of Romantic Partner, and Adolescent Risk Behavior

Early pubertal timing and advanced physical maturity for age confer elevated risk for problem behaviors for both boys and girls. However, examinations of possible biological and social mediators have been limited. Using more than 4,000 adolescents under age 15 who participated in Waves I and II of the National Longitudinal Study of Adolescent Health (Add Health), authors examined the relationship between perceived physical maturity and membership in risk behavior clusters, and tested whether having a romantic partner mediates the maturity/risk behavior relationship. Results of multinomial regression models indicated that for both boys and girls, advanced physical maturity was associated with membership in higher risk clusters, and

that having a romantic partner plays an important mediating role in this association. For females, the additional impact of having an older partner, versus any partner at all, was substantial and particularly important for the highest risk clusters. The role of partner age could not be tested for males. Because romantic partners elevate risk for young adolescent males and females, there is a need to identify and understand facets and developmental functions of adolescent romantic relationships that play a role in substance use and sexual decisions. Halpern, C., Kaestle, C., and Hallfors, D. Perceived Physical Maturity, Age of Romantic Partner, and Adolescent Risk Behavior. Prevention Science, 8(1), pp. 1-10, 2006.

Predictors of Engagement and Retention in Parent-Centered Prevention

This study examined predictors of engagement and retention into a parent-centered, ecodevelopmental HIV preventive intervention for Hispanic adolescents and their families. The influence of retention on changes in adolescent HIV-risk attitudes was also examined. Participants in this study were 91 Hispanic adolescents and their primary parents. Structural equation modeling was used to identify predictors of initial engagement, the effects of group processes on retention, and the effects of retention on change in HIV-risk attitudes in adolescents. Although some participant characteristics predicted engagement, the parent-facilitator relationship quality at the initial contact was found to be the strongest predictor of engagement. Furthermore, within-group processes such as group cohesion positively predicted retention. Finally, parent retention predicted decreases in adolescent HIV-risk attitudes. The results may have important implications for engagement and retention in parent-centered interventions, as well as for reducing risks for HIV transmission in Hispanic adolescents. Prado, G., Pantin, H., Schwartz, S., Lupei, N., and Szapocznik, J. Predictors of Engagement and Retention into a Parent-Centered, Ecodevelopmental HIV Preventive Intervention for Hispanic Adolescents and their Families. J Pediatr Psychol, 31(9), pp. 874-890, 2006.

Targeting Adolescents' Norm-Related Beliefs About Marijuana Use

The integrative model of behavior prediction and priming theory were used to evaluate the effects of anti-marijuana advertisements in an experimental context. In 1 original study and 2 replications, 435 adolescents (42% male; mean age 15.2 years) were randomly assigned to condition, and those in the experimental condition viewed 3 ads that challenged undesirable normative beliefs about marijuana use. Results showed that ad exposure had small but positive (antidrug) effects on adolescents' considerations of the outcomes of using marijuana and their perceptions of the social normative climate surrounding marijuana use. These findings suggest that the normative ads used in this study were able to bring about some desirable changes in adolescents' considerations of using marijuana and their perceptions of the social normative climate surrounding marijuana use. Unfortunately, these changes were not strong enough to translate into statistically significant differences in the more proximal determinants of behavior (i.e., intention, attitude, subjective norm, and self-efficacy). Priming effects also were observed but generally ran counter to predictions. Such findings should be evaluated within the context of a general appreciation of the difficulty involved in persuading adolescents not to use marijuana. The evaluations of the National Youth Antidrug Media Campaign, for example, have shown either no effects or effects in an unfavorable direction over the course of the campaign. Zhao, X., Sayeed, S., Cappella, J., Hornik, R., Fishbein, M., and Ahern, K.R. Targeting Norm-Related Beliefs About Marijuana Use in an Adolescent Population. Health Commun, 19(3), pp. 187-196, 2006.

Synergistic Effect of Anti-Drug Ad Campaign & ALERT Plus

Program

This analysis examined the possible synergistic effect of exposure to the National Youth Anti-Drug Media Campaign and a classroom-based drug prevention curriculum among 9th grade students participating in a randomized trial of ALERT Plus. A total of 45 South Dakota high schools and their middle-school feeder(s) were randomly assigned to an ALERT condition (basic prevention curriculum delivered in 7th and 8th grades), an ALERT Plus condition (basic curriculum with booster lessons added for 9th and 10th grades), or a control condition. Marijuana use in the past month was significantly less likely among ALERT Plus students reporting at least weekly exposure to anti-drug media messages. The National Youth Anti-Drug Media Campaign may have led to reductions in marijuana use among youth who simultaneously received school-based drug prevention. Longshore, D., Ghosh-Dastidar, B., and Ellickson, P. National Youth Anti-Drug Media Campaign and School-Based Drug Prevention: Evidence for a Synergistic Effect in ALERT Plus. Addict Behav, 31(3), pp. 496-508, 2006.

Who Benefited from an Efficacious Intervention for Youth Living with HIV: A Moderator Analysis

An efficacious intervention that results in young people living with HIV (YPLH) reducing their transmission risk has been identified. The present study identifies who is most likely to benefit from the intervention. Regression models were used to examine whether background contextual factors moderated the intervention's success. Percentage of protected sex was moderated by ethnicity, use of antiretroviral medications (ARV), healthcare utilization and mental health. Number of partners was moderated by anxiety and depression. When deciding if an intervention is appropriate and beneficial for an individual young person, consideration must be given to type of services the youth currently accesses and the youth's mental health. Lightfoot, M., Tevendale, H., Comulada, W. and Rotheram-Borus, M. Who Benefited From an Efficacious Intervention For Youth Living with HIV: A Moderator Analysis. AIDS Behav, 11(1), pp. 61-70, 2007.

Effects of School Social Climate on Student Alcohol Use

The school is a primary context for social interaction, cultivation of interpersonal skills, formation of peer groups, self-expression, and development of self. Several studies have demonstrated that the social context of the school has important implications for determining the likelihood that an adolescent will follow a prosocial path through adolescence as opposed to becoming involved in delinquent behavior. Using a data set of 4,216 youth who participated in a prevention trial in 32 middle schools and junior high schools across the United States, this paper examines the effect of a student's own level of school attachment as well as the contextual level of school attachment (the normative level of school attachment in a school) on 5 alcohol-related measures: recent use of alcohol, intention to use alcohol, normative beliefs about peer use of alcohol, attitudes toward alcohol use, and aspirations consistent with alcohol use. The data used in this paper represent the pretest assessment before any interventions were implemented. The results indicated that regardless of a student's own level of school attachment, students who attended schools where the pupils overall tended to be well attached to school were less likely to use alcohol. In addition, they also had lower intentions to use alcohol, perceived that fewer of their peers at school use alcohol, and more strongly held aspirations that were inconsistent with alcohol use. These findings, along with the findings of related studies, provide support for the hypothesis that improvement of school climate may result in less substance use among students. Henry, K., and Slater, M. The Contextual Effect of School

Attachment on Young Adolescents' Alcohol Use. J Sch Health, 77(2), pp. 67-74, 2007.

Adolescent Girls Offending and Health-Risking Sexual Behavior: The Predictive Role of Trauma

Several studies have highlighted high levels of risk for girls who have been exposed to traumatic experiences, but little is known about the exact relationship between traumatic experiences and problems with delinquency and health-risking sexual behavior (e.g., precipitory and/or exacerbatory roles). However, numerous short- and long-term detrimental effects have been linked to trauma, delinquency, and health-risking sexual behavior. The utility of diagnostic and experiential trauma measures in predicting the greatest risk for poor outcomes for delinquent girls was examined in this study. Results indicate that the experiential measures of trauma (cumulative and composite trauma scores) significantly predicted adolescent offending and adolescent health-risking sexual behavior, whereas the diagnostic measures of trauma (full and partial diagnostic criteria) did not. Smith, D., Leve, L.D., and Chamberlain, P. Adolescent Girls' Offending and Health-Risking Sexual Behavior: The Predictive Role of Trauma. Child Maltreat, 11, pp. 346-353, 2006.

Spirituality as One-Year Predictor of Drug Use Among High Risk Youth

The present article explored two different dimensions of spirituality that might tap negative and positive relations with adolescent drug use over a 1-year period. Non-drug-use-specific spirituality measured how spiritual the person believes he or she is, participation in spiritual groups, and engagement in spiritual practices such as prayer, whereas drug-use-specific spirituality measured using drugs as a spiritual practice. Self-report questionnaire data were collected during 1997-1999 from a sample of 501 adolescents in 18 continuation high schools across southern California. Participants ranged in age from 14 to 19 and were 57% male, with an ethnic distribution of 34% White, 49% Latino, 5% African American, 7% Asian, and 5% other. A series of general linear model analyses were conducted to identify whether or not two different spirituality variables predict drug use (cigarettes, alcohol, marijuana, hallucinogens, and stimulants) at 1-year follow-up. After controlling for baseline drug use, non-drug-use-specific spirituality was negatively predictive of alcohol, marijuana, and stimulant use, whereas drug-use-specific spirituality failed to be found predictive of these variables one year later. Conversely, drug-use-specific spirituality was positively predictive of cigarette smoking and hallucinogen use, whereas non-drug-use spirituality failed to be found predictive of these variables. These results provide new evidence that suggests that spirituality may have an effect on drug use among adolescents. The drug-use-specific measure of spirituality showed "risk effects" on drug use, whereas the other measure resulted in "protective effects," as found in previous research. Knowledge of the risk and protective patterns and mechanisms of spirituality may be translated into future drug use prevention intervention programs. Sussman, S., Skara, S., Rodriguez, Y., and Pokhrel, P. Non Drug Use- and Drug Use-specific Spirituality as One-year Predictors of Drug Use Among High-Risk Youth. Subst Use Misuse, 41(13), pp. 1801-1816, 2006.

Brief Interventions for Behavior Change

This theoretical discussion addresses the potential of brief intervention (BI) as a modality for translating health behavior intervention research into practice. A brief intervention is any intervention that is purposely limited in the number and length of contacts and provides personalized information designed to increase motivation to improve health-related behavior. Systematic reviews of

BIs have been conducted that demonstrate their potential applications across disease conditions. Findings from 13 systematic reviews of BI effects are described by the authors. Basic research on motivation, decision making, and persuasion may be applied to the design of BIs (Type 1 translation). Suggestions for translating BI research into practice (Type 2 translation) are discussed by the authors. The article concludes that efforts to use BIs to translate research into practice are currently underdeveloped. Recommendations are provided for using BI in translating research into practice. Werch, C., Grenard, J., Burnett, J., Watkins, J., Ames, S., and Jobli, E. Translation as a Function of Modality: The Potential of Brief Interventions. Eval Health Prof, 29(1), pp. 89-125, 2006.

Reading Problems, Psychiatric Disorders, and Functional Impairment from Mid to Late Adolescence

The goal of this study was to examine psychiatric morbidity and functional impairment of adolescents with and without poor reading skills during mid- to late adolescence. The sample consisted of 188 adolescents, 94 with poor reading skills and 94 with typical reading skills, screened from a larger sample in the public schools at age 15. To assess psychiatric disorders, participants were assessed annually with the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic Version (up to 4.5 years; maximum age, 20 years). Functional impairment was assessed with the Child and Adolescent Functional Assessment Scale. Adolescents with poor reading skills evidenced higher rates of current attention-deficit/ hyperactivity, affective, and anxiety disorders, particularly social phobia and generalized anxiety disorder. Anxiety disorders but not affective disorders were related to reading status after controlling for attention-deficit/hyperactivity disorder. Adolescents with poor reading evidenced more functional impairment across multiple areas than youths with typical reading skills, even after considering the presence of comorbid attention-deficit/hyperactivity disorder. The increased psychiatric morbidity and functional impairment of adolescents with reading problems highlight the importance of developing interventions that help these youths address reading deficits and associated vulnerabilities during the last years of secondary school. Goldston, D., Walsh, A., Mayfield Arnold, E., Reboussin, B., Sergent Daniel, S., Erkanli, A., Nutter, D., Hickman, E., Palmes, G., Snider, E., and Wood, F. Reading Problems, Psychiatric Disorders, and Functional Impairment from Mid- to Late Adolescence. J Am Acad Child Adolesc Psychiatry, 46(1), pp. 25-32, 2007.

Oppositional Defiant Disorder Toward Adults and Oppositional Defiant Disorder Toward Peers: Initial Evidence for Two Separate Constructs

Confirmatory factor analysis of 25 items on the Child and Adolescent Disruptive Behavior Inventory (CADBI, Version 2.3; G. L. Burns, T. K. Taylor, & J. C. Rusby, 2001) was conducted on teacher ratings of 824 kindergarten children and replicated on 534 children. Model fit was improved when correcting for 2 method effects: (a) adjacent items and (b) identical behaviors (e.g., argues with adults, argues with peers). The results show that the 25 items loaded on 3 distinct but correlated factors: Hyperactivity, Oppositional to Adults, and Oppositional to Peers. These more refined constructs from the CADBI may be useful for practitioners in identifying children who are at risk and for helping define appropriate contexts in which to intervene. The CADBI and analytic procedures also may contribute to future psycho educational research on the development of problem behavior. Taylor, T., Burns, G., Rusby, J., and Foster, E. Oppositional Defiant Disorder toward Adults and Oppositional Defiant Disorder toward Peers: Initial Evidence for Two Separate Constructs. Psychol Assess, 18(4), pp. 439-443, 2006.

The Relationship Between Cultural Practices and Commonly Used Markers of Acculturation

The current study was conducted to ascertain the validity of two commonly used markers of acculturation (nativity and years in the receiving culture). Relationships between these markers and a bidimensional measure of acculturation were examined in a convenience sample of Hispanic immigrant adolescents and their caregivers in Miami. Nativity was examined using adolescent-reported data; approximately half of the youth were U.S.-born and half foreign-born, but all of the caregivers were foreign-born. Years in the receiving culture was examined using both adolescent and caregiver data. Results indicated that nativity was significantly associated with adoption of receiving-culture practices, with a small to moderate effect size. Years in the receiving culture was significantly associated with adoption of receiving-culture practices only for adolescent girls and for female caregivers who immigrated as youth. Neither nativity nor years in the receiving culture explained even moderate amounts of variance in retention or loss of culture-of-origin practices. Schwartz, S.J., Pantin, H. and Sullivan, S. Nativity and Years in the Receiving Culture as Markers of Acculturation in Ethnic Enclaves. J Cross Cult Psychol, 37(3), pp. 345-353, 2006.

Research on the Caretaking of Children of Incarcerated Parents: Findings and Their Service Delivery Implications

This paper reviews research findings on caretaking-related problems associated with the absence of parents from the home following incarceration. It focuses on the impact of incarceration on the welfare and adjustment of urban African American children and on the assumption of caretaking responsibilities by other caretakers, principally maternal grandmothers. Noting the complex situational difficulties involved and the potential burdens associated with surrogate parenting in general, and with this population in particular, the service-provider implications of this parenting arrangement are considered in this review. Findings indicate that problems associated with incarceration of parents tend to be intergenerational and vary considerably in complexity and severity. To the extent that they impact the children involved, these issues should be addressed in coordinated service delivery focusing on prevention. Hanlon, T.E., Carswell, S.B., and Rose, M. Research on the Caretaking of Children of Incarcerated Parents: Findings and Their Service Delivery Implications. Child and Youth Services Review, 29(3), pp. 348-362, 2006.

Prenatal Care Providers Differ in Approaches to Preventing Substance Use Risk During Pregnancy

This study explored prenatal care providers' methods for addressing four behavioral risks in their pregnant patients: alcohol use, smoking, drug use, and domestic violence. Qualitative, purposively sampled, focus group data were used. Groups met in professional focus group settings. Six focus groups (five with OB/GYN physicians, one with nurse practitioners and certified nurse midwives), with a total of N = 49 were conducted. The moderator used a focus group guide with open-ended questions, with probes where appropriate. Results demonstrated that providers' discussions reflected differences in how they approach each risk, including: (1) ambivalence about abstinence messages for alcohol; (2) relative comfort and confidence about assessing smoking and counseling to reduce smoking; (3) disparities across practice settings for toxicology screening for drugs; and (4) discomfort and pessimism with domestic violence. Investigators also analyzed providers' statements for each risk within the framework of the "Five A's" construct (Assess, Advise, Agree, Assist, and Arrange) for evaluating risk behavior interventions. A comparison of each risk across the Five A's illuminates the gaps between

recommended and actual prevention methods and suggests directions for development of interventions and educational efforts. Herzig, K., Huynh, D., Gilbert, P., Danley, D., Jackson, R., and Gerbert, B. Comparing Prenatal Providers ' Approaches to Four Different Risks: Alcohol, Tobacco, Drugs, and Domestic Violence. Women Health, 43(3), pp. 83-101, 2006.

Sex Differences in Overt Aggression and Delinquency

Given the recent debate over whether differential pathways to overt aggression and delinquency exist between boys and girls, this study examined sex differences in overt aggressive and delinquent acts along with potential differences in precursors (anger, self-control, family disruption) to antisocial behaviors among a sample of urban minority adolescents (N = 1559). Overall the sample was 54% girls, 47% African American, 27% Latino/Hispanic, 5% Asian American, 7% Caucasian, and 13% biracial or other race/ethnicity. Almost all of the students (85%) attended public schools. Using a longitudinal design with data from 6th to 7th grade, results showed that girls had greater increases in rates of aggression relative to boys. Delinquency increased over time for both boys and girls, with boys consistently engaging in more delinquency. Girls and boys did not differ on the level of risk factors experienced except for a greater increase in anger over time for girls relative to boys. Across sex, anger and self-control predicted increases in both overt aggression and delinquency; family disruption also predicted increases in delinquency. Implications for subsequent studies on developmental process and preventive interventions are discussed. Nichols, T.R., Graber, J.A., Brooks-Gunn, J., and Botvin, G.J. Sex Differences in Overt Aggression and Delinquency Among Urban Minority Middle School Students. Applied Developmental Psychology, 27, pp. 78-91, 2006.

Effects of the Strengthening Washington DC Families Project

The Strengthening Washington DC Families study examined implementation fidelity and effectiveness of a selective, evidence-based prevention program implemented with a sample of 715 predominantly African American families. The prevention program, based on cognitive-behavioral and family systems theories, was designed to reduce child antisocial behavior and its precursors. Families were randomized to four conditions: child skills training only, parent skills training only, parent and child skills training plus family skills training, and minimal treatment control. Major challenges with recruitment and retention of participants and uneven program coverage were experienced. No statistically significant positive effects for any of the program conditions were observed, and a statistically significant negative effect on child reports of Negative Peer Associations was observed for children of families assigned to the family skills training condition. Two marginally significant findings were observed: Child's positive adjustment favored families assigned to family skills training condition relative to minimal treatment and child training only, and family supervision and bonding was lower for children in family skills training than in the other three conditions. Despite its lack of effects, this work provides important lessons for the implementation of family-based prevention. Gottfredson, D., Kumpfer, K., Polizzi-Fox, D., Wilson, D., Puryear, V., Beatty, P., and Vilmenay, M. The Strengthening Washington D.C. Families Project: A Randomized Effectiveness Trial of Family-based Prevention. Prev Sci, 7(1), pp. 57-74, 2006.

Latino Students Perceptions of School Environment

This study describes results from an investigation of Latino students attending a Hispanic Education Summit (HES) in North Carolina. Findings from data gathered from 275 middle and high school students are presented (n= 142

female; n = 121 male). Self-report data assessed level of acculturation, as well as students' perceptions with regard to a variety of issues, including school programs, barriers to participation in programs, problems in the school environment, and academic aspirations. Results revealed that students reported few perceived barriers to school and aspirations. However, there was a significant relationship between acculturation level and the frequency with which students reported selected barriers and future life goals. Results indicated that low-acculturated students more often reported language-related problems as barriers to school involvement. Also reported by those students in the low-acculturation group were perceived discrimination, parental lack of time as a barrier, and low or no community involvement. These results indicate that high acculturation provides some students with a greater sense of belonging to their community and fewer barriers, including perceived discrimination. Gender differences were found with regard to acculturation level, perception of barriers, and academic aspirations. Specifically, with the exception of lack of interest, females reported more barriers than males and were rated as low in acculturation more frequently than males. Females also reported higher levels of academic aspirations, desires to do well in school, and a desire to be successful more frequently than males. Being female seems to promote resiliency with regard to academic aspirations for Latinos/as. These results lend support to previous research findings that females' higher value of academic achievement is related to being less acculturated or less vulnerable to assimilation of adversarial attitudes and behaviors responsible for academic failure. Overall this study suggests that there is not a linear relationship between acculturation and academic aspirations but, rather, this relationship may be mediated by a variety of factors including students' beliefs and attitudes, family cohesion, parental monitoring, parental attitudes concerning education, cultural identity, perceived stereotypes, and discrimination. Future studies examining acculturation would benefit from a framework that clearly captures the complex dynamics of acculturation and how this phenomenon affects academic achievement and the overall adjustment of Latino immigrant students into their environment. Valencia, E.Y., and Johnson, V. Latino Students in North Carolina: Acculturation, Perceptions of School Environment, and Academic Aspirations. Hispanic Journal of Behavioral Sciences, 28(3), pp. 350-367, 2006.

Attitudes Toward Alcohol and Cocaine Among Black and White Elementary School Students

To trace the origins of race differences in substance use, this study examined differences between Black and White elementary school children's knowledge of alcohol and cocaine, beliefs about their short- and long-term effects, and attitudes toward and intentions to use them across three independent samples of students in grades 1 through 6 (N = 181, N = 287, N = 234). Black children were more negatively oriented toward alcohol and cocaine than White children from an early age. Most notably, in all samples Black children had less positive attitudes toward adult alcohol use and lower intentions to use alcohol. Black children were also more likely to attribute negative long-term health and social effects to alcohol and cocaine use, but there were few significant race differences in knowledge or in expectancies regarding short-term effects of use. Since race differences in beliefs, exposure to alcohol, and socioeconomic factors could not explain race differences in attitudes toward substance use, other cultural differences must be considered. Rinehart, C., Bridges, L., and Sigelman, C. Differences between Black and White Elementary School Children's Orientations Toward Alcohol and Cocaine: A Three-study Comparison. J Ethn Subst Abuse, 5(3), pp. 75-102, 2006.

Director's Report to the National Advisory Council on Drug Abuse - May, 2007

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

Doubling Voucher Incentive Amount during Initial Weeks of Treatment Produces Greater During Treatment and Longer-Term Cocaine Abstinence

Cocaine dependent outpatients were randomly assigned to receive Community Reinforcement Approach Behavioral Treatment with either a high value ($1995) or low value ($499) of voucher incentives available during the first twelve weeks of a twenty-four week treatment period. The voucher incentives were contingent upon providing drug negative urine specimens and could be exchanged for non-drug related goods or services. Results show that duration of continuous abstinence was higher across the entire 24 week treatment period in the higher condition. Additionally, the point prevalence rates of abstinence assessed every three weeks across an eighteen month follow-up period showed higher rates in the high than the low condition. Additional analyses indicate that few people in the low voucher value condition achieved 1 month or more of continuous abstinence. These results are significant because they indicate that larger voucher values early in treatment may maximize outcomes for cocaine dependent people receiving a comprehensive behavioral intervention. Higgins, S.T., Heil, S.H., Dantona, R., Matthews, M., and Badger, G. Addiction, 102 (2), pp. 271-281, 2007.

Contingency Management Improves Adherence to HIV Medication and Reduces Viral Load

Individuals with poor compliance to antiretroviral medication were randomized to either sixteen weeks of supportive counseling or sixteen weeks of a contingency management (CM) intervention. In the contingency management condition, bottle caps that monitored pill opening, a Medication Event Monitoring System (MEMS), were placed on up to three bottles of participants HIV medications for four weeks. Participants MEMS data was reviewed weekly and those whose data indicted that medication was taken in a timely manner were given the opportunity to draw cards from a bowl. Cards were printed with values ranging as follows: $1.00 (26% of cards), $20.00 (7.6% of cards) and $100.00 (0.2% of cards). The remaining cards did not have a value associated with them but had the words "good job" printed on them. Participants drawing winning cards had the opportunity to exchange these cards for goods worth the winning denomination in an on-site prize closet. Participants in the CM group attended significantly more counseling sessions than those assigned to supportive counseling. On average CM participants earned approximately $24.00/week of the intervention. Adherence in the CM group grew significantly higher over time while the control group drifted lower. At week 16 viral load had significantly improved for CM group participant indicating that review and

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contingent reinforcement of MEMS data likely resulted in better adherence. Rosen, M.I., Dieckhaus, K., McMahon, T.J., Valdes, B., Petry, N.M., Cramer, J., and Rounsaville, B. AIDS Patient Care STDS, 21(1), pp. 30-40, 2007.

Adding MEMS Feedback to Behavioral Smoking Cessation Therapy Increases Compliance with Bupropion: A Replication and Extension Study

This study was conducted to replicate and extend initial positive findings on the usefulness of a Medication Event Monitoring System (MEMS) to assess pill-taking behavior and enhance compliance with Bupropion for smoking cessation. Participants were 55 women aged 20-65, smoking a minimum of 10 cigarettes per day. All participants received MEMS bottles containing Bupropion-SR (150 mg) to be taken twice daily for 7 weeks, then randomized into one of two conditions, Usual Care (UC) or Enhanced Therapy (ET). In the UC condition, participants received individual cognitive behavioral therapy for smoking cessation. In the ET condition, weekly smoking cessation therapy sessions included additional 10 min of MEMS feedback and counseling using CBT techniques. Compliance outcomes included total doses taken and number of doses taken within the prescribed time interval. Results indicated significantly higher compliance over time for the Enhanced Therapy group. Smoking abstinence rates did not differ between the two groups, but pooled sample analysis showed a significant association between level of medication compliance and abstinence status at treatment weeks 3 and 6. Findings recommend incorporating MEMS-based compliance interventions into smoking pharmacotherapy trials. Mooney, M.E., Sayre, S.L., Hokanson, P.S., Stotts, A.L., and Schmitz, J.M., Addictive Behaviors, 32, pp. 875-880, 2007.

An Internet-based Abstinence Reinforcement Treatment for Cigarette Smoking

Dr. Jesse Dallery and colleagues at the University of Florida conducted this study to test a practical method of providing abstinent reinforcement treatment to smokers. Using a within-subject reversal design, the present study tested an Internet-based method to obtain objective evidence of smoking status and to deliver voucher incentives for evidence of abstinence. Twenty heavy smokers completed this 4-week study. Twice a day, participants made video recording of themselves providing a breath carbon monoxide sample with a web-camera. The video was made at home and sent electronically to the smoking clinic. Participants could earn vouchers for gradual reductions in breath CO during a 4-day shaping condition, and then for achieving abstinence (CO

Abstinence Rates Following Behavioral Treatments for Marijuana Dependence

Dr. Kadden and colleagues at the University of Connecticut conducted this dismantling study to determine whether adding contingency management (ContM) to motivational enhancement therapy plus cognitive behavioral therapy (MET+CBT), an intervention used in previous studies, would enhance abstinence outcomes in marijuana-dependent subjects. Two-hundred forty marijuana dependent participants were randomly assigned to one of four treatments, all of which lasted nine sessions: 1) MET+CBT, 2) ContM only, 3) MET+CBT+ContM, or 3) to a case-management control condition (CaseM). All interventions involved 1-hour individual sessions, except for the ContM-only condition whose sessions were about 15 minutes. ContM provided reinforcement for marijuana-free urine specimens, in the form of vouchers redeemable for goods or services. Follow-up data were collected at post treatment and at 3-month intervals for 1 year. The two ContM conditions had superior outcomes: ContM- only had the highest abstinence rates at post

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treatment, and the MET+CBT+ContM combination had the highest rates at later follow-ups and the longest periods of continuous abstinence. These findings support the prediction that maintenance of abstinence over the course of the follow-up year would require the coping skills development offered by CBT. Kadden, R.M., Litt, M.D., Kebela-Cormier, E., and Petry, N.M., Addictive Behaviors, 32(6), pp. 1220-1236, 2007.

Does Smoking Reduction Increase Future Cessation and Decrease Disease Risk? A Qualitative Review

Drs. Hughes and Carpenter conducted this qualitative review to determine whether smoking reduction in smokers not currently interested in quitting (a) will undermine motivation to quit smoking in the future and (b) produce a clinically-significantly decrease in risks of smoking-related diseases. Systematic computer searches and other methods located 19 studies examining reduction and subsequent cessation and ten studies examining reduction and disease risk. Across 19 studies reviewed, none found that reduction decreased later cessation in smokers not currently trying to quit. In fact, 16 found reduction was associated with greater future cessation including two randomized trials of reduction versus non-reduction. The ten trials of disease risk found conflicting results and none was an adequate test. The authors concluded that (a) smoking reduction increases probability of future cessation and (b) whether smoking reduction decreases the risks of smoking-related diseases has not been adequately tested. Hughes, J.R., and Carpenter, M.J., Nicotine & Tobacco Research, 8, pp. 739-749, 2006.

Developmental Course(s) of Lifetime Cigarette Use and Panic Attack Comorbidity: An Equifinal Phenomenon?

The primary objective of this investigation was to better understand the developmental course(s) of lifetime cigarette use and panic attacks. Specifically, the ages of onset and temporal patterns of onset between daily cigarette smoking and panic attacks was examined. A second objective was to evaluate the developmental features of smoking-panic comorbidity in relation to other comorbid psychiatric and substance outcomes. Participants included 4,409 adults, ages 15-54 years from the National Comorbidity Survey. One key finding was that among those with lifetime history of comorbid daily smoking and panic attacks, the onset of daily smoking preceded the onset of panic attacks in 64% of cases. In a large minority of cases (33%) panic attacks preceded the onset of daily smoking. Another finding indicates that whereas daily smoking demonstrates a relatively consistent mean age of onset in mid- to late adolescence, the mean ages of onset of panic attacks differ markedly between the comorbid subsamples (age 27.8 years among the smoking-to-panic subsample and age 11.4 years among the panic-to-smoking subsample). A third finding indicates that comorbidity of smoking and panic attacks, relative to unimorbid smoking or unimorbid panic attacks, was significantly associated with greater risk for substance abuse and/or dependence. The observed findings underscore the importance of delineating the developmental course(s) of smoking and panic comorbidity as well as specific course-related variables in understanding the nature of smoking-panic attack comorbidity. Bernstein, A., Zvolensky, M.J., Schmidt, N.B., and Sachs-Ericcson, N. Behavior Modification, 31, pp. 117-135, 2007.

Attrition in a Multi-Component Smoking Cessation Study for Females

Attrition is a major challenge faced by researchers when implementing clinical trials. Investigators conducted this study to determine which baseline smoking-related, demographic and psychological participant characteristics were

associated with attrition. Data were from a clinical trial evaluating exercise as an adjunctive treatment for nicotine gum among female smokers (N=246). There were a number of significant demographic predictors of attrition. Participants with at least one child living at home were at increased risk of both early and late dropout. Non-Whites were at increased risk of early dropout, while not having a college degree put one at increased risk of late dropout. Age was found to be a protective factor in that the older a participant was, the less likely she was to drop out in the early stages of the trial. With respect to psychological variables, weight concerns and guilt increased risk of attrition. In terms of smoking-related variables, mean cigarettes per day was not a significant predictor of attrition, although length of longest prior quit attempt was a significant predictor of early dropout when age was removed from the regression. Leeman, R.F., Quiles, Z.N., Molinelli, L.A., Medaglia Terwal, D., Nordstrom, B.L., Garvey, A.J. and Kinnunen, T. Tobacco Induced Diseases, 3, pp. 59-71, 2006.

Challenges and Potential Benefits of Using Email Communication to Treat Drug Abuse

Dr. Susanna Nemes of Social Solutions, Incorporated, and colleagues review the ethical, legal, logistical and clinical challenges and potential benefits in using email communication as a form of drug abuse treatment. A growing body of literature supports the potential efficacy of online communication (interactive internet-based support groups, web-based self-help, computerized medicine, etc.) for managing health-related problems. Email communication between counselors and patients in drug abuse treatment might be another application with potential benefits. Such communication brings with it concerns about generating a permanent written record of discussions, breeches of privacy, lag time in responses, and generally providing an appropriate level of care for patients. Professional organizations such as the American Medical Association and the American Psychological Association have offered guidelines for appropriate use of email communication. Dr. Nemes and colleagues stress the importance of the content of emails, and provide some guidance about the appropriate content and components of a therapeutic email intervention. Among the key elements of a therapeutic email intervention for drug abuse treatment are: 1) establishing contact; 2) assessing the patient's status; 3) identifying the consequences of drug use; 4) developing a plan for recovery; 5) mobilizing support for change; 6) identifying problematic interpersonal relationships; 7) adjusting daily routines through group action; 8) creating a sense of spirituality and/or community through group action; 9) identifying substitute routines through group action; 10) sharing success with others; 11) addressing the cycle of relapse; and 12) making amends and offering help to others. Research is underway to develop and test therapeutic email interventions to optimize the benefits of this technology to patients and the health care system. Alemi, F., Haack, M.R., Nemes, S., Aughburns, R., Sinkule, J., and Neuhauser, D. Substance Abuse Treatment, Prevention, and Policy, 2, pp. 1-18, 2007.

Director's Report to the National Advisory Council on Drug Abuse - May, 2007

Research Findings - Research on Pharmacotherapies for Drug Abuse

Urine Drug Screens (UDS) and Cocaine Selective Severity Assessment (CSSA) Scores are Powerful Outcome Predictors in Cocaine Dependence Treatment Trials

This study extended findings based on current predictors of response to psychosocial treatment, i.e., cocaine withdrawal symptom severity and results of a urine drug screen (UDS), by examining outcome predictors in a large number (n=402) of subjects participating in a series of outpatient cocaine pharmacotherapy trials while selecting three separate criteria to define successful outcome. Predictor variables included results from the baseline Addiction Severity Index (ASI), initial UDS results, and cocaine withdrawal symptom severity at treatment entry, as measured by scores on the Cocaine Selective Severity Assessment (CSSA). Baseline variables that most consistently predicted treatment outcome were the initial UDS results and initial CSSA scores, indicating that baseline UDS results and CSSA scores are powerful predictors of outcome and should be used as stratifying variables in outpatient cocaine medication trials. Ahmadi, J., Kampman, K. and Dackis, C. Outcome Predictors in Cocaine Dependence Treatment Trials. Am J Addiction, 15, pp. 434-439, 2006.

Benztropine Does Not Alter Cocaine-induced Effects

In this human laboratory study, benztropine was evaluated for its ability to block cocaine's physiological and subjective effects in 16 healthy, adult male volunteers who were recreational users of cocaine. Placebo or benztropine (1, 2, and 4 mg orally) was given 2 hours before subjects self-administered 0.9 mg/kg cocaine intranasally. Measurements (increases in heart rate and alterations in self-reports measured by visual analog scales) were made 2 hours following cocaine administration and plasma cocaine and cocaine metabolites were assayed. Benztropine alone did not produce changes on these measures, and responses to cocaine with and without benztropine pretreatment were similar. The results of this study suggest that benztropine does not alter cocaine-induced effects, and does not produce adverse behavioral or physiological effects. Penetar, D., Looby, A.R., Su, Z., Lundahl, L.H., Eroes-Sarnyai, M., McNeil, J.F., and Lukas, S.E. Benztropine Pretreatment Does Not Affect Responses to Acute Cocaine Administration in Human Volunteers. Hum Psychopharmacol Clin Exp, 21, pp. 549-559, 2006.

Divalproex May Be A Possible Treatment for Patients with Comorbidity of Bipolar Disorder and Primary Cocaine Dependence

Index

This report describes the result of an open-label pilot study with divalproex to evaluate its utility in decreasing cocaine use and stabilizing mood symptoms in 15 adult subjects with a DSM-IV diagnosis of comorbid bipolar disorder and cocaine dependence. Patients were started on open-label divalproex. After stabilization, weekly assessments, with counseling, were undertaken for 8 weeks. The results showed significant improvement on % cocaine abstinent days, dollars spent on cocaine, ASI's drug use severity index, % alcohol abstinent days, drinks per drinking day, marijuana use and cigarette smoking. Results also showed significant improvement on manic, depressive, and sleep symptoms and on functioning, with no reported adverse events, or increases in liver function tests. Double-blind, placebo-controlled studies to fully evaluate the efficacy of divalproex in this patient population are warranted, based on the results of this pilot study. Salloum, I.M., Douaihy, A., Cornelius, J.R., Kirisci, L., Kelly, T.M. and Hayes, J. Divalproex Utility in Bipolar Disorder With Co-occurring Cocaine Dependence: A Pilot Study. Addictive Beh, 32, pp. 410-415, 2007.

Cocaine Withdrawal Symptoms May Predict Treatment Response to Medications

This study examined the influence of cocaine withdrawal symptoms on addiction severity and treatment outcomes in 85 methadone-stabilized cocaine users who participated in pharmacotherapy trials using GABA medications. Subjects who fulfilled DSM-IV cocaine withdrawal criteria (n=45) compared to those who did not (n=40) showed a greater increase in cocaine free urines in response to pharmacotherapy with GABA medications. The results of this and previous studies support the clinical utility of cocaine withdrawal symptoms in predicting treatment response to GABA medications, while high withdrawal severity may predict better response to adrenergic blockers. Sofuoglu, M., Poling, J., Gonzalez, G., Gonsai, K., and Kosten, T. Cocaine Withdrawal Symptoms Predict Medication Response in Cocaine Users. Am J Drug Alcohol Abuse, 32, pp. 617-627, 2006.

Gabapentin Does Not Reduce Smoked Cocaine Self-administration

This 48-day inpatient/outpatient study examined the effects of gabapentin maintenance on cocaine self-administration using a purchase-cocaine choice procedure in 12 nontreatment- seeking cocaine abusers maintained on gabapentin (0, 600, 1200 mg.day). Four doses of cocaine (0, 12, 25, 50 mg) were each tested twice under each gabapentin condition. Participants were provided with 25 dollars before the start of each session, and smoked the sample cocaine dose once. Subsequently, participants were given five opportunities to purchase the sampled dose of cocaine at 5 dollars per dose or to keep 5 dollars for that choice trial. Choice to self-administer cocaine increased significantly with escalating cocaine doses. Gabapentin maintenance did not alter choice to self-administer cocaine. Along with other study results, the data indicate that gabapentin does not show promise as a treatment medication for cocaine dependence. Hart, C.L., Haney, M., Vosburg, S.K., Rubin, E., and Foltin, R.W. Gabapentin Does Not Reduce Smoked Cocaine Self-Administration: Employment of a Novel Self-Administration Procedure. Behav Pharmacol, 18, pp. 71-5, 2007.

No Associations Between Polymorphisms in the Par-4 Gene and the Cocaine-dependent Phenotype

The purpose of this study was to test the hypothesis that polymorphisms in the human Par-4 gene contribute to the etiology of cocaine dependence, based on other studies which have investigated the genes underlying dopamine, serotonin and glutamine neurotransmitter systems in order to find a genetic

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basis for the pathology of cocaine dependence. The study employed a case-control design in which the genotype and allele frequencies for five single nucleotide polymorphisms in the human Par-4 gene were compared between 172 cocaine-dependent individuals and 92 controls, of African descent. The genotype results failed to detect any associations between polymorphisms in the Par-r gene and the cocaine-dependent phenotype, suggesting that variations in the human Par-4 gene are unlikely to play a major role in the pathophysiology of cocaine dependence. The authors suggest that the study should be repeated in larger cocaine-dependent and control populations to determine if this is the case. Weller, A.E., Dahl, J.P., Lohoff, F.W., Kampman, K.M., Oslin, D.W., Dackis, C., Ferraro, T.N., O'Brien, C.P., and Berrettini, W.H. No Association Between Polymorphisms in the Prostate Apoptosis Factor-4 Gene and Cocaine Dependence. Psychiatric Genetics, 16, pp. 193-196, 2006.

Characteristics of Individuals Presenting for Substance Abuse Treatment Can Provide Important Information to Help Focus Treatment Services

In this study, demographic and clinical characteristics of individuals presenting for medication trials for the treatment of cocaine or marijuana dependence were compared, to highlight the significant impairments associated with marijuana and cocaine dependence. In general, marijuana-dependent subjects were younger than cocaine-dependent subjects, more likely to be Caucasian, and completed more years of education. Marijuana-dependent subjects also reported significantly more days using than cocaine-dependent subjects and higher levels of craving. Cocaine-dependent subjects were more likely to report anxiety symptoms and marijuana-dependent subjects, more past depressive episodes. Past and current other drug use was similar between the two groups. McRae, A.L., Hedden, S.L., Malcolm, R.J., Carter, R.E., and Brady, K.T. Characteristics of Cocaine- and Marijuana-Dependent Subjects Presenting for Medication Treatment Trials. Addictive Behaviors, 2006 (e-publication ahead of print).

Interaction Between Opioid Antagonists and Cannabinoid Agonists Varies as a Function of Marijuana Use History

The purpose of this study was to test whether a low dose of naltrexone (12 mg) in combination with THC has the same reported reinforcing effect as a higher (50 mg) dose of naltrexone. Naltrexone (0, 12 mg) was administered 30 minutes before oral THC (0-40 mg) or methadone (0--10 mg) capsules, and subjective effects, task performance, pupillary diameter, and cardiovascular parameters were assessed in marijuana smoking (n=22) and nonmarijuana smoking (n=21) men and women. The results showed that in marijuana smokers, low-dose naltrexone blunted the intoxicating effects of a low THC dose (20 mg) while increasing ratings of anxiety at a higher THC dose (40 mg). In nonmarijuana smokers, low-dose naltrexone enhanced the intoxicating effects of a low THC dose (2.5 mg) and decreased anxiety ratings following a high dose of THC (10 mg). There were no sex differences in these interactions, although among nonmarijuana smokers, men were more sensitive to the effects of THC alone than women. To conclude, a low, opioid-selective dose of naltrexone blunted THC intoxication in marijuana smokers, while in nonmarijuana smokers, naltrexone enhanced THC intoxication. Haney, M. Opioid Antagonism of Cannabinoid Effects: Differences Between Marijuana Smokers and Nonmarijuana Smokers. Neuropsychopharmacology 2006 (e-publication ahead of print).

Mood Disorders Affect Drug Treatment Success of Drug-dependent Pregnant Women

This study examined the impact of co-occurring Axis I disorders on drug treatment outcomes of drug-dependent pregnant women. Participants (N =106) were women who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for opioid dependence and were receiving methadone. Based on DSM-IV Axis I criteria, participants were categorized into three groups: (1) absence of mood/anxiety disorder (ND, n = 29), (2) primary mood disorder (MD, n = 39), or (3) primary anxiety disorder (AD, n = 38). Demographically, the groups were similar. The MD group was significantly more likely to be positive for drugs while in treatment compared with both the ND and AD groups. The MD and AD groups had more psychosocial impairment and higher incidence of suicidal ideation compared with the ND group. Interestingly, the AD group spent more days in treatment compared with the ND or MD group. These findings highlight the need to treat co-occurring Axis I disorders, particularly given the higher relapse risk for those with mood disorders. Fitzsimons, H.E., Tuten, M., Vaidya, V., and Jones, HE. Mood Disorders Affect Drug Treatment Success of drug-dependent pregnant women. J Subst Abuse Treat. 32(1), pp. 19-25, 2007. Epub 2006 October 13, 2006.

Simultaneous Determination of Buprenorphine, Norbuprenorphine and the Enantiomers of Methadone and its Metabolite (EDDP) in Human Plasma by Liquid Chromatography/ Mass Spectrometry

Buprenorphine (Bu) is a semi-synthetic oripavine derivative which is 25-50 times more potent than morphine. In humans, Bu is N-dealkylated by cytochrome P450 3A4 to form norbuprenorphine (norBu). A previously reported enantioselective LC-MS assay for the determination of (R)- and (S)-methadone [Met] and (R)- and (S)-2-ethylidene-1,5-dimethyl-3,3-diphenyl-pyrrolidine [EDDP] (the primary metabolite of Met) has been adapted for use in the simultaneous determination of the plasma concentrations of Met, EDDP, buprenorphine (Bu) and norbuprenorphine (norBu). All of the target compounds were separated within 15min using an alpha(1)-acid glycoprotein chiral stationary phase, a mobile phase composed of acetonitrile: ammonium acetate buffer [10mM, pH 7.0] in a ratio of 18:82 (v/v), a flow rate of 0.9ml/min at 25 degrees C. Deuterium labeled compounds were used as internal standards [d(4)-Bu, d(3)-norBu, (R,S)-d(3)-Met and (R,S)-d(3)-EDDP] and linear relationships between peak height ratios and drug concentrations were obtained for Bu and norBu in the range 0.2-12ng/ml with correlation coefficients greater than 0.999. The relative standard deviations (%R.S.D.) for the intra- and inter-day precision of the method were <4.5% and for accuracy was <4.0%. The bioanalytical assay reported in this manuscript is a simple, sensitive, accurate, rapid and reproducible LC/MS method for the simultaneous determination of Bu, norBu and the enantiomers of Met and EDDP in human plasma obtained from opioid dependent methadone-maintained adults. The method was validated and used to analyze plasma samples obtained from opioid dependent methadone-maintained adults enrolled in a research study. Rodriguez-Rosas, M.E., Lofwall, M.R., Strain, E.C., Siluk, D., and Wainer, I.W. Simultaneous Determination of Buprenorphine, Norbuprenorphine and the Enantiomers of Methadone and its Metabolite (EDDP) in Human Plasma by Liquid Chromatography/Mass Spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci., November 30, 2006 [Epub ahead of print].

Lofexidine May have Potential in Reducing Stress-Related Opioid Craving and Relapse Outcomes in Humans

This preliminary study examined whether lofexidine decreases stress-induced and cue-induced opioid craving and improves opioid abstinence in naltrexone-treated opioid-dependent individuals. Eighteen opioid-dependent patients were stabilized for 4 weeks with naltrexone (50 mg/day) and lofexidine (2.4 mg bid) before entering a 4-week randomized, double-blind placebo-controlled

discontinuation study where one group continued on lofexidine for an additional 4 weeks, and the second was tapered to placebo. Ten patients also participated in guided imagery exposure to stress, drug cue, and neutral scenarios in a single laboratory session. The results showed that lofexidine-naltrexone patients had higher opioid abstinence rates and improved relapse outcomes as compared to the placebo-naltrexone group, as well as significantly lower heart rates and an attenuated stress and drug cue-induced opioid craving response in the laboratory as compared to the placebo-naltrexone group. Further development of lofexidine to address stress-related opioid craving and relapse is warranted. Sinha, R., Kimmerling, A., Doebrick, C., and Kosten, T.R. Effects of Lofexidine on Stress-Induced and Cue-Induced Opioid Craving and Opioid Abstinence Rates: Preliminary Findings. Psychopharmacology, 190, pp. 569-574, 2007.

Effects of Acute Abstinence, Reinstatement, and Mecamylamine on Biochemical and Behavioral Measures of Cigarette Smoking in Schizophrenia

Schizophrenics have higher rates of smoking than the general population, and more difficulty with smoking cessation. However, there has been little study of differences between schizophrenics and controls with respect to biochemical and behavioral indices of smoking. This study compared smokers with schizophrenia (SS; n=27) and control smokers (CS; n=26) on smoking and psychiatric outcomes at baseline, during acute smoking abstinence and reinstatement, and with pre-treatment using the nicotinic acetylcholine receptor (nAChR) antagonist mecamylamine (MEC) in a human laboratory setting. Biochemical (e.g., plasma nicotine) and behavioral (e.g., craving, withdrawal) outcomes were assessed at baseline, after overnight abstinence, and after smoking reinstatement during three consecutive test weeks. Each week, participants received one of three doses of MEC (0.0, 5.0, or 10.0 mg/dayx3 days) in a randomized, counterbalanced manner. Compared to CS, SS displayed similar levels of craving and withdrawal, but higher plasma nicotine and cotinine levels, and cotinine/CPD ratio. During reinstatement, SS consumed significantly more cigarettes than CS, but MEC did not significantly alter indices of smoking, psychiatric symptoms, or cigarette consumption during reinstatement. 1) The reinforcing effects of smoking may be increased in SS versus CS after overnight abstinence; 2) the lack of effects of nAChR antagonism may suggest that non-nicotinic components of cigarettes may contribute to the behavioral effects of smoking in both SS and CS; and 3) consistent with previous studies, SS may exhibit higher baseline levels of nicotine and cotinine, and greater extraction of nicotine per cigarette than CS. Weinberger, A.H., Sacco, K.A., Creeden, C.L., Vessicchio, J.C., Jatlow, P.I., and George, T.P. Effects of Acute Abstinence, Reinstatement, and Mecamylamine on Biochemical and Behavioral Measures of Cigarette Smoking in Schizophrenia. Schizophr Res. 91(1-3), pp. 217-225, 2007.

Nicotine Dependence, Symptoms and Oxidative Stress in Male Patients with Schizophrenia

The high rate of smoking in schizophrenia may reflect patients' attempts to reduce the side effects of antipsychotic medications, and one mechanism for this reduction may be a decrease in oxidative stress and free radical-mediated brain damage that may contribute to schizophrenic symptoms and to complications of its treatment. Symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS), side effects were assessed with the Simpson and Angus Rating Scale (SAS), and malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT) activities were measured in plasma. All of these measures were compared in 130 male inpatients with DSM-IV schizophrenia: 104 smokers and 26 non-smokers. The results showed that the positive PANSS symptoms were

lower in smokers than non-smokers (14.5 vs 17.5), while the negative symptoms were lower in those who smoked more cigarettes (r=-0.23). The SAS showed no differences. The CAT activity was correlated with both GSH-Px and SOD activities. Of the three enzymes only the CAT activity was significantly higher in smokers than non-smokers (2.9 vs 1.6 U/ml), but greater SOD activity was correlated with more cigarettes smoked (r=0.24). Consistent with some protection against oxidative stress, MDA also was significantly lower in smokers than non-smokers (9.2 vs 14.4 nmol/ml). The fewer positive symptoms in smokers and fewer negative symptoms in those who smoked more cigarettes may be a selection bias, but appears to be associated with decreased oxidative stress and lipid peroxidation in schizophrenics who smoke tobacco. Zhang, X.Y., Tan, Y.L., Zhou, D.F., Haile, C.N., Wu, G.Y., Cao, L.Y., Kosten, T.A., and Kosten, T.R. Nicotine Dependence, Symptoms and Oxidative Stress in Male Patients with Schizophrenia. Neuropsychopharmacology advance online publication, January 17, 2007.

Effects of High Dose Transdermal Nicotine Replacement in Cigarette Smokers

Nicotine replacement therapies (NRT) have been evaluated to facilitate cigarette smoking reduction in smokers unwilling or unable to quit. In most of these studies, only conventional doses of NRT have been tested and higher doses may be required to result in significant reductions in smoking and in biomarkers of exposure. The purpose of this study was to determine if higher NRT doses in conjunction with smoking are safe and may promote significant reductions in cigarette smoking and biomarkers of exposure. A dose-ranging, within-subject design was implemented to evaluate the effects of 15, 30 and 45 mg nicotine-patch treatment on measures of safety and the extent of smoking reduction and biomarker exposure per cigarette in smokers (N=20 completers) not immediately interested in quitting. Concurrent smoking and NRT were generally tolerated and resulted in no changes in blood pressure or heart rate. Slightly less than 10% of the study sample was not given the highest dose of NRT due to side effects. Self-reported cigarette smoking decreased with increasing doses of nicotine replacement and significant reductions were observed for total NNAL (a carcinogen biomarker) and carbon monoxide. However, even at the 45 mg dose, increased carbon monoxide and total NNAL per cigarette occurred, even though cotinine levels increased on average, 69.3% from baseline. The present results suggest that the use of high dose NRT is safe, leads to significant reductions in smoking (-49%), significant but less reductions in total NNAL (-24%) and carbon monoxide (-37%) due to compensatory smoking. Hatsukami, D. Mooney, M., Murphy, S., LeSage, M., Babb, D. and Hecht, S. Effects of High Dose Transdermal Nicotine Replacement in Cigarette Smokers. Pharmacol Biochem Behav. 86(1), pp. 132-139, 2007.

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Research Findings - Research on Medical Consequences of Drug Abuse and Co-Occurring Infections (HIV/AIDS, HCV)

Associations Between Methamphetamine Use and HIV among Men who have Sex with Men: A Model for Guiding Public Policy

Among men who have sex with men (MSM) in Los Angeles County, methamphetamine use is associated with high rates of HIV prevalence and sexual risk behaviors. In four separate samples of MSM who differed in the range of their intensity of methamphetamine use, from levels of recreational use to chronic use to those for MSM seeking drug abuse treatment, the association between methamphetamine use and HIV infection increased as the intensity of use increased. The lowest HIV prevalence rate (23%) was observed among MSM contacted through street outreach who mentioned recent methamphetamine use, followed by MSM who used at least once a month for six months (42%), followed by MSM seeking intensive outpatient treatment (61%). The highest rate (86%) was observed among MSM seeking residential treatment for methamphetamine dependence. The interleaving nature of these epidemics calls for comprehensive strategies that address methamphetamine use and concomitant sexual behaviors that increase risk of HIV transmission in this group already at high risk. These and other data suggest that MSM who infrequently use methamphetamine may respond to lower intensity/lower cost prevention and early intervention programs while those who use the drug at dependence levels may benefit from high intensity treatment to achieve goals of reduced drug use and HIV-risk sexual behaviors. Shoptaw, S., and Reback, C. Associations Between Methamphetamine Use and HIV among Men who have Sex with Men: A Model for Guiding Public Policy. J Urban Health, 83(6), pp. 1151-1157, 2006.

Social and Political Factors Predicting the Presence of Syringe Exchange Programs in 96 US Metropolitan Areas

Community involvement and engagement can be important in shaping public health policies. For example, political pressure and direct action from the local community has been credited with having a central role in shaping attitudes and acceptance of syringe exchange programs (SEPs) in the United States. This study explored why SEPs are present in some localities but not others, hypothesizing that programs are unevenly distributed across geographic areas as a result of political, socioeconomic, and organizational characteristics of localities, including needs, resources, and local opposition. Researchers examined the effects of these factors on whether SEPs were present in different US metropolitan statistical areas in 2000. Significant predictors of the presence of an SEP included percentage of the population with a college education, the existence of local AIDS Coalition to Unleash Power (ACT UP) chapters, and the percentage of men who have sex with men in the population.

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By contrast, need was not found to be a predictor. Tempalski, B., Flom, P., Friedman, S., Des Jarlais, D., Friedman, J., McKnight, C., and Friedman, R. Social and Political Factors Predicting the Presence of Syringe Exchange Programs in 96 US Metropolitan Areas. Am J Public Health, 97(3), pp. 437-447, 2007.

Needle Exchange Program Utilization and Entry into Drug User Treatment: Is There a Long-Term Connection in Baltimore, Maryland?

This study examined the relationship between Needle Exchange Program (NEP) utilization and treatment entry in Baltimore, Maryland. The sample was composed of 440 drug injectors with disadvantaged backgrounds. Face-to-face interviews, focusing on HIV risk behaviors, drug use, and health, were conducted between June 1997 and June 2002. Multivariate logistic analyses revealed that entering treatment was associated with NEP utilization, being female, and being HIV-positive. Cocaine sniffers/snorters were less likely to enter treatment. These findings highlight the importance of NEPs in linking injectors to treatment. They also suggest that treatment programs should be prepared and capable of addressing co-occurring problems, like HIV and mental illness. Study limitations are noted. Latkin, C., Davey, M., and Hua, W. Needle Exchange Program Utilization and Entry into Drug User Treatment: Is There a Long-Term Connection in Baltimore, Maryland? Subst Use Misuse, 41(14), pp. 1991-2001, 2006.

Delayed Diagnosis and Elevated Mortality in an Urban Population with HIV and Lung Cancer: Implications for Patient Care

Lung cancer is more common in HIV-infected patients than in the general population. In this study, researchers examined how effectively lung cancer was being diagnosed in HIV-infected patients. Retrospective review was undertaken to assess clinical diagnosis of lung cancer in HIV-infected patients at Johns Hopkins Hospital between 1986 and 2004. Ninety-two patients were identified. Compared to HIV-indeterminate patients (n=4973), HIV-infected individuals were younger, with more advanced cancer. CD4 counts and HIV-1 RNA levels indicated preserved immune function. Mortality was higher in HIV-infected patients, with 92% dying of lung cancer (hazard ratio, 1.57; 95% confidence interval, 1.25-1.96), compared to HIV-uninfected patients. Advanced stage and black race were associated with worse survival. After adjustment for these factors, HIV infection was not associated with increased mortality (hazard ratio, 1.04; 95% confidence interval, 0.83-1.32). Of 32 patients followed in the HIV clinic, 60% of chest radiographs had no evidence of neoplasm within 1 year of diagnosis compared to only 1 (4%) of 28 chest computed tomography scans. Nonspecific infiltrates were observed in 9 patients in the same area that cancer was subsequently diagnosed. The findings show that HIV-infected lung cancer patients have shortened survival mainly due to advanced stage. Low clinical suspicion and over reliance on chest radiographs hindered earlier detection. Aggressive follow-up of nonspecific pulmonary infiltrates in these patients is warranted. Brock, M., Hooker, C., Engels, E., Moore, R., Gillison, M., Alberg, A., Keruly, J., Yang, S., Heitmiller, R., Baylin, S., Herman, J., and Brahmer, J. Delayed Diagnosis and Elevated Mortality in an Urban Population with HIV and Lung Cancer: Implications for Patient Care. J Acquir Immune Defic Syndr, 43(1), pp. 47-55, 2006.

Risk of Non-AIDS-Related Mortality May Exceed Risk of AIDS-Related Mortality among Individuals Enrolling into Care with CD4+ Counts Greater than 200 cells/mm3

To quantify cause-specific mortality risk attributable to non-AIDS-related and

AIDS-related causes before and after the advent of highly active antiretroviral therapy (HAART). Competing-risk methods were used to determine the cumulative AIDS-related and non-AIDS-related risk of mortality between 1990 and the end of 2003 in the Johns Hopkins HIV Clinical Cohort, a prospective cohort study. Beginning in 1997 with the introduction of HAART, all-cause mortality declined and has remained stable at approximately 39 deaths per 1000 person-years. AIDS-related mortality continued to decline in this period ($P = 0.008$), whereas non-AIDS-related mortality increased ($P < 0.001$). Using competing-risk methods, the risk of dying attributable to AIDS-related causes remains significantly higher than the risk of dying attributable to non-AIDS-related causes for patients with a CD4 count 200 cells/mm, however, non-AIDS-related mortality was greater than AIDS-related mortality, particularly among injection drug users. Other transmission categories had similar AIDS-related and non-AIDS-related cumulative mortalities. HAART has reduced mortality rates among HIV-infected individuals, but further efforts to reduce mortality in this population require increased attention to conditions that have not traditionally been considered to be HIV related. Lau, B., Gange, S., and Moore, R. Risk of Non-AIDS-Related Mortality May Exceed Risk of AIDS-Related Mortality among Individuals Enrolling into Care with CD4+ Counts Greater than 200 cells/mm3. J Acquir Immune Defic Syndr, 44(2), pp. 179-187, 2007.

Incidence of, Risk Factors for, Clinical Presentation, and 1-Year Outcomes of Infective Endocarditis in an Urban HIV Cohort

Previous studies described infective endocarditis (IE) in the era before highly active antiretroviral therapy (HAART); however, IE has not been well studied in the current HAART era. In this study, researchers evaluated the incidence of, risk factors for, clinical presentation, and 1-year outcomes of IE in HIV-infected patients. All cases of IE diagnosed between 1990 and 2002 in patients followed at the Johns Hopkins Hospital outpatient HIV clinic were evaluated. To identify factors associated with IE in the current era of HAART, a nested case-control analysis was employed for all initial episodes of IE occurring between 1996 and 2002. Logistic regression analyses were used to assess risk factors for IE and factors associated with 1-year mortality. IE incidence decreased from 20.5 to 6.6 per 1000 person-years (PY) between 1990 and 1995 and 1996 and 2002. The majority of IE cases were male (66%), African American (90%), and injection drug users (IDUs) (85%). In multivariate regression, an increased risk of IE occurred in IDUs (AOR, 8.71), those with CD4 counts <50 cells/mm, and those with HIV-1 RNA >100,000 copies/mL (AOR, 3.88). Common presenting symptoms included fever (62%), chills (31%), and shortness of breath (26%). The most common etiologic organism was Staphylococcus aureus (69%; of these 11 [28%] were methicillin resistant). Within 1 year, 16% had IE recurrence, and 52% died. Age over 40 years was associated with increased mortality. These findings show that IE rates have decreased in the current HAART era, but that IDUs and those with advanced immunosuppression are more likely to develop IE. In addition, there is significant morbidity and 1-year mortality in HIV-infected patients with IE, indicating the need for more aggressive follow-up, especially in those over 40 years of age. Future studies investigating the utility of IE prophylaxis in HIV patients with a history of IE may be warranted. Gebo, K., Burkey, M., Lucas, G., Moore, R., and Wilson, L. Incidence of, Risk Factors for, Clinical Presentation, and 1-Year Outcomes of Infective Endocarditis in an Urban HIV Cohort. J Acquir Immune Defic Syndr, 43(4), pp. 426-432, 2006.

CD4+ Cell Count 6 Years after Commencement of Highly Active Antiretroviral Therapy in Persons with Sustained Virologic Suppression

Sustained suppression of the human immunodeficiency virus (HIV) type 1 RNA load with the use of highly active antiretroviral therapy (HAART) results in

immunologic improvement, but it is not clear whether the CD4(+) cell count increases to normal levels or whether it reaches a less-than-normal plateau. In this study, researchers characterized the increase in the CD4(+) cell count in patients in clinical practice who maintained sustained viral suppression for up to 6 years. All patients were from the Johns Hopkins HIV Clinical Cohort, a longitudinal observational study of patients receiving primary HIV care in Baltimore, Maryland, who were observed for >1 year while receiving HAART and who had sustained suppression of the HIV RNA load at <400 copies/mL. Annual change in the CD4(+) cell count for up to 6 years after the start of HAART was analyzed, stratified by baseline CD4(+) cell counts of < or =200, 201-350, >350 cells/microL. The development of clinical events was assessed (death and new acquired immunodeficiency syndrome-defining illness) by Kaplan-Meier analysis. A total of 655 patients were observed for a median of 46 months (range, 13-72 months). The median change from baseline to most recent CD4(+) cell count was +274 cells/microL, with 92% of patients having an increase in CD4(+) cell count. By 6 years, the median CD4(+) cell count was 493 cells/microL among patients with baseline CD4(+) cell counts < or =200 cells/microL, 508 cells/microL among those with baseline CD4(+) cell counts of 201-350 cells/microL, and 829 cells/microL among those with baseline CD4(+) cell counts >350 cells/microL. In addition to baseline CD4(+) cell count, injection drug use and older age were associated with a lesser CD4(+) cell count response, and duration of therapy was associated with a greater CD4(+) cell count response. These findings show that only patients with baseline CD4(+) cell counts >350 cells/microL returned to nearly normal CD4(+) cell counts after 6 years of follow-up. Significant increases were observed in all CD4(+) cell count strata during the first year, but there was a lower plateau CD4(+) cell count at lower baseline CD4(+) cell strata. These data suggest that waiting to start HAART at lower CD4(+) cell counts will result in the CD4(+) cell count not returning to normal levels. Moore, R., and Keruly, J. CD4+ Cell Count 6 Years after Commencement of Highly Active Antiretroviral Therapy in Persons with Sustained Virologic Suppression. Clin Infect Dis, 44(3), pp. 441-446, 2007.

Hazardous Alcohol Use: A Risk Factor for Non-Adherence and Lack of Suppression in HIV Infection

Researchers examined the independent effect of alcohol and combined effects of drug and alcohol use on antiretroviral (ART) utilization, adherence, and viral suppression in an urban cohort of HIV-infected individuals. In an observational clinical cohort, alcohol use, active drug use, and adherence were prospectively assessed at 6-month intervals. Hazardous alcohol use was classified as >7 drinks/week or >3 drinks/occasion in women, and >14 drinks/week or >4 drinks/occasion in men and active drug use as any use in the previous 6 months. Study outcomes included ART utilization, 2-week adherence, and viral suppression. Generalized estimating equations were used to analyze the association between independent variables and outcomes. Analyses were adjusted for age, sex, race, years on ART, and clinic enrollment time. Between 1998 and 2003, 1711 participated in 5028 interviews, of whom 1433 received ART accounting for 3761 interviews. The prevalence of any alcohol use at the first interview was 45%, with 10% classified as hazardous drinkers. One-third of the sample used illicit drugs. In multivariate analyses adjusting for age, sex, race, active drug use, years on ART, and clinic enrollment time, hazardous alcohol use was independently associated with decreased ART utilization (AOR, 0.65; 95% CI: 0.51 to 0.82), 2-week adherence (AOR, 0.46; 95% CI: 0.34 to 0.63), and viral suppression (AOR, 0.76; 95% CI: 0.57 to 0.99) compared to no alcohol use. Concurrent injection drug use (IDU) exacerbated this negative effect on ART use, adherence, and suppression. These findings demonstrate that hazardous alcohol use alone and combined with IDU was associated with decreased ART uptake, adherence, and viral suppression. Interventions are needed to improve HIV outcomes in individuals with hazardous alcohol use.

Chander, G., Lau, B., and Moore, R. Hazardous Alcohol Use: A Risk Factor for Non-Adherence and Lack of Suppression in HIV Infection. J Acquir Immune Defic Syndr, 43(4), pp. 411-417, 2006.

Multiperson Use of Syringes among Injection Drug Users in a Needle Exchange Program: A Gene-Based Molecular Epidemiologic Analysis

Syringe-sharing behaviors among injection drug users (IDUs) are typically based on self-reports and subject to socially desirable responding. In this study, researchers used 3 short tandem repeat (STR) genetic biomarkers to detect sharing in 2,512 syringes exchanged by 315 IDUs in the Baltimore needle exchange program (NEP; 738 person-visits). Demographic characteristics as well as direct and indirect needle-sharing behaviors corresponding to the closest AIDS Link to Intravenous Experience (ALIVE) study visits were examined for association with multiperson use (MPU) of syringes. Overall, 56% of the syringes exchanged at the Baltimore NEP had evidence of MPU. Less MPU of syringes (48% vs. 71%; P < 0.0001) was seen with more rapid syringe turnaround (<3 days). IDUs always exchanging their own syringes ("primary" syringes) were less likely to return syringes with evidence of MPU (52%) than those who exchanged syringes for others ("secondary" syringes; 64%; P = 0.0001) and those exchanging primary and secondary syringes (58%; P = 0.004). In a multivariate analysis restricted to primary exchangers, MPU of syringes was associated with sharing cotton (adjusted odds ratio [AOR] = 2.06, 95% confidence interval [CI]: 1.30 to 3.28), lending syringes (AOR = 1.70, 95% CI: 1.24 to 2.34), and injecting less than daily (AOR = 0.64, 95% CI: 0.43 to 0.95). These findings support additional public health interventions such as expanded syringe access to prevent HIV and other blood-borne infections. Testing of STRs represents a promising and innovative approach to examining and accessing complex behavioral data, including syringe sharing. Shrestha, S., Smith, M., Broman, K., Farzadegan, H., Vlahov, D., and Strathdee, S. Multiperson Use of Syringes among Injection Drug Users in a Needle Exchange Program: A Gene-Based Molecular Epidemiologic Analysis. J Acquir Immune Defic Syndr, 43(3), pp. 335-343, 2006.

Design and Feasibility of a Randomized Behavioral Intervention to Reduce Distributive Injection Risk and Improve Health-Care Access Among Hepatitis C Virus Positive Injection Drug Users: The Study to Reduce Intravenous Exposures (STRIVE)

Hepatitis C virus (HCV) is hyperendemic among injection drug users (IDUs). However, few scientifically proven interventions to prevent secondary transmission of HCV from infected IDUs to others exist. This report describes the design, feasibility, and baseline characteristics of participants enrolled in the Study to Reduce Intravenous Exposure (STRIVE). STRIVE was a multisite, randomized-control trial to test a behavioral intervention developed to reduce distribution of used injection equipment (needles, cookers, cottons, and rinse water) and increase health-care utilization among antibody HCV (anti-HCV) positive IDUs. STRIVE enrolled anti-HCV positive IDU in Baltimore, New York City, and Seattle; participants completed behavioral assessments and venipuncture for HIV, HCV-RNA, and liver function tests (LFTs) and were randomized to attend either a six-session, small-group, peer-mentoring intervention workshop or a time-matched, attention-control condition. Follow-up visits were conducted at 3 and 6 months. At baseline, of the 630 HCV-positive IDUs enrolled (mean age of 26 years, 60% white, 76% male), 55% reported distributive needle sharing, whereas 74, 69, and 69% reported sharing cookers, cottons, and rinse water, respectively. Health-care access was low, with 41% reporting an emergency room as their main source of medical

care. Among those enrolled, 66% (418/630) were randomized: 53% (222/418) and 47% (196/418) to the intervention and control conditions, respectively. Follow-up rates were 70 and 73% for the 3- and 6-month visits, respectively. Distributive sharing of used injection equipment was common but care for HCV remained low, indicating the importance of developing effective HCV-related interventions with IDUs to avert their potential new spread of the infection and improve their health care access and use. Kapadia, F., Latka, M., Hagan, H., Golub, E., Campbell, J., Coady, M., Garfein, R., Thomas, D., Bonner, S., Thiel, T., and Strathdee, S. Design and Feasibility of a Randomized Behavioral Intervention to Reduce Distributive Injection Risk and Improve Health-Care Access Among Hepatitis C Virus Positive Injection Drug Users: The Study to Reduce Intravenous Exposures (STRIVE). J Urban Health, 84(1), pp. 99-115, 2007.

Impact of HIV Testing on Uptake of HIV Therapy among Antiretroviral Naive HIV-infected Injection Drug Users

Improving access to antiretroviral therapy among injection drug users remains an urgent public health concern. This study examined the time to antiretroviral therapy (ART) use among antiretroviral naive HIV-infected IDUs who were unaware of their HIV status to examine the impact of receipt of HIV test results on uptake of ART. Time to ART use was examined using Kaplan-Meier methods, and factors associated with the time to ART were evaluated using Cox proportional hazards regression. Between May 1996 and May 2003, 312 HIV-infected individuals were enrolled into the Barriers to Antiretroviral Therapy (BART) cohort, among whom 105 (33.7%) reported not knowing their HIV status at baseline. At 24 months post-baseline, those participants who returned for test results within 8 months initiated ART at a significantly elevated rate [adjusted relative hazard = 1.87 (95% CI: 1.05 - 3.33)]. These findings demonstrate the potential to improve uptake of ART among IDUs through targeted HIV testing and counseling initiatives that encourage the receipt of HIV test results, and suggest that strategies to improve awareness of HIV infection may improve access to antiretroviral therapy. Wood, E., Kerr, T., Hogg, R., Palepu, A., Zhang, R., Strathdee, S., and Montaner, J. Impact of HIV Testing on Uptake of HIV Therapy among Antiretroviral Naive HIV-infected Injection Drug Users. Drug Alcohol Rev, 25(5), pp. 451-454, 2006.

Frequent Needle Exchange Use and HIV Incidence in Vancouver, Canada

Researchers evaluated possible explanations for the observed association between elevated HIV rates and frequent needle exchange attendance that had been reported from a prior study in Vancouver. They used a prospective observational cohort study of injection drug users in Vancouver, BC, and examined HIV incidence rates with stratified Kaplan-Meier methods and Cox proportional hazards regression. Between May 1996 and December 2004, 1035 individuals were recruited. At 48 months after recruitment, the cumulative HIV incidence rate was 18.1% among those reporting daily needle exchange use at baseline compared with 10.7% among those who did not report this behavior (P<.001). However, comparing HIV incidence among daily vs. non-daily exchange users, while stratifying the cohort into those who did (23.2% vs. 16.8%; P=.157) and did not (11.4% vs. 9.0%; P=.232) report daily cocaine injection at baseline, the association between daily exchange use and HIV incidence was no longer significant. In an adjusted Cox model, daily exchange use was not associated with the time to HIV seroconversion (relative hazard=1.41 [95% confidence interval, 0.95-2.09]). These findings indicate that differential HIV incidence rates between frequent and nonfrequent needle exchange attendees can be explained by the higher risk profile of daily attendees. Causal factors, including the high rates of cocaine injection and other local injection drug user characteristics, explain the Vancouver HIV

outbreak. Wood, E., Lloyd-Smith, E., Li, K., Strathdee, S., Small, W., Tyndall, M., Montaner, J., and Kerr, T. Frequent Needle Exchange Use and HIV Incidence in Vancouver, Canada. Am J Med, 120(2), pp. 172-179, 2007.

Frequent Methamphetamine Use is Associated with Primary Non-nucleoside Reverse Transcriptase Inhibitor Resistance

Researchers determined whether methamphetamine use is associated with the increased prevalence of primary HIV drug resistance among a cohort of 300 men who have sex with men recently infected with HIV. Of the 300, 83 (28%) reported recent meth use; 12% reported weekly use; and 77 (26%) had resistance to at least one antiretroviral drug. Among frequent meth users, 34% were resistant to at least one class of antiretroviral drug compared to 21% of infrequent users and 25% of non-users. In a multivariate model, controlling for multiple sex partners, race/ethnicity, other illicit drug use, and previous use of antiretrovirals, researchers found that frequent methamphetamine use was strongly associated with primary non-nucleoside reverse transcriptase inhibitor resistance, but not with protease inhibitor or nucleoside reverse transcriptase inhibitor resistance. These findings are a concern, particularly because research has shown that resistance to NNRTIs is associated with a significantly greater mortality risk compared to resistance to PIs. The authors postulate that their findings may be caused by methamphetamine-associated treatment interruptions among source partners. Colfax, G., Vittinghoff, E., Grant, R., Lum, P., Spotts, G., and Hecht, F. Frequent Methamphetamine Use is Associated with Primary Non-nucleoside Reverse Transcriptase Inhibitor Resistance. AIDS, 21(2), pp. 239-241, 2007.

Limited Effectiveness of Antiviral Treatment for Hepatitis C in an Urban HIV Clinic

Researchers sought to evaluate predictors and trends of referral for hepatitis C virus (HCV) care, clinic attendance and treatment in an urban HIV clinic. They conducted a retrospective cohort analysis in which 845 of 1318 co-infected adults who attended the Johns Hopkins HIV clinic between 1998 and 2003 after an on-site viral hepatitis clinic was opened, attended regularly (>/= 1 visit/year for >/= 2 years). Logistic regression was used to examine predictors of referral. A total of 277 (33%) of 845 were referred for HCV care. Independent predictors of referral included percentage elevated alanine aminotransferase levels [adjusted odds ratio (AOR) for 10% increase, 1.16; 95% confidence interval (CI), 1.10-1.22] and CD4 cell count > 350 cells/microl (AOR, 3.20; 95% CI, 2.10-4.90), while injection drug use was a barrier to referral (AOR, 0.26; 95% CI, 0.11-0.64). Overall referral rate increased from < 1% in 1998 to 28% in 2003; however, even in 2003, 65% of those with CD4 cell count > 200 cells/microl were not referred. One hundred and eighty-five (67%) of 277 referred kept their appointment, of whom 32% failed to complete a pre-treatment evaluation. Of the remaining 125, only 69 (55%) were medically eligible for treatment, and 29 (42%) underwent HCV treatment. Ninety percent of 29 were infected with genotype 1 and 70% were African American; six (21%) achieved sustained virologic response (SVR). Only 0.7% of the full cohort achieved SVR. These findings indicate that, although the potential for SVR and the recent marked increase in access to HCV care are encouraging, overall effectiveness of anti-HCV treatment in this urban, chiefly African American, HCV genotype 1 HIV clinic is extremely low. The findings highlight the urgent need for new therapies and treatment strategies for HCV. Mehta, S., Lucas, G., Mirel, L., Torbenson, M., Higgins, Y., Moore, R., Thomas, D., and Sulkowski, M. Limited Effectiveness of Antiviral Treatment for Hepatitis C in an Urban HIV Clinic. AIDS, 20(18), pp. 2361-2369, 2006.

Effects of Pegylated Interferon alfa-2b on the Pharmacokinetic

and Pharmacodynamic Properties of Methadone: A Prospective, Nonrandomized, Crossover Study in Patients Coinfected with Hepatitis C and HIV Receiving Methadone Maintenance Treatment

Hepatitis C (HCV) is common among methadone-maintained HIV-positive individuals. Pegylated interferon (pegIFN) used in combination with ribavirin is conventional treatment for HCV. However, pegIFN has been associated with adverse effects (AEs) that may simulate opioid withdrawal and be confused with insufficient methadone dosage. The aim of this study was to determine, using methadone pharmacokinetic properties, whether methadone dosage adjustments are needed on initiation of treatment with pegIFN alfa-2b for HCV in methadone-maintained HIV-positive patients. Patients over age 18, coinfected with chronic HCV and HIV, who had been receiving methadone maintenance treatment (dosage, 40-200 mg/d PO) for at least 8 weeks prior to enrollment were eligible. Nine patients were included in the study (7 men, 2 women; 7 Hispanic, 2 black; mean [SD] age, 41 [8.3] years; mean [SD] weight, 75.0 [12.3] kg). No significant changes were observed from baseline in mean C(max), T(max), C(min), AUC, and CL/F values despite 80% power to detect a 30% change in either direction. Changes from baseline in SOWS and OOWS scores were not statistically significant. The only AEs reported were mild and consistent with those expected after pegIFN alfa-2b administration, such as inflammation at the injection site and mild, brief, flulike symptoms. Based on the results of this small, prospective, nonrandomized study, pegIFN alfa-2b did not appear to precipitate opioid withdrawal in this sample of methadone-maintained persons with HIV and chronic HCV coinfection; methadone dosage adjustments were unlikely to be needed. Berk, S.I., Litwin, A.H., Arnsten, J.H., Du, E., Soloway, I., Gourevitch, M.N. Clin Ther. 29(1), pp. 131-138, January 2007.

Feasibility and Acceptability of Rapid HIV Testing

For correctional HIV testing programs, delivery of HIV test results can be difficult because of short incarceration times for many inmates. Rapid HIV testing enables immediate delivery of test results and can be performed in conjunction with risk reduction counseling. The objective of this study was to determine the feasibility and acceptability of rapid HIV testing within the Rhode Island Department of Corrections jail. Jail detainees were randomly asked to participate in the study. The study included: (1) completing a questionnaire that investigated HIV risk behavior, incarceration history, HIV testing history, and attitudes toward routine HIV testing in jail and toward partner notification services; (2) individualized HIV risk reduction counseling; and (3) the option of rapid HIV testing with delivery of test results. One hundred thirteen inmates were asked to participate and 100 (88%) participated. Among the subjects, there was a high frequency of incarceration and subjects were at significant risk of HIV infection, yet there was low perceived risk. Ninety-five percent of participants underwent rapid HIV testing. Of those, 99% had negative test results and one subject had a preliminary positive result. All subjects received rapid test results and individualized risk reduction counseling. The majority of subjects supported routine HIV testing in jail and the concept of partner notification services. In this population of jail detainees, rapid HIV testing was feasible and highly acceptable. Further studies are needed to successfully incorporate rapid HIV testing into jail HIV screening programs. Beckwith, C.G., Atunah-Jay, S., Cohen, J., Macalino, G., Poshkus, M., Rich, J.D., Flanigan, T.P., and Lally, M.A. AIDS Patient Care STDS. 21(1), pp. 41-47, January 2007.

Specific Targeted Antiviral Therapy for Hepatitis C - Review

Since the discovery of the hepatitis C virus (HCV) as the major cause of non-A, non-B hepatitis in 1989, the search for specific targeted antiviral therapy for

HCV (STAT-C) has been underway. Recently, major advances in the understanding of HCV biology and the development of an in vitro system of HCV replication have contributed to the selection of multiple candidate drugs for the treatment of hepatitis C. In 2006, five such candidate drugs have entered phase II clinical trials in patients chronically infected with hepatitis C, including small molecule inhibitors of the HCV NS3 serine protease and NS5B RNA-dependent RNA polymerase. This review focuses on hepatitis C protease and polymerase inhibitors that have progressed to phase II clinical development, foreshadowing the era of STAT-Cs. Sulkowski, M.S. Curr Gastroenterol Rep. 9(1), pp. 5-13, February 2007.

Hepatitis C Management by Addiction Medicine Physicians: Results from a National Survey

Drug users are disproportionately affected by hepatitis C virus (HCV), yet they face barriers to health care that place them at risk for levels of HCV-related care that are lower than those of nondrug users. Substance abuse treatment physicians may treat more HCV-infected persons than other generalist physicians, yet little is known about how such physicians facilitate HCV-related care. A nationwide survey of American Society of Addiction Medicine physicians (n =320) was conducted to determine substance abuse physicians' HCV-related management practices and to describe factors associated with these practices. Findings showed that substance abuse treatment physicians promoted several elements of HCV-related care, including screening for HCV antibodies, recommending vaccinations against hepatitis A and B, and referring patients to subspecialists for HCV treatment. Substance abuse physicians who also provide primary medical or HIV-related care were most likely to facilitate HCV-related care. A significant minority of physicians were either providing HCV antiviral treatment or willing to provide HCV antiviral treatment. Litwin, A.H., Kunins, H.V., Berg, K.M., Federman, A.D., Heavner, K.K., Gourevitch, M.N., and Arnsten, J.H. J Subst Abuse Treat., March 20, 2007.

HIV Testing in Correctional Agencies and Community Treatment Programs: The Impact of Internal Organizational Structure

This study compares the provision of HIV testing in a nationally representative sample of correctional agencies and community-based substance abuse treatment programs and identifies the internal organizational-level correlates of HIV testing in both organizations. Using an organizational diffusion theoretical framework, Diffusion of innovations, the impact of Centralization of Power, Complexity, Formalization, Interconnectedness, Organizational Resources, and Organizational Size on HIV testing was examined in correctional agencies and treatment programs. Although there were no significant differences in the provision of HIV testing among correctional agencies (49%) and treatment programs (50%), the internal organizational-level correlates were more predictive of HIV testing in correctional agencies. Specifically, all dimensions, with the exception of Formalization, were related to the provision of HIV testing in correctional agencies. Implications for correctional agencies and community treatment to adopt HIV testing are discussed. Oser, C.B., Tindall, M.S., and Leukefeld, C.G. J Subst Abuse Treat. 32(3), pp. 301-310, April 2007.

Prevalence of Opioid Analgesic Injection Among Rural Nonmedical Opioid Analgesic Users

The purpose of this study was to examine the prevalence and correlates of opioid analgesic injection (OAI) in a cohort of opioid analgesic users through a cross-sectional study of 184 participants from rural Appalachian Kentucky. The majority of participants were male (54.9%), white (98.4%) and the median age was 30 years. The self-reported lifetime prevalence of injection drug use

(IDU) was 44.3%, with 35.3% of respondents reporting injection of oral opioid analgesic formulations. The prevalence of self-reported hepatitis C (HCV) was 14.8%, significantly greater than those not injecting opioid analgesics. Receptive needle sharing, distributive needle sharing and sharing of other injection paraphernalia was reported by 10.5%, 26.3%, and 42.1% of those currently injecting, respectively. Opioid analgesic injection was more prevalent in this rural population than has been found in previous reports. This study suggests a rising problem with injecting among rural opioid users, a problem more typically associated with urban drug users. Educating injectors of opioid analgesics on safe needle practices is necessary in order to curb the transmission of HIV, HCV, and other infectious diseases. Further study on the longitudinal course of opioid analgesic injection in this population appears warranted. Havens, J.R., Walker, R., and Leukefeld, C.G. Drug Alcohol Depend. 87(1), pp. 98-102, February 23, 2007.

Multi-sample Standardization and Decomposition Analysis: An Application to Comparisons of Methamphetamine Use Among Rural Drug Users in Three American States

This study demonstrates the use of standardization and decomposition analysis (SDA) techniques to compare outcome measures simultaneously among multiple populations. Methamphetamine use among rural stimulant drug users in three geographically distinct areas of the US (Arkansas, Kentucky, and Ohio) is presented as an example of applying SDA. Findings show that the observed crude rate of 'ever used' methamphetamine in the past 30 days and the frequency of methamphetamine use in the past 30 days were much higher in Kentucky than in the other two states. However, after the compositions of socio-demographic confounding factors were standardized across the samples, the two measures of methamphetamine use ranked highest in Arkansas, followed by Kentucky, and then Ohio. Confounding factors contributed in various dimensions to the differences in the observed outcome measures among the distinct samples. The study shows that SDA is a useful technique for multi-population comparisons, providing an opportunity to look at data from a different perspective in medical studies. Wang, J., Carlson, R.G., Falck, R.S., Leukefeld, C., and Booth, B.M. Stat Med. January 23, 2007.

Survivors of Violence-related Facial Injury: Psychiatric Needs and Barriers to Mental Health Care

This study examined mental health needs, receptivity to psychosocial aftercare, and barriers to care among survivors of violence-related facial injuries. Face-to-face interviews were conducted with 25 consecutively treated individuals at a hospital-based specialty outpatient clinic one month after a violence-related facial injury. To participate in the study, patients had to screen positive for a substance use disorder, major depression or posttraumatic stress disorder (PTSD). Participants were questioned about receptivity to an aftercare program and perceived barriers to care. Of those screened for study eligibility (n=62), a substantial proportion met probable criteria for AUD (31%), PTSD (34%) and major depression (35%). Among those completing the core interview (n=25), 80% met probable criteria for two or more psychiatric disorders. The majority (84%) expressed interest in psychosocial aftercare. However, barriers such as cost, insufficient information about counseling and obtaining services, transportation and preferences for self-reliance were commonly endorsed. Survivors of violence-related facial injuries have substantial mental health needs and appear receptive to psychosocial aftercare. However, significant treatment barriers must be addressed. Findings underscore the value of a collaborative care model for treating violence-related facial trauma patients seeking care in specialty outpatient oral and maxillofacial clinics. Wong, E.C., Marshall, G.N., Shetty, V., Zhou, A., Belzberg, H., and Yamashita, D.D. Gen Hosp Psychiatry. 29(2), pp. 117-122, March-April 2007.

Director's Report to the National Advisory Council on Drug Abuse - May, 2007

Research Findings - Services Research

Interim Methadone Maintenance Enhances Patient Engagement in Treatment

A total of 319 individuals meeting the criteria for current heroin dependence and methadone maintenance treatment were randomly assigned to either interim methadone maintenance, consisting of an individually determined methadone dose and emergency counseling only for up to 120 days, or referral to community-based methadone treatment programs. Significantly more participants assigned to the interim methadone maintenance condition entered comprehensive methadone maintenance treatment by the 120th day from baseline (75.9%) than those assigned to the waiting list control condition (20.8%) (P<.001). Overall, in the past 30 days at follow-up, interim participants reported significantly fewer days of heroin use (P<.001), had a significant reduction in heroin-positive drug test results (P<.001), reported spending less money on drugs (P<.001), and received less illegal income (P<.02) than the waiting list participants. Thus Interim methadone maintenance results in a substantial increase in the likelihood of entry into comprehensive treatment, and is an effective means of reducing heroin use and criminal behavior among opioid-dependent individuals awaiting entry into a comprehensive methadone treatment program. Schwatz, R.P., Brady, J.V., and Callaman, J.M. A Randomized Controlled Trial of Interim Methadone Maintenance. Arch Gen Psychiatry, 63(Jan), pp. 102-109, 2006.

Higher Syringe Coverage is Associated with Lower Odds of HIV

The purpose of this study was to determine if adequate syringe coverage - "one shot for one syringe" - among syringe exchange program (SEP) clients is associated with injection-related HIV risk behaviors and syringe disposal. HIV risk assessments with 1577 injection drug users (IDUs') recruited from 24 SEPs' in California between 2001 and 2003 were analyzed for the study. Individual syringe coverage was calculated as a proportion of syringes retained from SEP visits to total number of injections in the last 30 days. Participants were divided into four groups based on syringe coverage: <50%, 50-99%, 100-149%, and 150% or more. In multivariate logistic regression, SEP clients with less than 50% syringe coverage had significantly higher odds of reporting receptive syringe sharing in the last 30 days (adjusted odds ratio [AOR] = 2.3; 95% confidence interval [CI] = 1.4, 3.6) and those with 150% or more coverage had lower odds of reporting receptive syringe sharing (AOR= 0.5; 95%CI = 0.3, 0.8) as compared to SEP clients with adequate syringe coverage of 100-149%. Similar associations were observed for other main outcomes of distributive syringe sharing and syringe re-use. No differences in safe syringe disposal were observed by syringe coverage. Individual syringe coverage is strongly associated with safer injection behaviors without impacting syringe

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disposal among SEP clients. Syringe coverage is a useful measure for determining if IDUs' are obtaining sufficient syringes to lower HIV risk. Bluthenthal, R.N., Anderson, R., Flynn, N.M., and Kral, A.H. Higher Syringe Coverage Is Associated with Lower Odds of HIV. Drug Alcohol Depend, 12 pp. 1-9, 2006.

Examination of the Association Between Syringe Exchange Program (SEP)

Dispensation Policy and SEP Client-level Coverage This study explores whether syringe exchange programs' (SEPs') dispensation policy is associated with syringe coverage among SEP clients. The study used a cross-sectional sample of 24 SEPs and their injection drug using clients (IDU) (n=1546) in California, USA. Clients were classified as having adequate syringe coverage if they received at least as many syringes from the SEP as their self-reported injections in the last 30 days. SEPs' were classified based on their syringe dispensation policy. Dispensation schemes ranging from least restrictive to most are: unlimited needs-based distribution; unlimited one-for-one exchange plus a few additional syringes; per visit limited one-for-one plus a few additional syringes; unlimited one-for-one exchange; and per visit limited one-for-one exchange. Adequate syringe coverage among SEP clients by dispensation policy is as follows: unlimited needs-based distribution = 61%; unlimited one-for-one plus = 50%; limited one-for-one plus = 41%; unlimited one-for-one = 42%; and limited one-for-one = 26%. In multivariate analysis, adequate syringe coverage was significantly higher for all dispensation policies compared to per visit limited one-for-one exchange. Using propensity scoring methods, the study compared syringe coverage by dispensation policies while controlling for client-level differences. Providing additional syringes above one-for-one exchange (50% versus 38%, P = 0.009) and unlimited exchange (42% versus 27%, P = 0.05) generally resulted in more clients having adequate syringe coverage compared to one-for-one exchange and per visit limits. Providing less restrictive syringe dispensation is associated with increased prevalence of adequate syringe coverage among clients. This study suggests that SEPs' should adopt syringe dispensation policies that provide IDUs sufficient syringes to attain adequate syringe coverage. Bluthenthal, R.N., Ridgeway, G., Schell, T., Anderson, R., Flynn, N.M., and Kral, A.H. Examination of the Association between Syringe Exchange Program (SEP) and SEP Client-level. Addiction, 10, pp. 1-9, 2007.

Patient Engagement in Treatment is Enhanced When Staff Beliefs and Associated Practices are Widely Shared

Two nonspecific organizational factors--consensus, defined as agreement within staff and client groups about treatment and other practices, and concordance, defined as agreement between staff and client groups--were shown to influence client engagement in treatment in a national sample of 80 residential substance abuse treatment programs including 595 staff and 3,732 clients. Agreement was tested using a combined therapeutic community, cognitive-behavioral therapy, and 12-step treatment scale completed by staff and clients. Treatment engagement was measured by the combined scores on the three scales completed by the clients addressing engagement, rapport with the counseling process, and confidence in treatment. Within-group consensus was measured by the standard deviations of the mean scores, whereas between-groups concordance was measured by the standard error of the difference between staff and client mean scores. Regression analyses showed that staff consensus was a significant independent predictor of client treatment engagement ($p < .05$), whereas client consensus approached significance ($p < .10$). Concordance was also a significant predictor of client engagement ($p < .002$) after controlling for staff and client consensus. Melnick, G., Wexler, H.K., Chaple, M., and Banks, S. The Contribution of Consensus within Staff and

Client Groups as well as Concordance between Staff and Clients to Treatment Engagement. J Subst Abuse Treat, 31(3), pp. 277-285, 2006.

Public Sector Managed Care Did Not Result in Poorer Care for Most Clients

This study of publicly funded substance abuse treatment systems compared Mid-State, a county that reorganized its treatment system using managed care principles, to two other California counties that took different approaches, North-State and South-State. It was hypothesized that Mid-State would have better outcomes due to its emphasis on quality of care. This natural experiment compared the ''experimental'' county, Mid-State, to two ''control '' counties, assessing client outcomes following treatment. Administrative and historical exigencies that may affect system differences were explored in interviews with treatment program managers and staff. Comparison counties were selected using treatment system and county census data, maximizing similarities to enhance internal validity. The study participants consisted of adult clients (n = 681) who were interviewed when beginning treatment and 12 months later (81% response rate). In addition, 50 treatment program managers and staff members across the three counties were interviewed during the year of client recruitment. Outcome was assessed using client interviews that assessed functioning in the seven Addiction Severity Index domains-alcohol, drug, psychiatric, legal, employment, medical and family/social. It was found that the outcomes (differences between baseline and 12 month composite scores) did not differ between counties in six of seven domains; in the seventh, psychiatric functioning, South-State had better outcomes than Mid-State. Staff interviews indicated generally similar treatment strategies across counties, with Mid-State supplying greater oversight and performance standards. In this study managed care in public sector treatment generally did not result in poorer outcomes. The authors suggested that future attention in Mid-State to the barriers to successful implementation of individualized treatment, and to dual diagnosis treatment, might bring more positive results. Beattie, M., McDaniel, P., and Bond, J. Public Sector Managed Care: A Comparative Evaluation of Substance Abuse Treatment in Three Counties. Addiction, 101(6), pp. 857-872, 2006.

Impact of Enhanced Services on Virologic Outcomes for HIV-Infected Drug Users

Directly administered antiretroviral therapy (DAART) is a promising intervention for improving HIV outcomes among active drug users, but the elements associated with successful DAART programs remain largely unknown. This study aimed to assess the impact of co-located medical, case management, and referral to substance abuse services (DAART-Plus) among the subjects receiving DAART as part of a larger randomized controlled trial comparing DAART with self-administered therapy. The health services utilization of 72 subjects receiving DAART was analyzed for its impact on changes in HIV-1 RNA levels at 6 months. The primary outcome was virologic success, defined as achieving an HIV-1 RNA level 400 copies/mL or a 1.0 log10 reduction in HIV-1 RNA level. A second analysis consisted of linear regression assessing the effect of covariates on log10 HIV-1 RNA reduction from baseline to 6 months. In multivariate analyses, achieving virologic success at 6 months was associated with high medical services utilization [adjusted odds ratio [AOR] = 10.0 (1.4, 73.9); P = 0.02] and with the use of case management services [AOR = 5.8 (1.1, 30.5); P = 0.04]. Both services resulted in a larger reduction in log10 HIV-1 RNA from baseline (difference in slopes: 20.9 and 21.0, respectively; P = 0.02 for both). Referral to off-site substance abuse services treatment did not significantly predict either virologic outcome. Among individuals who receive DAART, the utilization of on-site medical and case management services was independently associated with improved virologic outcomes. These results suggest the potential utility of integrating these

services into DAART interventions (DAART-Plus) targeting HIV-infected drug users with problematic adherence. Smith-Rohrberg, D., Mezger, J., Walton, M., Bruce, D., and Altice, F. Impact of Enhanced Services on Virologic Outcomes in a Directly Administered Antiretroviral Therapy Trial for HIV-Infected Drug Users. J Acquir Immune Defic Syndr, 43(S1), pp. S48-S53, 2006.

Adolescent Health Care Utilization and Costs Do Not Diminish Following 1 Year of CD Treatment

This paper examined utilization and cost in the 1 year pre- and post-intake among a sample of adolescents (N = 419) entering chemical dependency (CD) treatment in a private, not-for-profit HMO. Multivariate analyses showed that these youth used significantly more medical services than a demographically matched sample of members without substance use (SU) problems. Their utilization and costs were higher than matched members, and they did not show the same reductions in post-treatment costs that adults do. This is of concern since it would appear that the medical and mental health problems of adolescents entering CD treatment may be so severe that there are no short-term reductions in post-treatment cost, including ER and hospitalizations. Parthasarathy, S., and Weisner, C. Health Care Services Use by Adolescents with Intakes into an Outpatient Alcohol and Drug Treatment Program. Am J Addict, 15 Suppl 1, pp. 113-121, 2006.

Teenage Marijuana and Hard Drug Use Increases in a Weak Economy

This research examines how teenage drug and alcohol use responds to changes in the economy. In contrast to the recent literature confirming pro-cyclical alcohol use among adults, this research offers strong evidence that a weaker economy leads to greater teenage marijuana and hard-drug use and some evidence that a weaker economy also leads to higher teenage alcohol use. The findings are based on logistic models with state and year fixed effects, using teenagers from the NLSY-1997. The evidence also indicates that teenagers are more likely to sell drugs in weaker economies. This suggests one mechanism for counter-cyclical drug use - that access to illicit drugs is easier when the economy is weaker. These results also suggest that the strengthening economy in the 1990s mitigated what would otherwise have been much larger increases in teenage drug use. Arkes, J. Does the Economy Affect Teenage Substance Use? Health Econ, 16 pp. 19-36, 2007.

Economic Evaluations Done Alongside RTCs Could be Improved

This article evaluates the statistical methods used for economic evaluations of medical interventions based on patient level data collected during randomized controlled trials. Only 42 (37%) of the 115 economic evaluations presented a cost-effectiveness ratio or estimated net benefits and 24 (57%) of these reported the uncertainty of this statistic. A comparison of costs alone was more common with 92 (80%) of the 115 studies statistically comparing costs between treatment groups. Of these, about two-thirds (62; 68%) used at least one statistical test appropriate for drawing inferences for arithmetic means. Incomplete cost data were reported in 67 (58%) studies with only two using a published statistical approach for handling censored cost data. The quality of statistical methods used in economic evaluations conducted alongside randomized controlled trials was poor in the majority of studies published in 2003. Adoption of appropriate statistical methods is required before the results from such studies can consistently provide valid information to decision-makers. Doshi, J., Glick, H., and Polsky, D. Analyses of Cost Data in Economic Evaluations Conducted alongside Randomized Controlled Trials. Value Health, 9(5), pp. 334-340, 2006.

Medical Conditions of Adolescents in AOD Treatment

This study compares the prevalence of medical conditions among 417 adolescent alcohol and drug treatment patients with 2082 demographically matched controls from the same managed care health plan and examines whether comparisons vary among substance-type subgroups. Approximately one-fourth of the comorbid conditions examined were more common among adolescent alcohol and drug patients than among matched controls, and several were highly costly conditions (e.g., asthma, injury). Pain-related diagnoses, including headache and abdominal pain, were more prevalent among these alcohol and drug patients. These findings point to the importance of examining comorbid medical and chemical dependency in both adolescent primary care and specialty care. Moreover, optimal treatment of many common medical disorders may require identification, intervention, and treatment of a substance use problem. Mertens, J., Flisher, A., Fleming, M., and Weisner, C. Medical Conditions of Adolescents in Alcohol and Drug Treatment: Comparison with Matched Controls. J Adolesc Health, 40(2), pp. 173-179, 2007. Payee Assignment Does Not Reduce Substance Abuse among Those with Serious Mental Illness Approximately 700,000 Social Security beneficiaries in the U.S. with psychiatric disabilities have been assigned a representative payee to manage their funds but it is unclear how those judged to need a payee differ from others and whether payee assignment improves clinical outcomes, especially substance abuse. Participants in this observational 12-month cohort study (n=1457) received SSI or SSDI and had serious mental illness. They were subsequently enrolled at eighteen community-based sites that provided Assertive Community Treatment. Social Security administrative records were used to determine whether a payee had been assigned. At baseline, participants who were assigned a payee were more likely to have schizophrenia and had more severe clinician-rated drug and alcohol use than those not assigned a payee. In GEE models that adjusted for these and other potentially confounding covariates, participants assigned a payee between 4 and 12 months after program entry subsequently used significantly more psychiatric services than participant's not assigned payees but showed no greater reduction in substance use. Although substance use is associated with being assigned a payee, substance use does not decline substantially following payee assignment. Participants assigned payees made greater subsequent use of psychiatric services, suggesting the potential for benefit from payee assignment. Rosen, M., McMahon, T., and Rosenheck, R. Does Assigning a Representative Payee Reduce Substance Abuse? Drug Alcohol Depend, 86(2-3), pp. 115-122, 2007.

Clients Smoking Five Years After Alcohol and Drug Abuse Treatment Have Worse Long-Term Treatment Outcomes

This prospective study examined the relationship between cigarette smoking and five-year substance abuse treatment outcomes. Of 749 individuals who began private outpatient treatment, 598 (80%) were re-interviewed by telephone at five years. At five-year follow-up, 53% reported smoking cigarettes in the prior 30 days. Those smoking at that time were less likely to be abstinent from alcohol and drugs in the prior 30 days (48.3% vs. 64.0%), and had higher Addiction Severity Index (ASI) scores in employment, alcohol, drug, psychiatric, and family-social problems; worse self-reported health; and greater self-reported depression. Satre, D.D., Kohn, C.S., and Weisner, C. Cigarette Smoking and Long-Term Alcohol and Drug Treatment Outcomes: A Telephone Follow-Up at Five Years. Am J Addict, 16, pp. 32-37, 2007.

Higher Contingency Management Payouts are More Cost Effective

Contingency management has been shown to be effective in improving

treatment outcomes. This paper assesses the relative cost-effectiveness of lower versus higher cost prize-based contingency management (CM) treatments for cocaine abuse as implemented in two community-based treatment centers. One hundred twenty patients who enrolled in out-patient treatment for cocaine abuse were randomly assigned to one of three 12-week treatment conditions: standard treatment (STD) alone or two variants of STD combined with prize based CM. In CM, drawing for prizes was available to those submitting drug-free urine samples and completing goal-related activities. There were two levels of pay-out (referred to as $80 versus $240) based on the potential value of prizes won. The higher magnitude CM produced outcomes at a lower per unit cost than did the lower magnitude prize CM treatment. This was the case for all three outcome measures examined (longest duration of consecutive abstinence, percentage completing treatment, and percentage of samples drug-free) and held across various assumptions in the sensitivity analysis. Sindelar, J., Elbel, B., and Petry, N. What Do We Get for Our Money? Cost-Effectiveness of Adding Contingency Management. Addiction, 102(2), pp. 309-316, 2007.

Buprenorphine Use: The International Experience

The confluence of the heroin injection epidemic and the human immunodeficiency virus (HIV) infection epidemic has increased the call for expanded access to effective treatments for both conditions. Buprenorphine and methadone are now listed on the World Health Organization's Model Essential Drugs List. In France, which has the most extensive experience, buprenorphine has been associated with a dramatic decrease in deaths due to overdose, and buprenorphine diversion appears to be associated with inadequate dosage, social vulnerability, and prescriptions from multiple providers. Other treatment models (in the United States, Australia, Germany, and Italy) and buprenorphine use in specific populations are also reviewed in the present article. In countries experiencing a dual epidemic of heroin use and HIV infection, such as former states of the Soviet Union and other eastern European and Asian countries, access to buprenorphine and methadone may be one potential tool for reducing the spread of HIV infection among injection drug users and for better engaging them in medical care. Carrieri, M. P., Amass, L., Lucas, G. M., Vlahov, D., Wodak, A., and Woody, G. E. Buprenorphine Use: The International Experience. Clin Infect Dis, 43, pp. S197-S215, 2006.

Limited Effectiveness of Antiviral Treatment for Hepatitis C in an Urban HIV Clinic

This study evaluated predictors and trends of referral for hepatitis C virus (HCV) care, clinic attendance and treatment in an urban HIV clinic. A retrospective cohort analysis in which 845 of 1318 co-infected adults who attended the Johns Hopkins HIV clinic between 1998 and 2003 after an onsite viral hepatitis clinic was opened attended regularly (1 visit/year for 2 years). Logistic regression was used to examine predictors of referral. A total of 277 (33%) of 845 were referred for HCV care. Independent predictors of referral included percentage elevated alanine minotransferase levels [adjusted odds ratio (AOR) for 10% increase, 1.16; 95% confidence interval (CI), 1.10-1.22] and CD4 cell count >350 cells/ml (AOR, 3.20; 95% CI, 2.10-4.90), while injection drug use was a barrier to referral (AOR, 0.26; 95% CI, 0.11-0.64). Overall referral rate increased from <1% in 1998 to 28% in 2003; however, even in 2003, 65% of those with CD4 cell count >200 cells/ml were not referred. One hundred and eighty-five (67%) of 277 referred kept their appointment, of whom 32% failed to complete a pre-treatment evaluation. Of the remaining 125, only 69 (55%) were medically eligible for treatment, and 29 (42%) underwent HCV treatment. Ninety percent of 29 were infected with genotype 1 and 70% were African American; six (21%) achieved sustained virologic response (SVR). Only 0.7% of the full cohort achieved SVR. Although

the potential for SVR and the recent marked increase in access to HCV care are encouraging, overall effectiveness of anti-HCV treatment in this urban, chiefly African American, HCV genotype 1 HIV clinic is extremely low. New therapies and treatment strategies are an urgent medical need. Mehta, S.H., Lucas, G.M., Mirel, L.B., Torbenson, M., Higgins, Y., Moore, R.D., Thomas, D.L., and Sulkowski, M.S. Limited Effectiveness of Antiviral Treatment for Hepatitis C in an Urban HIV Clinic. AIDS, 20(18), pp. 2361-2369, 2006.

Invasive Pneumococcal Disease in a Cohort of HIV-Infected Adults: Incidence and Risk Factors, 1990-2003

This study investigated the association between the introduction of HAART and invasive pneumococcal disease (IPD) in HIV-infected patients. Incidence of IPD was determined from 1990 to 2003 in a cohort of HIV infected individuals and a nested case-control study assessed risk factors of IPD. There were 72 cases over 19,020 person-years of follow-up (overall IPD rate, 379/100 000 person-years). In the calendar periods 1990-1995, 1995-1998, and 1998-2003, the IPD incidence per 100,000 person-years was 279 [95% confidence interval (CI), 150-519], 377 (95% CI, 227-625) and 410 (95% CI, 308-545), respectively (P _ 0.516). CD4 cell count < 200 cells/ml [odds ratio (OR), 3.0; 95% CI, 1.2-7.6), HIV RNA > 50 000 copies/ml (OR, 2.8; 95% CI, 1.2-6.5), hepatitis C (OR, 4.9; 95% CI, 1.7-14.9), serum albumin (OR, 0.1; 95% CI, 0.04-0.5), injection drug use in women (OR, 3.8; 95% CI, 1.6-8.8), and education beyond high school (OR, 0.2; 95% CI, 0.05- 0.8) were significantly associated with IPD in multivariate analysis. No treatment factor, including HAART (OR, 0.7; 95% CI, 0.3-1.5) and pneumococcal vaccination (OR, 0.9; 95% CI, 0.5-1.6), was associated with IPD. IPD incidence did not change significantly during the widespread dissemination of HAART in this cohort. IPD risk was associated with several socio-demographic and clinical factors. Barry, P.M., Zetola, N., Keruly, J.C., Moore, R.D., Gebo, K.A., and Lucas, G.M. Invasive Pneumococcal Disease in a Cohort of HIV-Infected Adults: Incidence and Risk Factors,1990-2003. AIDS, 20, pp. 437-444, 2006.

Substance Abuse Treatment Prevention and Policy

It has been proposed that the substance abuse treatment delivery system cut across different components of the criminal justice continuum in order to reduce criminal recidivism and drug use. Arrest, at the front end of this continuum, may represent a critical moment to motivate people with substance use disorders (SUD) to seek treatment but is often over looked as an intervention point. Data from the 2002 National Survey on Drug Use and Health (NSDUH) were used to compare treatment need and recent treatment admission for participants with no criminal justice (CJ) involvement in the past year, past-year arrest, and CJ supervision (i.e., probation or parole status). Of those arrested, 44.8% met criteria for an SUD. However, only 14% of those arrested with an SUD received treatment in the year of their arrest. In multivariate modeling, arrest was an independent predictor of treatment admission (odds ratio (OR) = 8.74) similar in magnitude to meeting criteria for an SUD (OR = 8.22). Those further along the continuum - under supervision - were most likely to receive treatment (OR = 22.62). Arrest involves the largest number of individuals entering the criminal justice system. The NSDUH suggests that nearly 6 million individuals in the US experience an arrest annually and that nearly half meet criteria for an SUD. Although arrest involves the largest number of individuals entering the criminal justice system, it is also the most fleeting point as individuals can move in and out rather quickly. Minimally, arrest imposes contact between the individual and a law enforcement person and can be an opportunity for early intervention strategies such as pre-arraignment diversion into treatment or brief intervention strategies. Using brief intervention at this early point in the continuum may motivate a greater number of individuals to seek treatment or decrease drug

and alcohol use. Training and procedural shifts at this point of contact could have important policy implications in reducing the number of subsequent arrests or preventing individuals moving further along the criminal justice continuum, as well as decreasing the fiscal and resource burdens associated with criminal justice processing and confinement. Pimlott Kubiak, S., Arfken, C.L., Swartz, J.A., and Koch, A.L. Substance Abuse Treatment Prevention, and Policy. BioMed Central, 1(20), pp. 1-10, 2006.

Initial Strategies for Integrating Buprenorphine into HIV Care Settings in the United States

The Centers for Disease Control and Prevention's HIV Prevention Strategic Plan through 2005 advocated for increasing the proportion of persons with human immunodeficiency virus (HIV) infection and in need of substance abuse treatment who are successfully linked to services for these 2 conditions. There is evidence that integrating care for HIV infection and substance abuse optimizes outcomes for patients with both disorders. Buprenorphine, a recently approved medication for the treatment of opioid dependence in physicians' offices, provides the opportunity to integrate the treatment of HIV infection and substance abuse in one clinical setting, yet little information exists on the models of care that will most successfully facilitate this integration. To promote the uptake of this type of integrated care, the current review provides a description of 4 recently implemented models for combining buprenorphine treatment with HIV primary care: (1) an on-site addiction/HIV specialist treatment model; (2) a HIV primary care physician model; (3) a nonphysician health professional model; and (4) a community outreach model. Sullivan, L.E., Bruce, R.D., Haltiwanger, D., Lucas, G.M., Eldred, L., Finkelstein, R., and Fiellin, D.A. Initial Strategies for Integrating Buprenorphine into HIV Care Settings in the United States. Clin Infect Dis, 43, pp. S191-S196, 2006.

Reasons for Condom Use or Non-use Among Drug Users

In this study, Rosengard, Anderson, and Stein, interviewed two hundred and seventy-seven drug using adults regarding details of their most recent sexual encounter. Demographic, attitudinal, and context variables were associated with condom use and non-use. Greater perceived risk of STDs/HIV and positive attitudes toward condoms' effect on sexual pleasure were associated with greater likelihood of reporting condom use. Common reasons for not using condoms included lower perceived risk of contracting HIV/STDs, negative attitudes toward condoms' effect on pleasure, and lack of condom availability. Tailoring messages to modifiable perceptions of risk and condom attitudes may be useful in reducing sexual risk among drug-using individuals. Rosengard, C., Anderson, B., and Stein, M. Correlates of Condom Use and Reasons for Condom Non-use Among Drug Users. Am J Drug Alcohol Abuse, 32(4), pp. 637-1441, 2006.

DSM-III-R and DSM-V Diagnoses are Generally Concordant in Drug Users with Chronic and Severe Problems

This study determined the rates of concordance between the Diagnostic and Statistical Manual of Mental Disorders Version III-R (DSM-III-R) and the next version (DSM-IV) lifetime diagnoses for Substance Abuse and Dependence in a population (N=900) homogeneous for chronic and severe substance use disorder. The substance use disorder sections of the Structured Clinical Interview for DSM-III-R and DSM-IV were combined into a single interview and administered by trained clinical research interviewers. Analysis for each drug class was restricted to patients who reported prior use of the substance. Kappa values indicated excellent agreement between the 2 classification systems for Dependence diagnoses and fair to excellent concordance for Abuse diagnoses.

However for cannabis the DSM-IV nosology resulted in lower rates of Dependence and higher rates of Abuse diagnoses. Stoller, K. B., King, V.L., Kidorf, M.S., Neufeld, K.S., and Brooner, R.K. DSM-III-R Versus DSM-IV Substance Use Disorders: Concordance in Drug Users Homogeneous for Chronic and Severe Problems. Addictive Disorders & Their Treatment, 5(4), pp. 165-171, 2006.

Research is Needed to Overcome Policy and Financing Barriers to Integrated Buprenorphine and HIV Primary Care

Treatment for substance abuse and human immunodeficiency virus (HIV) infection historically have come from different providers, often in separate locations, and have been reimbursed through separate funding streams. This paper describes policy and financing challenges faced by health care providers seeking to integrate buprenorphine, a new treatment for opioid dependence, into HIV primary care. Regulatory challenges include licensing and training restrictions imposed by the Drug Addiction Treatment Act of 2000 and confidentiality regulations for alcohol and drug treatment records. Potential responses include the development of local training programs and electronic medical records. Addressing the complexity of funding sources for integrated care will require administrative support, up-front investments, and federal and state leadership. A policy and financing research agenda should address evidence gaps in the rationales for regulatory restrictions and should include cost-effectiveness studies that quantify the "value for money" of investments in integrated care to improve health outcomes for HIV-infected patients with opioid dependence. Schackman, B.R., Merrill, J.O., McCarty, D., Levi, J., and Lubinski, C. Overcoming Policy and Financing Barriers to Integrated Buprenorphine and HIV Primary Care. Clin Infect Dis, 43, pp. S247-S253, 2006.

If You Build It, They Will Come: Practitioner Interest in CM for Youth

This publication addresses the science-service gap by examining the amenability of a large heterogeneous sample of community-based therapists in state mental health and substance abuse treatment sectors to learn about an evidence-based practice (EBP) for adolescent substance abuse (i.e., contingency management [CM]) when such learning was supported administratively and logistically. Leadership in most (44 of 50) public sector agencies supported practitioner recruitment, and 432 of 543 eligible practitioners subsequently attended a 1-day workshop in CM. Workshop attendance was predicted by organizational factors but not by practitioner demographic characteristics, professional background, attitudes toward EBPs, or service sector. Moreover, the primary reason for workshop attendance was to improve services for adolescent clients; the primary barriers to attendance, for those who did not attend, were practical in nature and not due to theoretical incompatibility. The findings demonstrate a considerable amount of interest practitioners showed in both the substance abuse and mental health sectors in learning about an EBP. Henggeler, S., Chapman, J., Rowland, M., Halliday-Boykins, C., Randall, J., Shackelford, J., and Schoenwald, S. If You Build It, They Will Come: Statewide Practitioner Interest in Contingency Management for Youths. J Subst Abuse Treat, 32(2), pp. 121-131, 2007.

Excess Medical Costs and Health Problems of AOD Family Members

The researchers estimate the excess medical costs and prevalence of diagnosed health conditions of family members of persons with an alcohol or drug diagnosis (AOD) compared with the family members of similar persons

without an AOD, utilizing a large health plans administrative 2001-2004 databases. Using a hierarchical linear mixed model, they compared the cost and utilization of the family members of the AOD and non-AOD patients in the 2 years prior to the AOD patient's first AOD. Using logistic regression, they determined whether the family members of patients with AODs' were more likely than comparison family members to be diagnosed with medical conditions. As hypothesized, family members of patients with AODs' had greater health care costs than comparison family members in the second year before the index date (490 dollars) and in the year before the index date (433 dollars). This was the case for both adult and child family members. They also were more likely to be diagnosed with many medical conditions, especially substance abuse and depression. Ray, G., Mertens, J., and Weisner, C. The Excess Medical Cost and Health Problems of Family Members of Persons Diagnosed with Alcohol or Drug Problems. Med Care, 45(2), pp. 116-122, 2007.

Potential Role of Buprenorphine in Treatment of Opioid Dependence in HIV-Infected Individuals

Untreated opioid dependence is a major obstacle to the successful treatment and prevention of human immunodeficiency virus (HIV) infection. In this review, the authors examine the interwoven epidemics of HIV infection and opioid dependence and the emerging role of buprenorphine in improving HIV treatment outcomes among infected individuals, as well as its role in primary and secondary prevention. This article addresses some of the emerging issues about integrating buprenorphine treatment into HIV clinical care settings and the various strategies that must be considered. Specifically, it addresses the role of buprenorphine in improving HIV treatment outcomes through engagement in care, access to antiretroviral therapy and preventive therapies for opportunistic infections, and the potential benefits of and pitfalls in integrating buprenorphine into HIV clinical care settings. Authors discuss the key research questions regarding buprenorphine in the area of improving HIV treatment outcomes and prevention, including a review of published studies of buprenorphine and antiretroviral treatment and currently ongoing studies, and provide insight into and models for integrating buprenorphine into HIV clinical care settings. Dialogue among practitioners and policy makers in the HIV care and substance abuse communities will facilitate an effective expansion of buprenorphine and ensure that these beneficial outcomes are achieved. Altice, F., Sullivan, L., Smith-Rohrberg, D., Basu, S., Stancliff, S., and Eldred, L. The Potential Role of Buprenorphine in the Treatment of Opioid Dependence in HIV-Infected Individuals and in HIV Infection Prevention. Clin Infect Dis, 206:43 (S4), pp. S178-S183, 2006.

Lack of HIV Seropositivity Among a Group of Rural Probationers: Explanatory Factors

Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) in rural America has been described as an epidemic, and the HIV prevalence rate among criminal justice populations is higher than the general population. Thus, criminally involved populations in Southern rural areas are at elevated risk for contracting HIV because of drug and sexual practices; however, little is known about HIV/AIDS in the fastest growing criminal justice population -- probationers. This study examined possible explanations for the lack of HIV seropositivity found in a purposive sample of rural probationers. Data were examined from 800 felony probationers from 30 counties in Kentucky's Appalachian region. Measures included HIV prevalence within the 30 counties, migration patterns, HIV knowledge, substance use, and sexual risk behaviors. These probationers had a high level of HIV knowledge, reported minimal injection drug use, practiced serial monogamy, and reported minimal engagement in transactional sex. However, these probationers also reported

negligible condom use, and injection drug users shared needles and works. Findings suggest the importance of developing programs targeting safe sex practices in rural areas. Oser, C.B., Smiley McDonald, H.M., Havens, J.R., Leukefeld, C.G., Webster, J.M., and Cosentino-Boehm, A.L. Lack of HIV Seropositivity Among a Group of Rural Probationers: Explanatory Factors. J Rural Health, 22(3), pp. 273-275, 2006.

Recruiting Drug-Using Men who Have Sex With Men into Behavioral Interventions: A Two-Stage Approach

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. MSMs' 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. J Urban Health, 2, pp. 109-119, 2005.

Buprenorphine Therapy Models for the HIV Care Setting

Buprenorphine maintenance therapy has been associated with reductions in opiate use, increased social stability, improved adherence to antiretroviral therapy, and lowered rates of injection drug use. The authors describe 4 models for the integration of buprenorphine maintenance therapy into HIV care: (1) a primary care model, in which the highly active antiretroviral therapy-administering clinician also prescribes buprenorphine; (2) a model that relies on an on-site specialist in addiction medicine or psychiatry to prescribe the buprenorphine; (3) a hybrid model, in which an on-site specialist provides the induction (with or without stabilization phases) and the HIV care provider provides the maintenance phase; and (4) a drug treatment model that provides buprenorphine maintenance therapy services with HIV services in the substance abuse clinic setting. Basu, S., Smith-Rohrberg, D., Bruce, R., and Altice, F. Models for Integrating Buprenorphine Therapy into the Primary HIV Care Setting. Clin Infect Dis, 42(5), pp. 716-721, 2006.

Buprenorphine and HIV Primary Care: New Opportunities for Integrated Treatment

NIDA, the Centers for Disease Control and Prevention, and other agencies, presented a workshop entitled "Buprenorphine in the Primary HIV Care Setting." Participants reviewed and discussed current issues, such as the introduction of and sources for the provision of buprenorphine in HIV primary care settings and strategies for integrating treatment of HIV-infected drug abusers, all of which are covered in this supplement. Data presented at this

conference suggest that the most effective way to integrate the use of buprenorphine for the treatment of opioid dependence with antiretroviral therapy for HIV is to bridge two medical fiends - addiction medicine and infectious disease - and then develop supportive policies. Research is needed to develop effective ways to blend these two different medical disciplines and improve the quality of care delivered to individuals who are both HIV positive and opioid dependent. Khalsa, J., Vocci, F., Altice, F., Fiellin, D., and Miller, V. Buprenorphine and HIV Primary Care: New Opportunities for Integrated Treatment. Clin Infect Dis, 43(S4), pp. S169-S172, 2006.

Demonstration and Evaluation of a Method for Assessing Mediated Moderation

When interaction terms are correlated, the power needed to detect mediated moderation can be problematic. Mediated moderation occurs when the interaction between two variables affects a mediator, which then affects a dependent variable. In this article, authors describe the mediated moderation model and evaluate it with a statistical simulation using an adaptation of product-of-coefficients methods to assess mediation. The authors also demonstrate the use of this method with a substantive example from the adolescent tobacco literature. In the simulation, relative bias (RB) in point estimates and standard errors did not exceed problematic levels of +/- 10% although systematic variability in RB was accounted for by parameter size, sample size, and nonzero direct effects. Power to detect mediated moderation effects appears to be severely compromised under one particular combination of conditions: when the component variables that make up the interaction terms are correlated and partial mediated moderation exists. Implications for the estimation of mediated moderation effects in experimental and non-experimental research are discussed. Morgan-Lopez, A., and MacKinnon, D. Demonstration and Evaluation of a Method for Assessing Mediated Moderation. Behav Res Methods, 38(1), pp. 77-87, 2006.

Deaf Recovering Addicts Residing in Oxford Houses Have Similar Aftercare Outcomes to Hearing Residents

Deaf individuals seeking substance abuse recovery are less likely to have access to treatment and aftercare services because of a lack of culturally and linguistically specific programs and insufficient information about existing services. This study found no significant differences between 10 randomly selected Deaf and 10 hearing men, matched for age, ethnicity, and time spent living in Oxford Houses (OH) in terms of sense of community and abstinence self-efficacy. This led to the conclusion that integrating deaf recovering addicts into OH aftercare is not problematic. However, consistent with previous studies, there was a significant difference between the two groups in levels of employment, with all deaf residents being under-employed whereas all hearing residents were fully employed. Results suggest that special employment help may be needed to sustain recovery and a return to independent living. Alvarez, J., Adebanjo, A.M., Davidson, M.K., Davis, M.I., and Jason, L.A. Oxford House: Deaf-Affirmative Support. Project Muse Scholarly Journal Online, 151(4), pp. 418-422, 2006.

Director's Report to the National Advisory Council on Drug Abuse - May, 2007

Clinical Trials Network Research

Attitudes Toward the Integration of Smoking Cessation Treatment into Drug Abuse Clinics

This article examines the variables associated with the presence of smoking cessation interventions in drug abuse treatment units, as well as staff attitudes toward the integration of smoking cessation services as a component of care. Surveys were administered to 106 organizations, 348 treatment clinics, and 3,786 employees in agencies that participated in the National Drug Abuse Treatment Clinical Trials Network. Use of smoking cessation interventions was associated with the number of additional services offered at clinics, residential detoxification services, and attitudes of the staff toward smoking cessation treatment. Staff attitudes toward integrating smoking cessation services in drug treatment were influenced by the number of pregnant women admitted, the number of ancillary services provided, the attitudes of staff toward evidence-based practices, and whether smoking cessation treatment was offered as a component of care. Fuller, B.E., Guydish, J., Tsoh, J., Reid, M.S., Resnick, M., Zammarelli, L., Ziedonis, D.M., Sears, C., and McCarty, D. Attitudes Toward the Integration of Smoking Cessation Treatment into Drug Abuse Clinics. J Subst Abuse Treat. 32(1), pp. 53-60, 2007. Epub September 26, 2006.

Substance Abuse Treatment Entry, Retention, and Outcome in Women: A Review of the Literature

A search of the English language literature from 1975 to 2005 using Medline and PsycInfo databases found 280 relevant articles. Ninety percent of the studies investigating gender differences in substance abuse treatment outcomes were published since 1990, and of those, over 40% were published since the year 2000. Only 11.8% of these studies were randomized clinical trials. A convergence of evidence suggests that women with substance use disorders are less likely, over the lifetime, to enter treatment compared to their male counterparts. Once in treatment, however, gender is not a significant predictor of treatment retention, completion, or outcome. Gender-specific predictors of outcome do exist, and individual characteristics and treatment approaches can differentially affect outcomes by gender. While women-only treatment is not necessarily more effective than mixed-gender treatment, some greater effectiveness has been demonstrated by treatments that address problems more common to substance-abusing women or that are designed for specific subgroups of this population. There is a need to develop and test effective treatments for specific subgroups such as older women with substance use disorders, as well as those with co-occurring substance use and psychiatric disorders such as eating disorders. Future research on effectiveness and cost-effectiveness of gender-specific versus standard treatments, as well

as identification of the characteristics of women and men who can benefit from mixed-gender versus single-gender treatments, would advance the field. Greenfield, S.F., Brooks, A.J., Gordon, S.M., Green, C.A., Kropp, F., McHugh, R.K., Lincoln, M., Hien, D., and Miele, G.M. Substance Abuse Treatment Entry, Retention, and Outcome in Women: A Review of the Literature. Drug Alcohol Depend. 86(1), pp. 1-21, 2007. Epub June 8, 2006.

Direct Care Workers in the National Drug Abuse Treatment Clinical Trials Network: Characteristics, Opinions, and Beliefs

Individuals with direct care responsibilities in 348 drug abuse treatment units were surveyed to obtain a description of the workforce and to assess support for evidence-based therapies. Surveys were distributed to 112 programs participating in the National Drug Abuse Treatment Clinical Trials Network (CTN). Descriptive analyses characterized the workforce. Women made up two-thirds of the CTN workforce. One-third of the workforce had a master's or doctoral degree. Responses from 1,757 counselors, 908 support staff, 522 managers-supervisors, and 511 medical staff (71% of eligible participants) suggested that the variables that most were most consistently associated with responses were job category and education. Managers-supervisors were the most supportive of evidence-based therapies, and support staff were the least supportive. Generally, individuals with graduate degrees had more positive opinions about evidence-based therapies. Support for using medications and contingency management was modest across job categories. The relatively traditional beliefs of support staff could inhibit the introduction of evidence-based practices. Programs initiating changes in therapeutic approaches may benefit from including all employees in change efforts. McCarty, D., Fuller, B.E., Arfken, C., Miller, M., Nunes, E.V., Edmundson, E., Copersino, M., Floyd, A., Forman, R., Laws, R., Magruder, K.M., Oyama, M., Prather, K., Sindelar, J., and Wendt, W.W. Direct Care Workers in the National Drug Abuse Treatment Clinical Trials Network: Characteristics, Opinions, and Beliefs. Psychiatr Serv. 58(2), pp. 181-190, 2007.

Training and Fidelity Monitoring of Behavioral Interventions in Multi-site Addictions Research

Methods for the training and fidelity monitoring of behavioral interventions in multi-site addictions research were reviewed, including five published studies and seven ongoing studies sponsored by the National Institute on Drug Abuse-funded Clinical Trials Network. Topics include: therapist selection, training, certification, and supervision; selection, training, and certification of supervisors; scales and processes used for monitoring of the quality of treatment; and processes followed to provide new training for replacement staff once trials have begun. The review reveals both a wide array of procedures and emerging standards for multi-site trials. Methodological weakness was observed with respect to limited empirical support for many adherence scales, little or no evaluation of supervisory processes, and no evaluation of re-training practices. Methods used in multi-site trials are important not only to ensure validity of those trials, but also to inform the wider dissemination of empirically based treatment into community agencies. Training and fidelity models that delegate responsibility to participating sites appear most relevant for establishing best practices for dissemination of behavioral interventions. The effectiveness of these distributed training and supervision models should be subjected to empirical study at a level of rigor comparable to the evaluation of their corresponding treatments. Baer, J.S., Ball, S.A., Campbell, B.K., Miele, G.M., Schoener, E.P., and Tracy, K. Training and Fidelity Monitoring of Behavioral Interventions in Multi-site Addictions Research. Drug Alcohol Depend. 87(2-3), pp. 107-118, 2007. Epub October 4, 2006.

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Cost-effectiveness of Prize-based Incentives for Stimulant Abusers in Outpatient Psychosocial Treatment Programs

This cost-effectiveness analysis is based on a randomized clinical trial implemented within the National Drug Abuse Treatment Clinical Trials Network. The trial was conducted at eight community-based outpatient psychosocial drug abuse treatment clinics. Four hundred and fifteen stimulant abusers were assigned to usual care (N=206) or usual care plus abstinence-based incentives (N=209) for 12 weeks. Participants randomized to the incentive condition earned the chance to draw for prizes for submitting substance negative samples; the number of draws earned increased with continuous abstinence time. Incremental cost-effectiveness ratios were estimated to compare prize-based incentives relative to usual care. The primary patient outcome was longest duration of confirmed stimulant abstinence (LDA). Unit costs were obtained via surveys administered at the eight participating clinics. Resource utilizations and patient outcomes were obtained from the clinical trial. Acceptability curves are presented to illustrate the uncertainty due to the sample and to provide policy relevant information. The incremental cost to lengthen the LDA by 1 week was US$ 258 (95% confidence interval, US$ 191-401). Sensitivity analyses on several key parameters show that this value ranges from US$ 163 to 269. Compared with the usual care group, the incentive group had significantly longer LDAs and significantly higher costs. Olmstead, T.A., Sindelar, J.L., and Petry, N.M. Cost-effectiveness of Prize-based Incentives for Stimulant Abusers in Outpatient Psychosocial Treatment Programs. Drug Alcohol Depend. 87(2-3), pp. 175-182, 2007. Epub September 12, 2006.

'Tweaking 12-Step': The Potential Role of 12-Step Self-Help Involvement in Methamphetamine Recovery

The authors reviewed the literature on outcomes associated with 12-Step meeting attendance and involvement in 12-Step activities among substance abusers, particularly those who abuse stimulants. There are few if any data available on methamphetamine abusers and their use of 12-Step approaches. Evidence derived from work with alcohol-and cocaine-dependent individuals indicates that involvement in 12-Step self-help groups, both attending meetings and engaging in 12-Step activities, is associated with reduced substance use and improved outcomes. Although involvement in 12-Step fellowship improves outcome, many individuals do not engage on their own in 12-Step activities, and there are high rates of dropout from such groups. There are a number of evidence-based therapies available to assist clinicians in facilitating 12-Step involvement; however, these have not been used with methamphetamine abusers. More actively integrating 12-Step approaches into the treatment process may provide low-or no-cost options for methamphetamine abusers and increase the capacity for providing treatment. Further research and evaluation are necessary to determine the extent to which methamphetamine abusers do engage in 12-Step self-help programs, whether they prefer more general (e.g. Alcoholics Anonymous, Narcotics Anonymous, Cocaine Anonymous) or drug-specific (e.g. Crystal Meth Anonymous) meetings, the rate of dropout and the outcomes associated with their involvement. Donovan, D.M., and Wells, E.A. 'Tweaking 12-Step': The Potential Role of 12-Step Self-Help Involvement in Methamphetamine Recovery. Addiction, 102 (Suppl.1), pp. 121-129, 2007.

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Director's Report to the National Advisory Council on Drug Abuse - May, 2007

Research Findings - International Research

U.S. - Netherlands Researchers Demonstrate that Manualized Behavior Therapy for Children May Prevent Adolescent Substance Use

A binational research team has published their findings that a cognitive-behavioral intervention, the Coping Power Program (CPP), may prevent children diagnosed with Disruptive Behavior Disorder (DBD) in middle childhood from progressing to substance abuse in early adolescence. In studies supported by a NIDA International Program - Netherlands administrative supplement to Dr. John E. Lochman, University of Alabama, and Dr. Walter Matthys, Rudolf Magnus Institute of Neuroscience, Utrecht, the CPP was adapted for use with Dutch children diagnosed with DBD and seen in outpatient psychiatry clinics and mental health centers. The Utrecht Coping Power Program (UCPP) randomly assigned children to either the UCPP or the care as usual (CU) conditions, and compared them to a matched healthy control sample. The researchers report that in a five-year follow-up, children in the UCPP group not only smoked fewer cigarettes and were less likely to have ever used marijuana than children in the CU group, the UCPP group's substance use rates also fit within the range of those reported for the control group. The authors conclude that manualized behavior therapy with DBD-diagnosed children may be a preventive tool for substance use later in adolescence. Journal of the American Academy of Child and Adolescent Psychiatry, 46(1), pp. 33-39, 2007.

DISCA-Supported Research Finds Depression Predicts Failure to Quit Smoking

2004 NIDA Distinguished International Scientist Ivan Berlin, Groupe Hospitalier Universitaire Pitie-Salpetriere, France, and his DISCA partner Dr. Lirio S. Covey, New York State Psychiatric Institute, report that a Beck Depression Inventory score > or = 10, even in smokers who do not meet a current diagnosis of major depression, directly predicts inability to quit smoking. The pair assessed 600 smokers without currently diagnosed depression who participated in a smoking cessation study at 8 centers. The researchers examined whether mood, personality, and coping predict smoking cessation and whether the associations of personality and coping are mediated through depressed mood. The researchers concluded that neither personality traits nor coping skills predicted directly smoking cessation. However, they found that low levels of problem focusing and social support seeking predicted a negative outcome via depressed mood, suggesting that clinicians assess depression symptoms in routine smoking cessation care. Addiction,101(12), pp. 1814-1821, 2006.

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Research Publications by International Program Alumni

Alumni of the NIDA International Program research training and exchange programs authored or coauthored the following articles indexed by PubMed:

Former NIDA INVEST Drug Abuse Research Fellows

Habituation Deficits Induced by mGlu2/3 Receptor Blockade in Mice: Reversal by Antipsychotic Drugs
INVEST Fellow: Anton Bespalov, Russia, 1994-1995
Cortical metabotropic glutamate receptors (mGluRs) appear to be involved in habituation of simple stimulus-bound behaviors (e.g., habituation to acoustic startle or odor-elicited orienting response). Habituation deficits may contribute to the cognitive symptoms of schizophrenia. In the present study, male NMRI mice were injected with mGluR2/3 antagonist, LY-341495, thirty min prior to being placed into novel arenas for automatic motor activity recording (two-hour sessions). Administration of LY-341495 (1-10 mg/kg, s.c.) dose-dependently prevented the habituation of the locomotor activity. Effects of LY-341495 (10 mg/kg) were fully and dose-dependently reversed by i.p. administration of haloperidol (0.03-0.3 mg/kg), clozapine (1-10 mg/kg), risperidone (0.01-0.1 mg/kg), olanzapine (0.3-3 mg/kg), aripiprazole (1-10 mg/kg), and sulpiride (3-30 mg/kg), each of which was given 15 min prior to the test. Effects of antipsychotic drugs were observed at the dose levels that did not affect spontaneous motor activity. LY-341495-induced delayed hyperactivity was also partially attenuated by lithium (50-200 mg/kg), amisulpride (1-10 mg/kg), and the selective dopamine D3 antagonist, SB-277011A (3-30 mg/kg). Application of diazepam, imipramine, or several agonists and/or antagonists acting at various receptors that are thought to be relevant for antipsychotic treatment (e.g., 5-HT2A, 5-HT3 and 5-HT6 antagonists, 5-HT1A agonist, D4 antagonist, CB1 antagonist, AMPAkines, glycine transporter inhibitor) had no appreciable effects. Thus, behavioral deficits induced by mGluR2/3 blockade (such as delayed motor hyperactivity) are selectively reversed by clinically used antipsychotic drugs. Bespalov, A.Y., Jongen-Relom A.L., van Gaalen, M., Harich, S., Schoemaker, H., and Gross, G. J Pharmacol Exp Ther. November 29, 2006. [Epub ahead of print].

Naltrexone With or Without Fluoxetine for Preventing Relapse to Heroin Addiction in St. Petersburg, Russia
INVEST Fellow: Anton Bespalov, Russia, 1994-1995
This randomized placebo-controlled trial tested the efficacy of oral naltrexone with or without fluoxetine for preventing relapse to heroin addiction and for reducing HIV risk, psychiatric symptoms, and outcome. All patients received drug counseling with parental or significant-other involvement to encourage adherence. Patients totaling 414 were approached, 343 gave informed consent, and 280 were randomized (mean age, 23.6 +/- 0.4 years). At 6 months, two to three times as many naltrexone patients as naltrexone placebo patients remained in treatment and had not relapsed, odds ratio (OR) = 3.5 (1.96-6.12), p < .0001. Overall, adding fluoxetine did not improve outcomes, OR = 1.35 (0.68-2.66), p = .49; however, women receiving naltrexone and fluoxetine showed a trend toward a statistically significant advantage when compared to women receiving naltrexone and fluoxetine placebo, OR = 2.4 (0.88-6.59), p = .08. HIV risk, psychiatric symptoms, and overall adjustment were markedly improved among all patients who remained on treatment and did not relapse, regardless of group assignment. More widespread use of naltrexone could be an important addition to addiction treatment and HIV prevention in Russia. Krupitsky, E.M., Zvartau, E.E., Masalov, D.V., Tsoy, M.V., Burakov, A.M., Egorova, V.Y., Didenko, T.Y., Romanova, T.N., Ivanova, E.B., Bespalov, A.Y., Verbitskaya, E.V., Neznanov, N.G., Grinenko, A.Y., O'Brien, C.P. and Woody, G.E. J Subst Abuse Treat. 31(4), pp. 319-328, 2006. Epub July 24, 2006.

Peri-response Pharmacokinetics of Remifentanil During a Self-administration Session Indicates that Neither Blood nor Brain Levels are Titrated

INVEST Fellow: Gerald Zernig, Austria, 1993-1994

An individual's drug abuse pattern is determined by a multitude of factors. Among these, simple pharmacological determinants of within-binge drug consumption are sorely under investigated. The authors therefore determined if within-session operant responsing to the ultra-short-acting mu opioid agonist remifentanil (RMF) was determined by blood or brain RMF levels or changes thereof. A peri-response analysis did not detect any "threshold" RMF level, either in blood or in the nucleus accumbens (NAc) core as a deep brain region that might determine a rat's "decision" to re-emit a response during a multiple-injection drug self-administration session. The peri-response analysis also failed to find any peak RMF level, either in blood or in the NAc core, which could serve as a "ceiling" level. Thus, these findings strongly suggest that titration of blood or brain RMF levels does not determine a rat's intra-session operant response. Crespo, J.A., Panlilio, L.V., Schindler, C.W., Sturm, K., Saria, A., Zernig, G. Ann N Y Acad Sci. 1074, pp. 497-504, 2006.

4-Amino-5-aryl-6-arylethynylpyrimidines: Structure-activity Relationships of Non-Nucleoside Adenosine Kinase Inhibitors

INVEST Fellow: Steve McGaraughty, Canada, 1995-1996

A series of non-nucleoside adenosine kinase (AK) inhibitors is reported. These inhibitors originated from the modification of 5-(3-bromophenyl)-7-(6-morpholin-4-ylpyridin-3-yl)pyrido[2,3-d]pyrimidin-4-ylamine (ABT-702). The identification of a linker that would approximate the spatial arrangement found between the pyrimidine ring and the aryl group at C(7) in ABT-702 was a key element in this modification. A search of potential linkers led to the discovery of an acetylene moiety as a suitable scaffold. It was hypothesized that the aryl acetylenes, ABT-702, and adenosine bound to the active site of AK (closed form) in a similar manner with respect to the orientation of the heterocyclic base. Although potent acetylene analogs were discovered based on this assumption, an X-ray crystal structure of 5-(4-dimethylaminophenyl)-6-(6-morpholin-4-ylpyridin-3-ylethynyl)pyrimidin-4-ylamine (16a) revealed a binding orientation contrary to adenosine. In addition, this compound bound tightly to a unique open conformation of AK. The structure-activity relationships and unique ligand orientation and protein conformation are discussed. Matulenko, M.A., Paight, E.S., Frey, R.R., Gomtsyan, A., Didomenico, S. Jr., Jiang, M., Lee, C.H., Stewart, A.O., Yu, H., Kohlhaas, K.L., Alexander, K.M., McGaraughty, S., Mikusa, J., Marsh, K.C., Muchmore, S.W., Jakob, C.L., Kowaluk, E.A., Jarvis, M.F. and Bhagwat, S.S. Bioorg Med Chem. December 20, 2006 [Epub ahead of print].

Culturally Specific Adaptation of a Prevention Intervention: An International Collaborative Research Project

INVEST Fellow: Tatiana Tsarouk, Russia, 2001-2002

This study adapted a U.S. drug use prevention program for use with Russian at-risk adolescents, and explored directions for further development of programs addressing prevention of substance abuse and other health risk behaviors including risk of HIV infection. The adaptation process was conducted in phases, initially carried out in Seattle with 23 bilingual (English-Russian) youth and then further adapted in two Moscow schools with 44 "typical" youth. In the final phase, program adaptation for the Russian at-risk adolescents was achieved by conducting a pilot test of the adapted program lessons with Moscow at-risk adolescents (n=10), who met criteria of poor school performance and/or truancy. Observations and experience were used throughout to adapt and refine the program for at-risk youth. Modifications were made to represent more accurately colloquial Russian and to capture teen experiences common to Russian culture. Both U.S. and Russian youth characterized the lessons as engaging and valuable. They also expressed a need to learn about sexuality, drug use, and health; peer and romantic

relationships; and problem-solving strategies. Tsarouk, T., Thompson, E.A., Herting, J.R., Walsh, E. and Randell, B. Addict Behav. December 29, 2006 [Epub ahead of print].

Different Effects of Opioid Antagonists on _, D, and _ Opioid Receptors With and Without Agonist Pretreatment

INVEST Fellow: Danxin Wang, China, 1996-1997

Opioid receptors display basal signaling (constitutive, agonist-independent activity), which appears to be regulated by agonist exposure. Whereas agonist pretreatment desensitizes receptors to subsequent agonist stimulation, basal signaling of micro opioid receptor (MOR) was shown to increase. Moreover, agonist pretreatment converts the neutral antagonists naloxone and naltrexone into inverse agonists, suppressing basal signaling, while analogues with reduced C-6 position, e.g., 6beta-naltrexol, remain neutral antagonists at MOR under any condition. This study compares the regulation of basal signaling of MOR, delta (DOR), and kappa (KOR) opioid receptors after pretreatment with morphine or receptor-selective agonists, in transfected HEK293 cell membranes. Moreover, naloxone, naltrexone and related antagonists were compared for binding potency and effect on basal and agonist-stimulated receptor signaling, measuring (35)S-GTPgammaS binding. The results demonstrate basal activity for each opioid receptor, which is modulated by pretreatment with agonists. Even closely related opioid antagonists display distinct patterns of neutral and inverse effects before and after agonist pretreatment, including distinct efficacies between naloxone and naltrexone at agonist-pretreated DOR and KOR. Pretreatment with different agonists has varying effects on inverse and neutral activities of some analogues tested. These results demonstrate that antagonist efficacy is context-dependent, possibly accounting for paradoxical pharmacological effects. Activity profiles at the three opioid receptors under different conditions could lead to antagonists with optimal clinical properties in treatment of addiction and adverse opioid effects. Wang, D., Sun, X. and Sadee, W. J Pharmacol Exp Ther. January 31, 2007 [Epub ahead of print].

CCK(B) Receptor Antagonist L365,260 Potentiates the Efficacy to and Reverses Chronic Tolerance to Electroacupuncture-induced Analgesia in Mice

INVEST FELLOW: You Wan, China, 1998-1999

Cholecystokinin octapeptide (CCK-8) is a physiological antagonist of endogenous opioids in the central nervous system (CNS). The authors' previous work has shown that CCK-8 plays an important role in the development of tolerance to morphine analgesia and electroacupuncture (EA) analgesia in the rat. The present studies were designed to examine whether the CCK(B) receptor is involved in the modulation of EA analgesia and the development of EA tolerance in mice. The latency to flick the tail in the radiant heat was used as index to assess the efficacy of EA analgesia. Subcutaneous (s.c.) injection of the CCK(B) receptor antagonist L365,260 produced a dose-dependent (0.125-2.0mg/kg) potentiation of the analgesia induced by 100Hz EA, with a maximal effect occurred at 0.5mg/kg. In addition, L365,260 (0.5mg/kg) significantly reversed chronic tolerance to 100Hz EA in mice. These results suggest that the CCK(B) receptor might play a role in the tonic inhibition of 100Hz EA-induced analgesia and in the mediation of chronic tolerance to 100Hz EA in mice. The results opened a way for further investigation of the function of CCK-8 in pain modulation using inbred strains of mice. Huang, C., Hu, Z.P., Jiang, S.Z., Li, H.T., Han, J.S. andWan, Y. Brain Res Bull. 71(5), pp. 447-451, 2007. Epub December 11, 2006.

Effect of Memantine on Cue-induced Alcohol Craving in Recovering Alcohol-dependent Patients

INVEST Fellow: Anton Bespalov, Russia, 1994-1995

Increased NMDA receptor function may contribute to motivational disturbances that contribute to alcoholism. The authors assessed whether the NMDA

receptor antagonist memantine reduces cue-induced alcohol craving and produces ethanol-like subjective effects. Thirty-eight alcohol-dependent inpatients participated in three daylong testing sessions in a randomized order under double-blind conditions. On each test day, subjects received 20 mg of memantine, 40 mg of memantine, or placebo, and subjective responses to treatment were assessed. The level of alcohol craving was assessed before and after exposure to an alcohol cue. Results indicatec that memantine did not stimulate alcohol craving before exposure to an alcohol cue, and it attenuated alcohol cue-induced craving in a dose-related fashion. It produced dose-related ethanol-like effects without adverse cognitive or behavioral effects. These data support further exploration of whether well-tolerated NMDA receptor antagonists might have a role in the treatment of alcoholism. Krupitsky, E.M., Neznanova. O., Masalov, D., Burakov, A.M., Didenko, T., Romanova, T., Tsoy, M., Bespalov, A., Slavina, T.Y., Grinenko, A.A., Petrakis, I.L., Pittman, B., Gueorguieva, R., Zvartau, E.E. and Krystal, J.H. Am J Psychiatry. 164(3), pp. 519-523, 2007.

Stimulation of the Metabotropic Glutamate 2/3 Receptor Attenuates Social Novelty Discrimination Deficits Induced by Neonatal Phencyclidine Treatment

INVEST Fellow: Anton Bespalov, Russia, 1994-1995

RATIONALE: Glutamatergic mechanisms are implicated in psychiatric disorders such as schizophrenia. Modulation of glutamatergic neurotransmission via stimulation of the metabotropic glutamate 2/3 receptors (mGluR2/3) has been shown to reverse a number of behavioral effects of NMDA receptor antagonists thus indicating potential antipsychotic activity of mGluR2/3 agonists. The present study aimed to evaluate the effects of LY-354740 (mGluR2/3 agonist) and LY-487379 (mGluR2 potentiator) on social novelty discrimination in male Wistar rats that were treated with PCP (10 mg/kg, s.c.) on postnatal days 7, 9, and 11. During each test session (twice a week, postnatal days 70-100), an adult experimental rat was presented with a juvenile, untreated rat (4 weeks old) for a period of 30 min. At the end of this period, a second (novel) juvenile rat was introduced for 5 min. Adult rats spent more time exploring the novel than the familiar juvenile. This capacity for social novelty discrimination was impaired in rats that received neonatal PCP treatment and the impaired discrimination could be reversed by acute treatment with antipsychotic drugs such as clozapine (0.3-3 mg/kg) and the glycine transporter GlyT1 inhibitor SSR-504734 (1-10 mg/kg). Acute pretreatment with LY-354740 (1-10 mg/kg) or LY-487379 (3-30 mg/kg) facilitated social discrimination in rats with PCP administration history without having appreciable effects in controls and without affecting total time spent in social interaction. These results suggest that targeting glutamatergic functions may reverse long-term developmental cognitive deficits produced by PCP. Harich, S., Gross, G. and Bespalov, A. Psychopharmacology (Berl). February 23, 2007 [Epub ahead of print].

Validity of Self-reported Drinking Before Injury Compared with a Physiological Measure: Cross-national Analysis of Emergency-department Data from 16 Countries

INVEST Fellow: Guilherme Borges, Mexico, 1997-1998

Self-reports of alcohol consumption among patients visiting an emergency department (ED) have been used extensively in the investigation of the relationship between drinking and injury. Little is known, however, about the associations between validity of self-reports with patient and injury characteristics and whether these relationships vary across regions or countries. Both of these issues are explored in this article. In the construct of a multilevel logistical model, validity of self-reports was estimated as the probability of a positive self-report given a positive blood alcohol concentration (BAC). The setting included 44 EDs across 28 studies in 16 countries. Participants included 10,741 injury patients from the combined Emergency Room Collaborative Alcohol Analysis Project (ERCAAP) and the World Health Organization Collaborative Study of Alcohol and Injuries. Data were analyzed

on self-reported drinking within 6 hours before injury compared with BAC results obtained from breath-analyzer readings in all but two studies, which used urine screens. Covariates included demographic, drinking, and injury characteristics and aggregate-level contextual variables. At the individual level, a higher BAC measurement was associated with a higher probability of reporting drinking, as was heavy drinking and sustaining injuries in traffic accidents or violence-related events. At the study level, neither aggregate BAC nor other sociocultural variables affected the validity of self-reported drinking. This study provides further evidence of the validity of self-reported drinking measures in crossnational ED studies based on the objective criterion of BAC estimates. Cherpitel, C.J., Ye, Y., Bond, J., Borges, G., Macdonald, S., Stockwell, T., Room, R., Sovinova, H., Marais, S. and Giesbrecht, N. J Stud Alcohol Drugs. 68(2), pp. 296-302, 2007.

Cannabinoid Receptor Antagonists Counteract Sensorimotor Gating Deficits in the Phencyclidine Model of Psychosis

Clinical and laboratory findings suggest that cannabinoids and their receptors are implicated in schizophrenia. The role of cannabinoids in schizophrenia remains however poorly understood, as data are often contradictory. The primary aim of this study was to investigate whether the cannabinoid CB1 receptor antagonists rimonabant and AM251 are able to reverse deficits of sensorimotor gating induced by phencyclidine and to mimic the 'atypical' antipsychotic profile of clozapine. The prepulse inhibition (PPI) of the startle reflex was used to measure deficits of sensorimotor gating. PPI-disruptive effects of phencyclidine and their antagonism by rimonabant, AM251, and clozapine were studied in rats. The effects of rimonabant were carefully examined taking into account dose ranges, vehicle, and route of administration. The authors also examined the ability of rimonabant to reduce the PPI-disruptive effects of dizocilpine and apomorphine. Rimonabant as well as AM251 significantly counteracted the phencyclidine-disruptive model of PPI, comparable to the restoring effect of clozapine; no augmentation effect was observed with rimonabant and clozapine as cotreatment. Rimonabant also significantly attenuated the PPI disruptive effects of dizocilpine and apomorphine. Taken together, our results indicate that CB1 receptor antagonists do produce 'atypical' antipsychotic profile mimicking that of clozapine in the phencyclidine disruption of sensorimotor gating. These findings further suggest that CB1 receptor antagonism may be involved in restoring disturbed interactions between the activity of the endocannabinoid system and glutamate neurotransmitter system implied in schizophrenia. Ballmaier, M., Bortolato, M., Rizzetti, C., Zoli, M., Gessa, G., Heinz, A. and Spano, P. Neuropsychopharmacology. February 14, 2007 [Epub ahead of print].

Analysis of Yearly Variations in Drug Expenditure for One Patient Using Data Warehouse in a Hospital

INVEST Fellow: Yufeng Chen, China, 2003-2004

Medical expense has grown rapidly in Japan. It could be caused by the increase of the patient number and the increase of medical expense per patient. The authors studied the latter factor on drug expenditure from 1996 to 2002 using the prescription data stored in the data warehouse of one hospital. They found that the drug expenditure per patient had increased 1.32 times. The mean number of prescriptions per patient increased 1.23 times and the mean expenditure of one medicine increased 1.08 times. These results demonstrated that drug expenditure for one patient had gradually increased. This was caused by both the rise in the number of medicines taken by one patient and the rise in the prices of medicines. The data warehouse in the hospital was useful for the analysis of the trends in medical expenditure for one patient. Chen, Y., Matsumura, Y., Nakagawa, K., Ji, S., Nakano, H., Teratani, T., Zhang, Q., Mineno, T. and Takeda, H. J Med Syst. 31(1), pp. 17-24, 2007.

Roles of 5-HT Receptor Subtypes in the Inhibitory Effects of 5-HT on C-Fiber Responses of Spinal Wide Dynamic Range Neurons in Rats

INVEST Fellow: You Wan, China, 1998-1999
5-Hydroxytryptamine (5-HT, or serotonin) plays an important role in the descending control of nociception. 5-HT and its receptors have been extensively studied in the modulation of nociceptive transmission at the spinal level using behavioral tests that may be affected by the effects of 5-HT on motor performance and skin temperature. Using electrophysiological methods, the present study aimed to systematically investigate the roles of 5-HT receptor subtypes on the inhibitory effects of 5-HT on responses of the spinal wide dynamic range (WDR) neurons to C-fiber inputs in rats. Under basal conditions, topical application of 5-HT to the spinal cord inhibited the C-fiber responses of WDR neurons dose-dependently, whereas antagonists of 5-HT1A (WAY 100635), 5-HT1B (GR 55562), 5-HT2A (ketanserin), 5-HT2C (RS 102221), 5-HT3 (MDL 72222) and 5-HT4 (GR 113808) had no effect on their own. The inhibitory effects of 5-HT were reversed by antagonists of 5-HT1B (GR 55562), 5-HT2A (ketanserin), 5-HT2C (RS 102221), 5-HT3 (MDL 72222) and 5-HT4 (GR 113808), but not by 5-HT1A (WAY 100635), receptor antagonists. Topical administration of agonists of 5-HT1A (8-OH-DPAT), 5-HT1B (CGS 12066), 5-HT2A (alpha-m-5-HT), 5-HT2C (MK 212), 5-HT3 (mCPBG) and 5-HT4 (BZTZ) also inhibited the C-responses. These results suggest that under basal conditions there is no tonic serotonergic inhibition on the C-responses of dorsal horn neurons and multiple 5-HT receptor subtypes including 1B, 2A, 2C, 3 and 4 may be involved in mediating the inhibitory effects of 5-HT. Liu, F.Y., Xing, G.G., Qu, X.X., Xu, I.S., Han, J.S. and Wan, Y. J Pharmacol Exp Ther. February 28, 2007 [Epub ahead of print].

Cocaine-Induced Brain Activation Detected by Dynamic Manganese-enhanced Magnetic Resonance Imaging (MEMRI)
INVEST Fellow: Zhengxiong Xi, China, 1995-1996
Dynamic manganese-enhanced magnetic resonance imaging (MEMRI) detects neuronal activity based on the passage of Mn(2+) into active neurons. Because this mechanism is independent of any hemodynamic response, it is potentially ideal for pharmacological studies and was applied to investigate the acute CNS effects of cocaine in the rat. Dose-dependent, region-specific MEMRI signals were seen mostly in cortical and subcortical mesocorticolimbic structures. To verify the spatial accuracy and physiological mechanisms of MEMRI, neuronal activation following electrical forepaw stimulation revealed somatotopic signal enhancement in the primary and secondary somatosensory cortices, which was blocked by diltiazem, a Ca2+ channel antagonist. These data suggest that MEMRI may serve as a tool for investigating the effects of pharmacological agents and opens an application of MRI to study CNS drug effects at a systems level. Lu, H., Xi, Z.X., Gitajn, L., Rea, W., Yang, Y. and Stein, E.A. Proc Natl Acad Sci U S A. 104(7), pp. 2489-2494, 2007. Epub February 7, 2007.

Former Hubert H. Humphrey Drug Abuse Research Fellows

Predictors of HIV Sero-status Among Drug Injectors at Three Ukraine Sites
HHH Fellow: Sergey Dvoryak, Ukraine, 1999-2000
The objective of this study was to assess the HIV serostatus of injection drug users (IDU) in Ukraine, as well as associations between serostatus and selected demographic and risk factors. IDU were recruited from the streets in Kiev, Odessa and Makeevka/Donesk. Participants were interviewed using an HIV risk behavior assessment and tested for HIV with a finger-stick rapid test. Multiple logistic regression was used to identify determinants of HIV infection. Of the 891 IDUs surveyed, one-third came from each site and 22% were female. Their mean age was 29 years and on average they had been injecting for slightly more than 10 years. Seven hundred and seventy-eight of the total sample did not know their HIV status when first interviewed; they are the participants in this investigation. Overall, 33% tested positive for HIV, including 34% in Kiev, 51% in Odessa and 17% in Makeevka/Donesk. Independent predictors of HIV

included injecting a sedative/opiate mixture, female sex, having sex with a person who was HIV positive or whose HIV status was unknown and injecting daily. HIV-negative IDU were significantly younger than those infected, they were more likely to be from Makeevka/Donesk and they were more likely to have been sexually active. Rates of HIV infection among IDU vary considerably across Ukraine, although even in the site with the lowest rate nearly one in five was infected. The extent of drug and sex-related risk behaviors calls for interventions to reduce the spread of HIV and other infectious diseases. Booth, R.E., Kwiatkowski, C.F., Brewster, J.T., Sinitsyna, L. and Dvoryak, S. AIDS. 20(17), pp. 2217-2223, 2006.

Obstetric and Neonatal Outcomes in Women Who Live in an Urban Resettlement Area of Delhi, India: A Cohort Study

HHH Fellow: Arun Kumar Sharma, India, 2004-2005

The aim of the present research was to study the pregnancy outcome, namely mode and place of delivery, attendant at birth and perinatal mortality in an urban resettlement area of Delhi, India, and to determine factors that affect the outcome. Methods: All the pregnant women (n = 909) in the area were enrolled and followed until 7 days after delivery. The authors calculated the crude and adjusted odds ratios for predictors of pregnancy related obstetric and neonatal outcomes, using logistic regression analysis. A total of 884 (97.3%) women could be followed up. Approximately two-thirds of deliveries took place at home. Primigravida, more educated mothers and mothers with non-cephalic presentation or complications were more likely to deliver in a health facility ($P < 0.05$). Most deliveries (97%) were vaginal, 2.5% were cesarean and 0.5% forceps deliveries. Primigravida mothers, mothers with short stature, mothers with non-cephalic presentation or complications had cesarean and forceps delivery more often ($P < 0.05$). A perinatal mortality rate of 74.5 per 1000 live births was observed. Presentation of the fetus and complications in the mother remained important factors. The authors conclude that the majority of deliveries in the under-privileged sections in urban Delhi take place at home and the perinatal mortality remains high. Chhabra, P., Sharma, A.K. and Tupil, K.A. J Obstet Gynaecol Res. 32(6), pp. 567-573, 2006.

Alcohol Abuse-Duration Dependent Decrease in Plasma Testosterone and Antioxidants in Males

HHH Fellow: Amit Chakrabarti, India, 2002-2003

Ethanol is a testicular toxin and it causes fertility abnormalities with low sperm count and impaired sperm motility in men. The present study was designed to investigate plasma testosterone level and hypothalamic pituitary gonadal (HPG) axis function in alcoholic men and also effect of ethanol on systemic oxidative stress. Forty six male alcohol abusers in the age group 20-40 years were selected. Fifty five males in the same age group served as control. Alcohol abusers had significantly low plasma testosterone with low luteinizing hormone and follicle stimulating hormone. In addition they had significantly high thiobarbituric acid reactive substances (TBARS), superoxide dismutase and glutathione S-transferase, and low glutathione, ascorbic acid, catalase, glutathione reductase and glutathione peroxidase. Moreover, serum testosterone level in alcoholics negatively correlated with duration of alcohol abuse, and TBARS. Duration dependent decreased serum testosterone level in alcohol abusers might be due to 1) increased oxidative stress which can damage Leydig and supporting Sertoli cells and 2) impaired HPG axis. Maneesh, M., Dutta, S., Chakrabarti, A. and Vasudevan, D.M. Indian J Physiol Pharmacol. 50(3), pp. 291-296, 2006.

Exposure to HIV in Brazilian Adolescents: The Impact of Psychiatric Symptomatology

HHH Fellow: Flavio Pechansky, Brazil, 1993-1994

The objective of this study was to examine associations between psychiatric symptomatology and HIV-positive status in adolescents who sought HIV testing at a public health center in Brazil. In a cross-sectional study, 388 adolescents

assessed for their HIV status were also evaluated for psychiatric symptomatology using the Symptom Checklist-90-R (SCL-90-R). The impact of potential confounding variables such as risk behaviors was ascertained using the Brazilian version of the Risk Assessment Battery (RAB). Overall seropositivity rate was 6.2%. Seropositives had significantly higher scores in all dimensions of psychiatric symptomatology in the SCL-90-R ($P < 0.05$ and effect sizes > 0.5 in all dimensions). In multiple analyses, with the inclusion of 3 composite variables (sex-risk, drug-risk, and psychiatric symptomatology), only psychiatric symptoms were associated with positive HIV status (OR = 1.88, CI95% = 1.06-3.34; P = 0.032). The authors findings suggest that amongst young people asking for HIV testing in Brazil, seropositivity is associated with psychological symptoms and that screening for the latter would therefore be appropriate in this context. Bassols, A.M., Santos, R.A., Rohde, L.A. and Pechansky, F. Eur Child Adolesc Psychiatry. January 2, 2007 [Epub ahead of print].

Changing Patterns of Cocaine Use and HIV Risks in the South of Brazil
HHH Fellow: Flavio Pechansky, Brazil, 1993-1994
For well over a decade, researchers in Porto Alegre, Brazil, have been documenting the extent of the AIDS epidemic in the region, with a specific focus on the linkages between drug use and HIV seropositivity. Virtually all of the studies conducted during those years found injection drug use (IDU) to be the major vector for HIV seropositivity in this population. However, recent research found that the number of IDUs had declined significantly. Qualitative interviews and focus groups suggested many reasons for this decline: (1) many had died, because they had never heard of AIDS or HIV, and were unaware of how HIV is transmitted. As a result, they had become infected through the sharing of injection paraphernalia. (2) The quality of street cocaine had declined, making injection difficult. (3) Because of a fear of AIDS, some shifted to the smoking of crack, which had become a newly availability commodity in the street culture. Within this context, this article describes the qualitative data describing the decline of cocaine injecting and the corresponding emergence of crack use in Porto Alegre, Brazil, and related HIV risks. Inciardi, J.A., Surratt, H.L., Pechansky, F., Kessler, F., von Diemen, L., da Silva, E.M. and Martin, S.S. J Psychoactive Drugs. 38(3), pp. 305-310, 2006.

Influence of Clozapine on Platelet Serotonin, Monoamine Oxidase and Plasma Serotonin Levels
HHH Fellow: Berna Ulug, Turkey, 1995-1996
The purpose of this study was to investigate the influence of clozapine on plasma serotonin, platelet serotonin and monoamine oxidase (MAO) levels in schizophrenic patients and to compare their results with those of unmedicated healthy controls. Groups of 20 outpatients with schizophrenia and 20 healthy controls matched for age, sex and smoking status were recruited for the study. Psychopathology, neurocognitive functioning, plasma serotonin, platelet serotonin and MAO levels were assessed after 1-week drug free interval, and 8 weeks after initiation of clozapine treatment in an open design. The mean clozapine dose at week 8 was 382.5+/-96.4 (range: 250-600) mg/day. In the patient group, at baseline, plasma serotonin and platelet MAO levels were significantly lower, and platelet serotonin levels were significantly higher than in controls. After 8 weeks of clozapine treatment, plasma serotonin and platelet MAO levels increased significantly, while a significant decrease in platelet serotonin levels was detected compared with baseline values. Baseline platelet MAO levels explained 22% of the variance in Clinical Global Impression-Improvement (CGI-I) and improvement in attention, while baseline platelet serotonin predicted 23% of the variance in the improvement in positive symptoms during clozapine treatment. These data indicate that clozapine may be reversing or compensating for a pre-existing alteration in serotonergic neurotransmission in schizophrenic patients. The prediction of response to clozapine through peripheral biochemical markers may have important clinical implications if repeated in larger samples. Ertugrul, A., Ucar, G., Basar, K.,

Demir, B., Yabanoglu, S. and Ulug, B. Psychiatry Res. December 6, 2006 [Epub ahead of print].

Conformation-Dependent Stability of Junctophilin 1 (JP1) and Ryanodine Receptor Type 1 (RyR1) Channel Complex is Mediated by their Hyper-reactive Thiols

HHH FELLOW: Jozsef Lango, Hungary, 1997-1998

Junctophilin 1 (JP1), a 72 kDa protein localized at skeletal muscle triad, is essential for stabilizing the close apposition of T-tubule (TT) and sarcoplasmic reticulum (SR) membranes to form junctions. In the present study the authors report that rapid and selective labeling of hyper-reactive thiols found in both JP1 and ryanodine receptor type 1 (RyR1) with CPM, a fluorescent thiol reactive probe, proceeded 12-fold faster under conditions that minimize RyR1 gating (e.g., 10mM Mg(2+)) compared with conditions that promote high channel activity (e.g., 100microM Ca(2+)/10mM caffeine/5mM ATP). The reactivity of these thiol groups was very sensitive to oxidation by naphthoquinone, H(2)O{sub}2, NO, or O(2), all known modulators of the RyR1 channel complex. Using preparative SDS-PAGE, in-gel tryptic digestion, HPLC, and mass spectrometric based peptide sequencing, the authors identified CPM-thioether adducts on 3 cysteine residues of JP1 (101, 402 and 628); the remaining 5 cysteines of JP1 were unlabeled. Co-immunoprecipitation experiments demonstrated a physical interaction between JP1 and RyR1 that, like thiol reactivity, was sensitive to RyR1 conformation and chemical status of the hyper-reactive cysteines of JP1 and RyR1. These findings support a model in which JP1 interacts with the RyR1 channel complex in a conformationally sensitive manner and may contribute integral redox sensing properties through reactive sulfhydryls chemistry. Phimister, A.J., Lango, J., Lee, E.H., Ernst-Russell, M., Takeshima, H., Ma, J., Allen, P.D. and Pessah, I.N. J Biol Chem. January 19, 2007 [Epub ahead of print].

Director's Report to the National Advisory Council on Drug Abuse - May, 2007

Research Findings - Intramural Research

Development and Plasticity Section, Cellular Neurobiology Research Branch

Transcriptional Changes Common to Human Cocaine, Cannabis and Phencyclidine Abuse A major goal of drug abuse research is to identify and understand drug-induced changes in brain function that are common to many or all drugs of abuse. As these may underlie drug dependence and addiction, the purpose of the present study was to examine if different drugs of abuse effect changes in gene expression that converge in common molecular pathways. Microarray analysis was employed to assay brain gene expression in postmortem anterior prefrontal cortex (aPFC) from 42 human cocaine, cannabis and/or phencyclidine abuse cases and 30 control cases, which were characterized by toxicology and drug abuse history. Common transcriptional changes were demonstrated for a majority of drug abuse cases (N = 34), representing a number of consistently changed functional classes: Calmodulin-related transcripts (CALM1, CALM2, CAMK2B) were decreased, while transcripts related to cholesterol biosynthesis and trafficking (FDFT1, APOL2, SCARB1), and Golgi/endoplasmic reticulum (ER) functions (SEMA3B, GCC1) were all increased. Quantitative PCR validated decreases in calmodulin 2 (CALM2) mRNA and increases in apolipoprotein L, 2 (APOL2) and semaphorin 3B (SEMA3B) mRNA for individual cases. A comparison between control cases with and without cardiovascular disease and elevated body mass index indicated that these changes were not due to general cellular and metabolic stress, but appeared specific to the use of drugs. Therefore, humans who abused cocaine, cannabis and/or phencyclidine share a decrease in transcription of calmodulin-related genes and increased transcription related to lipid/cholesterol and Golgi/ER function. These changes represent common molecular features of drug abuse, which may underlie changes in synaptic function and plasticity that could have important ramifications for decision-making capabilities in drug abusers. Lehrmann, E., Colantuoni, C., Deep-Soboslay, A., Becker, K.G., Lowe, R., Huestis, M.A., Hyde, T.M., Kleinman, J.E., and Freed. W.J. PLoS ONE, 1:e, pp. 114, 2006.

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

PKA Activation Downregulates whereas ERK Activation Upregulates Sigma-1 Receptors in B-104 Cells: Implication for Neuroplasticity The sigma-1 receptor (Sig-1R) can bind psychostimulants and was shown to be upregulated in the brain of methamphetamine self-administering rats. Upregulation of Sig-1Rs has been implicated in neuroplasticity. However, the mechanism(s) whereby Sig-1Rs are upregulated by psychostimulants is unknown. Here, IRP investigators employed a neuroblastoma cell line B-104,

devoid of dopamine receptors and transporter, and examined the effects of psychostimulants as well as cAMP on the expression of Sig-1Rs in this cell line, with a specific goal to identify signal transduction pathway(s) that may regulate Sig-1R expression. Chronic treatments of B-104 cells with physiological concentrations of cocaine or methamphetamine failed to alter the expression of Sig-1Rs. Dibutyryl cAMP (dB-cAMP), when used at 0.5 mM, caused a downregulation of Sig-1Rs that could be blocked by a protein kinase A (PKA) inhibitor H-89. However, dB-cAMP, when used at 2 mM, caused an upregulation of Sig-1Rs that was insensitive to the H-89 blockade but was partially blocked by an extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK) inhibitor PD98059. Further, 2 mM of dB-cAMP induced an ERK phosphorylation lasting at least 90 min, at which time the phosphorylation caused by 0.5 mM of dB-cAMP had already diminished. PD98059, applied 90 min after addition of 2 mM of dB-cAMP, attenuated the Sig-1R upregulation. These results indicate that cAMP is bimodal in regulating Sig-1R expression: a downregulation via PKA and an upregulation via ERK. Results also suggest that psychostimulants may manipulate the cAMP-PKA-Sig-1R and/or the cAMP-ERK-Sig-1R pathways to achieve a neuroplasticity that favors addictive behaviors. Cormaci, G., Mori, T., Hayashi, T., and Su, T.P. The Journal of Pharmacology and Experimental Therapeutics, 320(1), pp. 202-210, 2007.

Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Parkinson's Disease Model Mitochondrial dysfunction is implicated in the pathophysiology of Parkinson's disease (PD), a common age-associated neurodegenerative disease characterized by intraneuronal inclusions (Lewy bodies) and progressive degeneration of the nigrostriatal dopamine (DA) system. It has recently been demonstrated that midbrain DA neurons of PD patients and elderly humans contain high levels of somatic mtDNA mutations, which may impair respiratory chain function. However, clinical studies have not established whether the respiratory chain deficiency is a primary abnormality leading to inclusion formation and DA neuron death, or whether generalized metabolic abnormalities within the degenerating DA neurons cause secondary damage to mitochondria. IRP scientists have used a reverse genetic approach to investigate this question and created conditional knockout mice (termed MitoPark mice), with disruption of the gene for mitochondrial transcription factor A (Tfam) in DA neurons. The knockout mice have reduced mtDNA expression and respiratory chain deficiency in midbrain DA neurons, which, in turn, leads to a parkinsonism phenotype with adult onset of slowly progressive impairment of motor function accompanied by formation of intraneuronal inclusions and dopamine nerve cell death. Confocal and electron microscopy show that the inclusions contain both mitochondrial protein and membrane components. These experiments demonstrate that respiratory chain dysfunction in DA neurons may be of pathophysiological importance in PD. Ekstrand, M., Terzioglu, M., Galter, D., Zhu, S., Hofstetter, C., Lindqvist, E., Thams, S., Bergstrand, A., Hansson, F.S., Trifunovic, A., Hoffer, B., Cullheim, S., Mohammed, A.H., Olson, L., and Larsson, N.G. PNAS, 104, pp. 1325-1330, 2007.

Glutamatergic Neurons are Present in the Rat Ventral Tegmental Area The ventral tegmental area (VTA) is thought to play an important role in reward function. Two populations of neurons, containing either dopamine (DA) or gamma-amino butyric acid (GABA), have been extensively characterized in this area. However, recent electrophysiological studies are consistent with the notion that neurons that utilize neurotransmitters other than DA or GABA are likely to be present in the VTA. Given the pronounced phenotypic diversity of neurons in this region, IRP researchers have proposed that additional cell types, such as those that express the neurotransmitter glutamate may also be present in this area. Thus, by using in situ hybridization histochemistry the

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authors investigated whether transcripts encoded by genes for the two vesicular glutamate transporters, VGluT1 or VGluT2, were expressed in the VTA. They found that VGluT2 mRNA but not VGluT1 mRNA is expressed in the VTA. Neurons expressing VGluT2 mRNA were differentially distributed throughout the rostro-caudal and medio-lateral aspects of the VTA, with the highest concentration detected in rostro-medial areas. Phenotypic characterization with double in situ hybridization of these neurons indicated that they rarely co-expressed mRNAs for tyrosine hydroxylase (TH, marker for DAergic neurons) or glutamic acid decarboxylase (GAD, marker for GABAergic neurons). Based on the results described here, the authors concluded that the VTA contains glutamatergic neurons that in their vast majority are clearly non-DAergic and non-GABAergic. Yamaguchi, T., Sheen, W., and Morales, M. European Journal of Neuroscience, 25(1), pp. 106-118, 2007.

Alterations in Prodynorphin, Proenkephalin, and GAD67 mRNA Levels in the Aged Human Putamen: Correlation with Parkinson's Disease A real-time quantitative PCR approach was used to quantify mRNA levels corresponding to the neuropeptides enkephalin, dynorphin, and the 67-kDa isoform of glutamic acid decarboxylase (GAD67) in the human putamen from young and aged individuals as well as from aged patients affected by Parkinson's disease (PD). cDNA-specific primers were designed to amplify GAD67, proenkephalin (pENK), prodynorphin (pDYN), and the housekeeping genes glyceraldehydes-3-phosphate dehydrogenase (GAPDH) and guanine nucleotide binding protein, beta-peptide 2-like I (GNB2LI). GAPDH and GNB2LI mRNA levels were similarly expressed among the groups and were therefore used as endogenous reference genes. Normalized data showed that mRNA levels for both pENK and pDYN were reduced in the putamen of aged controls and aged individuals affected by PD, compared with young controls. In addition, the authors showed that GAD67 mRNA levels did not change during aging and PD. Further analyses showed no differences in mRNA levels, for pENK, pDYN, or GAD67 mRNA, between PD patients and aged matched controls. These findings contrast with animal models of parkinsonism, for which expression of pDYN, pENK, and GAD67 mRNA has been reported to change after striatal dopamine denervation. Compensatory mechanisms and regional differences within the human putamen as well as the severity index of the disease, clinical diagnosis, and response to pharmacological therapy are possible reasons for these results. The present study suggests that alteration of neuropeptide pathways in the human putamen may be involved in the functional deterioration of parts of the extrapyramidal system during aging. Backman, C.M., Shan, L., Zhang, Y., Hoffer, B.J., and Tomac A.C. Journal of Neuroscience Research, 85(4), pp. 798-804, 2007.

Electrophysiology Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Opposing Actions of Chronic Delta9-Tetrahydrocannabinol and Cannabinoid Antagonists on Hippocampal Long-Term Potentiation Memory deficits produced by marijuana arise partly via interaction of the psychoactive component, Delta(9)-tetrahydrocannabinol (Delta(9)-THC), with cannabinoid receptors in the hippocampus. Although cannabinoids acutely reduce glutamate release and block hippocampal long-term potentiation (LTP), a potential substrate for learning and memory, the consequences of prolonged exposure to Delta(9)-THC for hippocampal function are poorly understood. Rats were injected with Delta(9)-THC (10 mg/kg, i.p., q.d.) for 1, 3, or 7 d, and electrophysiological recordings were performed in hippocampal slices 1d after the final injection. At this time, Delta(9)-THC was undetectable in hippocampus using liquid chromatography-mass spectrometry (LC-MS). Hippocampal LTP generated using high-frequency (HFS) or theta burst stimulation was not observed in brain slices from the 7-d Delta(9)-THC-treated animals. Delta(9)-THC also blocked HFS-LTP after 3 d, but not 1 d of treatment. The complete

blockade of LTP persisted for 3 d after the last Delta(9)-THC injection, and full reversal of the LTP deficit was not observed up to 14 d following Delta(9)-THC withdrawal. The cannabinoid antagonist AM251 (2 mg/kg), administered before each Delta(9)-THC injection prevented the blockade of LTP, and 7-d treatment with AM251 alone significantly increased the level of LTP. Chronic Delta(9)-THC also produced tolerance to the inhibition of synaptic GABA, but not glutamate release by the agonist WIN55,212-2. These data define consequences of repeated Delta(9)-THC exposure for synaptic plasticity in the hippocampus that may help explain memory impairments in humans following chronic marijuana use. Hoffman, A.F., Oz, M., Yang, R., Lichtman, A.H., and Lupica, C.R.. Learning Memory, 14(1), pp. 63-74, 2007.

Proteomics Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Sulfation, the Up-and-Coming Post-Translational Modification: Its Role and Mechanism in Protein-Protein Interaction Tyrosine sulfation is a post-translational modification entailing covalent attachment of sulfate to tyrosine residues. It takes place in the trans-Golgi, is necessary for the bioactivity of some proteins, and improves their ability to interact with other proteins. In the present work, IRP scientists show that a protein containing a sulfated tyrosine with a delocalized negative charge forms a salt bridge with another protein if it has two or more adjacent arginine residues containing positive delocalized charges. These noncovalent complexes are so stable that, when submitted to collision induced dissociation, the peptides forming the complex dissociate. Just one covalent bond fragments, the covalent bond between the tyrosine oxygen and the SO3 sulfur, and is represented by the appearance of a new peak (basic peptide + SO3), suggesting that in some instances covalent bonds will break down before the noncovalent bonds between the arginine guanidinium and SO3 dissociate. The data implies that the dissociation pathway is preferred; however, fragmentation between tyrosine and the sulfate residue is a major pathway. Woods, A.S., Wang, H.Y., and Jackson, S.N. Journal of Proteome Research, 6(3), pp. 1176-1182, 2007.

In Situ Structural Characterization of Glycerophospholipids and Sulfatides in Brain Tissue Using MALDI-MS/MS Lipids are major structural components of biomembranes. Negatively charged species such as phosphatidylinositol, phosphatidylserine, sulfatides, and the zwitterionic phosphatidylethanolamines are major components of the cytoplasmic surface of the cellular membrane lipid bilayer and play a key role in several receptors signaling functions. Lipids are not just involved in metabolic and neurological diseases; negatively charged lipids in particular play crucial roles in physiological events such as signal transduction, receptors, and enzymatic activation, as well as storage and release of therapeutic drugs and toxic chemicals in the body. Due to the importance of their role in signaling, the field of lipidomics has rapidly expanded in recent years. In the present study, direct probing of tissue slices with negative ion mode matrix assisted laser desorption/ionization mass spectrometry was employed to profile the distribution of lipids in the brain. In total, 32 lipid species consisting of phosphatidylethanolamines, phosphatidylglycerol, phosphatidylinositols, phosphatidylserines, and sulfatides were assigned. To confirm the structure of lipid species, MALDI-MS/MS analysis was conducted. Product-ion spectra obtained in negative ion mode allow for the assignment of the head groups and the fatty acid chains for the lipid species. Jackson, S.N., Wang, H.Y., and Woods, A.S. Journal of the American Society for Mass Spectrometry, 18(1), pp. 17-26, 2007.

Abeta Peptides as one of the Crucial Volume Transmission Signals in the Trophic Units and their Interactions with Homocysteine: Physiological Implications and Relevance for Alzheimer's Disease

Amyloid peptides (Abeta) can operate as volume transmission (VT) signals since they are continuously released from cells of the central nervous system and diffuse in the extra-cellular space of the brain. They have both regulatory and trophic functions on cellular networks. In agreement with Abeta regulatory actions on glial-neuronal networks, the present paper reports new findings demonstrating that intrastriatal injections of Abeta peptides reduce striatal tyrosine hydroxylase, increase striatal GFAP immunoreactivities and lower pain threshold in experimental rats. Furthermore, it has been demonstrated that exogenous homocysteine (Hcy) binds Abeta(1-40) favoring its beta-sheet conformation both in vitro and in vivo and hence the formation of beta-fibrils and development of neurotoxicity. Thus, the hypothesis is discussed that Abeta peptides represent crucial VT-signals in the brain and their action is altered by dysmetabolic signals such as high Hcy extra-cellular levels, known to be an important risk factor for Alzheimer's disease. Agnati, L.F., Genedani, S., Leo, G., Forni, A., Woods, A.S., Filaferro, M., Franco, R., and Fuxe, K. Journal of Neural Transmission, 114(1), pp. 21-31, 2007.

Direct MALDI-MS Analysis of Cardiolipin from Rat Organs Sections Cardiolipins (CL) are mitochondria specific lipids. They play a critical role in ATP synthesis mediated by oxidative phosphorylation. Abnormal CL distribution is associated with several disease states. MALDI-MS and MALDI-MS/MS were used to demonstrate in situ analysis and characterization of CL from tissue sections of organs containing high concentrations of mitochondria. Once the experimental parameters were established, a survey of CL distribution in heart, liver, kidney, leg muscle, and testis was undertaken. The major CL specie in the heart muscle, leg muscle, liver, and kidney is the (18:2)(4) CL, while liver and kidney also contain a minor specie, (18:2)(3)/(18:1) CL. The major CL specie in testis is the (16:0)(4) CL. The CL species distribution in various organs appeared to be in agreement with prior reports. Overall, proper matrix selection, tissue section handling, instrument tuning, and the inclusion of cesium ion in matrix ensured successful in situ MALDI-MS and MALDI-MS/MS analysis of CL. Upon modification and standardization, this method could be streamlined for rapid pathological diagnosis with short turnaround time in clinical settings. Wang, H.Y., Jackson, S.N., and Woods, A.S. Journal of the American Society for Mass Spectrometry, 18(3), pp. 567-577, 2007.

Medicinal Chemistry Section, Medications Discovery Research Branch

Novel Metabotropic Glutamate Receptor Subtype 5 Antagonists The metabotropic glutamate receptor subtype 5 (mGluR5) has been implicated in drug abuse and other neuropsychiatric disorders. The lead compounds for this receptor subtype, MPEP and MTEP, have provided important tools with which to study the role these receptors play in the central nervous system, but have limited application as potential medications. In this report, IRP researchers design and synthesize a novel series of heterobicyclic amides that provide novel structural templates with sub-micromolar binding affinities at the mGluR5. In the functional assay measuring the hydrolysis of phosphoinositide at mGluR5 in CHO cells, the lead compound showed antagonist activity (IC50=0.26+/-0.05 micromolar). Hence this template provides a new lead for further structure-activity relationship investigation and these compounds may serve as molecular tools with which to further study the mGluR5. Kulkarni, S. S., Newman A. H. Bioorganic Medicinal Chemistry Letters, 17, pp. 2074-2079, 2007.

Clinical Psychopharmacology Section, Chemical Biology Research Branch

Salvinorin A: Allosteric Interactions at the Mu-Opioid Receptor Salvinorin A is a hallucinogenic kappa opioid receptor agonist that lacks the

usual basic nitrogen atom present in other known opioid ligands. IRP researchers' first published studies indicated that Salvinorin A weakly inhibited mu receptor binding and subsequent experiments revealed that Salvinorin A partially inhibited mu receptor binding. Authors therefore hypothesized that Salvinorin A allosterically modulates mu receptor binding. To test this hypothesis, IRP researchers used CHO cells expressing the cloned human opioid receptor. Salvinorin A partially inhibited [3H]DAMGO (0.5, 2.0 and 8.0 nM) binding with EMAX values of 78.6%, 72.1% and 45.7%, respectively and EC50 values of 955, 1124 and 4527 nM, respectively. Salvinorin A also partially inhibited [3H]diprenorphine (0.02, 0.1 and 0.5 nM) binding with EMAX values of 86.2%, 64%, and 33.6%, respectively and EC50 values of 1231, 866, 3078 nM, respectively. Saturation binding studies with [3H]DAMGO showed that Salvinorin A (10 and 30 uM) decreased the mu receptor Bmax and increased the Kd in a dose-dependent non-linear manner. Saturation binding studies with [3H]diprenorphine showed that Salvinorin A (10 and 40 uM) decreased the mu receptor Bmax and increased the Kd in a dose-dependent non-linear manner. Similar findings were observed in rat brain with [3H]DAMGO. Kinetic experiments demonstrated that Salvinorin A altered the dissociation kinetics of both [3H]DAMGO and [3H]diprenorphine binding to mu receptors. Additionally, Salvinorin A acted as an uncompetitive inhibitor of DAMGO-stimulated [35S]-GTP-g-S binding. Viewed collectively, these data support the hypothesis that Salvinorin A allosterically modulates the mu opioid receptor. Rothman, R.B., Murphy, D.L., Xu H., Godin J.A., Dersch C.M., Partilla J.S., Tidgewell K. Schmidt M., Prisinzano T.E. J Pharmacol Exp Ther 320, pp. 801-810, 2007.

Behavioral Neuroscience Section, Behavioral Neuroscience Research Branch

The Midbrain Raphe Nuclei Mediate Primary Reinforcement via GABA(A) Receptors Because rats learn to lever-press for brief electrical stimulation of the median and dorsal raphe nuclei (MRN and DRN, respectively), these brain sites have long been implicated in reward processes. However, it is not clear whether the MRN and DRN integrate reward-related signals or merely contain fibers of passage involved in reward processes. To shed light on this issue, the present study employed chemicals that selectively modulate neurotransmission, in particular the GABA(A) receptor agonist muscimol. Rats quickly learned to lever-press for muscimol infusions (50 and 100 microm) into the MRN or DRN. Muscimol was not self-administered when cannulae were placed just outside these nuclei. The reinforcing effects of muscimol appeared to be greater when the drug was administered into the MRN than into the DRN, as demonstrated by higher infusion rates and better response discrimination. These observations are consistent with the additional finding that muscimol administration into the MRN, but not the DRN, induced conditioned place preference. The reinforcing effects of muscimol administration into the MRN were blocked by coadministration of the GABA(A) antagonist picrotoxin (100 microm) and by pretreatment with the dopamine receptor antagonist SCH 23390 (0.025 mg/kg, i.p.). The present results suggest that median and dorsal raphe neurons presumably inhibited by muscimol via GABA(A) receptors are involved in integration of primary reinforcement, and that median raphe neurons exert tonic inhibition over dopamine-dependent reward circuitry. The midbrain raphe nuclei may be involved in a variety of reward-related phenomena including drug addiction. Liu, Z.H. and Ikemoto, S. European Journal of Neuroscience, 25, pp. 735-743, 2007.

Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch

High Reinforcing Efficacy of Nicotine in Non-human Primates Although tobacco appears highly addictive in humans, there has been persistent

controversy about the ability of its psychoactive ingredient nicotine to induce self-administration behavior in laboratory animals, bringing into question nicotine's role in reinforcing tobacco smoking. Because of ethical difficulties in inducing nicotine dependence in naive human subjects, IRP scientists explored reinforcing effects of nicotine in experimentally-naive non-human primates given access to nicotine for periods of time up to two years. Five squirrel monkeys with no experimental history were allowed to intravenously self-administer nicotine by pressing one of two levers. The number of presses on the active lever needed to obtain each injection was fixed (fixed-ratio schedule) or increased progressively with successive injections during the session (progressive-ratio schedule), allowing evaluation of both reinforcing and motivational effects of nicotine under conditions of increasing response cost. Over time, a progressive shift toward high rates of responding on the active lever, but not the inactive lever, developed. The monkeys' behavior was clearly directed toward nicotine self-administration, rather than presentation of environmental stimuli associated with nicotine injection. Both schedules of reinforcement revealed a high motivation to self-administer nicotine, with monkeys continuing to press the lever when up to 600 lever-presses were needed for each injection of nicotine. Thus, nicotine, by itself, in the absence of behavioral or drug-exposure history, is a robust and highly effective reinforcer of drug-taking behavior in a non-human primate model predictive of human behavior. This supports the use of nicotinic ligands for the treatment of smokers, and this novel preclinical model offers opportunities to test future medications for the treatment of nicotine dependence. Le Foll, B., Wertheim, C. and Goldberg, S. R. Plos One, 2, pp. e230, 2007.

Differential Glutamate-dependent and Glutamate-independent Adenosine A(1) Receptor-mediated Modulation of Dopamine Release in Different Striatal Compartments Adenosine and dopamine are two important modulators of glutamatergic neurotransmission in the striatum. However, conflicting reports exist about the role of adenosine and adenosine receptors in the modulation of striatal dopamine release. It has been previously suggested that adenosine A(1) receptors localized in glutamatergic nerve terminals indirectly modulate dopamine release, by their ability to modulate glutamate release. In the present study, using in vivo microdialysis, IRP researchers provide evidence for the existence of a significant glutamate-independent tonic modulation of dopamine release in most of the analyzed striatal compartments. In the dorsal, but not in the ventral, part of the shell of the nucleus accumbens (NAc), blockade of A(1) receptors by local perfusion with the selective A(1) receptor antagonist 8-cyclopentyl-1,3-dimethyl-xanthine or by systemic administration of the non-selective adenosine antagonist caffeine induced a glutamate-dependent release of dopamine. On the contrary, A(1) receptor blockade induced a glutamate-independent dopamine release in the core of the NAc and the nucleus caudate-putamen. Furthermore, using immunocytochemical and functional studies in rat striatal synaptosomes, the authors demonstrate that a fraction of striatal dopaminergic terminals contains adenosine A(1) receptors, which directly inhibit dopamine release independently of glutamatergic transmission. Borycz, J., Pereira, M. F., Melani, A., Rodrigues, R. J., Kofalvi, A., Panlilio, L., Pedata, F., Goldberg, S. R., Cunha, R. A. and Ferre, S. Journal of Neurochemistry, January 24, 2007, Epub ahead of print, PMID 17254024.

The Endogenous Cannabinoid Anandamide Produces THC-like Discriminative and Neurochemical Effects that are Enhanced by Inhibition of Fatty Acid Amide Hydrolase (FAAH) but Not by Inhibition of Anandamide Transport Anandamide is an endogenous ligand for brain cannabinoid CB1 receptors, but its behavioral effects are difficult to measure due to rapid inactivation. Here IRP scientists used a drug-discrimination procedure to test the hypothesis that anandamide, given intravenously (i.v.) or intraperitoneally, would produce discriminative effects like those of delta-9-tetrahydrocannabinol (THC) in rats when its metabolic inactivation was

inhibited. The authors also used an in-vivo microdialysis procedure to investigate effects of anandamide, given i.v. or intraperitoneally, on dopamine levels in the nucleus accumbens shell in rats. When injected i.v., methanandamide (AM-356), a metabolically stable anandamide analog, produced clear dose-related THC-like discriminative effects, but anandamide produced THC-like discriminative effects only at a high 10 mg/kg dose that almost eliminated lever-press responding. URB-597, an inhibitor of fatty acid amide hydrolase (FAAH), the main enzyme responsible for anandamide's metabolic inactivation, produced no THC-like discriminative effects alone but dramatically potentiated discriminative effects of anandamide, with 3 mg/kg anandamide completely substituting for the THC training dose. URB-597 also potentiated anandamide's ability to increase dopamine levels in the accumbens shell. The THC-like discriminative-stimulus effects of methanandamide and anandamide after URB-597 were blocked by the CB1 receptor antagonist rimonabant, but not the vanilloid VR1 receptor antagonist capsazepine. Surprisingly, the anandamide transport inhibitors AM-404 and UCM-707 did not potentiate anandamide's THC-like discriminative effects or its dopamine-elevating effects. Thus, anandamide has THC-like discriminative and neurochemical effects that are enhanced after treatment with a FAAH inhibitor but not after treatment with transport inhibitors, suggesting brain area specificity for FAAH vs. transport/FAAH inactivation of anandamide. Solinas, M., Tanda, G., Justinova, Z., Wertheim, C.E., Yasar, S., Piomelli, D., Vadivel, S.K., Makriyannis, A. and Goldberg, S.R. Journal of Pharmacology and Experimental Therapeutics, January 8, 2007, Epub ahead of print, PMID 17210800.

Neurobiology of Relapse Section, Behavioral Neuroscience Research Branch

Long-term Upregulation of Protein Kinase A and Adenylate Cyclase Levels in Human Smokers Repeated injections of cocaine and morphine in laboratory rats cause a variety of molecular neuroadaptations in the cAMP signaling pathway in nucleus accumbens and ventral tegmental area. Here IRP investigators report similar neuroadaptations in postmortem tissue from the brains of human smokers and former smokers. Activity levels of two major components of cAMP signaling, cAMP-dependent protein kinase A (PKA) and adenylate cyclase, were abnormally elevated in nucleus accumbens of smokers and in ventral midbrain dopaminergic region of both smokers and former smokers. Protein levels of the catalytic subunit of PKA were correspondingly higher in the ventral midbrain dopaminergic region of both smokers and former smokers. Protein levels of other candidate neuroadaptations, including glutamate receptor subunits, tyrosine hydroxylase, and other protein kinases, were within normal range. These findings extend our understanding of addiction-related neuroadaptations of cAMP signaling to tobacco smoking in human subjects and suggest that smoking-induced brain neuroadaptations can persist for significant periods in former smokers. Hope, B.T., Nagarkar, D., Leonard, S., and Wise, R.A. Journal of Neuroscience, 27, pp. 1964-1972, 2007.

Tolerance to Opiate Reward: Role of Midbrain IRS2-Akt Pathway Addicts report that opiate drugs lose their rewarding effects over time, but the molecular mechanisms underlying this effect are unknown. A study now reports that tolerance to morphine reward in rats is due to downregulation of IRS2-Akt signaling in the ventral tegmental area (VTA), the cell body region of the mesolimbic dopamine reward system. Harvey, B.K., Hope, B.T., and Shaham, Y. Nature Neuroscience, 10, pp. 9-10, 2007.

Role of ERK in Cocaine Addiction Cocaine addiction is characterized by compulsive drug-taking behavior and high rates of relapse. According to recent theories, this addiction is due to drug-induced adaptations in the cellular mechanisms that underlie normal learning and memory. Such mechanisms involve signaling by extracellular signal-regulated kinase (ERK). As IRP

scientists review here, evidence from rodent studies also implicates ERK in cocaine psychomotor sensitization, cocaine reward, consolidation and reconsolidation of memories for cocaine cues, and time-dependent increases in cocaine seeking after withdrawal (incubation of cocaine craving). The role of ERK in these behaviors involves long-term stable alterations in synaptic plasticity that result from repeated cocaine exposure, and also rapidly induced alterations in synaptic transmission events that acutely control cocaine-seeking behaviors. Pharmacological manipulations that decrease the extent to which cocaine and cocaine cues induce ERK activity might therefore be considered as potential treatments for cocaine addiction. Lu, L., Koya, E., Zhai, H., Hope, B.T., and Shaham, Y. Trends in Neurosciences, 29, pp. 695-703, 2006.

Cocaine-induced Locomotor Activity and Fos Expression in Nucleus Accumbens are Sensitized for 6 Months After Repeated Cocaine Administration Outside the Home Cage Induction of the immediate early gene protein product Fos has been used extensively to assess neural activation in the striatum after repeated cocaine administration to rats in their home cages but rarely after repeated administration outside the home cage, which produces more robust locomotor sensitization. In the present study, IRP investigators found cocaine-induced Fos expression in nucleus accumbens, but not caudate-putamen, was enhanced 1 and 6 months after repeated drug administration in locomotor activity chambers. Double-labeling of Fos protein and enkephalin mRNA indicated that Fox expression in nucleus accumbens was enhanced in enkephalin-positive, but not enkephalin-negative, medium spiny neurons. In contrast, cocaine-induced Fos expression was absent altogether in nucleus accumbens and unaltered in caudate-putamen 1 month after repeated cocaine administration in the home cage. As cocaine-induced locomotor activity was also enhanced 1 and 6 months after repeated cocaine administration in locomotor activity chambers, the authors wanted to confirm that neuronal activity in nucleus accumbens mediates cocaine-induced locomotor activity using our particular treatment regimen. Bilateral infusions of the GABA agonists baclofen and muscimol (1 microg/side) into nucleus accumbens of sensitized rats blocked cocaine-induced Fos expression and locomotor activity. Thus, while neuronal activity in both D1- and D2-type neurons in nucleus accumbens can mediate acute cocaine-induced locomotor activity, the enhanced activation of enkephalinergic D2-type neurons suggests that these latter neurons mediate the enhancement of cocaine-induced locomotor activity for up to 6 months after repeated drug administration outside the home cage. Hope, B.T., Simmons, D.E., Mitchell, T.B., Kreuter, J.D., and Mattson, B.J. European Journal of Neuroscience, 24, pp. 867-875, 2006.

Systemic and Central Amygdala Injections of the mGluR(2/3) Agonist LY379268 Attenuate the Expression of Incubation of Cocaine Craving IRP investigators and others reported time-dependent increases in cue-induced cocaine seeking after withdrawal, suggesting that craving incubates over time. Recently, the authors found that central amygdala extracellular signal-regulated kinases (ERK) and glutamate are involved in this incubation. Here, they further explored the role of central amygdala glutamate in the incubation of cocaine craving by determining the effect of systemic or central amygdala injections of the mGluR(2/3) agonist LY379268 (which decreases glutamate release) on cue-induced cocaine seeking during early and late withdrawal. Rats were trained to self-administer cocaine for 10 days (6 hours/day); infusions were paired with a tone-light cue. Cocaine seeking and craving after systemic or central amygdala injections of LY379268 were then assessed in extinction tests in the presence of the cocaine-associated cues during early (day 3) or late (day 21) withdrawal. Systemic (1.5 or 3 mg/kg) or central amygdala (.5 or 1.0 mug/side) injections of LY379268 attenuated enhanced extinction responding on day 21 but had no effect on lower extinction responding on day 3. Results confirm the authors previous findings on the role of central amygdala glutamate in the incubation of cocaine craving and together with previous reports suggest that mGluR(2/3) agonists should be considered in the

treatment of drug relapse. Lu, L., Uejima, J., Gray, S., Bossert, J., and Shaham, Y. Biological Psychiatry, 61, pp. 591-598, 2007.

The Anxiogenic Drug Yohimbine Reinstates Palatable Food Seeking in a Rat Relapse Model: a Role of CRF1 Receptors The major problem in treating excessive eating is high rates of relapse to maladaptive eating habits during diet treatments; this relapse is often induced by stress or anxiety states. Preclinical studies have not explored this clinical problem. Here, IRP scientists adapted a reinstatement model (commonly used to study relapse to abused drugs) to examine the role of stress and anxiety in relapse to palatable food seeking during dieting. Rats were placed on restricted diet (75 - 80% of daily standard food) and for 12 intermittent training days (9 h/day, every other day) lever-pressed for palatable food pellets (25% fat, 48% carbohydrate) under a fixed ratio 1 (20-s timeout) reinforcement schedule. Subsequently, the rats were given 10 daily extinction sessions during which lever presses were not reinforced, and were then injected with yohimbine (an alpha-2 adrenoceptor antagonist that induces stress and anxiety in humans and non-humans) or given a single food pellet to assess reinstatement of food seeking. The rats rapidly learned to lever press for the palatable pellets and across the training days the ratio timeout nonreinforced lever presses to reinforced lever presses progressively increased more than three-fold, suggesting the development of compulsive eating behavior. After extinction, yohimbine injections and pellet priming reliably reinstated food seeking. The corticotropin-releasing factor1 (CRF1) receptor antagonist antalarmin attenuated the reinstatement induced by yohimbine, but not pellet priming. Antalarmin also reversed yohimbine's anxiogenic effects in the social interaction test. These data suggest that CRF is involved in stress-induced relapse to palatable food seeking, and that CRF1 antagonists should be considered for the treatment of maladaptive eating habits. Ghitza, U.E., Gray, S.M., Epstein, D.H., Rice, K.C., and Shaham, Y. Neuropsychopharmacology, 31, pp. 2188-2196, 2006.

Activation of Group II Metabotropic Glutamate Receptors in the Nucleus Accumbens Shell Attenuates Context-induced Relapse to Heroin Seeking Using a rat relapse model, IRP investigators previously reported that re-exposing rats to a drug-associated context, following extinction of operant responding in a different context, reinstates heroin seeking. In an initial pharmacological characterization, the authors found that the mGluR2/3 agonist LY379268, which acts centrally to reduce evoked glutamate release, attenuates context-induced reinstatement of heroin seeking when injected systemically or into the ventral tegmental area, the cell body region of the mesolimbic dopamine system. Here, the authors tested whether injections of LY379268 into the nucleus accumbens (NAc), a terminal region of the mesolimbic dopamine system, would also attenuate context-induced reinstatement of heroin seeking. Rats were trained to self-administer heroin; drug infusions were paired with a discrete tone-light cue. Subsequently, lever pressing was extinguished in the presence of the discrete cue in a context that differed from the drug self-administration context in terms of visual, auditory, tactile, and circadian cues. After extinction of responding, LY379268 was injected to different groups of rats into the NAc core or shell or into the caudate-putamen, a terminal region of the nigrastriatal dopamine system. Injections of LY379268 into the NAc shell (0.3 or 1.0 microg) dose-dependently attenuated context-induced reinstatement of heroin seeking. Injections of 1.0 microg of LY379268 into the NAc core had no effect, while a higher dose (3.0 microg) decreased this reinstatement. Injections of LY379268 (3.0 microg) 1.5 mm dorsal from the NAc core into the caudate-putamen were ineffective. Results suggest an important role of glutamate transmission in the NAc shell in context-induced reinstatement of heroin seeking. Bossert, J.M., Gray, S.M., Lu, L., and Shaham, Y. Neuropsychopharmacology, 31, pp. 2197-2209, 2006.

Nicotine Psychopharmacology Unit, Treatment Section, Clinical Pharmacology and Therapeutics Research Branch

Effect of Tobacco Deprivation on the Attentional Blink in Rapid Serial Visual Presentation When two targets are imbedded in rapid serial visual presentation (RSVP), identification of the second target (T2) is impaired if it occurs within 500 ms of the first target (T1). This attentional blink (AB) is thought to involve interference of resources in processing T1 and T2. The deleterious effect of tobacco deprivation on attention has been documented, but no studies have examined the AB. Nonsmokers (n = 30), 12-hr tobacco-deprived smokers (n = 30), and nondeprived smokers (n = 30) were randomly assigned to perform the RSVP with one of three stimulus-duration conditions (96, 113, or 130 ms). Participants completed 48 RSVP trials. Each trial consisted of 16 individually presented words (T1, T2, and 14 distractors), and T2 lagged T1 at serial positions 1 to 8. Participants verbalized T1 and T2 in order immediately after each trial. Identification of T2 (for correct T1 trials) was impaired at early vs. late lag positions, which was especially pronounced in the most difficult (96 ms) condition. There was no evidence for group differences on the AB; however, deprived smokers were worse identifying T1 in the 113-ms condition. These results suggest that the AB is influenced by stimulus duration, but not by 12 hr of tobacco deprivation. Heinz, A., Waters, A.J., Taylor, R.C., Myers, C.S., Moolchan, E.T., and Heishman, S.J. Human Psychopharmacology: Clinical and Experimental, 22, pp. 89-96, 2007.

Director's Report to the National Advisory Council on Drug Abuse - May, 2007

Program Activities

New NIDA PAs

On February 16, 2007, NIDA issued the PA entitled **NIDA Research Education Grants in Drug Abuse and Addiction (R25) (PAR-07-221)**. This FOA invites applications focused on research education and research curriculum development and/or program building in the area of drug abuse and addiction research. The focus should be primarily on clinical research, with preclinical research included to directly inform or provide a mechanistic foundation and/or for the purposes of supporting translational research training.

On February 21, 2007, NIDA issued the PA entitled **Neuroscience Research on Drug Abuse (R01) (PA-07-226)**. Through this PA, the National Institute on Drug Abuse (NIDA) requests research grant applications in the areas of neuroscience and behavioral neuroscience research that are relevant to the understanding of the process(es) and mechanisms underlying drug abuse and addiction, including use, dependence, addiction, withdrawal, and treatment, and may be conducted using model systems, animals, and/or humans.

On February 21, 2007, NIDA issued the PA entitled **Neuroscience Research on Drug Abuse (R21) (PA-07-227)**. Through this PA, the National Institute on Drug Abuse (NIDA) requests research grant applications in the areas of neuroscience and behavioral neuroscience research that are relevant to the understanding of the process(es) and mechanisms underlying drug abuse and addiction, including use, dependence, addiction, withdrawal, and treatment, and may be conducted using model systems, animals, and/or humans.

On February 22, 2007, NIDA issued the PA entitled **Neuroscience Research on Drug Abuse (R03) (PA-07-228)**. Through this PA, NIDA requests research grant applications in the areas of neuroscience and behavioral neuroscience research that are relevant to the understanding of the process(es) and mechanisms underlying drug abuse and addiction, including use, dependence, addiction, withdrawal, and treatment, and may be conducted using model systems, animals, and/or humans.

On February 23, 2007, NIDA issued a PA entitled **Collaborative Clinical Trials in Drug Abuse (R01) (PAR-07-232)**. Through this PA NIDA seeks to increase the collaboration of investigators at different sites in order to address critical issues in the treatment of substance-related disorders that require sample sizes greater than a single site can reasonably attain. The expectation for the collaborative effort is that there will be implementation of common clinical trials across different sites in order to study patient outcomes, patient factors, provider factors, setting characteristics, interactions of these, or other effects where pooled samples are appropriate and necessary for the

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hypotheses under consideration.

On March 22, 2007, NIDA issued a PA entitled **Medications Development for the Treatment of Amphetamine and Amphetamine-Like Related Disorders (R01) (PA-07-333)**. The goal of this program announcement is to encourage preclinical and clinical research directed towards the identification, evaluation and development of safe and effective medications for the treatment of Amphetamine and Amphetamine-like Related Disorders (ARDs), most importantly methamphetamine abuse and methamphetamine dependence. According to the DSM-IV-TR, the class of amphetamine and amphetamine-like substances includes all substances with a substituted-phenylethylamine structure, such as amphetamine, dextroamphetamine, methamphetamine, and MDMA (3,4-methylenedioxymethamphetamine). Also included are those substances that are structurally different but have amphetamine-like action, such as methylphenidate, some agents used as appetite suppressants, and khat. Amphetamines, amphetamine-like substances and methamphetamine especially, are highly addictive central nervous system stimulants that can be injected, snorted, smoked, or ingested orally. Of all the ARDs, prevalence data is most readily available for methamphetamine abuse and dependence. This data indicates that methamphetamine use continues to be a major public health concern in the United States for all segments of the population. Methamphetamine is unique in that it can be easily manufactured in clandestine laboratories using store-bought materials and is the most prevalent synthetic drug manufactured in the United States. The ease of manufacturing methamphetamine and its highly addictive potential has caused the use of the drug to greatly increase throughout the Nation. The methamphetamine problem was originally concentrated in the West of the United States, but has since spread throughout almost every major metropolitan area in the country, due to the low cost, high availability, and addictive properties of this substance. There are currently no effective pharmacological treatments for ARDs and there has been limited research focused on the identification and development of medications to treat these disorders, as well as research on the health effects of chronic abuse. For these reasons, the NIDA is encouraging research in this area.

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Planned Meetings

Publications

Staff Highlights

Grantee Honors

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On March 30, NIDA issued a PA entitled **NIDA Mentored Clinical Scientists Development Program Award in Drug Abuse and Addiction (K12) (PAR-07-346)**. The goal of NIH-supported career development programs is to help ensure that a diverse pool of highly trained scientists is available in adequate numbers and in appropriate research areas to address the Nation's biomedical, behavioral, and clinical research needs. The purpose of the NIDA Mentored Clinical Scientists Development Award in Drug Abuse and Addiction (K12) is to support the career development of clinical investigators who have made a commitment to research independence.

On April 3, 2007, NIDA issued a PA entitled **AIDS-Science Track Award for Research Transition (R03) (PA-07-349)**. HIV/AIDS research is a major focus at NIDA, and this funding opportunity announcement (FOA) is designed to facilitate the entry of new investigators and early career investigators to the area of drug abuse research on HIV/AIDS. This FOA, AIDS--Science Track Award for Research Transition (A-START), solicits Small Research Grant (R03) applications to support feasibility, secondary data analysis, and small, self-contained studies on drug abuse and HIV/AIDS. This funding opportunity announcement (FOA) seeks to facilitate the entry of both newly independent and early career investigators to the area of drug abuse research on HIV/AIDS.

On April 24, 2007, NIDA issued a PA entitled **Medications Development for the Treatment of Cannabis-Related Disorders (R01) (PA-07-365)**. This Funding Opportunity Announcement (FOA) solicits new or competing renewal Research Project Grant (R01) applications from institutions/ organizations that propose to conduct preclinical and clinical research directed towards the identification, evaluation and development of safe and effective medications for the treatment of Cannabis Related Disorders (CRDs) and their medical and psychiatric consequences. They include the Cannabis Use Disorders (CUDs) such cannabis abuse and dependence, the Cannabis Induced Disorders (CIDs) such as intoxication, psychosis, and anxiety, as well as the comorbidity of these disorders with other medical and psychiatric disorders (e.g., depression). Cannabis use includes marijuana, hashish, and other tetrahydrocannabinol (THC) containing substances. NIDA is encouraging research in this area because there is a high prevalence of marijuana use in the general population accompanied with an increasing misperception that its use poses low health risk, there is limited research in this area, and there are no effective pharmacological treatments available for these disorders.

On April 25, 2007, NIDA issued a PA entitled **Medications Development for the Treatment of Cannabis-Related Disorders (R21) (PA-07-366)**. This funding opportunity announcement (FOA) solicits Exploratory/Developmental (R21) grant applications from applicant organizations that propose to conduct preclinical and clinical research directed towards the identification, evaluation and development of safe and effective medications for the treatment of Cannabis Related Disorders (CRDs) and their medical and psychiatric consequences. They include the Cannabis Use Disorders (CUDs) such cannabis abuse and dependence, the Cannabis Induced Disorders (CIDs) such as intoxication, psychosis, and anxiety, as well as the comorbidity of these disorders with other medical and psychiatric disorders (e.g., depression). Cannabis use includes marijuana, hashish, and other tetrahydrocannabinol (THC) containing substances. NIDA is encouraging research in this area because there is a high prevalence of marijuana use in the general population accompanied with an increasing misperception that its use poses low health

risk, there is limited research in this area, and there are no effective pharmacological treatments available for these disorders.

International Program Announcement Expanded to R03 and R21 Grants

NIDA has expanded its Program Announcement (PA) on **International Research Collaboration on Drug Addiction** to use two additional funding mechanisms. In addition to the traditional Research Project Grants, known as R01 awards, scientists are now invited to submit grant applications that propose international collaborative research using the Small Grant Award, also known as an R03, and the Exploratory/Developmental Research Grants, or R21 awards. NIDA issues PAs to formally express ongoing interest in funding a particular area of science. Applications under the three PAs on International Research Collaboration may be for new or continuing funding and must:

Take advantage of special opportunities that exist outside the United States - such as unusual talent, resources, populations, or environmental conditions.

Be conducted by U.S. investigators in collaboration with non-U.S.-based investigators.

Address NIDA's scientific priority areas, which currently include linkages between HIV/AIDS and drug abuse, adolescent and prenatal tobacco exposure, methamphetamine abuse, inhalant abuse, and drugged driving.

Specific application requirements and deadlines differ for the three grant mechanisms and are available in the *NIH Guide for Grants and Contracts*:

R01: **PA-07-275** (http://grants.nih.gov/grants/guide/pa-files/PA-07-275.html).

R03: **PA-07-311** (http://grants.nih.gov/grants/guide/pa-files/PA-07-311.html).

R21: **PA-07-310** (http://grants.nih.gov/grants/guide/pa-files/PA-07-310.html).

PAs and RFAs with Other NIH Components/Agencies

On March 23, 2007, NIDA, in collaboration with numerous other NIH components, issued a PA entitled I**nternational Research Collaboration - Basic Biomedical (FIRCA-BB) (R03)(PA-07-335)**. This funding opportunity facilitates collaborative basic biomedical research between scientists supported by the National Institutes of Health (NIH) and investigators in developing countries. For behavioral and social sciences research, see the companion Funding Opportunity Announcement (FOA), Fogarty "International Research Collaboration - Behavioral, Social Sciences" Research Award program (FIRCA-BSS) (PAR-06-437).

On March 27, 2007, NIDA, in collaboration with NIMH and NINR, issued a PA entitled **HIV Treatment Adherence Research (R01) PA-07-338**. This funding opportunity announcement (FOA) invites grant applications from applicant organizations to advance scientific research and intervention regarding HIV treatment adherence.

On March 27, 2007, NIDA, in collaboration with NIMH and NINR, issued a PA entitled **HIV Treatment Adherence Research (R03) PA-07-339**. This funding opportunity announcement (FOA) invites grant applications from applicant organizations to advance scientific research and intervention regarding HIV treatment adherence.

On March 27, 2007, NIDA, in collaboration with NIMH and NINR, issued a PA entitled **HIV Treatment Adherence Research (R21) PA-07-340**. This

funding opportunity announcement (FOA) invites grant applications from applicant organizations to advance scientific research and intervention regarding HIV treatment adherence.

On March 29, 2007, NIDA in conjunction with numerous other NIH components, issued a PA entitled **Innovations in Biomedical Computational Science and Technology (R01) (PA-07-344)**. The NIH is interested in promoting research and developments in computational science and technology that will support rapid progress in areas of scientific opportunity in biomedical research. As defined here, biomedical computing or biomedical information science and technology includes database design, graphical interfaces, querying approaches, data retrieval, data visualization and manipulation, data integration through the development of integrated analytical tools, and tools for electronic collaboration, as well as computational and mathematical research including the development of structural, functional, integrative, and analytical models and simulations.

On March 29, 2007, NIDA, in collaboration with NIEHS, issued a PA entitled **Mechanism for Time-Sensitive Research Opportunities (R21) (PA-07-345)**. This Funding Opportunity Announcement (FOA) is intended to support substance abuse services research or hazard exposure - related 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 April 2, 2007, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **AIDS International Training and Research Program (D43) (PAR-07-348)**. The purpose of this Funding Opportunity Announcement (FOA) is to invite applications from eligible institutions for innovative, collaborative research training programs that would contribute to the long-term goal of building sustainable research capacity in HIV-related conditions at institutions in low- and middle-income countries.

On February 21, 2007, NIDA, in collaboration with NIMH and NICHD, issued a PA entitled **Developmental Psychopharmacology (R21) (PA-07-222)**. The purpose of this Funding Opportunity Announcement (FOA) is to request research applications to examine the neurobiological impact of psychotherapeutic medications upon the immature brain, with particular emphasis upon mapping the precise developmental profile of physiological response to psychotropic agents used in the treatment of mental disorders in children. Appropriate research includes studies in model systems, including animals, and in human populations.

On February 23, 2007, NIDA, in collaboration with numerous other NIH components issued a PA entitled **Continued Development and Maintenance of Software (R01) (PAR-07-235)**. Biomedical research laboratories increasingly undertake a software development project to solve a problem of interest to that laboratory. These software packages sometimes become useful to a much broader community of users that can include translational and clinical researchers. The goal of this program announcement is to support the continued development, maintenance, testing and evaluation of existing software. The proposed work should apply best practices and proven methods for software design, construction, and implementation to extend the applicability of existing biomedical informatics/computational biology software to a broader biomedical research community.

On March 15, 2007, NIDA, in collaboration with NIAAA, issued a PA entitled **Women and Sex/Gender Differences in Drug and Alcohol Abuse/Dependence (R01) (PA-07-329)**. The purpose of this Funding Opportunity Announcement (FOA) is to promote research on women and sex/gender differences in drug/alcohol abuse and dependence.

On March 15, 2007, NIDA, in collaboration with NIAAA, issued a PA entitled **Women and Sex/Gender Differences in Drug and Alcohol Abuse/Dependence (R03) (PA-07-330)**. The purpose of this Funding Opportunity Announcement (FOA) is to promote research on women and sex/gender differences in drug/alcohol abuse and dependence.

On March 15, 2007, NIDA, in collaboration with NIAAA, issued a PA entitled **Women and Sex/Gender Differences in Drug and Alcohol Abuse/Dependence (R21) (PA-07-331)**. The purpose of this Funding Opportunity Announcement (FOA) is to promote research on women and sex/gender differences in drug/alcohol abuse and dependence.

On Feburary 3, 2007, NIDA issued a Request for Information (RFI) entitled **Community Input for Nominating Single Nucleotide Polymorphisms or Genes Associated with Drug Abuse and Related Psychiatric Co-morbidities to Develop a Custom SNP Neuroarray (NOT-DA-07-010)**. The purpose of this RFI is to solicit community input to develop and generate a single nucleotide polymorphism (SNP) array platform for studies investigating the genetics and pharmacogenetics of drug abuse and addiction and related psychiatric disorders. The Neuroarray would be made available competitively through standard NIH mechanisms to advance the understanding of genetic vulnerability to these specific public health disorders, and the genetic profiles of patients for targeted/tailored pharmacotherapies.

Response to PAs/RFAs

There has been a substantial response to the NIH Roadmap RFA entitled **Facilitating Interdisciplinary Research via Methodological and Technological Innovation in the Behavioral and Social Sciences.** http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-07-004.html. NIDA is partnering with OBSSR on this Roadmap initiative, and is the lead Institute. Dr. Lisa Onken of DCNBR has been leading the effort on this RFA. The applications will be reviewed in June 2007.

Other Program Activities

Clinical Trials Network (CTN) Update

The CCTN received proposals in response to a NIH SBIR Contract Solicitation for **Topic 089, Development of Practical Training Materials for Evidence-Based Treatment**. A review meeting was held on March 13, 2007. Two awards are planned for this solicitation.

A total of 27 protocols have been initiated since 2001. A total of 7,732 participants enrolled in studies as of February 28, 2007. Of these studies, 19 have completed enrollment and locked the data; two completed enrollment and are in the follow-up phase; and four are currently enrolling. Two new protocols are in the development phase.

Primary outcome papers are published and dissemination materials have been developed with CSAT's ATTC on the following:

Protocol CTN 0001, Buprenorphine/Naloxone versus Clonidine for Inpatient Opiate Detoxification

Protocol CTN 0002, Buprenorphine/Naloxone versus Clonidine for Outpatient Opiate Detoxification

Protocol CTN 0005, MI (Motivational Interviewing) To Improve Treatment Engagement and Outcome in Subjects Seeking Treatment for Substance Abuse

Protocol CTN 0006, Motivational Incentives for Enhanced Drug Abuse Recovery: Drug Free Clinics

Protocol CTN 0007, Motivational Incentives for Enhanced Drug Abuse Recovery: Methadone Clinics

The following protocols have locked the data:

Protocol CTN 0003, Bup/Nx: Comparison of Two Taper Schedules

Protocol CTN 0004, MET (Motivational Enhancement Treatment) To Improve Treatment Engagement and Outcome in Subjects Seeking Treatment for Substance Abuse

Protocol CTN 0008, A Baseline for Investigating Diffusion of Innovation

Protocol CTN 0009, Smoking Cessation Treatment with Transdermal Nicotine Replacement Therapy in Substance Abuse Rehabilitation Programs

Protocol CTN 0010, (Buprenorphine/Naloxone Facilitated Rehabilitation for Opioid Dependent Adolescents/Young Adults)

Protocol CTN 0011, A Feasibility Study of a Telephone Enhancement Procedure (TELE) to Improve Participation in Continuing Care Activities

Protocol CTN 0012, Characteristics of Screening, Evaluation, and Treatment of HIV/AIDS, Hepatitis C Viral Infection, and Sexually Transmitted Infections in Substance Abuse Treatment Programs

Protocol CTN 0013, (Motivational Enhancement Therapy to Improve Treatment Utilization and Outcome In Pregnant Substance Abusers)

Protocol CTN 0016, Patient Feedback: A Performance Improvement Study in Outpatient Addiction Treatment

Protocol CTN 0017, (HIV and HCV Intervention in Drug Treatment Settings)

Protocol CTN 0018, (Reducing HIV/STD Risk Behaviors: A Research Study for Men in Drug Abuse Treatment)

Protocol CTN 0019, (Reducing HIV/STD Risk Behaviors: A Research Study for Women in Drug Abuse Treatment)

Protocol CTN 0020, (Job Seekers Training for Substance Abusers). This study was also 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). This is the first Spanish-only protocol in the CTN.

These protocols have ended new enrollment and are in either follow-up or data-lock phase:

Protocol CTN 0014, Brief Strategic Family Therapy for Adolescent Drug Abusers (BSFT), has been implemented at eight sites. The study reached its enrollment target of 480 randomized participants in January 2007.

Protocol CTN 0015, (Women's Treatment for Trauma and Substance Use Disorder: A Randomized Clinical Trial) began in March 2004. The study reached its enrollment target in October 2005, and follow-up continues until spring 2007.

Four protocols are currently enrolling:

Protocol CTN 0027, Starting Treatment with Agonist Replacement Therapies (START) is a randomized, open-label, multi-center study that was developed in collaboration with the Division of Pharmacotherapies & Medical Consequences of Drug Abuse (DPMCDA). Enrollment began in April 2006. As of February 28, 2007, there were 216 randomized participants.

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). Enrollment is now open at 11 sites. Sixty-five participants have been randomized.

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). This study is being carried out at six community treatment sites across five Nodes. There are a total of 165 randomized participants.

Protocol CTN 0030, Prescription Opioid Addiction Treatment Study (POATS) is a randomized 2-phase, open-label, multi-center study in outpatient treatment settings. Pre-screening began in May 2006. The study is being carried out in 11 sites. Sixty-eight participants have been randomized.

Two protocols are in the development phase:

Protocol CTN 0031, Stimulant Abuser Groups to Engage in 12-Step (STAGE-12): Evaluation of a Combined Individual-Group Intervention to Reduce Stimulant and Other Drug Use by Increasing 12-Step Involvement. The DSMB approved the protocol on January 29, 2007. The process for selecting Community Treatment Programs (CTPs) to serve as research sites has proceeded in two waves for implementation. Three CTPs were selected for Wave 1, based on combined ranking of interviews and Executive Committee consensus. The three CTPs selected for Wave 1 are Maryhaven from the Ohio Valley Node, ChangePoint from the Oregon/Hawaii Node, and Recovery Centers of King County from the Washington Node. Currently, the protocol Executive Committee is working to finalize the Standard Operations Manual and the Therapy Training Manual.

Protocol CTN 0032, HIV Rapid Testing and Counseling Protocol. This protocol is under development. This study seeks to evaluate the most effective strategy to ensure that persons in drug treatment programs are tested for HIV and receive their HIV test results. The Centers for Disease Control and Prevention (CDC) has made it a priority to bring HIV rapid testing and counseling into outpatient health care settings for high-risk populations. Protocol 0032 was approved for development in late November 2006, and the

protocol team meets regularly by conference call. The DSMB is being formed for possible submission of the completed protocol during summer/fall 2007.

In addition to the primary CTN trials, there are currently 28 funded studies supported by independent grants that use CTN studies as a platform.

NIDA's New and Competing Continuation Grants Awarded Since February 2007

Abrams, Donald I. -- University of California San Francisco
Opioid and Cannabinoid Pharmacokinetic Interactions

Abrantes, Ana M. -- Butler Hospital, Providence, RI
Behavioral Exercise Intervention For Smoking Cessation

Aharonovich, Efrat -- Columbia University Health Sciences
Cognition In Cocaine Dependence: Assessment & Therapy

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

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

Aldrich, Jane V. -- University of Kansas Lawrence
Affinity Labels For Opioid Receptors

Aldrich, Jane V. -- University of Kansas Lawrence
Peptidic Ligands For Kappa Opioid Receptors

Aldridge, J. Wayne -- University of Michigan at Ann Arbor
Neural Coding of Reward In Ventral Forebrain

Alger, Bradley E. -- University of Maryland Baltimore Professional School
Endocannabinoids and GABAergic Control Of Plasticity

Allen, Sharon S. -- University of Minnesota Twin Cities
Menstrual Phase and Depression Symptoms In Acute Smoking Abstinence

Amen, Shelley L. -- Medical College of Wisconsin
Glutamate-Mediated Attenuation Of Cocaine Craving

Angulo, Jesus A. -- Hunter College
Methamphetamine and the Striatal Nk-1 Receptors

Aragona, Brandon J. -- University of North Carolina Chapel Hill
Dopamine, Accumbens Signaling & Associative Learning

Aston-Jones, Gary S. -- Medical University of South Carolina
Alterations In Reward Processing During Drug Abstinence

Balda, Mara A. -- University of Miami-Medical School
The Roles Of NNOS, Ontogeny, and Gender In Cocaine Sensitization

Balster, Robert L. -- Virginia Commonwealth University
The Behavioral Pharmacology Of Phencyclidine

Bank, Lewis I. -- Oregon Social Learning Center, Inc.
Motivational Parent Training In Community Corrections

Bannon, Michael J. -- Wayne State University
Cocaine-Binding Dopamine Transporter: Molecular Biology

Barker, Eric L. -- Purdue University West Lafayette
Psychostimulant Recognition By Serotonin Transporters

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

Bartlett, Selena E.. -- Multispan, Inc.
Targeting Opioid Receptor Heterodimers For Pain Treatment

Baumann, Stephen B. -- Psychology Software Tools, Inc.
Virtual Reality and Functional MRI To Study Drug Craving

Bauzo, Rayna M. -- Emory University
Role Of Glutamate In Cocaine Behavioral Pharmacology

Bayer, Barbara M. -- Georgetown University
Lymphocyte Activity During Stress: Effects Of Morphine

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

Beckham, Jean C. -- Duke University
Optimal Smoking Cessation Treatment In PTSD

Beckham, Jean C. -- Duke University
The Effect Of Smoking On Startle & PPI In PTSD

Beckstead, Michael J. -- Oregon Health & Science University
Methamphetamine Effects On Dendrodendritic Dopamine Transmission In the VTA

Beeler, Jeff A. -- University of Chicago
Genetic Manipulation Of Phasic Dopaminergic Activity

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

Benavides, David R. -- University of Texas Southwest Medical Center, Dallas
Minority Predoctoral Fellowship Program

Bergman, Jack -- Mc Lean Hospital, Belmont, MA
Behavioral Effects and Abuse Of Dopaminergic Drugs

Berridge, Craig W.-- University of Wisconsin Madison
Neurochemistry Of Amphetamine Induced Arousal

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

Bidlack, Jean M. -- University of Rochester
Opioid Receptors On Lymphocytes and Brain

Biederer, Thomas -- Yale University
Mechanisms Of Syncam-Induced Synapse Formation

Bierut, Laura J. -- Washington University
Case Control Candidate Gene Study Of Addiction

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

Blackler, Adele R. -- University of Colorado Denver/Health Sciences

Center Aurora
Proteomic Characterization Of The Dopamine Transporter

Blakely, Randy D. -- Vanderbilt University
Regulation Of Serotonin Transporters

Blanco, Carlos -- New York State Psychiatric Institute
Smart: Improving Detection & Outcome Of Psychiatric Comorbidity In Drug Treatment

Blendy, Julie A. -- University of Pennsylvania
Molecular Genetic Analysis Of Drug Addiction

Blough, Bruce E. -- Research Triangle Institute
Potential Treatment Medications For Drug Abuse

Boeri, Miriam W. -- Kennesaw State University
Methamphetamine Use In the Suburbs: An Exploratory Study

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

Bonci, Antonello -- Ernest Gallo Clinic and Research Center
Synaptic Plasticity In the VTA After Behavioral Sensitization & Cocaine Self-Administration

Borenstein, Michael -- Biostatistical Programming Associates, Inc.
Forest Plots For Meta Analysis

Borenstein, Michael -- Biostatistical Programming Associates, Inc.
Power Analysis For Meta Analysis

Bosco, Giovanni -- University of Arizona
Fos, Jun & Synaptic Plasticity

Bost, Kenneth L. -- University of North Carolina Charlotte
Alters Immunity To Infections Of the Peripheral and Central Nervous Systems

Boudreau, Amy C. -- Rosalind Franklin University of Medicine & Science
Cocaine-Induced Plasticity In the Nucleus Accumbens

Boudreaux, Edwin D. -- Polaris Health Directions, Inc.
The Computer Assisted Brief Intervention For Tobacco (CABIT)

Bouhamdan, Mohamad -- Wayne State University
Rgs9-2 Protein: Novel Partners and Functional Roles

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

Boutros, Nashaat N. -- Wayne State University
Cortical Excitability In Cocaine-Dependent Subjects

Bradberry, Charles W. -- University of Pittsburgh at Pittsburgh
CNS Consequences Of Chronic Cocaine Self-Administration

Brady, Kathleen T. -- Medical University of South Carolina
South Carolina Consortium Of the Clinical Trials Network

Brady, Kathleen T. -- Medical University of South Carolina
Drug Abuse Research Training (DART) Program

Brady, Kathleen T. -- Medical University of South Carolina
South Carolina Consortium Of the Clinical Trials Network

Bridges, Robert S. -- Tufts University Boston
Parenting and the Brain

Bromberg, Jonas I. -- Inflexxion, Inc.
Web-Based Support To Self-Manage Migraine Pain

Brook, Judith S. -- New York University School of Medicine
Drug Use and Problem Behaviors In Minority Youth

Brook, Judith S. -- New York University School of Medicine
Etiology and Consequences Of Adolescent Drug Use (K05)

Brooner, Robert K. -- Johns Hopkins University
Services Research: Psychiatric Comorbidity In Drug Abuse

Brown, Alison H. -- University of California Los Angeles
Women, Methamphetamine and Sex

Brown, Lawrence S. -- Addiction Research and Treatment Corp
Electronic Information System To Enhance Practice At An Opioid Treatment Program

Bruno, John P. -- Ohio State University
High-Speed Detection Of Stimulant-Induced Cortical ACH Release

Buch, Shilpa J. -- University of Kansas Medical Center
HIV-Encephalitis and Cocaine Abuse: Mechanism Of Synergy and Therapy

Bucholz, Kathleen K. -- Washington University
Gene Environment In Outcomes Of Offspring Of Twins With Substance Use Disorders

Bunt, Gregory -- Daytop Village
International Society Of Addiction Medicine Conference

Burdzovic Andreas, Jasmina -- Brown University
Substance Use In Adolescents From High-Risk Neighborhoods: Risk and Protection

Burke, Kathryn A. -- University of Maryland Baltimore Professional School
Associative Basis Of Conditioned Reinforcement

Butelman, Eduardo R. -- Rockefeller University
Kappa-Agonist Effects Of the Hallucinogen Salvinorin A

Cabral, Guy A. -- Society on Neuroimmune Pharmacology
13th-17th Conferences: Drug Abuse, Immune Modulation and AIDS

Cabral, Guy A. -- Virginia Commonwealth University
Cannabinoid Modulation Of Macrophage Function

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

Campbell, William. B -- Medical College of Wisconsin
Biochemistry Of Anandamide, and Endogenous Cannabinoid

Capaldi, Deborah M. -- Oregon Social Learning Center, Inc.
Risk For Dysfunctional Relationships For Young Adults

Carlezon, William A. -- McLean Hospital, Belmont, MA.
Biobehavioral Mechanisms Of Drug Reward and Addiction

Carr, Kenneth D. -- New York University School of Medicine
CNS Mechanisms That Modulate Reward

Carroll, Kathleen M. -- Yale University
Maximizing CBT's Efficacy With Medication & CM

Carroll, Marilyn E. -- University of Minnesota Twin Cities
Primate Model Of Drug Abuse: Intervention Strategies

Carroll, Marilyn E. -- University of Minnesota Twin Cities
Animal Models For the Prevention and Treatment Of Drug Abuse

Caster, Joseph M. -- Duke University
Adolescent Vulnerbility To Neuroplastic Changes Induced By High Dose Cocaine

Chamberlain, Patricia -- Oregon Social Learning Center, Inc.
Preventing Behavior and Health Problems In Foster Teens

Chambers, Robert Andrew -- Indiana University-Purdue University at Indianapolis
Integrated Neurobiology Of Addiction and Mental Illness

Chang, Linda -- University of Hawaii at Manoa
Neuroimaging and Mentoring In Drug Abuse Research

Chang, Sulie L. -- Seton Hall University
Morphine Actions On the Immune System

Chang, Sulie L. -- Seton Hall University
Opiate's Effects On the Inflammation and Cytotoxicity In HIV-1 Transgenic Rat

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

Chavkin, Charles -- University of Washington
Opioid Mediation Of Stress-Potentiated Cocaine Response

Cinciripini, Paul M. -- University of Texas MD Anderson Cancer Center
A Mood Management Intervention For Pregnant Smokers

Clark, Ann S. -- Dartmouth College
AAS and the Neurobiology Of Social Behaviors

Clatts, Michael C. -- National Development & Research Institutes
Ethno-Epidemiology In An Emergent MSM Risk Environment

Cochran, Susan D. -- University of California Los Angeles
Drug Use, HIV, and Other Comorbidities In A Vulnerable Population

Cohen, Mardge H. -- Hektoen Institute For Medical Research
Chicago Consortium Women's Interagency HIV Study LII

Colbern, Deborah L. -- Beemnet, Inc.
National Kids Judge! Neuroscience Fairs Partnership

Colder, Craig R. -- State University of New York at Buffalo
Motivation In Context: Risk For Early Substance Use

Colfax, Grant N. -- San Francisco Department of Public Health
Club-Drugs and HIV Risk Behavior In High-Risk Men

Collins, Allan C. -- University of Colorado at Boulder
Studies With Nicotinic Null Mutant Mice

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

Conger, Rand D. -- Iowa State University
Economic Stress & Child Development Across 3 Generations

Cooper, Donald C. -- University of Texas Southwest Medical Center/Dallas
DNA Microarray Analysis Of Neuronal Excitability

Corbin, Joshua G. -- Children's Research Institute
Development Of the Basal Telencephalic Limbic System

Cottler, Linda B. -- Washington University
Prescription Drug Misuse, Abuse and Dependence

Coviello, Donna M. -- University of Pennsylvania
Employment Intervention For Offenders

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

Crowley, Thomas J. -- University of Colorado Denver/Health Science Center Aurora
Substance Dependent Adolescents: Imaging Risk-Taking

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

Dallery, Jesse -- University of Florida
Effects Of Nicotine On Environmental Stimuli

Dallery, Jesse -- University of Florida
A Home-Based Behavioral Treatment For Cigarette Smoking

Davies, Robert D. -- University of Colorado Denver/Health Science Center Aurora
Martial Arts As Early Intervention For Teen Drug Abuse

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

Day, Nancy L. -- University of Pittsburgh at Pittsburgh
Prenatal Marijuana Exposure: Long-Term Outcomes

De Wit, Harriet -- University of Chicago
Drug Abuse and Impulsivity: Human Laboratory Models

Deadwyler, Samuel A. -- Wake Forest University Health Sciences
Hippocampus Correlates Of Drug Abuse In Rats

Decharms, Christopher -- Omneuron, Inc.
Measurement and Control Of Patterned Brain Activation Using Real Time FMRI

Deleo, Joyce A. -- Dartmouth College
Alternatives To Opioids For Chronic Pain: Part IV

Deren, Sherry -- National Development & Research Institutes
High Risk Drug Use & HIV-Learning From The NYC Epidemic

Desbiens, Sophie C. -- Boston University Medical Campus
CREB Mediated GABA-B Receptor Regulation In the Nucleus Accumbens

D'esposito, Mark -- University of California Berkeley

Dopaminergic Modulation Of Frontostriatal Function

Diamond, Adele D. -- University of British Columbia
Cognitive Functions Linked To Frontal Lobe

Diantonio, Aaron -- Washington University
Molecular Pathways Regulating Synaptic Growth

Dietz, David M. -- Florida State University
Individual Differences In Sensitization To Amphetamine

Dimeff, Linda A. -- Behavioral Tech Research, Inc.
Computer Based Training In DBT-S Behavioral Analysis

Dominguez, Hector D. -- San Diego State University
Behavioral Effects Of Neonatal Methamphetamine Exposure

Dorn, Lorah D. -- Children's Hospital Medical Center, Cincinnati
Smoking and Metabolic Complications In Adolescent Girls

D'souza, Deepak C. -- Yale University
Neurobiology Of Cannabis Effects

Dunlap, Eloise E. -- National Development & Research Institutes
Disruption and Reformulation Of Illicit Drug Markets Among New Orleans Evacuees

Dykstra, Linda A. -- University of North Carolina Chapel Hill
Opioid Analgesics: Pharmacological & Behavioral Factors

Eby, Lillian T. -- University of Georgia
Clinical Supervision and Turnover In Substance Abuse Treatment

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

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

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

Epperson, Cynthia N. -- Yale University
Sex, GABA and Nicotine: A 1h-MRS Study

Ettenberg, Aaron -- University of California Santa Barbara
Mechanisms Of Opiate and Stimulant Drug Reinforcement

Evans, Suzette M. -- New York State Psychiatric Institute
Vulnerability To Anxiolytic Abuse In Women

Fanous, Sanya -- Tufts University Boston
Social Defeat Stress and Cross-Sensitization: The Role Of Mesocorticolimbic BDNF

Fantegrossi, William E. -- Emory University
Effects Of Self-Administered On Brain and Behavior In Rhesus Monkeys

Feelisch, Martin -- Boston University Medical Campus
A Nitric Oxide(No)-Based Metabonomic Approach To Investigate Tobacco Addiction

Fendrich, Michael -- University of Wisconsin Milwaukee
Secondary Analysis Of Substance Use In Men

Ferguson, Susan M. -- University of Washington
Role Of 5HT6 Receptors In Drug Reward

Feske, Ulrike -- University of Pittsburgh at Pittsburgh
Drug Abuse and Risky Sex In Borderline Personality

Field, Julie R. -- Vanderbilt University
Structure-Guided Analysis Of the Serotonin Transporter

Filizola, Marta -- Weill Medical College of Cornell University
Opioid Receptor Oligomerization: Prediction & Validation

Filizola, Marta -- Weill Medical College of Cornell University
Informatics Of GPCR Dimers In Drug Abuse Mechanisms

Finn, Peter R. -- Indiana University Bloomington
Attention-Biases and Hot Cognition In Drug Dependence

Firpo, Meri T. -- University of Minnesota Twin Cities
Essential Human Embryonic Stem Cell Culture Methods

Fite, Paula J. -- State University of New York at Buffalo
Pathways From Subtypes Of Aggression To Substance Use

Fleckenstein, Annette -- University of Utah
Psychostimulants and Monoamine Transporters

Fleckenstein, Annette -- University of Utah
Drug Abuse and Regulatory Enzymes Of Biogenic Amines

Fleckenstein, Annette -- University of Utah
K02 Application

Foltin, Richard W. -- New York State Psychiatric Institute
Anorectic Drugs: Abuse and Behavioral Mechanisms Of Action

Fontanilla, Dominique A. -- University of Wisconsin Madison
Characterization Of the Sigma-1 Receptor

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

Fowler, Melissa A. -- University of Texas Southwest Medical Center, Dallas
TRPC Channels In Dopamine Regulation Of Prefrontal Cortical Excitability

Fox, Nathan A. -- University of Maryland
Early Temperament and Social Behavior In Adolescence

France, Charles P. -- University of Texas Health Sciences Center San Antonio
Behavioral Pharmacology Of Drug Dependence

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

Friedman, Jeffrey M. -- Rockefeller University
Mapping Neural Circuits Using Pseudorabie Virus Vectors

Fuchs Lokensgard, Rita A. -- University of North Carolina Chapel Hill
Neural Bases Of Drug Context-Induced Cocaine Seeking

Gabuzda, Dana H. -- Dana-Farber Cancer Institute
Monocyte Viral Reservoirs In HIV-1 Dementia

Galloway, Matthew P. -- Wayne State University
High Field MRS Assessment Of Stimulant Exposure In Rats

Garner, Craig C. -- Stanford University
Sap97 Isoforms In Trafficking Synaptic Glur1

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

Gebhart, Gerald F. -- University of Pittsburgh at Pittsburgh
Mediators and Modulation Of Nociception

Gelberg, Lillian -- University of California Los Angeles
Homeless Women: Drugs, Race/Ethicity, and Health Care

Gelernter, Joel E. -- Yale University
Approaches To the Genetics Of Substance Dependence

Gerak, Lisa R. -- University of Texas Health Science Center San Antonio
Behavioral Effects Of Neuroactive Steroids

Gewirtz, Jonathan C. -- University of Minnesota Twin Cities
Neural Substrates Of Anxiety In Acute Opiate Dependence

Gifford, Elizabeth J. -- Duke University
Multilevel Modeling Of Inpatient Care: Comorbid Youth

Gilbert, David G. -- Southern Illinois University Carbondale
NRT & Bupropion Mechanisms Of Efficacy In Smokers

Glass, Michael J. -- Weill Medical College of Cornell University
Opioids and Conditional Amygdala NMDA Receptor Knockout

Glennon, Richard A. -- Virginia Commonwealth University
Chemical/Behavioral Studies On Hallucinogenic Agents

Glenzer, Vicky Ann -- Oregon Center For Applied Science, Inc.
Internet Stepparent Training For Parents Of Adolescents

Goeders, Nicholas E. -- Louisiana State University Health Science Center Shreveport
Environmental Influences On Cocaine Self-Administration

Gordon, Judith S. -- Oregon Research Institute
Tobacco Cessation Via Doctors Of Chiropractic

Grace, Anthony A. -- University of Pittsburgh at Pittsburgh
Stress-Induced Alterations In Amygdala-LC Interactions

Greengard, Paul -- Rockefeller University
Drugs Of Abuse -- Role Of Protein Phosphorylation

Greenwell, Thomas N. -- Scripps Research Institute
Role Of the Bed Nucleus In Opiate Dependence

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

Guydish, Joseph R. -- University of California San Francisco
Organizational Change and Nicotine Dependence Treatment

Gwaltney, Chad J. -- Brown University
Ecological Momentary Assessment Of Adolescent Smoking Cessation

Haber, Suzanne N. -- University of Rochester
Reward, Compulsions and Habit Formation

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

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

Hanlon, Colleen A. -- Wake Forest University Health Sciences
Neuroimaging Of Motor Control In Chronic Cocaine Users

Hanson, Glen R. -- University of Utah
Pharmacology and Toxicology Of Methamphetamine Abuse

Hanson, Glen R. -- University of Utah
Neurochemical Alterations By Designer Drugs

Harden, Kathryn P. -- University of Virginia Charlottesville
Religiosity and Adolescent Problem Behavior

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Drug Use, Disorder & HIV/AIDS Risk In Juvenile Justice Youth:A Longitudinal Study

Thatcher, Dawn L. -- University of Pittsburgh at Pittsburgh
Adult Neurobehavioral Outcomes Of Adolescent Drug Abuse

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

Thomas, Mark J. -- University of Minnesota Twin Cities
Synaptic Plasticity In Animal Models Of Addiction

Thompson, Barbara L. -- Vanderbilt University
Developmental Consequences Of In Utero Cocaine

Thompson, Sanna J. -- University of Texas Austin
Family-Based Substance Use Treatment For Runaway Youth

Tidey, Jennifer W. -- Brown University
Biological and Behavioral Mechanisms Of Smoking In Schizophrenia

Tietz, Elizabeth I. -- University of Toledo Health Sciences Campus
Benzodiazepine-Induced Glutamate Receptor Plasticity

Toll, Lawrence R. -- SRI International
Subtype-Selective Nicotinic Receptor Ligands As Smoking Cessation Pharmacotherapy

Tranel, Daniel T. -- University of Iowa
Drug Abuse, Social Decision-Making, and Sex-Related Functional Brain Asymmetry

Traynor, John R. -- University of Michigan at Ann Arbor
Opioid Receptor Mechanisms

Tucker, Joan S. -- Rand Corporation
Drugs Use, Social Context, and HIV Risk In Homeless Youth

Tueckmantel, Werner -- Acenta Discovery, Inc.
Nicotinic Ligands As Smoking Cessation Agents

Tull, Matthew T. -- University of Maryland
Predictors Of Drug Related Attentional Biases Among Crack/Cocaine Users With PTSD

University of Utah -- University of Utah
Quantitation Of Drugs Of Abuse By GC/MS

University of Miami -- University of Miami
The National Hispanic Science Network On Drug Abuse

University Of Mississippi -- University Of Mississippi
Production, Analysis & Distribution Of Cannabis & Marijuana

Unterwald, Ellen M. -- Temple University
Regulation Of Delta Opioid Receptor Function By Cocaine

Valdez, Avelardo -- University of Houston
Substance Use and Other Health Consequences Among Katrina Evacuees In Houston

Van Bockstaele, Elisabeth J. -- Thomas Jefferson University
Opioid Modulation Of the Coeruleo-Cortical Pathway

Van Bockstaele, Elisabeth J. -- Thomas Jefferson University
Modulation Of Norepinephrine By Cannabinoids

Van Den Oord, Edwin -- Virginia Commonwealth University
In Silico Genome Scan With High-Throughput Addiction Related Phenotypes In Mice

Vanderah, Todd W. -- University of Arizona
Brain Stem Mechanisms Of Opioid Induced Pain

Vanderschuren, Louk J.M.J. -- University Medical Center Utrecht
Social Play Behavior In Periadolescent Rats In Relation To Later Drug Abuse

Vaughan, Roxanne A. -- University of North Dakota
Phosphorylation and Regulation Of Dopamine Transporters

Vezina, Paul R. -- University of Chicago
Nicotine Exposure: Molecular To Behavioral Consequences

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

Virginia Commonwealth University -- Virginia Commonwealth University
Preclinical Abuse Liability and Medications Discovery Testing

Virginia Commonwealth University -- Virginia Commonwealth University
Medication Discovery Using Rat Models Of Relapse To Drug Self Administration

Virk, Michael S. -- Oregon Health & Science University
Agonist Specific Mu-Opioid Receptor Regulation

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

Voigt, Robin M. -- Loyola University Chicago
GABAbeta Regulation Of Meth-Induced Associative Learning

Von Korff, Michael R. -- Center For Health Studies
Long-Term Opioid Management Of Chronic Pain: Trends and Risks

Von Zastrow, Mark E. -- Gordon Research Conferences
2007 Molecular Pharmacology Gordon Research Conference

Vorhees, Charles V. -- Children's Hospital Medical Center, Cincinnati
Developmental Effects Of Methamphetamine-Like Stimulants

Vorhees, Charles V. -- Children's Hospital Medical Center, Cincinnati
Effects Of Neonatal On Brain and Behavior

Vujanovic, Anka A. -- University of Vermont & State Agricultural College

Nicotine Withdrawal and Panic Responding

Wade, Carrie A. -- University of Minnesota Twin Cities
Neuropharmacology Of Neuropathic Pain and Addiction

Wagner, John J. -- University of Georgia
Cocaine-Induced Metaplasticity In the Hippocampus

Wakschlag, Lauren S. -- University of Illinois at Chicago
Prenatal Smoking and Patterns Of Youth Problem Behavior

Walker, J. Michael -- Indiana University Bloomington
Role Of Endogenous Vanilloids and Cannabinoids In Pain

Walsh, Sharon L. -- University of Kentucky
Evaluation Of Novel Treatments For Stimulant Dependence

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

Wang, Qiang -- University of Missouri Kansas City
Metabotropic Glutamate Regulation Of Amphetamine Action

Wang, Zuoxin -- Florida State University
Dopamine Regulates Drug and Social Reward Interactions

Ward, Kenneth D. -- University of Memphis
Population-Based Assessment Of Post-Katrina Smoking Relapse

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

Watkins, Linda R. -- University of Colorado at Boulder
Pain Facilitation Via Neuron-To-Glia Signaling

Weerts, Elise M. -- Johns Hopkins University
Behavioral Pharmacology and GHB Physical Dependence

Wei, Li-Na L. -- University of Minnesota Twin Cities
Studies Of the Mouse Kappa Opioid Receptor Gene

Weisner, Constance M. -- University of California San Francisco
Integrated Drug and Medical Care-Cost and Effectiveness

Weisner, Constance M. -- University of California San Francisco
Course Of Problems In Adolescent Drug Treatment Intakes

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

Weiss, Roger D. -- McLean Hospital, Belmont, MA
CTN: Harvard University Northern New England Node

Weissman, Myrna M. -- Columbia University Health Sciences
Children At High and At Low Risk For Depression

Wheeler, Robert A. -- University of North Carolina Chapel Hill
The Nucleus Accumbens and Relative Reward

Whistler, Jennifer L. -- Ernest Gallo Clinic and Research Center
Role Of Opioid Receptor Trafficking In Tolerance and Dependence

Wiederhold, Mark D. -- Virtual Reality Medical Center
Low-Cost FMRI-Safe Virtual Reality Glasses

Wiley, Jenny L. -- International Cannabinoid Research Society

ICRS Symposium On the Cannabinoids

Williams, John T. -- Oregon Health & Science University
Chronic Morphine: Regulation Of Ion Conductances

Williams, John T. -- Oregon Health & Science University
Cocaine Effecs On Single Neurons

Winsauer, Peter J. -- Louisiana State University Health Science Center New Orleans
Effects Of Chronic THC In Adolescence

Wolf, Marina E. -- Rosalind Franklin University of Medicine & Science
Glutamate Transmission and Behavioral Sensitization

Wolf, Marina E. -- Rosalind Franklin University of Medicine & Science
Glutamate and Psychostimulant-Induced Neuroadaptations

Wong, Frank Y. -- Georgetown University
Sexuality, HIV/Drug In 3 Groups Of Asian/Gay/Bi Men/MSM

Woods, James H. -- University of Michigan at Ann Arbor
Development Of Esterases For the Treatment Of Cocaine Overdose and Abuse

Woody, George E. -- University of Pennsylvania
Delaware Valley Node Of the Clinical Trials Network

Woolverton, William L. -- University of Mississippi Medical Center
Self-Administration Of Drug Combinations: Polydrug Abuse

Worley, Paul F. -- Johns Hopkins University
Effector IEG, Homer and Drug Addiction

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

Wu, Christine C. -- University of Colorado Denver/Health Sciences Center Aurora
Proteomic Tools For the Comprehensive Analysis Of Dopamine Transporter Topology

Wu, Elwin -- Columbia University New York Morningside
Service Use, ATI Program Outcomes, and Pro-Social Change

Wu, Li-Tzy -- Duke University
Hallucinogen Use: Onset and Abuse/Dependence

Wu, Ping -- Columbia University Health Sciences
Ecstasy "Epidemic" and Youth: Trends, Comorbidity, Risk and Protective Factors

Wu, Z. Helen -- University of Texas Medical Branch Galveston
Effects Of Stressors On Drug Use In Young, Poor Women

Xenotech, LLC - Xenotech, LLC
In Vitro Metabolism & Metabolite Quantification

Xian, Hong -- Washington University
Environmental Risks For Smoking: A Genetically Informed Children Of Twins Design

Xu, X. Z. -- University of Michigan at Ann Arbor
Mechanisms Of Nicotine-Induced Behaviors

Xu, Xiangmin -- Salk Institute For Biological Studies

Local Connections and In Vivo Physiology Of Inhibitory Cortical Neurons

Yaksh, Tony L. -- University of California San Diego
The Pharmacology Of Spinal Analgesics

Yamamoto, Bryan K. -- Boston University Medical Campus
Methamphetamine Toxicity and Corticostriatal Glutamate

Yano, Motoyo -- Rosalind Franklin University of Medicine & Science
Methylphenidate-Induced Gene Expression In the Cortex

Yu, John-Paul J. -- University of Illinois Urbana-Champaign
Treatment and Control Of Mycobacterial Infections

Zemlan, Frank -- P2d, Inc.
Cocaine Therapeutic: Pd2007

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

Zhang, Heping -- Yale University
Methodological Research On Substance Use

Zhao, Min -- Shanghai Mental Health Center
Gender Difference Of HIV Risks Among IDUs In China

Zweifel, Larry S. -- University of Washington
Genetic Dissection Of Brain Reward Circuits

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Extramural Policy and Review Activities

Receipt, Referral, and Review

NIDA received 1219 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 763 applications.

OEA arranged and managed 18 grant review meetings in which 300 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 13 contract proposal reviews.

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

Conflicts with the chartered committees
Center Grant Applications
Program Project Grant applications
Behavioral Science Track Award for Rapid Transition (B/START)
Imaging Science Track Awards for Research Transition (I/START)
Cutting-Edge Basic Research Awards (CEBRA) (R21)
Conference Grants (R13)
NIH Pathway To Independence (PI) Awards (K99/R00)
Requests for Applications (RFA)

OEA managed the following RFA reviews:

- DA07-001: Announcement of A Limited Competition of The National Drug Abuse Treatment Clinical Trials Network (U10)
- DA07-005: Field-Deployable Tools for Quantifying Exposures to Psychosocial Stress and to Addictive Substances for Studies of Health and Disease (U01)

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

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

- N01DA-7-1132: Technical Support for Constituency Outreach and Research Dissemination
- N01DA-7-2211: Administrative and Meeting support for the Clinical Trials Network

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- N01DA-7-8872: Rodent Drug Discrimination
- N01DA-7-9911: Research Support and Animal Care Services

Phase I SBIR Contract Reviews

- N43DA-7-1131 (Topic 092): Mechanisms and Methods to Maximize Data Utilization
- N43DA-7-1133 (Topic 076): Development of Science Literacy Materials or Programs
- N43DA-7-2210 (Topic 089): Development of Practical Training Materials for Evidence-Based Treatment
- N43DA-7-7760 (Topic 085): Metabolomics in Drug Abuse Research
- N43DA-7-8869 (Topic 082): Development of Novel Drug Delivery Systems for Treatment Medications

Phase II SBIR Contract Reviews

- N44DA-7-1128 (Topic 084): International Virtual Collaboration (First of 2 planned Awards)
- N44DA-7-5534 (Topic 080): Training and Infrastructure Development
- N44DA-7-7756 (Topic 064): Molecular Profiling of Tissues (First of 2 Planned Awards)
- N44DA-7-7759 (Topic 064): General Analytical Techniques (Second of 2 Planned Awards)

Certificates of Confidentiality

Between December 8, 2006 and April 5, 2007, OEA processed 83 Certificate applications, including 19 for extension of expiration dates and 6 for amended protocols.

Extramural Outreach

Dr. Gerald McLaughlin, OEA, is the NIDA Liaison to the NIH-wide committee dealing with all aspects of the NIH transition to electronic grant submission and also serves on the trans-NIH workgroups tasked with implementing the electronic transition of the R01, U01 grant mechanisms, and appendix guidelines, and serves as a NIDA resource for related issues.

Dr. Gerald McLaughlin is a member of the NIH Review Users Group and an associated workgroup to improve J2EE Peer Review functionalities and assure related training, as well as another associated workgroup dealing with subproject capabilities.

Dr. Gerald McLaughlin is a member of a trans-NIH Human Subjects committee that is developing a revised and updated Human Subjects reference manual. He is also updating NIDA guidelines for public and community reviewers, and summarizing a Cultural and Ethical Issues in Review workgroup for NIDA OEA.

Dr. Teresa Levitin, Director, OEA, continues to serve on the NIH Director's Pioneer Award implementation committee.

Dr. Mark Swieter, OEA, continues to serve as NIDA's representative on the NIH Review Policy Committee and was recently selected to be a member of the RPC Steering Committee.

Staff Training and Development

The OEA Symposium Series, a forum for staff training and sharing of ideas and

Planned Meetings

Publications

Staff Highlights

Grantee Honors

information, continued through the spring. Activities included open forums for discussions about electronic submission of R01 applications, proposed plans for shortening research plans in R01 applications, and new rules for appendix materials. There were presentations about Certificate of Confidentiality procedures by Dr. Mark Green and about the NIDA AIDS Program by Dr. Jacques Normand.

The CTN Data and Safety Monitoring Board(s) met: January 11, 2007 to discuss a safety update of study 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).

January 29, 2007 to review and discuss study protocol CTN 0031 Stimulant Abuser Groups to Engage in 12-Step (STAGE-12): Evaluation of a Combined Individual-Group Intervention to Reduce Stimulant and Other Drug Use by Increasing 12-Step Involvement.

March 22, 2007 to review and discuss the progress of study 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).

April 5, 2007 to review and discuss the progress of study protocol CTN 0027 Starting Treatment with Agonist Replacement Therapies (START) study implementation. The board discussed the Final Study Reports of four studies:

- CTN 0010: Bup/NX for Adolescents/Young Adults
- CTN 0013: MET for Pregnant Drug Users
- CTN 0017: HIV Intervention
- CTN 0020: Job Seekers

April 6, 2007 to review and discuss the progress of study protocol CTN 0030 Prescription Opioid Addiction Treatment Study (POATS).

Director's Report to the National Advisory Council on Drug Abuse - May, 2007

Congressional Affairs (Prepared May 2, 2007)

Appropriations

FY 2007: On February 15, the President signed into law H. J. Res. 20, the "Revised Continuing Appropriations Resolution, 2007," as P.L. 110-5. For NIH, the resolution appropriated an increase of approximately $620 million over FY 2006. NIDA received a slight budget increase ($584,000) for a final FY 2007 level of $999,422,000.

FY 2008: The President's budget proposes $28.621 billion for NIH, $310 million below the FY 2007 Joint Resolution level. Within this total, NIDA would receive a slight increase of $943,000 over the FY 2007 level, totaling $1,000,365,000.

110th Congress

Followup from 2/07 report: As a result of the November 2006 elections, both the Senate and House of Representatives are now under Democratic Party control. As a result of this shift, there are significant changes to both the leadership and membership of those committees most relevant to NIDA's work. Also, certain committee jurisdictions have changed.

Senate: In the Senate, primary focus is on the

- Committee on Appropriations (Subcommittee on Labor, Health and Human Services, and Education; Financial Services [now with ONDCP jurisdiction] and Commerce, Justice, Science);
- Committee on Health, Education, Labor, and Pensions (HELP);
- Committee on the Judiciary (Subcommittee on Crime and Drugs); and the
- Caucus on International Narcotics Control (this is an officially recognized Caucus, established by law in 1985).

House: In the House, primary focus is on the

- Committee on Appropriations (Subcommittee on Labor, Health and Human Services, Education, and Related Agencies; Financial Services [now with ONDCP jurisdiction], and Commerce, Justice, Science and Related Agencies);
- Committee on Energy and Commerce (Subcommittee on Health); and the
- Committee on Oversight and Government Reform (formerly Government Reform). (Subcommittee on Domestic Policy - formerly Criminal Justice, Drug Policy, and Human Resources).

Subcommittee Rosters - Senate

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Appropriations - Labor, Health and Human Services, and Education

Democrats	Republicans
Tom Harkin, IA (Chair)	Arlen Specter, PA (Ranking Member)
Daniel Inouye, HI	Thad Cochran, MS
Herbert Kohl, WI	Judd Gregg, NH
Patty Murray, WA	Larry Craig, ID
Mary Landrieu, LA	Kay Bailey Hutchison, TX
Richard Durbin, IL	Ted Stevens, AK
Jack Reed, RI	Richard Shelby, AL
Frank Lautenberg, NJ	

Appropriations - Financial Services

Democrats	Republicans
Richard Durbin, IL (Chair)	Sam Brownback, KS (Ranking Member)
Patty Murray, WA	Christopher Bond, MO
Mary Landrieu, LA	Richard Shelby, AL
Frank Lautenberg, NJ	Wayne Allard, CO
Ben Nelson, NE	

Appropriations - Commerce, Justice, Science

Democrats	Republicans
Barbara Mikulski, MD (Chair)	Richard Shelby, AL (Ranking Member)
Daniel Inouye, HI	Judd Gregg, NH
Patrick Leahy, VT	Ted Stevens, AK
Herbert Kohl, WI	Pete Domenici, NM
Tom Harkin, IA	Mitch McConnell, KY
Byron Dorgan, ND	Kay Bailey Hutchison, TX
Dianne Feinstein, CA	Sam Brownback, KS
Jack Reed, RI	Lamar Alexander, TN
Frank Lautenberg, NJ	

Health, Education, Labor, and Pensions (NIH jurisdiction retained by full committee)

Democrats	Republicans
Edward Kennedy, MA (Chair)	Mike Enzi, WY (Ranking Member)
Christopher Dodd, CT	Judd Gregg, NH
Tom Harkin, IA	Lamar Alexander, TN
Barbara A. Mikulski, MD	Richard Burr, NC
Jeff Bingaman, NM	Johnny Isakson, GA
Patty Murray, WA	Lisa Murkowski, AK
Jack Reed, RI	Orrin Hatch, UT
Hillary Rodham Clinton, NY	Pat Roberts, KS
Barack Obama, IL	Wayne Allard, CO
Bernard Sanders, (I), VT	Tom Coburn, OK
Sherrod Brown, OH	

Judiciary (Crime and Drugs)

Democrats	Republicans
Joseph Biden, DE (Chair)	Lindsey Graham, SC (Ranking Member)
Edward Kennedy, MA	Arlen Specter, PA
Herbert Kohl, WI	Orrin Hatch, UT
Dianne Feinstein, CA	Charles Grassley, IA
Russ Feingold, WI	Jeff Sessions, AL
Charles Schumer, NY	John Cornyn, TX
Richard Durbin, IL	

Caucus on International Narcotics Control

Democrats
Joseph Biden, DE
Diane Feinstein, CA
Appointment pending
Appointment pending

Republicans
Charles Grassley, IA
Jeff Sessions, AL
Norm Coleman, MN

Subcommittee Rosters - House

Appropriations - Labor, Health and Human Services, Education, and Related Agencies

Democrats
David Obey, WI (Chair)
Nita Lowey, NY
Rosa DeLauro, CT
Jesse Jackson, IL
Patrick Kennedy, RI
Lucille Roybal-Allard, CA
Barbara Lee, CA
Tom Udall, NM
Michael Honda, CA
Betty McCollum, MN
Tim Ryan, OH

Republicans
James Walsh, NY (Ranking Member)
Ralph Regula, OH
John Peterson, PA
Dave Weldon, FL
Michael Simpson, ID
Dennis Rehberg, MT

Appropriations - Commerce, Justice, Science, and Related Agencies

Democrats
Alan Mollohan, WV (Chair)
Patrick Kennedy, RI
Chaka Fattah, PA
C.A "Dutch" Ruppersberger, MD
Adam Schiff, CA
Michael Honda, CA
Rosa DeLauro, CT
John Olver, MA

Republicans
Rodney Frelinghuysen, NJ
John Culberson, TX
Harold Rogers, KY
Tom Latham, IA
Robert Aderholt, AL

Appropriations - Financial Services

Democrats
Jose Serrano, NY (Chair)
Carolyn Kilpatrick, MI
C.A "Dutch" Ruppersberger, MD
Debbie Wasserman Schultz, FL
Peter Visclosky, IN
Robert "Bud" Cramer, Jr., AL
Maurice Hinchey, NY
Lucille Roybal-Allard, CA

Republicans
Ralph Regula, OH
Tom Latham, IA
Mark Kirk, IL
Dennis Rehberg, MT
Rodney Alexander, LA

Energy and Commerce - Health

Democrats
Frank Pallone, NJ (chair)
Henry Waxman, CA
Edolphus Towns, NY
Bart Gordon, TN
Anna Eshoo, CA
Gene Green, TX
Diana DeGette, CO

Republicans
Nathan Deal, GA (Ranking Member)
Ralph Hall, TX
Charlie Norwood, GA
Barbara Cubin, WY
John Shadegg, AZ
Steve Buyer, IN

Lois Capps, CA
Tom Allen, ME
Tammy Baldwin, WI
Eliot Engle, NY
Jan Schakowsky, IL
Hilda Solis, CA
Mike Ross, AK
Darlene Hooley, OR
Anthony Weiner, NY
Jim Matheson, UT

Joseph Pitts, PA
Mary Bono, CA
Mike Ferguson, NJ
Mike Rogers, MI
Sue Myrick, NC
John Sullivan, OK
Tim Murphy, PA
Michael Burgess, TX

Oversight and Government Reform - Domestic Policy

Democrats	Republicans
Dennis Kucinich, OH (Chair)	Darrell Issa, CA (Ranking Member)
Tom Lantos, CA	Dan Burton, IN
Elijah Cummings, MD	Christopher Shays, CT
Diane Watson, CA	John Mica, FL
Christopher Murphy, CT	Mark Souder, IN
Danny Davis, IL	Chris Cannon, UT
John Tierney, MA	Brian Bilbray, CA
Brian Higgins, NY	
Bruce Braley, IA	

HEARINGS, BRIEFINGS, AND EVENTS OF INTEREST

Friends of NIDA Congressional Briefing - Blending Research and Practice

On February 22, 2007, the Friends of the National Institute on Drug Abuse held its seventh in a series of educational briefings on Capitol Hill. The briefing, titled "Drug Abuse Treatment: The Blending of Research and Practice," drew an audience of over 100, including staff from a total of 50 different House and Senate offices, and was co-sponsored by 18 scientific and professional organizations.

The event focused on the issue of bridging the divide between scientific findings and their implementation and how to quicken the pace of real-world application of science-based research results. In order to accomplish this, the NIDA Research and Practice Blending Initiative has been developed, which is an innovative effort to translate research to practice and to incorporate feedback from multiple stakeholders to make the best treatments available to those who need them. Through the Blending Initiative, NIDA is able to directly address the challenge of connecting the science of drug abuse and addiction to real life practice.

NIDA Deputy Director Dr. Timothy Condon opened the briefing with an overview of the Institute's work in this crucial area. He was followed by Dr. Gregory Brigham, who shared his experiences as a member of a Blending Team, which provides the tools necessary to access and adopt NIDA research protocols. Brigham is the Chief Research Officer at Maryhaven, a Community Treatment Program (CTP) in Columbus, Ohio, and a Research Scientist in the College of Medicine at the University of Cincinnati. Maryhaven joined the NIDA Clinical Trials Network (CTN) in 2000 as a member of the Ohio Valley Node. Finally, Dr. Dennis McCarty, a professor in the Department of Public Health and Preventive Medicine at Oregon Health Sciences University, discussed his work as Principal Investigator for the Oregon Node of the CTN. These presenters did an excellent job in not only describing their own work, but in how the work of NIDA, the CTN research coordinators, and all of the CTPs continue to work together to discover, understand, and implement crucial approaches to successful drug abuse and addiction treatment. For additional details and some

photos, go to http://www.thefriendsofnida.org/briefing-2007-02.php.

House Appropriations Hearing for NIDA

On March 1, 2007, NIDA Director Dr. Nora Volkow testified in front of the House Appropriations Subcommittee on Labor, Health and Human Services, and Education. She joined NIH and SAMHSA colleagues in a "theme" hearing focusing on drug abuse and mental health. See full hearing report below.

House Appropriations Hearing for NIH

On March 6, 2007, NIH Director Dr. Elias Zerhouni testified in front of the House Appropriations Subcommittee on Labor, Health and Human Services, and Education. See full hearing report below.

Senate Appropriations Hearing for NIH

On March 19, 2007, NIH Director Dr. Elias Zerhouni testified in front of the Senate Appropriations Subcommittee on Labor, Health, and Human Services, and Education. See full hearing report below.

Senate Appropriations Hearing for NIDA

On March 26, 2007, NIDA Director Dr. Nora Volkow testified in front of the Senate Appropriations Subcommittee on Labor, Health and Human Services, and Education. She joined NIH colleagues in a "theme" hearing focusing on "mind, brain, and behavioral research." See full hearing report below.

BILLS OF INTEREST

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

Potential Institute Name Change -- H.R.1348/S. 101 - On March 6, 2007, Representatives Patrick Kennedy (D-RI) and John Sullivan (R-OK) introduced H.R.1348, to redesignate the National Institute on Drug Abuse as the National Institute on Diseases of Addiction, and to redesignate the National Institute on Alcohol Abuse and Alcoholism as the National Institute on Alcohol Disorders and Health. Similarly, on March 28, 2007, Senators Joseph Biden (D-DE), Edward Kennedy (D-MA) and Michael Enzi (R-WY) introduced S. 1011, the Recognizing Addiction as a Disease Act of 2007, which would make the same changes. In a press release, Senator Biden said the intent of the legislation is to recognize addiction as a preventable and treatable neurobiological disease, and to better identify the roles and missions of our research institutes. "Addiction is a neurobiological disease - not a lifestyle choice - and it's about time we start treating it as such," said Sen. Biden. "We must lead by example and change the names of our Federal research institutes to accurately reflect this reality. By changing the way we talk about addiction, we change the way people think about addiction, both of which are critical steps in getting past the social stigma too often associated with the disease." The House bill was referred to the Health Subcommittee of the Energy and Commerce Committee; the Senate bill was referred to the Health, Education, Labor and Pensions Committee.

Stem Cells -- H.R. 3/S. 5 - On January 5, 2007, Representative Diana DeGette (D-CO) introduced H.R. 3, the Stem Cell Research Enhancement Act of 2007. The Senate companion, S. 5, was introduced on January 4, 2007 by Senate Majority Leader Harry Reid (D-NV). The bills would require the Secretary of HHS to conduct and support research using human embryonic stem cells regardless of the date on which such cells were derived. The House passed its bill on January 11, 2007 and the Senate passed its bill on April 11, 2007. The Senate bill was amended prior to floor consideration. As amended, the bill would also require the Secretary to conduct and support research

involving methods of obtaining pluripotent stem cells that do not involve the use of human embryos. The White House has issued Statements of Administrative Policy in opposition to both S. 5 and H.R. 3.

Stem Cells -- S. 30 - On April 11, 2007, the Senate passed S. 30, the Hope Offered Through Principled and Ethical Stem Cell Research Act, by a roll call vote of 70-28. The bill, introduced on March 29, 2007, by Representative Norm Coleman (R-MN) would require the Secretary to support research to develop pluripotent stem cells using methods that do not involve either the creation of, harm to, or destruction of human embryos. The White House issued a Statement of Administrative Policy in support of S. 30.

Genetic Non-discrimination -- H.R. 493/S. 358 - On January 16, 2007, Representative Louise Slaughter (D-NY) introduced H.R. 493, the Genetic Information Nondiscrimination Act of 2007. The Senate companion, S. 358, was introduced by Senator Olympia Snowe (R-ME) on January 22, 2007. These bills, which would prohibit discrimination in health insurance and employment on the basis of predictive genetic information, are identical to legislation passed by the Senate during the 109th Congress. The bills would prohibit health insurers in both the group and individual markets from (1) using genetic information to impose enrollment restrictions or to adjust premium or contribution amounts, (2) requesting genetic testing or results except as necessary for treatment, payment, or health care operations, or (3) requesting or requiring the use of genetic information for the purposes of underwriting. The bills define a genetic test as an analysis of human DNA, RNA, chromosomes, proteins, or metabolites that detects genotypes, mutations, or chromosomal changes. The House passed its bill on April 25, 2007; the Senate Health, Education, Labor and Pensions committee has reported its bill favorably; floor action in the Senate is pending.

Insurance Parity for Mental Health and Substance Abuse -- H.R. 1424/S.558 - On February 12, 2007, Senator Pete Domenici (R-NM) introduced the Mental Health Parity Act of 2007, a bill to provide parity between health insurance coverage of mental health benefits and benefits for medical and surgical services. On March 9, 2007, Representative Patrick Kennedy (D-RI) introduced the Paul Wellston Mental Health and Addiction Equity Act of 2007, to amend section 712 of the Employee Retirement Income Security Act of 1974, section 2705 of the Public Health Service Act, and section 9812 of the Internal Revenue Code of 1986 to require equity in the provision of mental health and substance-related disorder benefits under group health plans. The Senate bill has been reported favorably from committee. The House bill awaits further committee action.

Community Re-entry for Prisoners -- H.R. 1593/S. 1060 - On March 20, 2007, Representative Danny Davis (D-IL) introduced the Second Chance Act of 2007, to reauthorize the grant program for reentry of offenders into the community in the Omnibus Crime Control and Safe Streets Act of 1968, to improve reentry planning and implementation, and for other purposes. The Senate version of this bill was introduced by Senator Joe Biden (D-DE) on March 29, 2007. The bills include a strong focus on drug treatment in the criminal justice system, and consultation with NIDA is required in several bill sections. The House bill has been reported favorably out of committee; the Senate bill awaits action.

Tobacco -- H.R. 1108/S. 625 - On February 15, 2007, Representative Henry Waxman (D-CA) introduced H.R. 1108, the Family Smoking Prevention and Tobacco Control Act - a bill to protect public health by providing the Food and Drug Administration with certain authority to regulate tobacco products. Senator Edward Kennedy (D-MA) introduced an identical bill in the Senate. There have been hearings in the Senate on this bill. Further action is pending in the House and Senate.

H.R. 1170 - On February 16, 2007, Representative Martin Meehan (D-MA) introduced H.R. 1170, the Comprehensive Awareness of Problem Gambling Act of 2007. H.R. 1170 includes a research provision which would require the President to establish a national program of research on problem gambling. The bill would require the President to appoint an advisory commission to coordinate activities of Federal agencies relating to research on problem gambling including the activities of the NIH. H.R. 1170 was referred to the House Committee on Energy and Commerce.

H.R. 1200 - On February 27, 2007, Representative Jim McDermott (D-WA) introduced H.R. 1200, the American Health Security Act of 2007. The purpose of the bill is "to provide for health care for every American and to control the cost and enhance the quality of the health care system." Of interest to NIH is section 722, which would establish the Office of Primary Care and Prevention Research within the Office of the Director; require the establishment of a data system of information regarding primary care and prevention research that is conducted or supported by the ICs; require the establishment of a clearinghouse to provide information on research and prevention activities of the ICs that relate to primary care and prevention research; require a biennial report on primary care and prevention research; and authorize $150 million for FY 2008, $180 million for FY 2009, and $216 million for FY 2010. In addition, the legislation would amend the authorities of the NIH Director to require that sufficient resources are sufficiently allocated for projects on primary care and prevention research. H.R. 1200 was jointly referred to the House Committees on Energy and Commerce; Ways and Means; Oversight and Government Reform; and Armed Services.

H.R. 1309 - On March 14, 2007, the House passed H.R. 1309, the Freedom of Information Act Amendments of 2007. Provisions of interest to NIH would shorten the time limits on which to act on requests, require agencies to establish a system to assign an individualized tracking number for each request for information, establish a telephone line or Internet service regarding the status of a request, institute additional reporting requirements regarding FOIA requests and processing times, and broaden "media status" to those who have "internet publications." The bill has been referred to the Senate.

H.R. 1663 - On March 23, 2007, Representative Pete Stark (D-CA) introduced HR 1663, The Medicare Mental Health Modernization Act of 2007, to amend title XVIII of the Social Security Act to expand and improve coverage of mental health services under the Medicare Program. The bill was referred to the Committee on Ways and Means, and the Committee on Energy and Commerce.

S. 884 - On March 14, 2007, Senator Richard Durbin (D-IL) introduced the Family-Based Meth Treatment Access Act of 2007, to amend the Public Health Service Act regarding residential treatment programs for pregnant and parenting women, a program to reduce substance abuse among nonviolent offenders, and for other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions.

S. 980 - On March 23, 2007, Senator Dianne Feinstein (D-CA) introduced the Online Pharmacy Consumer Protection Act of 2007, to amend the Controlled Substances Act to address online pharmacies. The bill was referred to the Judiciary Committee.

S. 1082 - On April 10, 2007, Senator Edward Kennedy (D-MA) introduced the Food and Drug Administration Revitalization Act. On April 18, 2007, the Senate Committee on Health, Education, Labor and Pensions reported out an amended version of the bill. The bill would expand the Clinicaltrials.gov registry to include mandatory reporting of certain drug and device clinical trials. The bill would also require that the ClinicalTrials.gov website provide corresponding linkages to peer-reviewed literature and certain publicly available FDA information regarding the results of those trials. S. 1082 also includes

provisions to reauthorize the Best Pharmaceuticals for Children Act. Senate floor action is pending.

HEARING REPORTS

House Appropriations Subcommittee on Labor-HHS and Education Holds Hearing on President's Budget Request for SAMHSA, NIDA, NIAAA and NIMH; Directors of Each Agency Testify

(Summary provided to NIDA by the Legal Action Center)

On Thursday, March 1, 2007, the House Appropriations Subcommittee responsible for funding programs within the Departments of Labor, Health and Human Services and Education convened a hearing to discuss the FY 2008 budget request for each of the key federal agencies responsible for administering drug and alcohol and mental health prevention, treatment, education and research programs. The witnesses representing each of the agencies were: Terry Cline, Ph.D., Administrator of the Substance Abuse and Mental Health Services Administration; Nora Volkow, M.D., Director of the National Institute on Drug Abuse, T.K. Li, M.D., Director of the National Institute on Alcohol Abuse and Alcoholism; and Thomas Insel, M.D., Director of the National Institute of Mental Health. Chairman of the Full House Appropriations Committee and the Subcommittee on Labor-HHS, Congressman David Obey (D-WI), chaired the hearing. Other Committee members in attendance included Subcommittee Ranking Member Representative James Walsh (R-NY), and Representatives Jesse L. Jackson, Jr. (D-IL), Patrick J. Kennedy (D-RI), Lucille Roybal-Allard (D-CA), Tom Udall (D-NM), Michael Honda (CA), Tim Ryan (D-OH), John E. Peterson (R-PA), and Dennis R. Rehberg (R-MT). Substance Abuse and Mental Health Services Administration.

Dr. Cline began his testimony by stating that despite the President's request to cut the budget of SAMHSA by $159 million from the FY 2007 continuing resolution funding level which would represent a five percent overall reduction for SAMHSA, an aggressive agenda has been set for the upcoming year. According to Dr. Cline's remarks the focus of SAMHSA's budget is on service delivery programs, such as the Mental Health and Substance Abuse Block and Formula Grants; resources will also be invested in program priority areas of children's mental health services, suicide prevention, school violence prevention, prevention and treatment of Post-Traumatic Stress Disorder, the Screening, Brief Intervention, Referral, and Treatment (SBIRT) program, HIV/AIDS and criminal and juvenile justice. In regards to expanding substance abuse treatment capacity, Dr. Cline articulated that the FY 2008 budget enhances accountability and improved performance outcomes by requiring States to report on the Community Mental Health Services (MHBG) and Substance Abuse Prevention and Treatment (SAPT) Block grant funds; States reporting on the SAPT Block Grant National Outcomes (NOMS) could receive an increase to their State allocation if some States do not report.

Dr. Cline testified that SAMHSA continues to expand treatment capacity through the Access to Recovery (ATR) program and provides increases for screening of drug addiction and treatment for those involved with the criminal justice system. Despite a cut of $36.4 million to the Center for Substance Abuse Prevention, Dr. Cline stated that the budget will continue to fully support the prevention activities of SAMHSA, including the Minority HIV/AIDS and Substance Abuse Prevention Grants, the Fetal Alcohol Spectrum Disorder Center for Excellence, and the Strategic Prevention Framework grant program. Citing the progress that has been made in reducing youth drug use in America Dr. Cline also stated that SAMHSA will continue to focus energy and take a leadership role in the prevention of underage drinking; alcohol remains the

drug of choice among adolescents and Dr. Cline acknowledged that more progress needs to be made in reducing underage drinking rates.

National Institute on Drug Abuse

Dr. Volkow began her remarks by highlighting the results of NIDA's latest Monitoring the Future survey which show a 23 percent decline over the last five years in any past-month illicit drug use by students in the 8th, 10th and 12th grade combined. Despite progress with rates of youth drug use, Dr. Volkow cited concern with misuse of prescription medications which has produced steep increases in abuse-related emergency room admissions; additionally, use of prescription medications, along with over the counter drugs (cough medicine), account for five of the top six drug abuse categories reported by 12th graders. Prevention was emphasized as critical and Dr. Volkow explained that NIDA continues to focus on adolescence, because that is typically when drug abuse and addiction begin. Since addiction results from a complex interaction of drugs, genes and environmental and developmental factors, NIDA has also made the study of these interactions a priority. NIDA's treatment research identifying the brain circuits that underlie addiction, such as craving, euphoria, and inhibitory control have opened the door to different treatment approaches, including the possibility of using neurofeedback, where patients learn to regulate specific regions in their brains by getting feedback from real-time brain images. Dr. Volkow also cited progress in the development of addiction medications, as well as immunotherapeutic strategies, which are based on the development of vaccines to generate antibodies to the drug that block its entry into the brain and thereby interfere with its effects.

Dr. Volkow emphasized one of NIDA's major objectives of translating research into practice by highlighting its Criminal Justice Drug Abuse Treatment Studies (CJ-DATS) initiative; this initiative is aimed at bringing new treatment models into the criminal justice system to improve outcomes for individuals with drug histories. Dr. Volkow also spoke about the Drug Abuse Treatment Clinical Trials Networks (CTN) which brings evidenced-based treatments to community settings, and the establishment of four Centers of Excellence for Drug Abuse Information, in collaboration with the American Medical Association. Another area of priority, according to Dr. Volkow's testimony, is HIV/AIDS where NIDA is supporting preclinical and clinical studies that examine the interactions between: drugs of abuse and HIV medication, HIV and the plasticity (relative to changes that lead to addiction), and HIV and neurotoxicity (with regard to the adverse drug effects that result in conditions such as dementia and Parkinsonian symptoms); NIDA is also supporting research to make testing more acceptable in communities nationwide.

National Institute on Alcohol Abuse and Alcoholism

Dr Li's testimony began with a reminder about the seriousness of excessive alcohol use which costs the Unites States an estimated $185 billion annually and is ranked by the Centers for Disease Control and Prevention as the third leading cause of preventable death in the United States. Dr. Li articulated NIAAA's strong research and prevention focus on pregnant women, children and adolescents, including the agency's work on the interplay between hormones, brain development, and alcohol use. Dr. Li also spoke about the work of the Interagency Coordinating Committee for the Prevention of Underage Drinking and the forthcoming Surgeon General's Call to Action on underage drinking. In addition to recent research findings that will improve the diagnoses of alcohol dependence, NIAAA is supporting research to improve treatment options, including identifying the next generation of medications, and understanding how individuals change harmful drinking patterns. In particular, Dr. Li emphasized that success can only be achieved if individuals have access to treatment and that coverage of mental health and drug and alcohol addiction services would allow a greater proportion of individuals to receive the care they need.

National Institute of Mental Health

Dr. Insel began his remarks by summarizing how research has transformed the understanding of mental disorders by defining mental disorders as brain disorders that begin early in life; mental disorders along with addictive disorders are the most common chronic illnesses of young people in the United States. NIMH's efforts have focused on predicting who is at risk for developing disease; pre-empting the disease process; personalizing interventions; and ensuring that clinical research involves participation from the diversity of people and settings involved in health care. Dr. Insel indicated that NIMH plans to expand its efforts in treatment development, with an enhanced focus on medications that reverse the cognitive deficits in schizophrenia, additional studies of novel antidepressants, and new efforts in autism, anxiety disorders, and eating disorders. Dr. Insel emphasized NIMH's collaboration with SAMHSA's Center for Mental Health Services (CMHS) on the Mental Health Transformation State Incentive Grant program.

Members' Remarks

Subcommittee Ranking Member Congressman James Walsh (R-NY) began his opening remarks by stating his concern with how the agencies are addressing the mental health issues of active duty troops and veterans. Rep. Walsh also stated that building a foundation for research is good, but only if it translates into practice, and that he would like to hear more about the agencies' efforts to turn research into practice. Chairman Obey (D-WI) began by expressing his frustration with the belief that level funding means that there will not be cuts, when in fact, it does not take into account inflation and population growth; Obey stated "we are headed in the wrong direction" with the Administration's budget request and asked the witnesses to explain the challenges that level funding would create for their agencies. Dr. Cline responded by highlighting the efforts of SAMHSA to develop a comprehensive data strategy, which will help translate data into outcomes to better show results; additionally, he emphasized the continued importance of investing in prevention. Dr. Volkow discussed the difficulty of bringing medications into medical practice, in part due to the lack of involvement of the pharmaceutical industry in this particular area of medication development, and also stated that clinical trials are delayed because of budget shortfalls. Dr. Li articulated that it is a struggle to change the culture of binge drinking in youth and that it remains important to identify those who are at high risk for alcohol dependence, both of which are priority areas of NIAAA.

Congresswoman Roybal-Allard (D-CA) and Congressman John Peterson (R-PA) both remarked that they are concerned about underage drinking. Rep. Peterson asked why there is not more information made available to young people about the damage excessive drinking can cause to the brain while it is in development. Dr. Cline confirmed that alcohol is the number one drug of choice for young people and that SAMHSA is investing resources in its Strategic Prevention Framework to combat underage drinking as well as focusing on the environmental factors such as schools, parents and peers that prevent underage drinking. Congressman Ryan (D-OH) offered his support for after school programs that prevent alcohol and drug use and keep youth involved in activities during that vulnerable time period. Rep. Ryan asked the witnesses about what efforts are being undertaken to study stress and the role it plays as a trigger for alcohol and drug use and mental health conditions. Dr. Volkow responded that stress is one of the most important environmental factors that contribute to drug use and poverty, that many prevention interventions work and that it is critical that such effective interventions are applied in communities.

Congressman Kennedy (D-RI) expressed his disappointment with the cuts proposed in the FY 2008 budget request by stating it is a departure from reality

and that it will result in shifting costs to other systems, including the criminal justice system, which is also receiving significant cuts in the FY 2008 budget request. Rep. Kennedy inquired as to how treatment of co-occurring disorders could be best administered in order to eliminate bureaucratic waste of resources and stated his position that the mental health and substance abuse block grants should be integrated. Dr. Cline responded by stating that SAMHSA is working on a number of best practices in the area of co-occurring disorders as well as supporting policy academies for information sharing. Additionally, Dr. Cline highlighted the flexibility that currently exists within SAMSHA to administer programs for co-occurring populations.

For more information on the House Appropriations Committee and the Appropriations process please visit: http://www.appropriations.house.gov/.

NIH Hearing Summary (provided by NIH/OLPA)

Overview of FY 2008 Budget Request for NIH
House Appropriations Subcommittee on Labor, HHS, and Education

March 6, 2007

Members: The hearing was attended by Representatives David Obey (D-WI), Chair; Jesse Jackson, Jr, (D-IL); Lucille Roybal-Allard (D-CA); Barbara Lee (D-CA); Michael Honda (D-CA); Betty McCollum (D-MN); Tim Ryan (D-OH); James Walsh (R-NY), Ranking Minority Member; Ralph Regula (R-OH); John Peterson (R-PA); Dave Weldon (R-FL); Dennis Rehberg (R-MT); and Jerry Lewis (R-CA).

Witnesses: Dr. Elias Zerhouni, Director, NIH, accompanied by Drs. Elizabeth G. Nabel, Director, NHLBI; John E. Niederhuber, Director, NCI; Anthony S. Fauci, Director, NIAID; Duane F. Alexander, Director, NICHD; John Ruffin, Director, NCMHD; Francis Collins, Director, NHGRI; Story Landis, Director, NINDS; Sam Wilson, Deputy Director, NIEHS; Griffin Rodgers, Acting Director, NIDDK; and Barbara Alving, Acting Director, NCRR.

Summary: In summary, the Chairman criticized the FY2008 President's budget, both because it did not take into account the actions of the FY2007 Joint Resolution which provided in excess of a $600 million increase over FY2006 for NIH, and especially absence of funding for the National Children's Study (NCS), which was explicitly funded in the Joint Resolution. The Chairman called the FY2008 request a "step backwards, " took issue with "OMB's plan to use NIH as the Bank of Bethesda when it comes to funding the Global AIDS Initiative," and with regard to the NCS, stated that "we're going to put that money back next year, too, and it will not squeeze other research, because we will expand the institutes' budget, just as we did last year."

There were questions about stem cells from Representative Walsh and also from Representative Ryan, which elicited the response from Dr. Zerhouni that it is important to pursue all lines of research (adult, human embryonic, etc.) and that as we look ahead, "we should find a way of allowing our scientists to have access to more experimental models, including embryonic stem cells, to understand the fundamental issue."

There were a number of questions about health disparities from Representatives Jackson, Roybal-Allard, Lee, and Honda. There was interest in other topics, including new and promising developments that would have an impact on the HIV/ AIDS vaccine; how NIH is progressing in the area of translational research, getting results into the hands of the health care providers; whether the budget could be devised to reflect future paradigm and priorities; genetic discrimination (to be provided for the record); and the third-generation anthrax vaccine research and RFP that was put out recently and

then rescinded.

Chairman Obey opened the hearing noting, as he has at the previous hearings, that he had charged all of the appropriation subcommittees to ask, "What will this country look like in 10 years? What will the demographic changes be, what will the traffic needs be, what will the environmental problems be, what are the scientific opportunities that we should be thinking about?" He also noted the increase provided to NIH in the FY2007 Joint Resolution and that "the budget presented by the President this year is actually a decrease from the previous year... the budget that it has presented is inadequate and needs to be augmented."

Mr. Walsh opened his statement with praise for the NIH, noting that NIH discoveries have the potential to change medicine, but also stated his concern with the pace at which those advances reach local doctors and community hospitals. "There are reasons for delays in taking this research to that level, including safety and cost. But I think we need to look for ways to move this research into practice as quickly as possible without sacrificing safety." He also mentioned that he would like to "underscore the need for sound financial management, which I know is something that you and your leadership staff have stressed" and "Congress has, I think, strongly -- over the last eight years or so -- and dramatically, increased National Institutes of Health funding to respond to the needs of the country, and we need to make sure the investment is being placed wisely and where it can do the most good."

The Director of NIH testified about where NIH has been over the past 30 years, where we are today, and what is our vision for the future. Due to the investment of Congress in biomedical research over the past 30 years, he reported that for the second consecutive year, annual cancer deaths in the United States have fallen. Furthermore, there has been a 60 percent drop in mortality for heart disease and stroke. There is a decline in the chronic disability indices that we have measured since the 1980s, and there has been a decrease of 30 percent in disability rates for Americans over the age of 65, a decrease which is actually accelerating. Life expectancy has risen to 78 years, up six years since 1974, or about one year every five years. He emphasized that we were poised to use NIH-supported discoveries to transform the medical treatment paradigm in the 21st Century, from one that responds to symptoms to one that predicts disease, personalizes treatment and preempts disease, striking it before it strikes the patient. He also noted that the new paradigm will require participation, because patients will have to participate, communities will have to participate, individuals will have to take more responsibility for their own care earlier than ever before. "This is the era of what we call precision medicine." He noted recent discoveries which are illustrative of the "four Ps," including remote glucose sensors; biomarkers from saliva; the development of the first anticancer vaccine, the HPV vaccine, the first FDA-approved vaccine against cancer; and the launching of a trial for a new class of HIV/AIDS vaccine. Also, he described the development of a genetic test to determine which patient would have intracranial bleeding from the use of immunoglobulin for treatments of certain diseases. He closed by noting that the scientific challenge before us is the one of biological complexity; that we are really in a race to understand in this century what the life sciences need to do, and to advance that understanding as we did with physical sciences in the 20th century. If we do not understand the biological circuitry, it will be very hard to advance our vision of the new health care system.

The first questions were a series of stem cell questions from Representative Walsh, who was attempting to elicit information on whether other than human embryonic stem cells (HESC) would be able to do all that HESC can do, without destruction of a human embryo. There was discussion about investigators who have reported that they can reprogram adult stem cells to produce pluripotent cells and the Congressman was looking for validation of this. Dr. Zerhouni

responded that understanding DNA programming and reprogramming is the largest challenge and that, from the scientific standpoint, and at this point, it is important to pursue both lines of research as vigorously as we can. This topic was visited again by Representative Ryan, who wondered if the United States and its scientists were falling behind in the quest to understand the action of stem cells.

There was extensive discussion of health disparities, beginning with the status of the strategic plans, and whether the coordinating role of the NCMHD is clear to the ICs by Representative Jackson, who stated that he wanted "to make sure that NIH does not overlook or misinterpret the intent of the Minority Health and Health Disparities Research Education Act of 2000." Representative Lee took issue with the positive statistics on cancer and heart disease decline, noting that this did not apply to African Americans and other minorities. Representative Honda was interested in Asian-Pacific Islanders and Representative Roybal-Allard was interested in a recently launched NHLBI longitudinal study, the Hispanic Community Health Study. Who pays for peer review of articles destined for deposition under the Public Access was raised by Representative Honda, and the response will be submitted for the record. The final, major topic was raised by Representative Obey, the National Children's Study. He pressed Dr. Zerhouni about reasons for the agency's unwillingness to fund the study and wanted to hear whether the decision was science or budget driven. Dr. Zerhouni responded that "unless there were additional resources, it wouldn't have been wise to sacrifice the next generation for this study, which is basically a budgetary decision. There's no opposition or scientific reluctance on our part."

NIH Hearing Summary (provided by NIH/OLPA)

Overview of FY 2008 Budget Request for NIH
House Appropriations Subcommittee on Labor, HHS, and Education

March 19, 2007

Members: The hearing was attended by Senators Tom Harkin (D-IA), Chairman, and Arlen Specter (R-PA), Ranking Member.

Witnesses: Panel 1: Dr. Elias Zerhouni, Director, NIH. Panel 2: Joan S. Brugge, Ph.D., Chair, Department of Cell Biology, Harvard Medical School; Brent Iverson, Ph.D., University Distinguished Teaching Professor of Organic Chemistry and Biochemistry, The University of Texas at Austin; Robert Siliciano, M.D., Ph.D., Professor of Medicine and Principal Investigator, Howard Hughes Medical Institute, Johns Hopkins University School of Medicine; Stephen Strittmatter, M.D., Ph.D., Professor of Neurology and Neurobiology, Yale University of Medicine.

Summary: This overview hearing with the NIH Director was held to address the overarching issues affecting NIH, with the promise that this was the first of six hearings on NIH and that the subcommittee looked forward to hearing from every Institute and Center (IC) Director. The major issues addressed were the inadequacy of the FY2008 President's budget, the fact that although the Joint Resolution provided funding to launch the National Children's Study, in the FY08 budget the NCS would be ceased. Senator Harkin said, "I think I can say we will not allow those cuts to take place." He then turned to the topic of stem cells and whether the current policy is restricting science and delaying cures. Dr. Zerhouni responded that embryonic stem cell research should be expanded beyond current restrictions.

There was then a request by Senator Specter for NIH to focus on the issue of cost savings resulting from research; what would it take to cure the many

strains of cancer; what would be the impact on NIH if the budget is cut by more than $500 million with an inflationary factor of 2 percent; and what research would be done by way of prevention (what savings would there be if many diseases were prevented). Senator Specter reiterated the need for something concrete to show the importance of health and how much NIH means to promoting health, and how much it means in reducing costs by preventing disease.

Senator Harkin asked what NIH could accomplish with an increase of $1.9 billion; what NIH hopes to accomplish with the Common Fund, examples of the kinds of initiatives that would be funded through the Fund and whether initiatives for particular diseases would be included; and what is the scientific value of public access and why it needs to be mandatory.

On public access, Dr. Zerhouni responded that NIH has tried a voluntary policy with very low rates of deposition of articles from NIH supported research; the publications that are being submitted represent less than 10 to 15 percent of the universe. He said further that he believes that we need to make this deposition of articles a condition of receiving NIH funds and said that "we need you to express the wish of Congress to do that."

Dr. Zerhouni thanked Senators Harkin and Specter for their efforts to provide NIH with an increase in FY2007, and discussed how our country's ability to compete globally will be based on our mastery of the biological world. He said that no country will excel without advances in the life sciences. He also explained how advances in research can make a difference in confronting the challenges of rising U.S. health expenditures, and predicted that advances in science will allow us to preempt diseases before they reach the critical stage. Dr. Zerhouni concluded by explaining that it is vitally important for our political leaders and research advocates to communicate the strategic importance of NIH, especially when the rest of the world is investing heavily in the life sciences.

Panel 2 was comprised of working scientists who gave a common message about the impact of flat budgets on the research enterprise. They participated in the creation of a document, released at a press conference at the conclusion of the hearing, entitled "Within our Grasp or Slipping Away-Assuring a New Era of Scientific and Medical Progress." Dr. Iverson spoke about the many researchers like himself, poised to make a difference with all the tools now in place, but limited by a flat budget. He said flat funding, as we have now, has the effect of making grant funding decisions overly conservative, stifling innovation and encouraging support for worthy, older ideas. Current graduate students are being dissuaded from an academic research career by the difficulty young faculty are having in receiving funding now. Fewer research grants means fewer opportunities for undergraduate researchers and consequently, undergraduate students. Dr. Brugge spoke about the promise of research and described particular opportunities in cancer research.

Dr. Siliciano spoke about the transformation in health care, a the direct result of the nation's investment in health science, and the vital importance of funding basic research. He spoke of his collaborative work with Dr. Anthony Fauci in HIV, in particular how HIV hides in the body and escapes from the drugs that are being used to combat the infection. He echoed earlier testimony about having difficulty taking on new students and beginning new projects, and said that investigators are leaving research altogether and fewer scientists want to tackle high risk problems because they know this kind of research will be difficult to fund. He pointed to the dramatic increase in time spent applying for grants.

Dr. Strittmatter also spoke to the impact of the recently flat NIH budget in stifling creative high-risk research. As a neurologist, he spoke about his research and that of others supported by NIH during the doubling, which today

would not likely be funded. As he put it, when researchers and peer review panels are faced with junior investigators not being funded at all or senior investigators losing funding, the shift is towards safe science. Scientists pursue those experiments that have the highest probability of success in the short term, which produces only incremental gains.

NIH Hearing Summary (provided by NIH/OLPA)

Fiscal 2008 Budget for Mind, Brain and Behavioral Research at NIH Senate Appropriations Subcommittee on Labor, HHS, and Education

March 26, 2007

Members: The hearing was attended by Senators Tom Harkin (D-IA), Chairman, and Arlen Specter (R-PA), Ranking Member.

Witnesses: Drs. Story Landis, Director, NINDS; Tom Insel, Director, NIMH; Nora Volkow, Director, NIDA; T. K. Li, Director, NIAAA; and James Battey, Director, NIDCD.

Summary: This hearing represented the first time in over a decade that this Subcommittee has heard testimony from individual institutes of the NIH. This is the first of 5 hearings expected over the next months where all of the NIH ICs will have the opportunity to sit before this Subcommittee. The witnesses for this hearing were unaccompanied by a Departmental representative and, in a departure from the previous years under the Chairmanship of Senators Specter and Harkin (briefly), the panel did not present all the testimony before the questioning, but rather spoke one at a time. The Chairman indicted that he wanted to have a more conversational interchange by hearing from each witness and then asking questions before moving on to the next witness.

Senator Specter had an opening statement similar to the one he offered at the NIH Overview hearing; he added that he and Senator Harkin had succeeded in attaching an amendment to the Senate Budget Resolution for $2.2 billion. He reiterated his need for quantification of the "best estimates you can make as to what this research means in terms of saving lives...how long it will take to find a cure for a given malady and how much it will save." In addition, he said, "And I know that Senator Harkin will endorse me in this. We will provide the kinds of resources you need to the maximum extent of our capabilities, which is now more limited than it used to be." Senator Harkin echoed this at the close of the hearing, noting that he hoped to have the finances and the budget and the money to encourage younger scientists to know that this is something that they to which they can dedicate their, but cautioned, "It's going to be very tough. It's going to be very tough."

True to his word, Senator Harkin asked his questions based on topics included in the statements of the witnesses. There were questions on the state of the science in areas of personal interest to the Senator such as the regeneration of hair cells to restore hearing; whether post-traumatic stress disorder is more prevalent now than it was in previous wars; where is the U.S. relative to other countries with controlling drug abuse; and what are we learning about the reasons for binge drinking among college students. He asked about new science such as ethogenetics, the discovery of the genes involved in spinal muscular atrophy, and who is supporting the neuroscience blueprint and what have we learned so far.

Senator Specter, who had to leave before he could ask all of the questions he wanted, did ask a few. He asked whether there is any answer from NIDA research to deal with drug addiction that is within the financial reach of what society is prepared to spend on corrections facilities. He also asked about brain

injuries incurred by soldiers and what should be the government response, so that these young men and women and their families do not have to bear the cost burden for a war not of their choosing or their making.

QUESTIONS

HARKIN

- (To Insel) So, you are saying that the mental health care piece of all health care costs (which represent 16 percent of the GDP) is about 6.2 percent of the overall health care costs?
- Are we putting too much into drugs development, or should we be looking at some of the underlying causes?
- With regard to eating disorders, are you looking into eating disorders and the underlying mental health problems that either lead to it or exacerbate it?
- What is ethogenetics? Have you done much about that area in the past?
- (To Volkow) If studies of childhood exposure to "stressors" has shown that they are 10 times more likely to become addicted than those that are not, what are some of these stressors? So, a factor of 10 is pretty important, and drug abuse leads a lot of times to mental illness?
- Have you looked at addiction in the United States versus other countries? How about state by state? What's it look like? When we look at addiction in this country, what does it look like compared to other countries?
- You talked about drug abuse being a chronic disease. How do we know it's related to disease?
- (To Li) You mentioned advances in knowledge of molecular medicine; we are developing better and better medications to treat alcohol dependence once it has developed. What medicines?
- Doctor, every institute out there needs to do outreach to the communities around the country. How well are you doing in reaching out to states and local communities to put into practice some of your findings? I'd like to know more about how that's done.
- Young people getting involved in drinking -- I wonder about messages that they receive about drinking -- all the advertising about the glamorizing of drinking alcohol. I just wonder about the impact of these messages and how they're reinforcing young people that it's all right to drink. Are you doing any research in this? Any results?
- What kind of research are you doing on binge drinking, especially among college students? Are you doing research on why they drink to intoxication? What's motivating young people to do this?
- (To Dr. Battey) Let's get into the whole thing of regeneration of hair cells. When I first chaired this committee in 1989, I engaged in questions with the then director about this. Now that's at least 17 years ago, and almost what I hear you saying is what I heard 17 years ago. Are you regenerating hair cells in mammals? How long have you been doing this? Is there more than one locus of this research going on right now? When do you think they'll be ready to go to higher mammals? Where is this research being funded? I'm just wondering how soon they might be ready to take it to a higher order of mammals. And this is a genetic intervention?
- I don't know much about how much regeneration they've had. Has it been a percentage? Is it like 10 percent of the hair cells are restored? Is it 20? Is it 30? Do you have any idea? Why are there differences from guinea pig to guinea pig?

(To Landis) Are you saying that diabetes is a leading indicator for having a stroke?

- About the debilitating effects of migraine headaches, how prevalent migraine headaches are; I don't know whether I'm just hearing more about it now and finding more people, or is it increasing?
- One disease that you know that I've been interested in is spinal muscular atrophy. Haven't you identified the gene? Tell me about the progress on spinal muscular atrophy, because I keep hearing that this has some lynchpin or some connectivity to other types of diseases.
- You mentioned that deaths have declined due to stroke, but I just wonder about the incidence of stroke. I don't think the incidence of stroke has. I think stroke remains still one of the feared things that can happen to someone, because they're just so unexpected and can happen to anyone at any time. And, it's that early intervention, and if you can get to it right away, that helps, you know, if you get that TPA.
- I'm also interested in Parkinson's disease. In your testimony, you talked about deep brain stimulation for Parkinson's. How much progress is being made in this area? What about a therapy in Greece where scientists had developed something like a helmet they put over a patient's head, but it didn't penetrate the skull (Transcranial magnetic stimulation).
- (To Insel) I've been told that one out of every three Iraqi veterans seeks mental health help sometime during the first year. Whether that's one out of three or one out of four, it's very high. And, that's just those who actively seek it. What about those that don't? How many more are out there that are trying to tough it out? Any thoughts on why it's so prevalent? Why these returning vets are having really mental health problems? Talk to me a little bit more about post-traumatic stress disorder. What is it? Is it more prevalent now than in the past? Is this more prevalent than any war in the past? Your institute is actually actively doing research in post-traumatic stress disorder?
- Your institute's budget for next year is $1.4 billion. What would be the largest sector where that money would go for research? What department or sector?
- Dr. Insel, would you be the proper person that I would ask this question? I'm going to ask about the effect that stress plays in diseases. So are you looking at stress? Is this part of your $1.4 billion, looking at stress and how stress levels affect a person's ability to ward off diseases and illnesses or become more susceptible because they have a higher level of stress? Is that you or is that somebody else? But somewhere in this $1.4 billion you do have research on stress that's ongoing?
- (To Volkow) You were talking about the environmental factors for drug abuse, but you said that 50 percent of the factors are genetic for addiction. I mean, you really hold that's 50 percent?
- Talk to me about what you've done in terms of looking at the role that stress plays in addiction to drugs to relieve stress.
- (To Landis) All the institutes today have been involved in a collaborative effort called the NIH blueprint for neuroscience research. Dr. Landis, what is this effort? What's been achieved? What are you doing and what are the plans for next year and how do you all participate? Who else is involved?

SPECTER

- (To Volkow) Is there any answer from your research to deal with drug addiction that is within the financial reach of what society is prepared to spend on corrections facilities? How do we deal with it effectively within some reasonable cost parameter?
- I'm not interested in how much you save. I'm interested in how much we spend.

'm interested in how we get my colleagues to spend money for corrections, and he inquiry goes to whether there is any answer within what the government is willing to spend, to ask the question more specifically. There's a willingness to spend money for incarceration?

- (To Li) I've heard martini drinkers illustratively express concern about killing brain cells with the alcohol. Is that a real risk? Alcohol kills brain cells? How many and at what rate? Is it a real danger?
- What would be consumption to avoid becoming an alcoholic or, to a lesser extent, impairing one's brain?
- How much more money do you need than $30 billion that Senator Harkin has provided for you?
- (To Insel) We talk a lot about the 3,200 or more men and women killed in Iraq. We now find that there is an enormous number coming back from Iraq with brain injuries. And, there are reports that these young men and women are coming back in their 20s, teens, and they're going to need care for a lifetime. To what extent can you evaluate those kinds of brain injuries and what might be done to provide therapy from the kind of research you're undertaking?
- What should be the government response, either through the Veterans Administration or the Department of Defense, so that these young men and women and their families don't have to bear the burden of the cost when it is really not a war of their choosing or their making, but a war for the government that ought to be borne by the government? What is an equitable response by the government to these kinds of injuries?

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International Activities

NIDA Introduces Methadone Research Web Guide

The NIDA International Program has introduced its Methadone Research Web Guide, which reviews methadone maintenance treatment research findings in an easy-to-use question and answer format. The new guide also includes a revised section on the history and evolution of methadone maintenance in the United States, and new information on regulatory requirements in the international community. This online version (http://international.drugabuse.gov/collaboration/guide_methadone/index.html) updates and revises a 1995 print version developed through the work of numerous NIDA-supported researchers, including many who voluntarily provided slides and data. David A. Fiellin, M.D., Associate Professor of Medicine, Yale University School of Medicine, updated the research portion of the Web guide and developed a new section on methadone treatment effectiveness. Dale S. Weiss, IP Program Analyst, managed the web guide development and implementation through a contract with IQ Solutions, Inc.; Dr. Ivan Montoya, DPMCDA, provided technical guidance and review.

NIDA-Supported Meetings

Italian Delegation Visits NIDA

Representatives of the Federazione Italiana degli Operatori dei Dipartimenti e dei Servizi delle Dipendenze (FeDerSerD), the Italian drug abuse prevention and treatment organization, visited NIDA in December 2006 to discuss opportunities for binational cooperation on drug abuse research and the development of science-based clinical interventions. At NIDA headquarters, the Italian delegation met with NIDA Director Dr. Nora D. Volkow as well as directors and staff from DBNBR, DESPR, DPMCDA, and CTN. The group also toured NIDA's Intramural Research Program in Baltimore, Maryland, meeting with staff in the Neuroimaging Branch, Molecular Neuropsychiatry Section, Teen Tobacco Addiction Research Clinic, Nicotine Psychopharmacology Unit, Treatment Research Program, and Molecular Neurobiology Unit. The Italian delegation included: Dr. Alfio Lucchini, Director, Milan Department of Addiction Medicine; Dr. Guido Faillace, Director, Alcamo - Palermo Department of Addiction Medicine; Dr. Pietro Fausto D'Egidio, Director, Pescara Department of Addiction Medicine; Dr. Claudio Leonardi, Director, Rome Department of Addiction Medicine; and Dr. Nava Felice, Castelfranco Veneto - Treviso Department of Addiction Medicine.

NIDA Meeting Focuses on Impact of Drug Abuse and Addiction on HIV/AIDS

Researchers discussed the successes, research challenges, and opportunities for addressing the evolving HIV/AIDS pandemic during the NIDA-sponsored meeting, *Drug Abuse and Risky Behaviors*, held May 8-9, 2007, on the NIH campus. Presenters provided a broad understanding of the multiple ways that

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drug abuse and addiction affect HIV/AIDS and how research can inform public health policy. The IP supported the participation of current Hubert H. Humphrey Drug Abuse Research Fellows Mr. Duc Nguyen, Vietnam; Dr. Kevin Goulbourne, Jamaica; Ms. Rehana Kader, South Africa; Ms. Desiree Molina, Venezuela; Dr. Peter Ndege, Kenya; Dr. Yasantha Ariyaratne, Sri Lanka; Mr. Amani Msami Kisanga, Tanzania; Mr. Md Alamgir, Bangladesh; Dr. Joseph E. Navarro, Philippines; Dr. Violet C. A. Okech, Kenya; and Dr. Mehboob Singh, India.

Planned Meetings

Publications

Staff Highlights

Grantee Honors

Research Training and Exchange Programs

Three Researchers Named Distinguished International Scientists
NIDA selected researchers from Finland, India, and South Korea as 2007 Distinguished International Scientists:

Petri Hyytiae, Ph.D., Finland National Public Health Institute, and his research partner, Gregory Mark, Ph.D., Oregon Health and Science Institute, will investigate the role of prefrontal cortex cholinergic neurotransmission in methamphetamine (MA) seeking. Using microdialysis techniques and inbred mice, the researchers will examine how passive vs. self-administered exposure to MA affects the release of acetylcholine (ACh) in the prefrontal cortex. Dr. Hyytiae's previous research has focused on alcohol and cocaine behavioral pharmacology in rats and neuronal circuits involved in stress and drug self-administration; Dr. Mark's, on rat and mouse drug self-administration models and microdialysis methods to study modulation of ACh levels in rats and mice.

Meera Vaswani, Ph.D., All India Institute of Medical Sciences, and her research partner, Nicholas Goeders, Ph.D., Louisiana State University, will investigate combinations of therapeutic drugs that affect the hypothalamo-pituitary-adrenal (HPA) axis through divergent mechanisms on the cue-induced reinstatement of extinguished cocaine-seeking in rats. By examining the role of environmental stress and the subsequent activation of corticotrophin-releasing hormone (CRH) and the HPA axis on intravenous cocaine self-administration in rats, the researchers hope to identify potential pharmacotherapies to treat cocaine addiction in humans. Dr. Vaswani has extensive research experience in the neurogenetics and treatment of alcohol and heroin dependence; Dr. Goeders, in the interactions between stress and cocaine addiction.

In Kyoon Lyoo, M.D., Ph.D., M.M.S., Seoul National University Hospital, and his research partner, Perry F. Renshaw, M.D., Ph.D., McLean Hospital Brain Imaging Center and Harvard Medical School, will investigate the impact of methamphetamine (MA) abuse on the developing brain and develop models to test the safety and efficacy of Cytidine 5'-diphosphocholine (CDP-choline) to repair aspects of neurobiological function damaged by MA dependence in adolescence. The researchers have published seven peer-reviewed papers that describe multimodal brain imaging studies involving a cohort of about 40 MA dependent subjects in South Korea, and their research collaborations have been supported by NIDA and matching funds from South Korea.

NIDA Selects INVEST Fellow
Sung Jin Cho, Ph.D., Korean Research Institute of Bioscience and Biotechnology, has been selected as 2006-2007 NIDA INVEST Drug Abuse Research Fellow. Dr. Cho will spend his Fellowship working with Dr. Alan P. Kozikowski, University of Illinois at Chicago, investigating novel serotonin receptor agonists to treat cocaine abuse and addiction and learning Dr. Kosikowski's methods for computer modeling in drug development. A chemist, Dr. Cho will focus on developing new analogues of the MAO inhibitor tranylcypromine, which has been identified as a candidate target for drug development, evaluating the *in vitro* pharmacological properties of the new analogues and the *in vivo* activity of the analogues in behavioral studies using rats. Dr. Cho received his doctoral degree from Yonsei University and published his research in the *Journal of Organic Chemistry* and *Bioorganic and Medicinal*

Chemistry Letters.

Iranian and South African Named 2007 WHO/NIDA/CPDD International Traveling Fellows

Dr. Azarakhsh Mokri, Iranian National Center for Addiction Studies (INCAS), and Dr. M.N. (Nancy) Phaswana-Mafuya, South African Human Sciences Research Council (HSRC), have been selected as the 2007 WHO/NIDA/CPDD International Traveling Fellows. The Fellowships provide travel support for international researchers to conduct research visits to NIDA grantees and participate in two scientific meetings: the NIDA International Forum and the CPDD Annual Scientific Meeting. Dr. Mokri will work with Dr. Richard Schottenfeld, Yale University, to complete analyses on their NIDA-supported clinical trial comparing buprenorphine with naltrexone maintenance treatment for opium- or heroin-dependent patients and plan further collaborative research. Dr. Mokri directs the INCAS drug abuse clinical research and training program, where the Institute has been selected as a WHO Middle East and Central Asia Knowledge Hub, and is an assistant professor of psychiatry at Tehran University of Medical Sciences. He has also served as the Iranian principal investigator for a WHO multi-site study of methadone maintenance. Dr. Phaswana-Mafuya will work with Dr. Bruce Johnson, National Development and Research Institutes, Inc. (NDRI), to plan and implement their institutions' memorandum of understanding for collaborative research on drug abuse and HIV/AIDS issues in South Africa and much of Sub-Saharan Africa and to develop scientific articles based on their current epidemiological studies of drug abuse treatment and illicit drug markets in South Africa. NIDA, the World Health Organization (WHO), and the College on Problems of Drug Dependence (CPDD) cosponsor the International Traveling Fellowships.

NIDA Hosts INVEST and HHH Fellows

NIDA introduced the 2006-2007 Hubert H. Humphrey Drug Abuse Research Fellows and NIDA INVEST Fellows to NIDA staff during an orientation program held January 18-19, 2007. The Fellows met with representatives from the IP and DESPR, and toured the Mark O. Hatfield Clinical Research Center, National Library of Medicine, and the IRP in Baltimore. INVEST Fellows also met individually with NIDA staff: Dr. Doug Han and Dr. Young Hoon Sung, South Korea, met with Dr. Thomas Aigner, DBNBR; Dr. Judice Wagner, Brazil, met with Dr. Rao Rapaka, DBNBR; Dr. Paula Mayock, Ireland, met with Dr. Elizabeth Lambert, DESPR; and Dr. Paulo Telles, Brazil, met with Dr. J.C. Comolli, DPMCDA. NIDA Visiting Scientist Dr. Michiel B. de Ruiter, Netherlands, met with Dr. Steve Grant, DCNBR. In Baltimore, the Fellows met with Drs. Yihong Yang and Thomas Ross, Neuroimaging Branch; Dr. Ron Herning, Molecular Neuropsychiatry Section; and Dr. Stephen Heishman, Nicotine Psychopharmacology Unit. The coordinator of the Humphrey Program at Virginia Commonwealth University, Dr. Robert Balster, and the Assistant Coordinator, Ms. Susan Webb, accompanied the Humphrey Fellows from Richmond: Kevin Goulbourne, Jamaica; Rehana Kader, South Africa; Desiree Molina, Venezuela; Peter Kenneth Ndege, Kenya; and Duc Cuu Nguyen, Vietnam. Humphrey Fellows from Johns Hopkins University who participated included: Fairuz Afram, Iraq; Md Alamgir, Bangladesh; Dr. Yasantha Ariyaratne, Sri Lanka; Amani Kisanga, Tanzania; Michelle Moore, Trinidad and Tobago; Dr. Joseph Navarro, Philippines; Dr. Violet Okech, Kenya; and Dr. Mehboob Singh, India.

Travel Support

NIDA-Supported Researcher Participates in Drug Abuse Epidemiology Course

NIDA supported Dr. Jorge Delva, University of Michigan, who served as an instructor in drug abuse epidemiology at the University of Chile International Summer School, January 15-19, 2007, in Santiago.

Chinese Researchers Present at Society on NeuroImmune

Pharmacology (SNIP) Conference
NIDA supported three Chinese scientists who presented their research findings in a session on opportunities and challenges in HIV/HCV research at the Society on NeuroImmune Pharmacology (SNIP) 13th Conference, held April 11-14, 2007, in Salt Lake City, Utah. Dr. Deyin Guo, Wuhan University, reported on host cell proteins, discussing their involvement in HIV replication and potential as targets for RNAi-based genetic therapies for AIDS. Dr. Hongkui Deng, Peking University, reviewed the development of novel mouse models to investigate HIV and HCV infection. Dr. Jianguo Wu, Wuhan University, described a potential animal model to replicate HCV infection using the tree shrew.

Two Researchers Participate in Iberoamerican College of Addictive Disorders
NIDA supported the participation of two U.S. researchers at the third congress of the Iberoamerican College of Addictive Disorders (CITA), April 12-14, 2007, in Buenos Aires, Argentina. Dr. Robert P Schwartz, Friends Research Institute, Inc., and Dr. Ronald Cowan, Vanderbilt University, attended the meeting.

International Visitors

Dr. Ruri Kikura-Hanajiri from the National Institute of Health Sciences, Japan visited NIDA on February 28, 2007. Dr. Kikura-Hanajiri met with Moira O'Brien, DESPR to discuss trends in drug abuse in the United States.

A delegation from Taiwan visited NIDA on April 25, 2007. The visitors included the U.S. liaison Dr. Shihlung Huang from Fayetteville State University, Dr. Shi-lung Yang, National Chung Cheng University, Dr. Su-Chuag Chiang, Taoyuan Institute of Mental Health and Tsung Hsien, National Chung Cheng University. NIDA participants in the meeting included Moira O'Brien, DESPR, Dr. Cecelia Spitznas, DPMCDA, and Dale Weiss, IP.

Dr. Wilson Compton, Director, DESPR, met with Dr. Maria Elena Medina Mora and colleagues in Mexico City to assist in developing prevention activities in Mexico. Dr. Compton then participated in the Joint NIH/American Psychiatric Assoction Meeting on Externalizing Disorders of Childhood, also in Mexico City, where he presented a paper on the links of externalizing disorders with substance use disorders.

Drs. Elizabeth Robertson and Augusto Diana of DESPR met with representatives of the Italian Federation of Operators of Departments and Services of Addictions to discuss implementation of effective prevention and best approaches for conducting prevention research.

Other International Activities

In early May 2007, Dr. Wilson Compton chaired a panel and presented at the International Federation of Psychiatric Epidemiology (IFPE), Goteburg, Sweden.

Dr. Peter Hartsock co-chaired a special international meeting sponsored by UNAIDS and the U.S. Department of Defense on AIDS in the military. The meeting had representatives from around the world and was held at the Uniformed Services University of the Health Sciences, Bethesda, MD, March 5 and 6, 2007. Dr. Hartsock presented on NIDA's AIDS modeling research, including those studies which have lead to recent major changes in U.S. HIV testing policy.

Dr. Augusto Diana, PRB, DESPR served as a Task Force member for the International Task Force on Prevention Evaluation Measures, part of the Inter-American Drug Abuse Control Commission (CICAD) of the Organization of American States (OAS). Dr. Diana presented the results of the Task Force, a compendium of prevention measures called the CICAD Toolkit for the Evaluation

of Universal Substance Abuse Prevention Programs for Youth, to the VIII meeting of the Expert Group on Demand Reduction, held in Bogota, Columbia, February 13 - 15, 2007. Dr. Diana served as a technical expert on a number of panels to refine the measures while at the meeting. The Expert Group meeting included state representatives from 20 OAS member nations, including Argentina, Bahamas, Barbados, Bolivia, Brazil, Canada, Chile, Colombia, Dominican Republic, El Salvador, Guatemala, Haiti, Mexico, Panama, Paraguay, Peru, St. Kitts and Nevis, Suriname, Trinidad and Tobago, and the United States. There was additional representation of experts from the European Monitoring Centre for Drugs and Drug Addiction, the Pan American Health Organization (PAHO), and the United Nations Office on Drugs and Crime (UNODC). The purpose of the meeting was to establish agreement on the use of a common set of measures for prevention programs across the participating member states. The Expert Group did support use of the measures and developed an implementation and training and technical assistance plan to facilitate their use.

Dr. Jonathan D. Pollock, DBNBR, is a scientific officer on the Knockout Mouse Project (KOMP) and participated in the steering committee meeting, March 14, 2007 at the Sanger Center, Hinxton, UK.

Dr. Jonathan D. Pollock participated in the founding meeting of the International Knockout Mouse Consortium in Brussels, Belgium, March 15-16, 2007.

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Meetings/Conferences

The NIH/NIDA/AMA jointly-supported meeting titled: **Pain, Opioids and Addiction: An Urgent Problem for Doctors and Patients** was held at the Natcher Auditorium, NIH, on March 5-6, 2007 and attended by over 500 participants. The purpose of this meeting was to bring together the research and clinical practice communities - through its co-sponsorship with the American Medical Association (AMA), and supported by the NIH Pain Consortium - to draw attention to the risk of prescription opioid misuse by patients with chronic non-malignant pain conditions. The goal of the meeting was to inform practitioners and scientists on the emerging research on pain and addiction and what we are learning about how to most effectively and compassionately treat these conditions, while minimizing the risk of abuse and addiction in these patients. The web cast of this meeting can be accessed though the link http://videocast.nih.gov/PastEvents.asp?c=1.

The NIH/NIDA meeting titled: **Drug Abuse and Risky Behaviors: The Evolving Dynamics of HIV/AIDS** was held at the Natcher Auditorium, NIH, on May 8-9, 2007. Drug abuse and addiction continue to fuel the spread of HIV/AIDS in the United States and abroad. To address this significant public health threat, research has focused on the multiple ways that HIV/AIDS and drug abuse are entwined, including: risk behaviors associated with both injection and non-injection drug abuse; how drugs of abuse alter brain function and impair decision making; and HIV prevention and treatment strategies for diverse groups. This conference provided a broad understanding of the multiple ways drug abuse and addiction impact HIV/AIDS and how research can inform public health policy. Presentations focused on successes, research challenges, and opportunities for addressing the evolving HIV/AIDS pandemic. Collaborators included: the National Institute on Alcohol Abuse and Alcoholism, the National Institute of Allergy and Infectious Diseases, the National Institute of Child Health and Human Development, the National Institute of Mental Health, and the Centers for Disease Control and Prevention.

NIDA provided support through the Genes and Environment Initiative for the **GWAS to Sequencing: Sequencing Think Tank and Training Workshop for the Genes and Environment Initiative (GEI)** meeting in Bethesda on January 18-19, 2007. Dr. Joni Rutter, DBNBR, was the lead organizer and co-chair for the meeting along with NHGRI.

Drs. Cecelia Spitznas, Melissa (Racioppo) Riddle, and Lisa Onken, all of DCNBR, organized a meeting on Augmenting HIV Prevention using Information Technology which was held on March 1 & 2, 2007 in Washington D.C. The meeting was sponsored by the Office of Science Policy and Communications (OSPC). A major purpose was to stimulate application development on community friendly HIV prevention interventions and combined behavioral treatment and HIV prevention using information technology for use in settings

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that treat drug abuse.

CAPT Steve Oversby, Psy.D., DPMCDA, convened a workshop on March 8-9, 2007 on **Pharmacotherapy Research for the Treatment of In Utero Substance Exposed Neonates: Advances and Future Directions**". The workshop brought together experts in the field to develop ideas, concepts, and research questions addressing new pharmacotherapy research for the treatment of in utero substance exposed neonates. Ivan Montoya, M.D., DPMCDA, gave a presentation on "The Public Health Scope of In Utero Drug Exposure" and Jamie Biswas, Ph.D., DPMCDA, gave a presentation on "In Utero Substance Exposure and the Division Portfolio".

NIDA's Special Populations Office hosted the **Southern Africa Initiative: Research Progress and Perspectives Meeting** in Bethesda, Maryland on April 16-17, 2007. The two day meeting convened U.S. principal investigators and their South African collaborators to discuss the impact of NIDA funding on research capacity development in South Africa. Research topics encompassed Neuroscience, Social and Behavioral Science, Drug Abuse Prevention/Intervention, and HIV. Attendees addressed the barriers encountered, success stories, and provided recommendations to NIDA for future research studies. Dr. Nora Volkow gave a welcoming presentation to the meeting attendees. Other members of NIDA senior staff also made presentations.

The National CTN Steering Committee Meetings were held March 19-22, 2007 in Bethesda, MD. The following meetings/committees convened:

- Members of the Study Teams: START (CTN 0027) and STAGE-12 (CTN 0031)
- Special Interest Groups: Health Services Research, Pharmacotherapy, Behavior/ Psychosocial and HIV
- CTP and PI Caucuses
- Executive Committee
- Research Utilization Committee
- Research Development Committee
- Node Coordinator Workgroup
- Steering Committee
- Two workshops: Exploring Collaborating Opportunities - what's new in NIMH, NIAAA and CSAT? (CTN Platform) and Adaptive Treatment Strategies
- Brief Study Report - CTN 0017
- DCRI Data & Statistics Center (DSC) Demos: The DSC and CTN Working Together

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Dr. Timothy P. Condon, Deputy Director, NIDA, 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 Enhancing State Capacity to Foster Adoption of Science-Based Practices conference on November 20, 2006, in Bethesda, Maryland.

Dr. Timothy P. Condon provided opening remarks and a brief overview at the National Institute on Drug Abuse sponsored "Substance Abuse, Criminal Justice and HIV in African Americans: Research Development Workshop" on December 11, 2006, in Silver Spring, Maryland.

Dr. Timothy P. Condon provided opening remarks at the Consequences of Marijuana Use on Brain and Behavioral Development meeting on December 15, 2006, in Bethesda, Maryland.

Planned Meetings

Publications

Staff Highlights

Grantee Honors

Dr. Timothy P. Condon presented "Translational Addiction Research and the AAPI Community" at the Asian American and Pacific Islander Scientific Conference/Workshop on February 12, 2007, in Santa Monica, California.

Dr. Timothy P. Condon presented "NIDA's Blending Initiative" at a Friends of NIDA Congressional briefing held on February 22, 2007, in Washington, D.C.

Dr. Timothy P. Condon addressed members of the press at the National Inhalants and Poison Awareness Press Conference on March 15, 2007, in Washington, D.C.

Dr. Timothy P. Condon delivered the plenary presentation entitled "Principles of Drug Abuse Treatment for Criminal Justice Populations" at the 2007 North Carolina TASC Conference on Community, Crime and Addiction on March 26, 2007, in New Bern, North Carolina.

Dr. Timothy P. Condon presented the keynote address entitled "Advances in Drug Abuse and Addiction from NIDA: Implications for Treatment" at the Pennsylvania Certification Board 8th Annual Conference on April 16, 2007, in Harrisburg, Pennsylvania.

Dr. Cindy Miner, Deputy Director, OSPC participated in the PRISM Nomination Review Committee for the 2007 PRISM Awards on January 27-28, 2007 in Los Angeles, CA.

Dr. Cindy Miner participated in a panel presentation on "Methamphetamine Abuse and Addiction" at the Midwest/Great Lakes Regional Methamphetamine Legislative and Policy Planning Conference on February 1, 2007 in Des Moines, Iowa.

Dr. Cindy Miner presented a workshop on the "Neurobiology of Addiction" at CADCA's National Leadership Forum on February 15, 2007, in Washington, D.C.

Dr. Cindy Miner attended and presented on funding opportunities at a planning session for the Development of a National Strategy for Drug Endangered Children on April 4-6, 2007, in Boulder, Colorado.

Dr. Cindy Miner presented "Neurobiology of Addiction" at the NIMH Outreach Partnership Program Annual Meeting on April 25, 2007, in Portland, Oregon.

Dr. Denise Pintello, OSPC, delivered a presentation addressing: Sources of Support for Social Work Doctoral Education and Dissertation Research at the Institute for the Advancement of Social Work Research (IASWR) and the Action Network for Social Work Education and Research (ANSWER) in Washington D.C., on April 25, 2007.

Dr. Lula Beatty, Chief, Special Populations Office, participated as a panelist at a session on conducting research in racial/ethnic minority populations at the National Multicultural Summit in Seattle, Washington in January 2007.

Dr. Lula Beatty served as a moderator and presenter at the Translational Addiction Research: Bench, Bedside, Community and Back conference in Santa Monica, California in February 2007. The title of her presentation was "NIDA/NIH Support for Minority Research and Researchers."

Dr. Lula Beatty was an invited speaker at the Southeastern Psychological Association meeting in New Orleans, Louisiana in February 2007. The title of her presentation was "Making a Difference through Drug Abuse Health Disparities Research."

Dr. Lula Beatty attended a meeting, The Federal Initiative on Juvenile Justice Health, sponsored by the Office of Juvenile Justice and Delinquency Prevention, held in Northern Virginia at George Mason University in March 2007.

Dr. Lula Beatty presented a pre-conference workshop on grant development at the Lonnie Mitchell HBCU Substance Abuse conference in Washington, DC in March 2007.

Dr. Lula Beatty organized a panel on "African Americans, Drugs and Criminalization" with representatives from NIDA, CSAT, and CSAP at the Lonnie Mitchell HBCU Substance Abuse conference in Washington, DC in March, 2007.

Dr. Lula Beatty and Derrick Prather, SPO, hosted a roundtable on the Special Populations Office and health disparities at the Addictions, Infectious Diseases and Public Health conference held in Baltimore, Maryland at Johns Hopkins University in April 2007.

Dr. Lula Beatty provided an overview of NIDA programs at the HHS African American Healthy Marriage Initiative Agency Partners Roundtable in Washington, DC in February 2007.

Ana Anders, M.S.W., Senior Advisor on Special Populations, attended and presented at the Translational Addiction Research: Bench, Bedside, Community and Back held in Santa Monica, California in February 2007.

Ana Anders attended a Steering Committee meeting of NIDA's National Hispanic Science Network on Drug Abuse in Miami, Florida on February 20-22, 2007 for the purpose of planning the annual conference in September 2007.

Ana Anders participated as a member of the CSAT Hispanic Stakeholders meeting in Los Angeles, California.

Ana Anders participated in a meeting representing NIH Hispanic employees called by the NIH Office of Equal Opportunity and Diversity Management in April 2007.

Dr. Donald Vereen, M.D., M.P.H., Special Assistant to the Director, NIDA, gave a keynote address at the Community Anti-Drug Coalitions of America (CADCA) annual meeting in Washington, D.C. on February 14, 2007.

Dr. Don Vereen, M.D., M.P.H. delivered Grand Rounds to the Department of Psychiatry at Temple University School of Medicine in Philadelphia, PA on February 28, 2007.

Dr. Don Vereen, M.D., M.P.H. gave the Keynote Address at the Indiana Judicial Center Court Alcohol and Drug Program in Indianapolis, IN on March 1, 2007.

Dr. Vereen gave a presentation on drug abuse and addiction and its treatment and prevention at the Tufts Dean's Gathering in Baltimore, MD on March 4, 2007.

Dr. Vereen delivered the Keynote Address and conducted a workshop on the developing adolescent brain and drug abuse at the Brain Development Conference in Portland, OR on March 23, 2007.

Dr. Vereen gave the Keynote Presentation at the George Washington School of Medicine Annual Research Day in Washington, DC on March 26, 2007.

Dr. Vereen presented an overview of NIDA treatment research with a special emphasis on vigabatrin to the National African American Drug Policy Coalition in Washington, DC on March 29, 2007.

Dr. Vereen gave a presentation at the St. Louis Science Center as part of a series in collaboration with the Dana Foundation in St. Louis, MO on April 26, 2007.

Dr. Vereen presented an overview of drug abuse research to The Sheridan School in Washington, DC on May 3, 2007.

Dr. Vereen gave a presentation on drug abuse, addiction, and brain development at the Saturday Academy in Washington, DC on May 5, 2007.

Dr. Vereen gave a presentation to the Arlington County Committee of 100, sponsored by Vanguard Services at Marymount College in Arlington, VA on May 9, 2007.

Dr. Allison Chausmer, DBNBR, was an invited presenter at a workshop entitled "Applying for and Obtaining a Job: Perspectives from Academia, Medical Centers, and Industry", held at the Feb 2007 annual meeting of the Society for Research on Nicotine and Tobacco in Austin, TX.

Drs. Allison Chausmer and Cora Lee Wetherington, DBNBR, co-organized and co-chaired a symposium entitled "A Translational Approach to Understanding Gender, Adolescence and Vulnerability to Nicotine Addiction" at the February 2007 annual meeting of the Society for Research on Nicotine and Tobacco in Austin, TX.

Dr. Allison Chausmer, DBNBR, and Debbie Grossman, DCNBR, co-organized and co-chaired (with Cathy Backinger, NCI, and Catherine Jo from the American Cancer Society), "The Future of Youth Tobacco Cessation Research", a meeting sponsored by the ACS, NCI and NIDA on May 7-8, 2007 in Rockville, MD.

Dr. Nancy Pilotte, DBNBR, served as a discussant to the Stress and Sensitization session at the Spring Brain Conference in Sedona, AZ, in March 2007.

Dr. Joni L Rutter, DBNBR, presented an overview of the NIDA Genetics Programs to the Pennsylvania State University on February 28, 2007.

Drs. Joni L. Rutter and John Satterlee, DBNBR, along with other NIH staff, were co-organizers of a session entitled "Environmental Influences on Complex Genetic Traits" in the Systems Medicine Workshop held by NHLBI on January 30-February 1, 2007 in Bethesda, MD.

Dr. Joni L. Rutter and Dr. Kevin Conway, DCNBR, presented a talk entitled, "The Genes, Environment, and Development Initiative in Addiction: The GEDI Approach" at the Community Anti-Drug Coalitions of America (CADCA) meeting in Washington DC on February 14, 2007.

Dr. Jonathan D. Pollock, DBNBR, and Dr. George Uhl, IRP, organized the panel, entitled, "Cell Adhesion Molecules and Addiction" at the 40th Winter Conference on Brain Research, Snowmass, CO, January 31, 2007.

Drs. John Satterlee, Joni L. Rutter and Christine Colvis, all of DBNBR, are NIDA's representatives to the Epigenetics Roadmap 1.5 Workgroup.

Drs. Jonathan D. Pollock and Christine Colvis, DBNBR, are NIDA representatives to the Proteome Roadmap 1.5 Workgroup.

Drs. Christine Colvis and Chris Pierce organized and chaired the panel, "Epigenetics of Cocaine Addiction" at the 40th Winter Conference on Brain Research, Snowmass, CO, January 28, 2007.

John Satterlee, Ph.D., DBNBR, NIDA, Susan Volman, Ph.D., DBNBR, NIDA, Andrea Beckel-Mitchner, Ph.D., NIMH, and Laurie Tompkins, Ph.D., NIGMS organized and co-chaired the NIH workshop, Genetics and Genomics of Social Behavior, Bethesda, MD. January 4-5, 2007.

Dr. Satterlee attended a Gordon Conference entitled "Quantitative Genetics and Genomics", Ventura, CA, February 19-22, 2007.

Dr. Rao Rapaka, DBNBR, visited the University of Kentucky, Lexington to the

NCDDG spring retreat to participate and follow the progress on drug development for treatment of nicotine addiction.

Dr. Rao Rapaka participated in the discussions on "Drug Discovery and Design Intiative" organized by the American Association of Pharmaceutical Scientists (AAPS).

Dr. David Shurtleff, Director, DBNBR, gave a key note address on "Research Priorities and Directions for the Division of Basic Neuroscience and Behavioral Research (DBNBR): Determining the Basis of Drug Addiction" at the Current Trends in Drug Abuse Research 5th Annual Symposium at the Center for Drug Discovery, Northeastern University; March 27, 2007.

Drs. David Shurtleff, Lynda Erinoff, Diane Lawrence, and Woody Lin organized and co-chaired two session on "HIV/HCV Research in China: Opportunities and Challenges" at the 13th annual meeting of the Society for NeuroImmune Pharmacology, April 11-12, 2007.

Dr. David Shurtleff gave a presentation on "Navigating the NIH System: How to Write Competitive Applications' at the 13th annual meeting of the Society for NeuroImmune Pharmacology, April 14, 2007.

Dr. Paul Schnur, Deputy Director, DBNBR, represented the Division t the 2007 National Scientific Conference planning committee meeting of the National Hispanic Science Network on Drug Abuse in Miami, FL, on February 21-23, 2007.

Dr. Paul Schnur presented a NIDA Grants Workshop at the 55th Annual Meeting of the Nebraska Symposium on Motivation, Lincoln Nebraska, April 12-14, 2007.

Dr. Kevin Conway, DCNBR, serves as the NIDA representative on the NIH Roadmap 1.5 Phenotype Working Group. Dr. Ruben Baler, OSPC, serves as alternate representative.

Dr. Kevin Conway, DCNBR (and Kay Wanke, DESPR), continue to serve as NIDA's representative(s) on the Exposure Biology Program for the NIH Genes and Environment and Health Initiative (GEI).

Dr. Kevin Conway, DCNBR, continues to serve as the NIDA representative on the NIH Blueprint Committee on Neuroepidemiology.

Dr. Joseph Frascella, Director, DCNBR, gave a presentation of the division's programs at the "NIDA Centers for Excellence for Physician Information" meeting held in Bethesda, MD on February 23, 2007.

Dr. Joseph Frascella, DCNBR, participated in the "Asian American and Pacific Islander Scientific Conference" and also presented a talk entitled The Myths and Realities of Writing an NIH Grant. This meeting was held in Santa Monica, CA on February 12-13, 2007.

Drs. Nicolette Borek and Karen Sirocco, DCNBR, co-organized and presented talks at the session "Grants 201 for Mid-Career and Senior Level Scientists: Mentoring the Next Generation of Child and Adolescent Researchers" at the Society for Research on Child Development meeting March 28th - April 1, 2007 in Boston, MA .

Dr. Nicolette Borek, DCNBR presented a talk on Consulting with NIH Program Officials at the Society for Research on Child Development meeting March 28th - April 1, 2007 in Boston, MA.

Dr. Nicolette Borek, DCNBR, presented a talk on Measurement and Outcomes of Prenatal Drug Exposure at the Pediatric HIV/AIDS Cohort Study (PHACS) network meeting, March 12-13th, Arlington, VA. Dr. Borek also participated as

a NIH scientific collaborator at the meeting.

Dr. Nicolette Borek, DCNBR presented a talk on Opportunities for Conducting HIV/AIDS Research at NIDA at the spring meeting of the Adolescent Trials Network for HIV/AIDS Interventions April 25th-April 27, 2007 in Vienna, VA.

Dr. Lisa Onken spoke about evidence-based treatments for drug abuse with the Behavioral Therapy Interest Group of the NIDA Clinical Trials Network at the CTN Steering Committee meeting in Bethesda, Maryland, on March 20, 2007.

Dr. Lisa Onken participated in the planning of a joint IAPAC-NIMH-NIDA 2nd International Conference on Adherence to HIV Treatment. She moderated a panel on adherence to ART within the context of substance use and abuse. The meeting took place in Jersey City on March 28-30, 2007.

Drs. Steven Grant, DCNBR, represented NIDA at the annual meeting of the Cognitive Neuroscience Society that was held in New York, New York, May 5-8, 2007.

Dr. Wilson Compton, Director, DESPR, attended the American Psychopathological Association Annual Meeting in New York City, March 1-3, 2007. The theme of this meeting was gene environment development interactions in psychiatric illnesses. Along with multiple NIDA colleagues, Dr. Wilson Compton chaired a panel and participated in the meeting on Pain, Opioids, and Addiction: An Urgent Problem for Doctors and Patients at the Natcher Center at NIH, March 5-6, 2007.

On March 21, 2007, Dr. Wilson Compton presented Grand Rounds at Temple University Department of Psychiatry. His presentation was titled: "Uncertainty & Discovery in the Neuroscience of Addiction".

On April 2, 2007, Dr. Wilson Compton presented a keynote address to the Johns Hopkins University epidemiology workshop on "Uncertainty and Discovery in Linking Drug Abuse Public Health Research to Neuroscience".

On April 11-12, 2007, Dr. Wilson Compton participated in the DSM-V Task Force Meeting of the American Psychiatric Association.

On April 18, 2007, Drs. Wilson Compton and Yonette Thomas co-chaired and presented at the Association of American Geographers (AAG) Annual Meeting in San Francisco. This presentation was conducted jointly with Drs. Ivan Cheung and Douglas Richardson of the AAG.

On April 23, 2007, Dr. Wilson Compton presented a keynote presentation to the NIATx Summit in San Antonio, Texas.

Dr. Wilson Compton presented on the epidemiology of stimulant abuse at the American Society of Addiction Medicine (ASAM) meeting in Miami, Florida.

Dr. Elizabeth Robertson, DESPR, presented a talk at the Pride Conference, convened in Lexington, KY on April 11, 2007. Her talk was titled: "Caution: Brain Under Construction."

Drs. Gina Hijjawi and Eve Reider, DESPR, co-chaired a symposium "Children of Parents Involved in the Criminal Justice System" at the Society for Research in Child Development biennial meeting in Boston, MA on April 1, 2007. The panel of presenters included Rebecca J. Shlafer and Julie A. Poehlmann (University of Wisconsin, Madison); Lew Bank (Oregon Social Learning Center); Mary Byrne (Columbia University School of Nursing) with J. Mark Eddy (Oregon Social Learning Center) as the discussant.

Dr. Elizabeth Ginexi, DESPR, served as a planning committee member and panel chair for the USC-IPR/NIH Conference on Interdisciplinary Science, Health Promotion & Disease Prevention Hosted by University of Southern

California Institute for Health Promotion and Disease Prevention Research (IPR) May 2-3, 2007 at the Westin Pasadena, California. This conference was support by the National Institutes of Health, National Cancer Institute, National Institute on Alcohol Abuse and Alcoholism, National Institute on Drug Abuse, National Institute on Aging, National Institute of Environmental Health Sciences, and the Office of the Provost and the Institute for Health Promotion and Disease Prevention Research at the University of Southern California.

Dr. Jessica Campbell Chambers presented on NIDA funding opportunities in two symposia held at the Society for Research on Child Development biennial meeting, March 29-April 1, 2007.

Dr. Augusto Diana, PRB, DESPR delivered a keynote address entitled "Prevention and Methamphetamine - What Do We Know?" to the 2nd Annual Drug Endangered Child Conference held from February 21-23, 2007, at Stephen F. Austin State University in Nacogdoches, Texas. Dr. Diana also facilitated a series of follow-up workshops at the conference, focused on the same topic. The conference was organized around juvenile substance abuse and juvenile crime and included participants from a wide variety of state and local agencies charged with addressing youth crime and substance abuse, representatives from Drug Courts, many local service provider agencies, health care providers, and many others.

Drs. Belinda Sims, Aria Crump, and Elizabeth Robertson, DESPR, participated in a Discussion Hour on NIH Research Priorities for Drug and Alcohol Abuse, and Addictions Research, at the biennial meetings of the Society for Research in Child Development in March/April 2007.

Dr. Belinda Sims, DESPR, presented at the SAMHSA/CSAP Prevention Fellowship Program, for second year fellows, on NIH/NIDA Research Opportunities, in March 2007.

Dr. Aria Crump presented a talk entitled "An Update on Extramural Program and E-Submission" at the Society for Research on Child Development Meeting on March 31, 2007.

Dr. Belinda Sims, DESPR, participated in a Discussion Hour on Mentoring and Training Priorities at NIDA, at the biennial meetings of the Society for Research in Child Development, in March/April 2007.

Dr. Dionne Jones presented on a panel "Drugs, African Americans and Criminal Justice Research: Implications for Career Choices and Job Excellence" at the Lonnie Mitchell Annual Conference, Washington, DC, March 29-31, 2007.

Dr. Elizabeth Robertson of DESPR is a member of the Society for Prevention Research Task Force on Basic Career Knowledge Development. The Task Force is currently developing guidelines for researchers and practitioners.

Dr. Elizabeth Robertson of DESPR is NIDA's representative to the IOM study titled "Reducing Risks for Mental Disorders."

Drs. Belinda Sims, Elizabeth Robertson and Eve Reider of DESPR served on the ACF Planning Committee for the meeting titled "The Application of Effect Sizes in Research on Children and Families" convened on March 5, 2007, in Bethesda, MD.

Dr. Elizabeth Robertson of DESPR serves as the NIDA Liaison to the Strategic Prevention Framework-State Incentive Grant Program administered by the Center for Substance Abuse Prevention. She attends monthly meetings of the Internal Workgroup.

Dr. Elizabeth Robertson is the NIDA liaison to the Center for Substance Abuse Prevention's Strategic Prevention Framework-State Incentive Grant Program

(SPF-SIG) Internal Work Group.

Dr. Frank Vocci, Director, DPMCDA, Dr. Kathy Backinger of NCI, and Dr. Caryn Lerman of the University of Pennsylvania co-organized and co-chaired a NCI/NIDA workshop on Translational Medication Development for Nicotine Dependence in Chevy Chase, MD, January 8-10, 2007.

Dr. Frank Vocci spoke at the Roskamp Institute on January 12, 2007 in Tampa, Florida. Dr. Vocci presented on addiction, medications, and new molecular targets for treatment of addictive disorders.

Dr. Frank Vocci organized, co-chaired, and presented at a NIDA symposium on treatments for stimulant dependence at the American Society of Addiction Medicine in Miami, Florida on April 28, 2007. The speakers included Drs. Nancy Petry, Kathleen Brady, Richard Rawson, Walter Ling, Ahmed Elkashef, Charles Dackis, Wilson Compton, and Kyle Kampman.

Dr. Frank Vocci attended the Consumer Demand Roundtable conference on May 3-4, 2007 in Washington, D.C. The goal of the conference was to develop innovations in building consumer demand for tobacco cessation products and services.

Dr. Jag Khalsa, DPMCDA, participated in the Annual Meeting of the Society of NeuroImmune Pharmacology (SNIP), Salt Lake City, Utah, April 11-15, 2007, and presented NIDA's International Research Program and also served as a Mentor for young travel awardee researchers.

Dr. Jag Khalsa presented a symposium on Neurobiology, Clinical Consequences and Treatment of Cannabis Dependence at the 38th Annual Conference of the ASAM, in Miami, April 29, 2007. Dr. Vocci presented on neurobiology of marijuana and Dr. Elkashef presented on treatment of cannabis dependence.

Dr. Petra Jacobs, CCTN, participated in the AATOD Workshop Committee Meeting on April 13, 2007.

Dr. Rita Liu, OEA, chaired a Research Career Development Session at the First Scientific Conference for Asian American and Pacific Islanders (AAPI), held from February 12 to 14, 2007, in Santa Barbara, CA. The session's topics included peer review, international support and health diversity issues that were presented by Drs. Joe Frascella, Steve Gust and Lula Beatty, while Dr. Liu's presentation was on mechanisms of support.

Dr. Gerald McLaughlin, OEA, presented three lectures for a 2007 FAES graduate course on the proteomics and genomics of mitochondria, and serves as a reviewer for J. Proteomics.

At the biennial meeting of the Society for Research on Child Development, Dr. Levitin, Director, OEA, joined other NIH staff on a symposium on mentoring the next generation of child and adolescent researchers. Her presentation focused on what reviewers of training applications look for in assessing the quality of mentoring proposed in fellowship and career development applications. She also was a discussant on a symposium she helped organize entitled "The Ethics of Giving Away Child Development Research: Opportunities, Problems, and Pitfalls". Dr. Levitin continues to serve on the SRCD Ethics Committee.

Dr. Amy Newman, IRP, was invited to give a lecture at Pfizer, Inc. in Groton CT in February, 2007.

Dr. Peter Grundt, IRP, was invited to give lectures in the Departments of Chemistry at Stevens Institute of Technology and New Jersey Institute of Technology in March 2007.

Dr. Roy Wise, IRP, presented a seminar entitled "The Role of Dopamine in Reward and Motivation" at the Drexel University in Philadelphia, PA on

November 20 - 22, 2006.

Dr. Yavin Shaham, IRP, presented a lecture on "Recent Research on Relapse to Food Seeking in a Rat Model" at the New York University School of Medicine on December 18, 2006.

Dr. Roy Wise presented a seminar entitled "The Normal Roles of Dopamine in Reward and Motivation" at the Department of Pharmacology of the University of Washington in Seattle, Washington on March 5-7, 2007.

Dr. Yavin Shaham chaired a session entitled "Orbitofrontal Cortex and Addiction" with NIDA Director, Dr. Nora Volkow at the NYAS Orbitofrontal Cortex Conference in New York, NY on March 11-14, 2007.

Director's Report to the National Advisory Council on Drug Abuse - May, 2007

Media and Education Activities

Press Releases

March 7, 2007 - NIDA Launches First Large-Scale National Study to Treat Addiction to Prescription Pain Medications.
Researchers funded by the National Institute on Drug Abuse are launching the first large-scale national study evaluating a treatment for addiction to prescription opioid analgesics such as Vicodin and OxyContin. NIDA's National Drug Abuse Treatment Clinical Trials Network (CTN) is conducting the multi-site study, known as the Prescription Opiate Addiction Treatment Study (POATS).

March 6, 2007 - NIH Partners with HBO on Groundbreaking Documentary on Addiction.
The National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism have collaborated with HBO to create the eye-opening documentary, ADDICTION that aired on March 15, 2007. The documentary, developed with funding support from the Robert Wood Johnson Foundation, seeks to help Americans understand addiction as a chronic yet treatable brain disease, and highlights promising scientific advancements.

March 5, 2007 - NIDA NewsScan #49 - Pain, Opioids, and Addiction

- Physician Concerns Regarding Prescribing Opiates for Chronic Pain
- Researchers Assess Adolescents' Motivations To Abuse Prescription Medications
- Study Reveals a New Cellular Adaptation that Contributes to Opiate Tolerance
- URB597 Relieves Pain in Rats Without Cannabinoid-Associated Side Effects
- Managing the Impact of Pain: Antidepressants May Be Useful Part of Pain Therapy

March 5, 2007 - NIDA Begins Its First-Ever Public Discussion on Pain Relief and Addiction.
Pain, Opioids, and Addiction: an Urgent Problem for Doctors and Patients, sponsored by the National Institute on Drug Abuse brought together more than 500 researchers, clinicians and interested consumers to discuss the growing problem of prescription painkiller abuse and the potential for addiction in patients with chronic pain conditions. The conference took place on the NIH campus, and was held in collaboration with the NIH Pain Consortium and the American Medical Association.

February 26, 2007 - NIDA NewsScan #48 - Hispanic Issue

- Identifying Research Opportunities To Improve Drug Treatment Services

among Hispanics
- Adapting Research To Prevent Substance Abuse among Hispanic Youth
- Scientists Identify Areas of Research To Prevent HIV in Hispanic Adolescents
- Researchers Suggest Directions for Biological Research on Drug Abuse and Addiction in Hispanics
- A Review of Drug Treatment Outcomes, Needs, and Scientific Opportunities among Hispanic Adults

February 13, 2007 - NIDA Unveils its First Consumer Publication to Explain the Science of Addiction.
Drugs, Brains, and Behavior: The Science of Addiction was unveiled by the National Institute on Drug Abuse. This 30-page full-color booklet explains in layman's terms how science has revolutionized the understanding of drug addiction as a brain disease that affects behavior. NIDA hopes this new publication will help reduce stigma against addictive disorders.

January 25, 2007 - Damage to Specific Part of the Brain May Make Smokers 'Forget' to Smoke.
Preliminary research supported by the National Institute on Drug Abuse, has found that some smokers with damage to a part of the brain called the insula may have their addiction to nicotine practically eliminated. The study was published the journal Science.

January 25, 2007 - NIDA Launches Centers of Excellence for Physician Information.
The National Institute on Drug Abuse announced the establishment of four Centers of Excellence for Physician Information - these Centers will serve as national models to support the advancement of addiction awareness, prevention, and treatment in primary care practices. The NIDA Centers of Excellence will target physicians-in-training, including medical students and resident physicians in primary care specialties.

December 11, 2006 - NIDA NewsScan #47 - International Issue

- Economic, Political Challenges Can Drive Drug Abuse, HIV
- New Research Examines Disclosure Norms and Risk Behaviors Among Young Hungarian Drug Injectors
- Ukrainian Injection Drug Users Respond To Risk Behavior Intervention, But Many Continue Habits
- Drug Abuse-HIV Connection Evident in Brazil
- Study Identifies Factors Associated With HIV Infection, Heroin Addiction, In Malaysian Men
- Drug Abuse on the Mexico-U.S. Border: Implications for HIV/AIDS Transmission
- HIV Transmission and Syringe-Sharing Practices Among Injection Drug Users in Dar es Salaam, Tanzania
- NIDA International Programs Foster Opportunities for Global Cooperation

December 5, 2006 -Young African American Adults at High Risk for HIV, STDs Even In Absence of High-Risk Behaviors.
Results of a study supported by the National Institute on Drug Abuse suggest that young African American adults - but not young white adults - are at high risk for HIV and other sexually transmitted diseases even when their relative level of risky behaviors is low. The findings imply that the marked racial disparities in the prevalence of these diseases are not exclusively affected by individual risk behaviors. The paper was published in the American Journal of Public Health.

December 4, 2006 - NIDA Researchers Complete Unprecedented Scan

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of Human Genome That May Help Unlock the Genetic Contribution to Tobacco Addiction.
Results of a genetic study bring scientists one step closer to understanding why some smokers become addicted to nicotine, the primary reinforcing component of tobacco. The research funded by the National Institute on Drug Abuse, represents the most powerful and extensive evidence to date of genetic risk factors for tobacco addiction. The study not only completed the first scan of the human genome to identify genes not previously associated with nicotine dependence (or addiction), it also focused on genetic variants in previously suspected gene families. The research results appeared in the Journal of Human Molecular Genetics.

Articles of Interest

March 12, 2007, *Associated Press*--"Experts Seek Options on Painkiller Abuse"--Interview with Nora D. Volkow, M.D.

February 6, 2007, *USA Today*--"Danger: Marijuana May Not Be Lesser Evil"--Interview with Nora D. Volkow, M.D.

January 25, 2007, *Associated Press*--"Brain Damage Can Curb Urge to Smoke"--Interview with Nora D. Volkow, M.D.

Educational Activities

NIDA Physician's Outreach Project

The purpose of NIDA Primary Care Physician Outreach Project is to increase primary care physicians' awareness of NIDA, NIDA-funded research, and the medical consequences of drug abuse and addiction and to provide physicians with the information and resources they need to incorporate research findings into clinical practice. As part of this physician outreach project, NIDA is collaborating with physician specialty organizations and State, county, and local medical societies. An overview of this project's key activities is provided below.

Physician Outreach Campaign: This campaign focuses on the development and dissemination of targeted materials for physicians and patients, including publication of articles in physician specialty society newsletters (e.g., American College of Obstetricians and Gynecologists, American Academy of Family Physicians, Society for Adolescent Medicine, American Medical Association); pasting NIDA materials on online physician resources (e.g., Medscape, Medpagetoday); creation of CMEs; dissemination of resources to State, county, and local medical societies; and creation of a NIDA physician Web page (anticipated launch in Spring, 2007). To ensure that the materials created will resonate with primary care physicians, a NIDA Physician Consultant Group was created. This consultant group is made up of practicing physicians from across the country and will be used to inform and guide the outreach activities in a cost-effective manner. Finally, a literature review has been submitted to the Journal of Addictive Diseases for publication.

NIDA Centers of Excellence for Physician Information (CoEs): To create the NIDA CoEs, NIDA has partnered with the American Medical Association and released a request for proposals to institutions at all 16 sites (representing 27 medical schools) that compose the American Medical Association's consortium on medical education research. The consortium focuses on transforming medical education across physician stages of learning. The NIDA CoEs are charged with the development of a portfolio of informational/educational materials and training resources that will impart the knowledge and skills essential for the prevention, diagnosis, and treatment of prescription and illicit drug abuse. The portfolios will be evaluated and implemented in the NIDA CoEs (i.e., medical schools). The centers opening in 2007 will be located at:

- Creighton University School of Medicine in Omaha, NE
- University of Pennsylvania School of Medicine (in collaboration with Drexel University College of Medicine)
- University of North Dakota School of Medicine and Health Sciences
- Massachusetts Consortium of Medical Schools (which includes the University of Massachusetts Medical School, Tufts University School of Medicine, Boston University School of Medicine, and Harvard Medical School/Cambridge Health Alliance)

The CoE kickoff meeting was held at NIDA on February 23, 2007. Dr. Timothy P. Condon and Ms. Carol Krause presented. Dr. Condon presented the state of the science, the implications for treatment, and the role the CoE can play in bringing science into clinical practice. Ms. Carol Krause opened the meeting by highlighting NIDA's effort to maximize physicians' effectiveness in treating substance use disorders and the partnership with the American Medical Association (AMA) to help implement NIDA's Physician Outreach Project. Following the kickoff meeting, a CoE intranet was created to support communication across the sites.

Interviews

Dr. Frank Vocci, Director, DPMCDA, was interviewed by Latitia Stern of the St. Petersburg Times on February 23, 2007 regarding the addictiveness of crack cocaine.

Dr. Frank Vocci was interviewed by Jennifer Pfeifer of CNN radio on February 13, 2007 regarding the abuse liability of methadone.

Dr. Frank Vocci was interviewed by Carlos Santos of the Richmond Times Dispatch on March 19, 2007 about medications for stimulant addiction.

On December 16, 2006, Dr. Joni L. Rutter, DBNBR, was interviewed by Wally Akinso for an NIH Radio address regarding the genetics of nicotine addiction. Drs. Shakeh Kaftarian and Elizabeth Robertson, DESPR, were interviewed by the University of Florida Radio Station on February 15, 2007. The topic of the interview was "How to Prevent Youth From Smoking." This interview was disseminated on a later date.

Dr. Steven Grant, DCNBR, was interviewed by a number of print and radio reporters including Scientific American On-Line and NPR Morning Edition with respect to the study by Bechara on "Damage to the insula disrupts addiction to cigarette smoking" that was published in Science (315 (5811): 531-534 January 26, 2007).

Upcoming Confernences/Exhibits

American Psychiatric Association 160th Annual Meeting, San Diego, CA	May 19-24, 2007
Association for Psychological Science 19th Annual Convention, Washington, DC	May 24-27, 2007
Society for Prevention Research 15th Annual Meeting, Washington, DC	May 30-June 1, 2007
National Association of Drug Court Professionals 13th Annual Drug Court Training Conference,	June 13-16, 2007

Washington, DC	
National Association of School Nurses 39th Annual Conference, Nashville, TN	June 28-July 1, 2007
NIH IC of the Month, Bethesda, MD	July 1-31, 2007

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Planned Meetings

The National Institute on Drug Abuse (NIDA) is collaborating with the **American Psychiatric Association (APA) to hold a major research based track at the APA Annual Meeting in San Diego, CA, May 19-24, 2007**. The first major NIDA/APA track was held at the 1998 APA meeting in Toronto and then again at the 2004 APA meeting in New York City. NIDA has organized a number of sessions for the upcoming track, including 5 symposia, 5 workshops, a forum for residents and medical students on ***Substance Abuse in Your Patients: Beyond What is Taught in Your Residency*** and a major lecture featuring NIDA Director, Nora Volkow, M.D. on ***The Neurobiology of Free Will in Addictive Disorders***. NIDA anticipates another highly successful program at the meeting in 2007.

The National Institute on Drug Abuse (NIDA) will again sponsor the "Grant Writing Workshop" and the "Tutorials Workshop" at the **College on Problems of Drug Dependence (CPDD) Annual Scientific Meeting**. This year's conference will be held in **Quebec City, Canada, on June 16-21, 2007**. The "Tutorials Workshop" provides junior investigators with fundamental information from a variety of scientific disciplines representing the breadth of drug abuse and addiction research. Speakers for this workshop are selected from amongst NIDA's T32 Training Directors to each give a presentation on a research topic within their field of expertise. The "Grant Writing Workshop" is designed to orient new research investigators to NIDA and the grant application process. NIDA will also be offering a limited number of travel awards to partially defray the cost of attending this conference.

The National Institute on Drug Abuse (NIDA) is organizing a program at this year's **American Psychological Association (APA) Annual Meeting in San Francisco, California, August 17-20, 2007**. A number of NIDA staff throughout the Institute are involved in organizing and/or presenting on a wide range of session topics. NIDA will also co-sponsor 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.

Dr. Lisa Onken of DCNBR is taking the lead on planning a meeting with other NIDA colleagues on **Social Neuroscience and the Development of Behavioral Interventions**. The meeting is planned for October 2007.

Dr. Steven Grant is leading the planning efforts for a workshop titled **Developing a Testing Battery for Cognitive Dysfunction in Substance Abuse** to be held in Chevy Chase, Maryland on July 12-13, 2007.

Dr. Steven Grant is leading the planning efforts for a workshop titled **Using Real Time fMRI for Neurofeedback Control of Craving** to be held in Chevy Chase, Maryland on July 25-26, 2007.

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Dr. Harold Gordon organized and will chair a mini-symposium titled **Understanding the Neurobiology of Drug Addiction by studying Sleep Disturbances and Circadian Rhythms** at the upcoming Annual Meeting of the Society for Neuroscience to be held in San Diego, CA, November 3-7, 2007.

Drs. Belinda Sims, Elizabeth Robertson, Eve Reider, and Aria Crump, PRB, DESPR are collaborating with staff from the National Institute on Child Health and Human Development, the National Institute on Mental Health, the NIH Office of Behavioral and Social Sciences Research, the Administration for Children and Families, and the Substance Abuse Mental Health Services Administration to plan a meeting entitled **Intervening Early: Progress and Opportunities in Child Service Settings**, scheduled for September 18-19, 2007. The purpose of this meeting is to review existing prevention programs for children 0-5 and their families that are designed to improve child, parent and family outcomes in a variety of domains (e.g., social and emotional development, mental health, education, parenting, substance use, family functioning), with a particular focus on programs delivered within child service settings. Goals of this meeting include identifying critical research gaps that need to be addressed to 1) foster novel program development through the translation of basic research on self-regulatory processes, and 2) increase the uptake and implementation of effective preventive interventions for young children and their families within child service settings, including setting characteristics.

The 28th annual meeting of the Society for Clinical Trials will be held in Montreal, Canada, May 20-23, 2007. Dr. Paul Wakim will chair an Invited Session on "Effect Size in Sample Size Determination: Clinical versus Statistical Significance". The session will include three speakers: Gordon Lan (Johnson & Johnson Pharmaceutical R&D), Carl Pieper (Duke University Medical Center) and Christopher Coffey (University of Alabama at Birmingham), and a discussant (Paul Wakim). Carmen Rosa will chair a symposium titled, "Safety Monitoring in Behavioral Trials: Challenges and Opportunities" that will present an overview of he design and safety monitoring of behavioral trials, a discussion of adverse events, and a discussion of challenges from the perspective of the principal investigator. The session will include four speakers: Kathleen Carroll (Yale University, New England Node), Greg Brigham (Maryhaven Inc., Ohio Valley Node), Felix Gyi (CEO, Chesapeake Research Review, Inc.); and Kenzie Preston (Acting Chief, Clinical Pharmacology and Therapeutic Research Branch, National Institute on Drug Abuse). NIDA CCTN staff, Jeng-Jong (JJ) Pan and David Liu, will present a poster entitled, "Analysis of Adverse Events in Clinical Trials Using Data Mining." Jeng-Jong (JJ) Pan is a co-author of the paper titled "Challenges of Establishing a Public Share Data Web Site", which will be presented in the contributed paper session. Janet Levy will deliver an oral presentation entitled "Sizing Simple Trials to Develop Adaptive Treatment Strategies". Coauthors include Susan Murphy of the University of Michigan and Carl Pieper of the Duke Clinical Research Institute.

At the College on Problems of Drug Dependence (CPDD) annual meeting in Quebec City, June 17-21, 2007, Don Calsyn and other CTN members will present a symposium on the results of three HIV protocols completed in the CTN in 2006.

The 115th annual convention of the American Psychological Association (APA) will be held August 17-20 in San Francisco, CA. The CTN Gender Special Interest Group (SIG) will present a symposium entitled, "Women's Issues in Substance Abuse Treatment." The symposium will be co-chaired by Susan Gordon (Delaware Valley) and Carmen Rosa (NIDA). Participants are Theresa Winhusen (Ohio Valley Node), Susan Tross (Long Island Node), and Denise Hien (Long Island Node); Kathleen Brady (Southern Consortium) will be the discussant. The CTN HIV Special Interest Group will present a symposium on the past and present HIV related studies conducted in the CTN. Dr. Don Calsyn

(Lead Investigator CTN 0018) will chair the session entitled, "HIV/AIDS Related Research in the NIDA Clinical Trials Network." The session will include five speakers: Robert Booth (Lead Investigator CTN 0017), Susan Tross (Lead Investigator CTN 0019), Don Calsyn, James Sorensen (California/Arizona Node PI), and Lisa Metsch (Lead Investigator CTN 0032). Presenters will discuss the primary outcome findings from their trials and challenges involved in conducting HIV risk reduction research protocols in community treatment programs, many who have not previously been involved in research studies. Member and affiliates of the CTN will present a symposium entitled, "Practical Challenges Integrating Evidence-Based Practices Into Addiction Treatment Programs." Participants include Joan Zweben (California/Arizona Node), Greg Brigham (Ohio Valley Node), Michael Levy (Northern New England Node), Dan Kivlahan (Washington Node), and Harold Perl (NIDA) and Dean Fixon, who is well known to the CTN. Janet Levy, NIDA/CCTN, will present a poster entitled "Biostatistical Versus Psychological Approaches to Longitudinal Clinical Trial Data Analysis." Dr. Paul Wakim is a coauthor.

The next National CTN Steering Committee Meeting is planned for September 23-28, 2007 in Rockville, Maryland.

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NIDA Publications

Epidemiologic Trends in Drug Abuse - Community Epidemiology Work Group - January 2007
NIH Pub. No.: 07- 6200
This report is a synthesis of findings and highlights of data reported at the semiannual meeting of the CEWG.

Monitoring the Future - National Results on Adolescent Drug Use, Overview of Key Findings: 2006
NIH Pub. No.: 07- 6202
Provides a summary of drug use trends from a survey of 8th-, 10th-, and 12th grade students nationwide. Also includes perceived risk, personal disapproval, and perceived availability of each drug by this group.

Science of Addiction
NIH Pub. No.: 07-5605
New advances in science demonstrate that addiction is a brain disease--a disease that is accompanied by disruption of the mechanisms responsible for generating, modulating and controlling an individual's cognitive, emotional, and social behavior.

Commonly Abused Drugs Chart (Revised)
NCADI #AVD137
Laminated 8.5" x 11" color chart lists drugs most widely abused, their trade names and street names, effects of intoxication, and long-term health consequences. Includes 13 "Principles of Drug Abuse Treatment" and graphs on drug use by students.

NIDA Notes

***NIDA Notes* Volume 21 Issue No. 2**
NIH Pub. No. 07-3478
The lead story looks at the correlation of response to novel objects and cocaine-induced dopamine release in rats. The Director's Perspective reports on the interplay of addiction and co-occurring mental disorders. Other research looks at cue responses in cocaine abusers; nicotine's effects on the developing rat brain; and cocaine craving and cocaine high's effects on brain reward structures. A NIDA at Work feature discusses the Division of Basic Neuroscience and Behavioral Research. Brief features look at acculturation studies, the impact of medical care during addiction treatment, and brain changes that accompany cocaine withdrawal.

***NIDA Notes* Volume 21 Issue No. 3**

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NIH Pub. No. 07-3478
The Director's Perspective will examine genes and smoking, and NIDA's work with Perlegen Sciences. Research findings will include how regional brain development contributes to adolescent risk-taking; animal studies looking at the serotonin system as a potential target for cocaine medications; endorphin derivative inhibiting reward from morphine and nicotine in rats; depot naltrexone's safety and efficacy for heroin addiction; and the use of standard treatments to help depressed smokers quit. The Bulletin Board discusses the NIDA International Program-sponsored special supplement to Drug and Alcohol Dependence, and What the Numbers Say will look at cocaine abstinence rates. The Bulletin Board will report on the recent Waletzky award presentation, the Blending Conference, and methadone research centers.

Science and Practice Perspectives

Science and Practice Perspectives Volume 3, Issue No. 2
Research Review articles will include "Assessing Organizational Functioning as a Step toward Innovation," by Drs. D. Dwayne Simpson and Donald F. Dansereau; "Imaging the Addicted Human Brain," by Dr. Joanna Fowler and NIDA Director Dr. Nora D. Volkow; "Clinical Perspectives: One Program's Experience Incorporating Research-Based Strategies into Methamphetamine Treatment," by Jay Hansen; "Quality and Performance Improvement: What's a Program to Do?" by Dr. Frank McCorry. The Science and Practice in Action feature is "Attending to Emotional Cues for Drug Abuse: Bridging the Gap between Clinic and Home Behaviors" by Drs. Michael Otto, Conall O'Cleirigh, and Mark Pollack.

CTN-Related Publications

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.

The **CTN Data Sharing Web Site** was established to support the NIH data sharing policy. The data sets of six protocols are available for public use; another five data sets will be available before the end of August 2007. Currently more than 30 research scientists have downloaded one or more data sets. These data sets are in compliance with HIPAA and CDISC (Clinical Data Interchange Standards Consortium) standards in support of the interoperability required by the NIH Roadmap.

CCTN developed two bookmarks for distribution to participants throughout the CTN: Informed Consent and Data Sharing.

International Program *E-News Letter*

The NIDA International Program issues an *E-News Letter* every other month to inform the international drug abuse research community about recent events, funding opportunities, NIDA's the research training and exchange programs for international scientists, and forthcoming meetings.

February 2007 - This issue announced the expansion of NIDA's Program Announcement on International Research Collaboration on Drug Abuse to the R01, R03, and R21 grants mechanisms; the new Methadone Research Web guide; and results of a NIDA-Dutch Addiction Program binational research project that concluded that children diagnosed with Disruptive Behavior Disorder in middle childhood benefit from a cognitive-behavioral intervention, the Coping Power Program (CPP), which may prevent the children from progressing to substance abuse in early adolescence.

Other Publications

Compton, W.M., Thomas, Y.F., Stinson, F.S., and Grant, B.F. Prevalence, Correlates, Disability, and Comorbidity of DSM-IV Drug Abuse and Dependence in the United States: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. Archives of General Psychiatry, May 2007.

Goldstein, R.B., Dawson, D.A., Saha, T.D., Ruan, W.J., Compton, W.M., and Grant, B.F. Antisocial Behavioral Syndromes and DSM-IV Alcohol Use Disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. Alcoholism: Clinical and Experimental Research, 31(5), pp. 814-828, 2007.

Ingraham, S.E., Lynch, R.A., Surti, U., Rutter, J.L., Buckler, A.J., Khan, S.A., Menon, A.G., and Lepont, P. Identification and Characterization of Novel Human Transcripts Embedded Within HMGA2 in t(12;14)(q15;q24.1) Uterine Leiomyoma. Mutation Res. 602, pp. 43-53, 2006.

Swan, G.E., Bierut, L.J., Li, M.D., Bergen, A., Lachman, H., Rutter, J.L., Pollock, J.D., and Caporaso, N. Letter to the Editor of JAMA Genetic Research and Smoking Behavior. JAMA, 297, p. 809, 2007.

International Mouse Knockout Consortium; Collins, F.S., Rossant, J., and Wurst, W. A Mouse For All Reasons. Cell, 128(1), pp. 9-13, January 12, 2007.

Vocci, F.J., Jr., and Appel, N.M. Approaches to the Development of Medications for the Treatment of Methamphetamine Dependence. Addiction 102(S1), pp. 96-106, 2007.

Elkashef, A., Rawson, R.A., Smith, E., Pearce, V., Flammino, F., Campbell, J., Donovick, R., Gorodetzky, C., Haning, W., Mawhinney, J., McCann, M., Weis, D., Williams, L., Ling, W. and Vocci, F. The NIDA Methamphetamine Clinical Trials Group: A Strategy to Increase Clinical Trials Research Capacity. Addiction 102(S1), pp. 107-113, 2007.

Vocci, F.J. Opiates and Addiction. In Handbook of Contemporary Neuropharmacology, eds. Sibley, D., Hanin, I., Kuhar, M., and Skolnick, P. .John Wiley and Sons, Inc, Vol. 2, pp. 691-705, 2007.

Tanda, G., Ebbs, A., Kopajtic, T., Campbell, B., Newman, A.H., and Katz, J.L. Effects of Muscarinic M1 Receptor Blockade on Cocaine-Induced Elevations of Brain Dopamine Levels and Locomotor Behavior in Rats. J. Pharmacol. Exp. Ther. 321, pp. 332-344, 2007.

Kulkarni, S.S. and Newman, A.H. Design and Synthesis of Novel Heterobiaryl Amides as Metabotropic Glutamate Receptor Subtype 5 Antagonists. Bioorg. Med. Chem Lett. 17, pp. 2074-2079, 2007.

Heinz, A., Waters, A.J., Taylor, R.C., Myers, C.S., Moolchan, E.T., and Heishman, S.J. Effect of Tobacco Deprivation on the Attentional Blink in Rapid Serial Visual Presentation. Human Psychopharmacology: Clinical and Experimental 22, pp. 89-96, 2007.

Director's Report to the National Advisory Council on Drug Abuse - May, 2007

Staff Highlights

Staff Honors and Awards

Ana Anders, SPO, was elected president of the NIH Hispanic Employee Organization.

Dr. Steven Grant, DCNBR, served on the fingerprint panel and as an expert reviewer on Knowledge Management for Disease Coding (KDMC) sub-committee on "Mind and Brain".

Dr. Rao Rapaka, DBNBR, has agreed to serve as the "Associate Editor" for the AAPS Journal (American Association of Pharmaceutical Scientists Journal).

Dr. Jerry Flanzer, Services Research Branch, Division of Epidemiology, Services and Prevention Research, received an award for Outstanding Leadership and Excellence in Advancing Social Work Research, Research Infrastructure and Knowledge from the National Association of Deans and Directors of Social Work (NADD) at their Annual Meeting, San Francisco, CA., January 2007.

Dr. Amy Newman, IRP, filed the following patent: Newman A. H.; Kulkarni, S. S. Modulators of the Metabotropic Glutamate Receptor Subtype 5 And Uses Thereof. *U.S. Patent Application* filed January 26, 2007.

Staff Changes

Dr. Kevin P. Conway has been appointed as Deputy Director of the Division of Epidemiology, Services, and Prevention Research (DESPR). Kevin returns to DESPR after serving as the Associate Director of DCNBR for nearly 2 years. Prior to that time, Kevin was a program official and deputy branch chief in the Epidemiology Research Branch in DESPR. Prior to joining NIDA in 2001, Dr. Conway was a faculty member in the Department of Epidemiology and Public Health at the Yale University School of Medicine. Dr. Conway earned the Ph.D. in Experimental Psychology from Temple University in 1998.

Dr. Mary Kautz joined the Clinical Neuroscience Branch, DCNBR as a program officer. Mary received her Ph.D. in Experimental Psychology from The American University in Washington, D.C. and was a post-doctoral fellow at Johns Hopkins University School of Medicine and Bowman Gray School of Medicine (of Wake Forest University). She subsequently conducted human behavioral pharmacology research on factors to maintain or improve cognitive performance during periods of simulated, sustained or continuous operations as a Commissioned Army Officer in the U.S. Army at Walter Reed Army Institute of Research.

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Dr. Liberman joined the Services Research Branch of DESPR where his focus will be on services research with criminal justice populations. Before joining NIDA, Dr. Liberman served as a Social Science Analyst at the National Institute of Justice (NIJ) of the U. S. Department of Justice. He is the editor of the forthcoming volume, The Long View: A Synthesis of Recent Longitudinal Studies of Crime and Delinquency, to be published by Springer. Dr. Liberman has published on topics including police stress, minority over-representation in the juvenile and criminal justice systems, and juvenile waiver to criminal court, as well as basic research in social psychology. He has conducted criminal justice research at Columbia University and the New York City Criminal Justice Agency, and taught in the Psychology Department at the University of Arizona. Dr. Liberman holds a Ph.D. in psychology from New York University.

Dr. Yu (Woody) Lin joined the Clinical Neurobiology Branch, DCNBR, where he will direct the portfolio in HIV/AIDS and Pain. Dr. Lin was formerly a program officer in DBNBR.

Dr. Samia Dawud Noursi has joined the Women and Sex/Gender Research Program as Deputy Coordinator. She is not new to NIDA as she was Special Assistant to the Director in DESPR for the past year. Dr. Noursi holds a Ph.D. in Applied Developmental Psychology from the University of Maryland and was awarded a Post-Doctoral Fellowship at NICHD during which she led a longitudinal study on the effects of domestic violence on children's development. Prior to joining NIDA, Dr. Noursi was a Social Science Analyst in the Division of Services and Intervention Research at NIMH and worked on a variety of projects including efforts to bridge science to services.

Eric P. Zatman, Contracts Review Branch, Office of Extramural Affairs, retired after 33 years of government service on May 2, 2007. Eric spent the last 30 years with NIDA, serving as a Public Health Advisor in the Prevention Branch in the 1970s and in the NIDA Treatment Research Branch, Division of Community Assistance, working as a state-wide Services Program Official responsible for the federal government match for the States of North Carolina, Tennessee and Alabama. He also served as a Contract Specialist in the Contracts Management Branch and, for the past 20 years, has served as a contract proposal review administrator. Eric also represented NIDA as a member of the NIH-wide team that drafted the updated NIH Policy Manual Issuance on Initiation, Review, Evaluation, and Award of Research & Development (R&D) Contracts. Eric is a recent recipient of the NIDA Director's Award of Merit for his contribution as the review administrator for the NIH Blueprint Neuroscience Information Framework Broad Agency Announcement.

Pamela K. Stokes, Office of Extramural Affairs, has retired after 36 years of government service, 29 of which were at NIDA. She started her government career with the Division of Research Grants, in the Career Development Research Branch at NIH. She next moved to NIMH, where she was a Grants Technical Assistant, and she then came to NIDA as a secretary in a program office and moved to extramural grants and contracts review in 1980. Most of her NIH career has been with the extramural review of grant and contract applications. She started as a fellowship clerk, became a Grants Technical Assistant, moved to a Lead Grants Technical Assistant position, and currently is serving as the Extramural Review Coordinator in OEA. As the Extramural Review Coordinator, Pam has supported the Institute's Advisory Council as well as the Institute's receipt and referral functions. She has worked closely with the Director, OEA as well as NIDA senior staff and she has been a source of information and advice for all NIDA, as well as the scientific community, answering questions and providing guidance about all aspects of extramural policy and procedures. Pam will be fondly remembered and greatly missed for her comprehensive knowledge of NIDA's program, review and grants management functions, for her competence and good humor, for her assistance throughout times of dramatic change in extramural policy and

procedures and for her dedication to the mission of NIDA and the NIH.

Director's Report to the National Advisory Council on Drug Abuse - May, 2007

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Dr. Linda M. Collins, Director of the NIDA funded Penn State Methodology Center, has been named a member of the Fulbright Senior Specialists Roster. This is a roster of scientists representing a wide variety of areas of expertise, who may be called upon to visit a foreign country for 2-6 weeks to collaborate with scientists there on targeted projects. More about the program may be found at http://www.cies.org/specialists/.

Dr. Douglas Owens (Stanford University and the U.S. Veterans Administration) was awarded the Veterans Administration's most prestigious national award for research, "The Under Secretary's Award for Health Services Research" (February 22, 2007, Washington, D.C. Dr. Owens received a personal special cash award of $5,000, and up to $50,000 annually for up to three years in VA research funds to augment his peer-reviewed research funding. Dr. Owens was particularly recognized for his advanced AIDS modeling research on expanded HIV screening which has been adopted by the CDC and significantly altered and bettered U.S. public health policy and practice.

Dr. Nancy Petry, Professor of Psychiatry at the University of Connecticut Health Center in Farmington, CT has won the 2007 Joseph Cochin Young Investigator Award from the College on Problems of Drug Dependence (CPDD). This award, in memory of the former Chairman and Executive Secretary of CPDD, recognizes research contributions in the field of drug abuse by an investigator who has not attained his/her 40th birthday by July 1 in the year of the award. Dr. Petry was recognized for her significant contributions to the field of behavioral drug abuse treatment. Dr. Petry's research has led to the development of a contingency management approach--prize-based contingency management, sometimes known as "The Fishbowl"--that is both a potent intervention for improving treatment engagement and outcomes, and is deliverable in community settings (i.e., is "community-friendly"). Dr. Petry's work also has clarified the association between problem gambling and drug abuse, and has developed treatments for this population. Dr. Petry has been funded as principal investigator on multiple research project grants from NIDA and NIMH, has had over 130 peer reviewed manuscripts accepted for publication, and has served as a reviewer on various NIH study sections. She is a valuable member of the scientific community, and well-deserving of this honor.

Dr. Judith Prochaska at the University of California San Francisco was awarded the Jarvik-Russell Young Investigator Award at the 2007 Conference of the Society for Research on Nicotine and Tobacco.

The Connecticut Renaissance (CT Renaissance), a CTP in the New England Node, was selected for an effectiveness award. The Joint Meeting on Adolescent Treatment Effectiveness (JMATE) presents awards in 5 categories.

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CT Renaissance will receive an award - "In recognition of constant commitment and movement towards evidence-based practice in adolescent substance abuse treatment." This award was selected from nominations made nationwide. Presentation of the award was in Washington DC during the JMATE April 2007 meeting.

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