Director's Report to the National Advisory Council on Drug Abuse - February, 2008

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Research Findings - Basic Neuroscience Research

Inhalant-Induced Epigenetic Changes Produce Drug Tolerance

Epigenetic changes are heritable or stable changes in gene expression potential that are not encoded by the DNA sequence itself. The role of epigenetic regulation in illicit drug responses is an emerging but still understudied area of scientific discovery. Dr. Nigel Atkinson and co-workers exploit the genetically powerful fruit fly model system to investigate the molecular basis of inhalant tolerance. Briefly, Dr. Atkinson showed that a single exposure to inhalant can lead to epigenetic changes in the chromatin (the DNA/protein complex in the nucleus of a cell) near the "slowpoke" potassium channel gene, leading to altered expression of the slowpoke gene and reduced sensitivity (tolerance) to additional inhalant exposures. These studies are based on the observation that animals become tolerant to sedation by organic solvents, which can be abused as inhalants, and this reduced sensitivity to inhalants requires increased expression of the slowpoke potassium channel which in turn alters neuronal function. What is the molecular mechanism behind this observation? Dr. Atkinson and co-workers found that a single exposure to an inhalant led to epigenetic changes in regulatory regions of the slowpoke gene. Specifically they observed that the pattern of acetylation of the DNA-binding protein histone H4 was altered across the slowpoke gene, which likely led to a more open localized chromatin structure and subsequent increased expression of the slowpoke gene. Exposure of the animals to a pharmacological inhibitor of histone deacetylases, the class of enzymes responsible for the H4 histone acetylation, also led to similar epigenetic and gene expression changes as well as tolerance of the animals to the inhalant. Interestingly, Dr. Atkinson and colleagues found DNA elements within the slowpoke promoter that could be bound by the CREB transcription factor. A number of labs have shown that the CREB transcription factor is important in the responses of organisms to illicit substances, as well as in other neuroplastic processes such as learning and memory. Using a genetic trick to "turn off" CREB, the researchers found that the epigenetic and expression changes to slowpoke, and the development of behavioral tolerance no longer occurred. This indicates that the CREB transcription factor is required for these processes. Overall this work clearly shows that exposure to a drug of abuse can alter future sensitivity to the drug via epigenetic regulatory mechanisms. It also provides insight into the precise mechanisms by which exposure to an inhalant can lead to epigenetic and gene expression changes of a single gene, resulting in altered neuronal function and altered behavioral responses of an animal to future inhalant exposure. Although this work was done using an inhalant, similar mechanisms may well be utilized for responses to other drugs of abuse. Small molecules that alter the activity of epigenetic regulatory proteins are already in clinical trials to treat some forms of cancer, so it is possible that a deeper understanding of the role of epigenetics in response to drug exposure could lead to the development

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of "epigenetic therapies" to treat addiction and other neuropsychiatric diseases. Wang, Y., Kishnan, H.R., Ghezzi, A., Yin, J.C.P., and Atkinson, N.S. Drug-Induced Epigenetic Changes Produce Drug Tolerance. PLoS Biology 5, pp. 2342-2353, 2007.

Molecular Adaptations Underlying Susceptibility and Resistance to Social Defeat in Brain Reward Regions

Why do some individuals manage to cope with stress while others develop psychopathologies such as post-traumatic stress disorder (PTSD) and depression in response to adverse circumstances? Both genetic and environmental factors contribute to resiliency of individuals to stress. By examining the response of genetically identical animals to stress, environmental and genetic factors can be separated. Yet, if genetically identical animals respond differently to the same environmental stimuli what molecular mechanism can account for the different response? In a recent paper in Cell, Dr. Eric Nestler and his group examined the different responses of genetically identical C57BL/6J mice to social defeat. In the social defeat paradigm a smaller mouse is forced to intrude on the territory of a larger mouse of a more aggressive strain. The larger mouse responds aggressively to the intrusion of the smaller mouse, resulting in subsequent subordination by the smaller intruder mouse. Repeated exposure of C57Bl/6J mice to social defeat produces long lasting reductions in social interactions. Dr. Nestler and his colleagues report that nearly 50% of the chronically defeated C57BL/6J showed similar amounts of social interaction to non-defeated C57BL/6J mice. Susceptible mice showed increased sensitivity to low doses of cocaine, weight loss, and abnormalities in circadian regulation of body temperature, increased anxiety and increased corticosterone reactivity in response to stress. Increased levels of brain derived neurotropic factor (BDNF) and enzymatic activity of BDNF signaling molecules [(phosphorylated akt thymoma viral oncogene (Akt), glycogen synthase kinase 3_ (Gsk-3_)], and extracellular signal regulated kinase (ERK1/2) in the Nucleus Accumbens (NAC) was observed in susceptible mice but not in resilient mice. The source of the increase in BDNF in the NAC comes from BDNF synthesized by ventral tegmental area (VTA) dopamine neurons that project and transport BDNF to the NAC. While upregulation of BDNF explains susceptibility to social defeat, the result does not explain the molecular mechanisms of resilience. To identify the molecular mechanism of resilence, Dr. Nestler and his colleagues conducted a gene expression profiling experiment of transcripts expressed in the VTA from susceptible and resilient mice. Gene expression profiling showed that increased expression histone deacetylase-2 (Hdac2) and adenylyl cyclase 7 (Adcy7), and galanin (Gal) in the VTA is associated with susceptibility while increase expression of three voltage-gated potassium (K+) channels (Kcnf1, Kcnh3, and Kcnq3) in the VTA was only observed in resilient animals. As expected decreased excitability was observed in VTA dopamine neurons in resilient mice and susceptibility in susceptible mice could be reversed by increasing the expression of a potassium channel with a viral vector. The experimentally increased potassium channel resulted in decreased expression of BDNF protein in the NAC. To further test the hypothesis that the release of BNDF from VTA neurons is responsible for susceptibility, Nestler and his colleagues used a "knockin" mouse that has either a val/val or met/met variant in the BDNF gene. Met/met mice, displaying impaired BDNF secretion without affecting neuronal firing, were resilient while val/val knockin mice were highly susceptible to social avoidance following social defeat. These finding are highly relevant to the human condition because levels of BDNF were increased by 40% in the post-mortem brains of depressed patients. These results suggest that individuals releasing BDNF from VTA dopamine neurons in response to adversity are susceptible to stress. These results provide a novel insight into the development of novel therapeutic agents to promote resilience. It is anticipated that further research will explain the mechanisms by which differential gene expression in the VTA is observed in

susceptible and resilient animals. Krishnan, V., Han, M.H., Graham, D.L., Berton, O., Renthal, W., Russo, S.J., Laplant, Q., Graham, A., Lutter, M., Lagace, D.C., Ghose, S., Reister, R., Tannous, P., Green, T.A., Neve, R.L., Chakravarty, S., Kumar, A., Eisch, A.J., Self, D.W., Lee, F.S., Tamminga, C.A., Cooper, D.C., Gershenfeld, H.K., and Nestler, E.J. Cell 131(2), pp. 391-404, 2007.

Histone Deacetylase 5 Epigenetically Controls Behavioral Adaptations to Chronic Emotional Stimuli

Although genetic mechanisms play an important role in vulnerability to addiction and psychiatric disorder, recent evidence suggest that epigenetic mechanisms such as enzymatic modification of histones or DNA methylation also play an important role in addiction and psychiatric illness. Epigenetic mechanisms permit long term changes in gene expression in response to environmental conditions without mutation or a change in the sequence of a gene. A recent paper in Neuron by Dr. Nestler and his colleagues focuses on the role of histone deacetylases (HDAC) that represses transcription by removing acetyl groups from histones in mediating responses to stress or cocaine. Previous work showed that systemic injections of HDAC inhibitors enhanced the rewarding effects of cocaine. Dr. Nestler and his colleagues show that the site of action of the systemic injection of the HDAC inhibitors on increased reward is the Nucleus Accumbens (NAC). HDAC5 and HDAC3 were found to have the highest level of expression in the NAC but their expression was not altered by acute or chronic cocaine treatment. Repeated injection of cocaine, however, was associated with increased phosphorylation of HDAC5 and transport of HDAC5 into the cytosol. The effect was specific to HDAC5. Nuclear export of HDAC5 in neurons of the NAC provides a mechanism by which genes induced by chronic cocaine can be regulated epigenetically. Over expression of HDAC5 in the NAC using viral vectors attenuated the response to cocaine and required the presence of the histone deacetylase domain in HDAC5. Knockout of the HDAC5 increased the rewarding properties of cocaine in mice following chronic but not acute cocaine treatment. Expressing HDAC5 in the nucleus accumbens restores normal sensitivity to the rewarding properties of cocaine. Gene expression profiling of HDAC5 knockout mice chronically treated with cocaine suggests that the enhanced sensititivity to the rewarding properties of cocaine is associated with increased expression and acetylation of the promoters of RapGEF6, Gnb4, Suv39H1, wnt5a and the NK1 receptor (NK1R). Chronic stress also resulted in decreasing HDAC5 activity by decreasing HDAC5 transcription, a mechanism distinct from the one through which cocaine decreases activity. Dr. Nestler and his colleagues suggest that chronic cocaine causes the phosphorylation of HDAC5 leading to the nuclear export of HDAC5 from the nucleus to the cytoplasm. This blocks the action of HDAC5 in the nucleus and increases histone acetylation and transcription of HDAC5 target genes. These results suggest that HDAC5 contributes to the behavioral transition between short-term physiological and long-term pathological responses to emotional stimuli and drug exposure. Renthal, W., Maze, I., Krishnan, V., Covington, H.E. 3rd, Xiao, G., Kumar, A., Russo, S.J., Graham, A., Tsankova, N., Kippin, T.E., Kerstetter, K.A., Neve, R.L., Haggarty, S.J,. McKinsey, T.A., Bassel-Duby, R., Olson, E.N., and Nestler, E.J. Neuron 56(3), pp. 517-529, 2007.

Hemopressin is an Inverse Agonist of CB1 Cannabinoid Receptors

Hemopressin, a nine amino acid peptide derived from the _-chain of hemoglobin, was originally isolated from rat brain. It had been previously shown to inhibit hyperalgesia by an opioid-independent mechanism. In this study, the researchers report that hemopressin exhibits antinociceptive properties through interaction with the cannabinoid receptor, CB1. The antinociceptive properties were observed using a variety of modes of

administering the peptide including oral administration. When the researchers looked at the effect of hemopressin on CB1 agonist activity, they found evidence that it blocks downstream signaling events suggesting that hemopressin is acting as an inverse agonist. Furthermore, hemopressin was selective for CB1 over the related receptor CB2 and was able to displace a known chemical antagonist for CB1 with sub-nanomolar affinity. Taken together, these properties make hemopressin a strong candidate for development of a new pain therapeutic. Heimann, A.S., Gomes, I., Dale, C.S., Pagano, R.L., Gupta, A., de Souza, L.L., Luchessi, A.D., Castro, L.M., Giorgi, R., Rioli, Ferro, E.S. and Devi, L.A. PNAS 104, pp. 20588-20593, December 18, 2007.

Tris-Azaaromatic Quaternary Ammonium Salts: Novel Templates as Antagonists at Nicotinic Receptors Mediating Nicotine-Evoked Dopamine Release

A series of tris-azaaromatic quaternary ammonium salts has been synthesized and evaluated for their ability to inhibit neuronal nicotinic acetylcholine receptors (nAChRs), which mediate nicotine-evoked [3H]dopamine release from superfused rat striatal slices, and for their ability to inhibit [3H]nicotine and [3H]methyl-lycaconitine binding to whole rat brain membranes. The 3-picolinium compound 1,3,5-tri-{5-[1-(3-picolinium)]-pent-1-ynyl}benzene tribromide (tPy3PiB), 3b, exhibited high potency and selectivity for nAChR subtypes mediating nicotine-evoked [3H]dopamine release with an IC50 of 0.2 nM and Imax of 67%. The IC50 values obtained for the mono-, bis-, and trispicolinium analogues, NDDPiI, bPiDDB, and tPy3PiB were 30 nM, 2.0 nM, and 0.2 nM, respectively, with Imax values of 62%, 68%, and 67%, respectively. These results clearly indicate that introduction of additional 3-picolinium head groups into the NDDPiI structure greatly augments inhibitory potency and may be attributed to an increase in the number of ionic interactions with putative negatively charged binding sites on nAChR proteins mediating nicotine-evoked DA release. However, one must also consider the potential contributions of the central planar aromatic moiety and triple bond in the linker units with respect to the improved potency of tPy3PiB compared with bPiDDB and NDDPiI. In summary, the novel tris-quaternary ammonium compounds described in the current study represent new leads in our search for subtype-selective nAChR antagonists as treatments for nicotine addiction. Zheng, G., Sumithran, S.P., Deaciuc, A.G., Dwoskin, L.P. and Crooks, P.A. tris-Azaaromatic Quaternary Ammonium Salts: Novel Templates as Antagonists at Nicotinic Receptors Mediating Nicotine-Evoked Dopamine Release. Bioorganic & Medicinal Chemistry Letters, 17, pp. 6701-6706, 2007.

Quantitative Analysis of Naltrexone and 6ss-Naltrexol in Plasma by Liquid Chromatography-Electrospray Ionization Tandem Mass Spectrometry

To improve the analysis of naltrexone and its primary metabolite 6ss-naltrexol, a sensitive and specific method for the analysis of subnanogram per milliliter concentrations of these analytes in human, rat and rabbit plasma was developed utilizing liquid chromatography coupled to electrospray ionization (ESI) tandem mass spectrometry (MS-MS). Plasma samples were extracted utilizing a liquid-liquid extraction technique. This method was compared to an existing gas chromatography (GC)-MS method by analyzing plasma samples collected from a clinical study. Specificity determined from comparing blank plasma fortified with internal standard and analyte at the lower limit of quantitation (LLOQ) from six different human, rat, and rabbit sources demonstrated sufficient signal-to-noise to set the LLOQ for both analytes and by less than 10, 10, and 9% at higher concentrations for human, rat and rabbit plasma, respectively. No loss of analyte was observed after 24 hours of room

temperature storage in human, rat, and rabbit plasma of three cycles of freezing and thawing of human plasma prior to extraction. Human plasma samples were stable for at least five days when stored frozen at -20_ C, and for at least two days when stored at room temperature. The GC-MS and LC-MS-MS methods correlated in the measured plasma concentrations of both naltrexone and 6ss-naltrexol. This method has been validated and subsequently used in the determination of the pharmacokinetics of Depotrex in rabbits. In rabbits, the parent compound shows dose dependent pharmacokinetics as seen in human, but rabbits have much lower conjugated metabolite, 6ss-nalrexol, than that seen in humans. Slawson, M.H., Chen, M., Moody, D.E., Comer, S.D., Nuwayser, E.S., Fang, W.B. and Foltz, R.L. Quantitative Analysis of Naltrexone and 6_-Naltrexol in Human, Rat, and Rabbit Plasma by Liquid Chromatography-Electrospray Ionization Tandem Mass Spectrometry with Application to the Pharmacokinetics of Depotrex(R) Rabbits. Journal of Analytical Toxicology, 31, pp. 453-461, 2007.

Cannabinoids and Pain

The CB2 receptor is of current interest in pain research because several studies have reported CB2 agonist efficacy in various animal models of nociceptive and neuropathic pain. One feature of this receptor is its high level of expression in the immune system and in peripheral organs, which suggests that CB2-selective ligands may not produce the side effects of catalepsy, sedation, and psychotropic action attributed to CB1 ligands, which affect the central nervous system. CB2 messenger RNA has also recently been reported in rat dorsal root ganglion neurons, and lumbar spinal cord, although the location of the receptor on neurons or microglia cells is controversial. At the supraspinal level, low levels of messenger RNA have been reported in various regions of animal brain, but not well correlated with CB2 protein localization. To date, studies of CB2 agonists having antinociceptive properties which NIDA has supported include "classical" tetrahydrocannabinols (HU210), a deoxy-delta-8-THC (JWH133), and cannabimimetic indoles (HU-308, AM 1241, and JWH 015). In a recent study, Dr. Alexandros Makriyannis and collaborators have reported on the preparation and preliminary properties of a new series of benzo(c)chromenones known as cannabilactones. These have been shown to bind preferentially to the CB2 versus the CB1 receptor in tissue binding assays, with one case of 500 fold selectivity for the CB2 receptor. They were shown to be partial agonists in terms of GTPgammaS stimulation, and they also decreased the level of forskolin-stimulated cAMP, indicative of agonist behavior. They did not affect ambulation in rats at ip dose injections of 3 mg/kg, as opposed to impaired ambulation shown by WIN 55,212-2 at the same dose. The 9-hydroxy and 9-methoxycannabi-lactones exhibited peripheral antinociception in the radiant tail-flick test in rats, which was blocked for the 9-hydroxy compound by injection of a CB2, but not a CB1 antagonist. Preliminary structural information from X-ray crystallography and modeling suggests that the presence of the 6-keto group rather than the 6-dimethyl substitution (found in classical THC) produces a planar three-ring structure, reduces affinity for the CB1 receptor, and modifies the interaction of the CB2 receptor with the cannabilactones at positions 3 and 9. It should be noted that the above CB2 selectivity found in animal tissue was much smaller when using the human CB2 receptor (82 % identity with the animal CB2 receptor) expressed in HEK cells. Additional structural modification and structure- activity relationship information will be needed to evaluate these cannabilactones as potential human therapeutics. Khanolkar, A.D., Lu. D. Ibrahim, M. Duclos, R.I., Thakur, G.A., Malan, P., Porreca, R. Veerappan, V., Tian, X., George, C., Parrish, D.A., Papahatjis, D.P., and Makriyannis, A. Cannabilactones: A Novel Class of CB2 Selective Agonists with Peripheral Analgesic Activity. Journal of Medicinal Chemistry, 50, pp. 6493-6500, 2007.

Antagonist to Improgan Discovered

Improgan is a highly effective non-opioid analgesic when injected into the CNS. Improgan has been extensively studied; however neither the improgan receptor, nor a pharmacological antagonist of improgan has been previously described. NIDA grantee Dr. Lindsay Hough (Albany Medical College) and colleagues have recently discovered that 4(5)-((4-iodobenzyl)thiomethyl)-1H-imidazole (CC12), produced a dose dependent attenuation of improgan analgesia in rats, while having no effect when given alone. Radioligand binding, receptor autoradiography, and electrophysiology experiments showed that CC12's effects are not explained by activity at 25 sites known to be relevant to analgesia, including sites where cannabinoids, opioids and histamine produce analgesia. Dr. Hough appears to have discovered a novel brain mechanism involved in pain and analgesia, which may provide a new target for the development of centrally acting analgesics. Hough, L.B., Nalwalk, J.W., Phillips, J.G., Kern, B., Shan, Z., Wentland, M.P., de Esch, I.J.P., Janssen, E., Barr, T. and Stadel, R. CC12, a High-Affinity Ligand for [3H]cimetidine Binding, is an Improgan Antagonist. Neuropharmacology, 52, pp. 1244-1255, 2007.

Studies of Drug Actions on Basic HIV Infection and Growth

Several different laboratories have recently published data on drug action on HIV proliferation in various mammalian systems. There are three papers recently published that describe different types of drug action (cannabinoid or opioid) on immune systems; the third paper describes the basic mechanism of action (describing enzyme systems conducting the message) through which these drugs exert their actions. (1) The first paper describes the inhibition of growth of HIV in cell cultures by a synthetic cannabinoid. NIDA researcher Guy Cabral and colleagues observed that this action was mediated primarily through the "peripheral" cannabinoid system. They also observed, unexpectedly, that the more "central" cannabinoid system, also present, exerted the opposite effect. This occurred not through the action of the agonist (the usual mode of "pro" action through a receptor), but via the antagonist. Rock, R.B., Gekker, G., Hu, S., Sheng, W.S., Cabral, G.A., Martin, B.R. and Peteron, P.K. WIN55,212-2-Mediated Inhibition of HIV-1 Expression in Microglial Cells: Involvement of Cannabinoid Receptors. Journal of Neuroimmune Pharmacology, 2, pp. 178-183, 2007. (2) The second study, reported by NIDA research Dr. S.L. Chang focuses on opioid actions. In a special rat model which expresses some HIV viral proteins, these circulating viral entities enhanced the expression of morphine receptor activity through which increased levels of HIV viral growth could occur, especially in humans. This would demonstrate that not only bacterial, but viral growth (including HIV) could be enhanced by opiates administered to humans. Chang, S.L., Beltran, J.A. and Swarup, S. Expression of the Mu Opioid Receptor in the Human Immunodeficiency Virus Type 1 Transgenic Rat Model. Journal of Virology, 81, pp. 8406-8411, 2007. (3) A CXCR4 receptor system resides on immune and neural supporting cells. This receptor plays a pivotal role in immune responses, the pathogenesis of infection such as HIV, and cellular trafficking. However, the signaling mechanisms regulating SDF-driven (the agent acting on the CXCR4 receptor) T cell migration are not well defined. Dr. Burt Sharp and colleagues have focused on understanding how the signal is transmitted from CXCR4 receptor to accomplish its actions: i.e. alter HIV actions and reproduction and have characterized the kinases involved (enzyme systems which are involved in many cellular functions), which are different from those primarily associated with HIV type actions. Shahabi, N.A., McAllen, K. and Sharp, B.M. Stromal Cell-Derived Factor 1-_ (SDF)-Induced Human T Cell Chemotaxis Becomes Phosphoinositide 3-Kinase (PI3K-Independent: Role of PKC-_. Journal of Leukocyte Biology, 83, 2008. (epub ahead of print)

Cell-specific Upregulation of 4 Nicotinic Receptor Subunits May Explain both Tolerance and Sensitization due to Chronic Nicotine

Exposure

Chronic nicotine induces at least two behavioral phenomena: sensitization, both locomotor and cognitive, and tolerance. Additional studies have shown that chronic nicotine upregulates nicotinic receptor levels throughout the brain, and that these receptors are functional. The conundrum is that increased nicotinic receptor activity produced by upregulation of receptors is consistent with sensitization but not tolerance. Conversely, desensitization of nicotinic receptors which would result in reduced activity would be consistent with tolerance but not sensitization. This study developed mice that express a normal functioning, fluorescently labeled 4 nicotinic receptor subunit and examined the brain region and cell type expression of this subunit, and the functional consequences of its expression. Focusing on the midbrain and hippocampus, it was found that 4 receptors localize to the GABAergic neurons of the VTA and substantia nigra while 4 receptor expression is little changed in dopaminergic neurons. Consequently, increased inhibitory inputs would reduce dopaminergic transmission and produce a decreased response to nicotine that may underlie the development of nicotine tolerance. In the hippocampus, chronic nicotine increased 4 receptors on glutamatergic neurons of the medial perforant path, thereby increasing excitability and consistent with the development of sensitization to nicotine. These different mechanisms provide a possible explanation for the development of tolerance of dopaminergic transmission in midbrain and sensitization of synaptic transmission in forebrain due to chronic nicotine exposure. Nashmi, R., Xiao, C., Deshpande, P., McKinney, S., Grady, S.R., Whiteake, P., Huang, Q., McClure-Begley, T., Lindstrom, J.M., Labarca, C., Collins, A.C., Marks, M.J., Lester, H.A. Chronic Nicotine Cell Specifically Upregulates Functional alpha 4* Nicotinic Receptors: Basis for Both Tolerance in Midbrain and Enhanced Long-term Potentiation in Perforant Path. Journal of Neuroscience, 27, pp. 8202-8218, 2007.

Haloperidol, after a Neurotoxic Regimen of Methamphetamine, Kills GABAergic Neurons in the Substantia Nigra Pars Reticulata of Rats

Methamphetamine-induced psychoses are often managed with haloperidol, a typical antipsychotic (neuroleptic) drug. Neuroleptics are dopamine D2 receptor antagonists. Since the loss of dopaminergic axons due to chronic methamphetamine in rats results in persistent elevated glutamate in the substantia nigra, Bryan Yamamoto's group hypothesized that D2 blockade by haloperidol following methamphetamine neurotoxicity might further disinhibit (i.e., enhance) glutamate release in the substantia nigra pars reticulata by D2 antagonism on striatal GABAergic output neurons and on subthalamo-nigral glutamatergic terminals in the substantia nigra, the combination of which results in the disinhibition of glutamate release from subthalamo-nigral terminals. Indeed, the researchers found that haloperidol, after a neurotoxic regimen of methamphetamine, killed GABAergic neurons in the substantia nigra pars reticulata by glutamatergic excitotoxicity, as reflected by loss of GAD67 mRNA expression, a marker for GABAergic neurons, and DNA fragmentation, accompanied by enhanced extracellular glutamate, and blocked by the glutamate NMDA (N-methyl-D-aspartate) receptor antagonist dizocilpine. While it is not known if this GABAergic neurotoxicity occurs in humans, these findings suggest that the current therapeutic management of methamphetamine psychoses with haloperidol may be contraindicated because of a resultant GABAergic cell death in the substantia nigra pars reticulata, which may predispose some individuals to the development of hyperkinetic movement disorders and seizures. Atypical antipsychotics or benzodiazepines may be a better option. Hatzipetros, T., Raudensky, J.G., Soghomonian, J.J. and Yamamoto, B.K. Haloperidol Treatment after High-Dose Methamphetamine Administration Is Excitotoxic to GABA Cells In The Substantia Nigra Pars Reticulata. Journal of Neuroscience, 27(22), pp. 5895-902, 2007.

Cocaine During Adolescence Enhances Dopamine in Response to a Natural Reinforcer

One of the most important questions in addiction research is whether the developmental period during which one begins to use drugs is important in determining an individual's vulnerability to future drug use. Increased dopamine release may be predictive of a substance's reinforcing properties. The present study investigated whether cocaine pretreatment in either adolescence or adulthood altered the dopaminergic response to a naturally reinforcing substance in adulthood. Animals were treated with cocaine for a single ten-day period as adolescents or as adults, and were prepared for microdialysis, with cannulae implanted in the nucleus accumbens septi (NAcc). One week later, all animals were exposed to sucrose in their drinking water and dialysate samples were collected. Regardless of age all saline-pretreated rats had significant increases in sucrose-induced extracellular dopamine (DA) levels in the NAcc compared to baseline levels. Rats pretreated with cocaine as adults also had significant increases in DA levels after sucrose. Interestingly, sucrose intake significantly enhanced DA levels in cocaine-pretreated adolescent rats as compared to all other conditions. The results from the present study show that rats given cocaine during adolescence have an enhanced dopaminergic response relative to adults when exposed to a naturally reinforcing substance, suggesting a greater sensitivity to sucrose in the younger animals. Cocaine exposure during adolescence produces long-term functional changes in the mesolimbic pathway. Future studies need to ascertain the underlying mechanisms and their potential role in cocaine addiction. Catlow, B.J. and Kirstein, C.L. Cocaine During Adolescence Enhances Dopamine in Response to a Natural Reinforcer. Neurotoxicology and Teratology, 1, pp. 57-65, 2007.

Gingko Biloba Extract Protects Against Astrocyte-Mediated Neurotoxicity in Mouse Model of HIV Neuropathogenesis

One factor believed to play a significant role in HIV-associated neuropathogenesis is the secretion of the HIV-1 Tat protein from infected cells in the brain. However, the mechanisms underlying Tat neurotoxicity are still not completely understood, and few therapeutics have been developed to specifically target HIV infection in the brain. Recent development of an inducible brain-specific Tat transgenic mouse model has made it possible to define the mechanisms of Tat neurotoxicity and evaluate anti-neuroAIDS therapeutic candidates in the context of a whole organism, as well as to study these issues in combination with models of drug abuse. This study showed that administration of EGb 761, a standardized formulation of Ginkgo biloba extract, markedly protected Tat transgenic mice from Tat-induced developmental retardation, inflammation, death, astrocytosis, and neuron loss. EGb 761 directly down-regulated glial fibrillary acidic protein (GFAP) expression, a marker of astrocyte activation, at both protein and mRNA levels. This down-regulation was, at least partially mediated by EGb 761 alteration of the interactions of the AP1 and NF-kappaB transcription factors with the GFAP promoter. Most strikingly, the characteristic Tat-induced macrophage/microglia activation, central nervous system infiltration of T lymphocytes, and oxidative stress were significantly alleviated in GFAP-null/Tat transgenic mice. Taken together, these results provide the first evidence to support the potential for clinical use of EGb 761 to treat HIV-associated neurological diseases. Moreover, these findings suggest for the first time that GFAP activation is directly involved in Tat neurotoxicity, supporting the notion that astrocyte activation or astrocytosis may directly contribute to HIV-associated neurological disorders. Zou,W., Kim, B.O., Zhou, B.Y., Liu, Y., Messing, A. and He, J.J. Protection Against Human Immunodeficiency Virus Type 1 Tat Neurotoxicity by Ginkgo biloba Extract EGb 761 Involving Glial Fibrillary Acidic Protein. American Journal of Pathology, 171, pp. 1923-1935, 2007.

Cocaine Directly Induces Breakdown of Blood-Brain Barrier and Increased Chemotactic Signaling of Monocytes, Factors Involved in Exacerbation of NeuroAIDS Pathogenesis

One of the hallmark features underlying the pathogenesis of HIV encephalitis is the disruption of the blood-brain barrier (BBB). Cocaine, often abused by HIV-infected patients, has been suggested to worsen the HIV-associated dementia (HAD) via unknown mechanisms. The present study examined the effects of cocaine on BBB permeability using human brain microvascular endothelial cells (HBMECs), as well as on the chemokine CCL2 and its receptor CCR2, which play crucial roles in the recruitment of inflammatory cells into the central nervous system in HIV-associated neurological disease. Exposure of HBMECs to cocaine correlated with the breakdown of ZO-1 tight junction protein and reorganization of the cytoskeleton resulting in stress fiber formation. Furthermore, cocaine also modulated upregulation of the CCL2/CCR2 axis in monocytes. These findings support the idea that cocaine exposure may lead to accelerated progression of HIV-1 neuropathogenesis. Dhillon N.K., Peng, F., Bokhari, S., Callen, S., Shin, S.H., Zhu, X., Kim, K.J. and Buch, S.J. Cocaine-Mediated Alteration in Tight Junction Protein Expression and Modulation of CCL2/CCR2 Axis Across the Blood-Brain Barrier: Implications for HIV-Dementia. Journal of Neuroimmune Pharmacology, 2007, epub ahead of print.

CYP2B6 Genotype Alters Abstinence Rates in a Bupropion Smoking Cessation Trial

Bupropion is a non-nicotine smoking cessation treatment medication. Although the efficacy of bupropion relative to placebo is firmly established, the majority of smokers relapse to smoking within 6 months after a quit attempt. It's known that CYP2B6 is the primary enzyme that metabolizes bupropion. Genetic variations in CYP2B6, such as the variant CYP2B6*6, can alter bupropion metabolism and may affect treatment outcome. To understand the pharmacogenetics of bupropion metabolism, Rachel Tyndale and her colleagues conducted a smoking cessation trial of bupropion versus placebo. Subjects were assessed for abstinence and other outcomes 10 weeks after start of treatment, and then again for a 6-month follow-up, and genotyped for CYP2B6. They showed that among smokers with *6 variants (n=147), bupropion treatment showed higher abstinence rates than placebo at the end of treatment (32.5% vs. 14.3%, p=0.01) and at the 6 month follow-up (31.2% vs. 12.9%, p=0.008). In contrast, bupropion was no more effective than placebo for smokers with the CYP2B6*1 gene variant (n=179), at the end of treatment (31% vs. 31.6%, p=.93) or at the 6-month follow up (22.0% vs. 21.5%, p=.94). Taken together, this study suggests that smokers with the CYP2B6*6 genotype may be especially 1.good candidates for bupropion treatment for smoking cessation. Lee, A.M, Jepson, C., Hoffmann, E., Epstein, L., Hawk, L.W., Lerman, C., and Tyndale, R.F. Biol. Psychiatry 62(6), pp. 635-641, 2007.

The Classical Complement Cascade Mediates CNS Synapse Elimination

During development synapses are initially formed and many inappropriate synapses are eliminated to establish the necessary circuitry for the proper function of the nervous system. Axons emanating from the retinas of both eyes initially connect to overlapping areas of the lateral geniculate nucleus, an area involved in processing visual information. Through a process of neuronal activity the overlap in the projections to the lateral geniculate nucleus is eliminated and the inputs from each eye become separated. This occurs during a specific time window, known as the critical period. If neuronal activity is

blocked and only occurs after the critical period, synaptic refinement cannot take place. The process by which inappropriate synapses are eliminated has not been understood up until now. Work by the Barres lab at Stanford led by Dr. Beth Stevens shows that a molecule used to fight infection, C1q, in the complement cascade is required for synapse elimination. C1q is expressed in postnatal neurons in response to immature astrocytes and is localized to synapses throughout the postnatal CNS and retina. In the adult mouse brain C1q is not expressed. Thus, the expression of C1q coincides with the critical period for synapse elimination. The knockout of the C1q blocks synapse elimination and prevents segregation of the connections by the two retinas to the lateral geniculate nucleus. The mechanism by which synapse elimination takes place appears to be mediated by the classical complement cascade because knockout out of C3 produces the same effect on synapse elimination and segregation of synaptic input from the two retinas. C3 is the next molecule in complement cascade activated by C1q. While C1q is normally down regulated in the adult nervous system, C1q is upregulated in the retina in a mouse model of glaucoma, a neurodegenerative disease. These results suggest that the complement cascade plays an important role in synapse elimination during normal development and that complement-mediated synapse elimination may become reactivated in neurodegenerative disease. Stevens, B., Allen, N.J., Vazquez, L.E., Howell, G.R., Christopherson, K.S., Nouri, N., Micheva, K.D., Mehalow, A., Huberman, A.D., Stafford, B., Sher, A., Litke, A.M., Lambris, J.D., Smith, S.J., John, S.W.M., and Barres, B.A. Cell, 131, pp. 1164-1178, 2007.

Serine Phosphorylation Controls PSD-95: A Mini-Switch for Learning and Memory

Long term potentiation (LTP) and long term depression (LTD) play major roles in the most basic neural mechanisms for learning and memory. In the hippocampal region of the brain, LTP is the long-lasting enhancement in communication between two neurons that results from stimulating them simultaneously. LTD has the opposite role in neuronal communication. The cellular and molecular biology of LTP and LTD are not fully understood. PSD-95 is a scaffold protein at the post synaptic density (PSD) of the neuron that regulates synaptic strength. Evidences suggests that synaptic (chemical) LTP promotes PSD-95 accumulation at PSD, increasing synaptic strength; and LTD induces dispersal of PSD-95, reducing synaptic strength. Therefore PSD-95 is functioning like a switch to turn communication on and off between neurons for memory and learning. How the synaptic activities results in PSD-95 switch being turned on and off is not known. A NIDA funded research team led by Dr. Yasunori Hayashi, researcher at MIT in collaboration with a research group at University of Bristol, UK, reports that synaptic activities regulate PSD-95 accumulation at the synaptic site through the phosphorylation and dephosphorylation of a specific serine residue on the protein. Thus, phosphorylation of ser-295 occurs in vivo, and it enhances the ability of PSD-95 to accumulate in the PSD, leading to the recruitment of AMPA receptors and the strengthening of synaptic transmission. On the other hand, over expression of a mutant, S295D-PSD-95, which mimics phosphorylation but cannot be "dephosphorylated", blocks the induction of LTD. They suggest that dephosphorylation of PSD-95 ser-295 is critical for LTD, presumably because this dephosphorylation is required for dispersal of PSD-95 from synaptic sites and subsequent mobilization and internalization of AMPA receptors. Using pharmacological blocking agents, the researchers further identified that the Rac1-JNK1 kinase pathway is the main mediator of the PSD-95 serine phosphorylation, and the activation of the PP1 and/or PP2A phosphatases are responsible for PSD-95 dephosphorylation. Kim, M.J., Futai, K., Jo, J., Hayashi, Y., Cho, K. and Sheng, M. Synaptic Accumulation of PSD-95 and Synaptic Function Regulated by Phosphorylation of Serine-295 of PSD-95. Neuron 56(3), pp. 488-502, 2007.

Navigating Neurons Get to Know Where and When in the Developing Cerebral Cortex through Lhx2

During the development of cerebral cortex, newly born neurons in the ventricular zone migrate towards the cortical area and form six cortical layers. How the navigating neurons know where they are during the migration and when to stop upon their destination have been important research topics. A NIDA supported research team at Mass General Hospital/Harvard University, led by Dr. Pradeep Bhide, previously reported that embryonic exposure to cocaine results in irregularity of neuronal migration in the developing cortex, indicating the consequences of drugs of abuse in causing brain disorders. In the most recent study, the team reveals a molecular mechanism that migrating neurons rely on for positioning. Thus, the projection neurons of the neocortex are produced in the pseudostratified ventricular epithelium (PVE) lining of the embryonic lateral ventricles. Over a 7 day period in mouse, these neurons arise in an overlapping layer VI-to-II sequence and in an anterolateral to posteromedial gradient [the transverse neurogenetic gradient (TNG)]. At any time in the 7 day neurogenetic interval, a given PVE cell must know what class of precursor cell or neuron to form next. How this information is encoded in the PVE has not been known. With comparative experiments in wild-type and double-transgenic mice, overexpressing the cell cycle inhibitor p27Kip1, they show that a gradient of expression of Lhx2, a LIM homeodomain transcription factor, together with a gradient in duration of the G1 phase of the cell cycle, are sufficient to specify a positional mapping system that informs the PVE cell what class of neuron to produce next. The researchers suggest that Lhx2 likely is representative of an entire class of transcription factors expressed along the TNG. This mapping system consisting of a combination of signals from two different sources is a novel perspective on the source of positional information for neuronal specification in the developing CNS. Bernhard, S.B., Nowakowski, R.S., Bhide, P.G., and Caviness, V.S. Navigating Neocortical Neurogenesis and Neuronal Specification: A Positional Information System Encoded by Neurogenetic Gradients. J. Neurosci. 27, pp. 10777-10784, 2007.

Alpha2-Chimaerin Is the Newly Discovered Player in Eph-Ephrin Signaling Pathways in Axonal Path-finding

Eph-ephrin, the ligand-receptor signaling pair, is a family of principal cell guidance system during vertebrate and invertebrate development. They play essential roles in determining body segmentation, axon guidance and fasciculation, cell migration, angiogenesis, and cancer. A well known phenotype observed in neurobiological research is that mice lacking EphA4 exhibit a pronounced locomotor defect that results in rabbit-like hopping of the hindlimbs, largely due to aberrant axonal path-finding and crossing in the spinal cord during CNS development. While many ephrins, as the receptors for Ephs, have been identified, little has been known on the downstream signaling events and players inside the cell as effectors for Eph-ephrin signaling. Dr. Peter Scheiffele, a NIDA researcher at Columbia University, reports that his team has recently identified an important player, alpha2-chimaerin, as the effector in EphA4-ephrin signaling. They observed that the RacGAP alpha2-chimaerin interacts with activated EphA4 and is required for ephrin-induced growth cone collapse in cortical neurons. Alpha2-chimaerin mutant mice exhibit the same rabbit-like hopping gait with synchronous hind limb movements that phenocopies mice lacking EphA4 kinase activity. Anatomical and functional analyses of corticospinal and spinal interneuron projections reveal that loss of alpha2-chimaerin results in impairment of EphA4 signaling in vivo. These findings identify alpha2-chimaerin as an indispensable effector for EphA4 in cortical and spinal motor circuits. Beg, A.A., Sommer, J.E., Martin, J.H., and Scheiffele, P. Alpha2-Chimaerin Is an Essential EphA4 Effector in the Assembly of Neuronal Locomotor Circuits. Neuron 55(5), pp. 768-778, 2007.

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Director's Report to the National Advisory Council on Drug Abuse - February, 2008

Research Findings - Basic Behavioral Research

Nicotinic Control of Axon Excitability Regulates Thalamocortical Transmission

Dr. Raju Metherate and his colleagues at the University of California, Irvine, have reported a new role for nicotinic acetylcholine receptors in regulating cortical information processing by an action on myelinated axons in a thalamocortical tract that carries sensory information from relay nuclei in the thalamus to the neocortex. Using both in vivo and in vitro preparations of the auditory thalamo-cortical pathway in adult mice, Dr. Metherate and his team showed that activation of nicotinic acetylcholine receptors in the initial portion of the path modulate transmission by means of regulating axonal excitability. Exogenously applied nicotine was found to increase the probability and synchrony of evoked action potential discharges in vitro, whereas blockade of the receptors in the pathway in vivo was accompanied by reduced sound-evoked cortical responses. Dr. Metherate proposes that this mechanism may be responsible for the facilitatory effect of nicotine on sound-evoked cortical potentials and the cholinergic regulation of sensory-cognitive function. Kawai, H., Lazar, R. and Metherate, R. Nicotinic Control of Axon Excitability Regulates Thalamocortical Transmission. Nature Neurosci., 10, pp. 1168-1175, 2007.

Repeated Cocaine in Rats Prior to Pregnancy Alters Subsequent Cortical Activation and Maternal Behavior

Drs. Marcelo Febo and Craig Ferris at the University of Massachusetts Medical Center administered cocaine to rats for 14 days and then withdrew treatment during breeding and pregnancy. On postpartum days 4-8 neural responses to suckling were measured with blood-oxygen-level-dependent (BOLD) MRI or microdialysis. Results showed that BOLD activation in the medial prefrontal cortex, septum, and auditory cortex was curtailed in these cocaine sensitized dams and the effect was long lasting. No differences were reported for other brain areas examined, including the nucleus accumbens and olfactory regions. Baseline, but not pup-stimulated, dopamine levels in the prefrontal cortex were lower in cocaine-sensitized dams. Cocaine-sensitized dams exhibited faster retrieval of pups, but no differences were seen in other maternal behaviors such as grouping, crouching or defending the nest. The authors proposed that this cocaine-associated change in pup retrieval behavior could be linked to hypo-responsivity of the medial prefrontal cortex. It is possible that cocaine's effect on neural activation associated with suckling reflects a cross-sensitization process, such as that previously observed by others when comparing drugs of abuse like cocaine with natural rewards. Febo, M. and Ferris, C.F. Development of Cocaine Sensitization Before Pregnancy Affects Subsequent Maternal Retrieval of Pups and Prefrontal Cortical Activity During Nursing. Neurosci, 148, pp. 400-412, 2007.

Planned Meetings

Publications

Staff Highlights

Grantee Honors

Chronic Nicotine Augments Hormonal Response to a Mild Stressor

NIDA grantee Dr. Burt Sharp has been investigating the effects of chronic nicotine self-administration (SA) on hypothalamo-pituitary-adrenal (HPA) responses to stress. In a recent study, he predicted that nicotine would act as a stressor, increasing plasma stress hormone levels and augmenting the increases produced by other stressors. Stress responsivity varies across rat strains, so Sprague-Dawley (SD) rats were comprehensively evaluated in this study and Lewis rats tested under limited conditions for comparison. Both strains were given the opportunity to self-administer (SA) nicotine or saline on a 23 hr/day schedule for 20 days. Blood samples were taken on the first and third day of access and analyzed for adrenocorticotropin (ACTH) and corticosterone (CORT). In both SD and Lewis rats, hormone levels increased on the first day of nicotine exposure, suggesting that acute drug activates a stress response, but normalized by the third day of nicotine SA. After 20 days of nicotine or saline SA, SD rats were exposed to one of three types of stress: mild or moderate foot shock stress, endotoxin [lipopolysaccharide; LPS], or immobilization. Foot shock was administered during a nicotine SA session, and lever-press behavior was assessed. Also, as all three types of stress have previously been observed to increase stress hormone levels, blood samples were taken for hormone level analysis. LPS and immobilization stressors were administered following a nicotine SA session, and only effects on plasma hormone levels were measured. For the Lewis rats, the only stressor tested was mild foot shock, which was also imposed during a nicotine SA session. In general, electric foot shock did not alter nicotine SA behavior regardless of strain or shock intensity. Chronic nicotine SA augmented the HPA hormonal response to mild foot shock in SD rats, and moderate foot shock-induced hormonal responses in this strain were not affected by chronic nicotine. Chronic nicotine also did not affect LPS- or immobilization-induced increases in ACTH or CORT. As predicted, nicotine activated the HPA axis in a similar manner to that produced by an imposed stressor -- initially increasing ACTH and CORT, with tolerance developing to this effect after several days of repeated administration. Although mild shock foot shock produced CORT increases in both SD and Lewis rats, their responses were not identical. Peak CORT responses were seen earlier in SD rats and nicotine's amplification of the CORT response in SD rats was greater than that seen in the Lewis strain. These findings indicate that type of stress, as well as its intensity, are important determinants of the stress-induced hormonal responses, and that nicotine augments the hormonal stress responses produced by these stressors. Taken together, the data suggest that nicotine may increase responses to a mild stressor in chronic cigarette smokers. Chen, H., Fu, Y., and Sharp, B.M. Chronic Nicotine Self-Administration Augments Hypothalamic-Pituitary-Adrenal Responses to Mild Acute Stress. Neuropsychopharm., pp. 1-10, 2007 (e-pub ahead of print).

Chronic Nicotine Increases _4 and _2-Containing- and Decreases _6-Containing-Nicotinic Acetylcholine Receptors

Nicotine regulates the expression of neuronal nicotinic acetylcholine receptors (nAChR). These receptors are typically heteromeric, containing both alpha- and beta-subtypes. Upregulation of _4_2 has been reported from human smokers, while nAChR receptors containing the _3_2 combination appear resistant to nicotine. Subunits of the _6 type in the striatum are involved in nicotine-stimulated dopamine release and levels of _6 are increased by long-term administration of nicotine. Dr. David Perry and colleagues have recently used three different approaches to assess the effects of chronic nicotine on _6 subunits and assess functional changes in striatal dopamine release that correspond to these changes: 1) autoradiographic binding of cone snail toxin _-conotoxin MII ([125I]_-CtxMII -- a radioligand predominantly selective for the

_6 subtype) and [125I]A-85380 -- a radioligand selective for the _4_2 subtype; 2) immunoprecipi-tation with a battery of subunit-selective antibodies; and 3) determination of _6-CtxMII-sensitive dopamine release from striatal synaptosomes. Immunoprecipitation using antibodies for _2, _3, _4, _5, _6, _2, _3, and _4 subunits found that _4 and _2 receptor subunits represented about 80% of the labeled receptors in the striatum and the superior colliculus. Levels of both _2 and _4 subunits were negligible, with levels of _3, _5, _6 and _3 subunits falling in the 10-25% range. Receptor subunit levels were quantified with these techniques after chronic nicotine treatment (14 days), with 1-30 days of "recovery" time. [125I]A-85380 binding was increased in both regions, indicating a nicotine-induced increase in _4_2 subtype levels. In nicotine treated animals, there was a 28% reduction of ([125I]_-CtxMII binding in the striatum only. Immunoprecipitation of the _6 subunit also indicated significantly reduced levels, which was also selective for the striatum. Specifically, levels of _6-containing receptors decreased up to 3 days post-treatment, but recovered to near control levels by day 7, with complete recovery by 30 days. The decrease in _6-containing nACh receptors was accompanied by a decline of approximately 54% in nicotine-stimulated dopamine release from striatal synaptosomes. Thus, after chronic treatment with nicotine, _-CtxMII appears to be less effective in blocking nicotine-induced dopamine release in a population of striatal _6-containing AChRs, presumably due to down-regulation of the subunit. As the researchers did not observe a 100% decrease in the ability of _6-CtxMII to block nicotine stimulated dopamine release, it appears that there is a separate population of striatal _6-containing striatal receptors, that may be differentiated on the basis of subunit complement, and that this receptor constellation is not changed by chronic nicotine. Nicotine receptors in these regions also contain a _3 subunit, associated primarily with _4_2. Interestingly, while nicotine increased the number of receptors immunoprecipitated by _4 and _2 antibodies, and decreased the number detected by _6 antibodies, _3 levels showed no change. Conclusions from the study are as follows: The decrease in _6 levels in the striatum appears to be driven by a reduction in a population of AChRs that are _-CtxMII-sensitive. Furthermore, the researchers hypothesize that the presence of a _3 subunit modulates the regulatory effects of nicotine on _6_2_3-containing receptors, such that _-CtxMII-resistance (seen in the striatal _6 containing receptors that did not change after nicotine) is associated with the presence of this _3 subunit. They also postulate that _3 may allow more efficient assembly of the receptor subtype or stabilize assembly in some way, conferring resistance to chronic nicotine-induced down-regulation. Thus, chronic nicotine decreases binding to _6-containing receptors, but only to those that do not also contain a _3 subunit. This shift in the nicotinic receptor profile following chronic nicotine exposure may be relevant for understanding the development of nicotine dependence and identifying molecular targets in treatment. Perry, D.C., Mao, D., Gold, A.B., McIntosh, M., Pezzulo, J.C., and Kellar, K.J. Chronic Nicotine Differentially Regulates _6- and _3-Containing Nicotinic Cholinergic Receptors in Rat Brain. JPET 322, pp. 306-315, 2007.

Topiramate Increases Nicotine Reward but Reduces Nicotine Intake

Recently, NIDA grantee Malcolm Reid and colleagues have been testing the drug topiramate, which has both GABA agonist and AMPA glutamate antagonist activity, as a putative smoking cessation agent. Previous findings indicate that glutamatergic antagonists and GABAergic agonists reduce the acute rewarding and reinforcing effects of nicotine, however little is known about this drug's effects on subjective and physiological responses to nicotine withdrawal, cue-elicited craving, and the acute effects of smoked cigarettes. A total of 40 treatment-seeking smokers were enrolled in this study and were randomly assigned to either the topiramate treatment (75 mg/day) or a placebo control in a double-blind design. Baseline evaluations were conducted 30 minutes after

a smoked cigarette and subjects were assessed with subjective rating scales such as the smoking urges-brief questionnaire (QSU), the withdrawal scale for tobacco (WST), and the cigarette evaluation questionnaire (CEQ). Following completion of a 9 day treatment schedule, subjects were re-evaluated at 3 hours of smoking abstinence. Post-treatment tests included skin temperature, blood pressure, heart rate and skin conductance, re-evaluation with the QSU and WST, and a choice procedure which asked patients to hypothetically choose between smoking a cigarette and receiving money. During cue exposure subjects were tested for craving with tactile, olfactory, visual, and audio smoking cues, or with neutral cues, and responses to the QSU, WST and choice test were again collected. In a post-treatment smoking test, subjects were asked to smoke a single cigarette. Cigarettes were smoked though a controlled- puff volume apparatus to measure number of puffs and volume per puff in to collect data on smoking topography. Before and after smoking, physiological measurements were again collected, and the QSU, WST, CEQ, and choice test were re-administered. After 3 hours of abstinence, subjects in the topiramate group reported greater QSU cigarette craving, WST craving, and WST withdrawal, suggesting that they experienced more withdrawal symptoms. There were no significant interactions between treatment condition and measures from the cue exposure test. The post-treatment cigarette reduced craving, withdrawal, and the amount of money chosen over a cigarette during the choice test, and medication did not alter these outcomes. Although topiramate-treated subjects reported increased smoking reward, they had lower puff volumes, total volume smoked, and plasma nicotine levels. These data suggest that topiramate augmented nicotine withdrawal following brief smoking abstinence, and enhanced the rewarding effects of nicotine when patients smoked. Given this observed enhancement of nicotine's rewarding effects, researchers question the utility of topiramate as putative aide in smoking cessation treatment. Reid, M.S., Palamar, J., Raghavan, S., and Flammino, F. Effects of Topiramate on Cue-induced Cigarette Craving and the Response to a Smoked Cigarette in Briefly Abstinent Smokers. Psychopharmacology, 192(1), pp. 147-158, 2007.

Social Reward in Juvenile Mice Reflects Genetic Variation

Vulnerability to drug abuse is different for adolescent humans and animals, compared to adults. We are beginning to understand some of the developmental factors that underlie this difference, including differences in the importance of social interactions. Dr. Garet Lahvis and his colleagues are developing a mouse model of social reward that can be used to investigate how social affiliative behavior and drug abuse vulnerability interact during different periods of development. In one study, they used a novel social conditioned place preference (SCPP) to examine social reward in juvenile mice and investigate its genetic basis by comparing different mouse strains. The SCPP procedure is similar to the conditioned place preference paradigm that is commonly used to study stimuli associated with drug rewards. In one type of environment with a particular type of bedding material, the mice were allowed to interact with their peers, while on alternate days, in the presence of different environmental stimuli, they experienced social isolation. Then on the test day, they were allowed to freely move between two compartments differentiated by the two types of bedding. The results showed that mice could be conditioned to prefer a stimulus previously associated with the availability of social interactions, and indicate that reward mediated by social contact is a fundamental aspect of juvenile mouse sociality. They also reveal that social proximity is rewarding for juvenile mice from three inbred strains (A/J, C57BL/6J and DBA/2J), but that mice from a fourth strain (BALB/cJ) were much less responsive to social contact (although the BALB mice can develop and demonstrate place conditioning for food). The SCPP phenotype was expressed early in development (postnatal day 25) and did not depend on the number of males or females in each conditioning group. They then conducted

additional experiments to compare the strain that conditioned best (C57BL/6J) with the BALB mice that did not show SCPP. In these experiments, they were able to determine that SCPP responses result from an interaction between two distinct processes; that is, conditioning resulted from both facilitated approach toward environments associated with social salience and avoidance of environments associated with social isolation. A follow-up investigation examined the developmental trajectory of preference for social affiliation and behaviors that mediate it, such as ultrasonic communication, and this experiment also incorporated strain comparisons. Strain differences were also found in this study. Overall, these studies identify genetically prescribed processes that attribute value to conditions which predict social contact in juvenile mice - a form of social valuation that is not specifically related to reproductive behavior. This behavioral paradigm, and the identification of phenotypes that can be linked to a genetic substrate, can be a valuable tool for future research in the behavioral genetics of drug abuse vulnerability and development. Panksepp, J.B. and Lahvis, G.P. Social Reward Among Juvenile Mice. Genes, Brain and Behavior, 6, pp. 661-671, 2007. Panksepp, J.B., Jochman, K.A., Kim, J.U., Koy, J.J., Wilson, E.D., Chen, Q.L., Wilson, C.R., and Lahvis, G.P. Affiliative Behavior, Ultrasonic Communication and Social Reward Are Influenced by Genetic Variation in Adolescent Mice. PLoS ONE, 2, e351, 2007.

Enhanced Nicotinic Receptor Activity Links Individual Differences in Novelty Response to Drug Abuse Vulnerability

Animals that have high activity levels in a novel environment are more likely to self-administer abused drugs including nicotine, cocaine, amphetamine, and morphine. Other studies show that activation of nicotinic acetylcholine receptors (nAChRs) contributes to the rewarding effects of addictive drugs. Dr. Daniel McGehee and colleagues hypothesized that nAChR activity may contribute to differences seen in drug abuse vulnerability between these high- (HR) and low-novelty (LR) responding rats. They screened adult rats for their behavioral response to a novel environment and selected animals in the top and bottom quartiles to conduct electrophysio-logical studies of nAChR function in brain slices that included the mesoaccumbens dopamine neurons of the ventral tegmental area (VTA). They found a positive correlation between response to novelty and nAChR modulation of glutamatergic and GABAergic synaptic inputs to VTA dopamine neurons, and in the somatic nAChR responses of VTA neurons. It is also known that response to novelty and sensitivity to addictive drugs are positively correlated with hormonal responses to stress, as HR rats have higher corticosterone (CORT) levels after a stress challenge than their LR counterparts. Thus, the researchers also hypothesized that CORT could enhance nAChR responses. Consistent with this hypothesis, they found that 48 h of CORT treatment of dopaminergic cells in vitro enhanced nAChR responses. Furthermore, when LR animals (but not HR animals) were subjected to stress (repeated forced swimming in cold water for two days), nAChR responses were enhanced in the VTA. Both of these effects were inhibited by pretreatment with a glucocorticoid receptor antagonist, suggesting that a steroid hormone receptor-dependent process was involved. These findings suggest that differences in nAChR function within the mesoaccumbens dopamine system may contribute to individual differences in drug abuse vulnerability and that these differences can be linked to differences in stress hormone levels. Exactly how differences in nAChR function contribute to drug sensitivity and the predisposition to self-administer drugs requires additional study. Fagen, Z., Mitchum, R., Vezina, P., and McGehee, D.S. Enhanced Nicotinic Receptor Function and Drug Abuse Vulnerability. J. Neurosci., 27, pp. 8771-8778, 2007.

Antidepressant Treatment can Normalize Adult Behavioral Deficits Induced by Early-Life Exposure to Methylphenidate in an Animal Model

Animal models have been used to assess whether methylphenidate (MPH), a psychostimulant commonly prescribed for the treatment of attention-deficit/hyperactivity disorder, alters subsequent sensitivity to drugs of abuse or has other neurobiological or behavioral consequences in later life. Rats exposed to MPH during preadolescence show a decreased sensitivity to cocaine in adulthood, but they also show enhanced reactivity to stressful or anxiety provoking situations and a reduced sensitivity to natural and drug rewards. In the current study, Bolanos and his colleagues examined the ability of fluoxetine, a selective serotonin reuptake blocker, to normalize these depression-like symptoms. Male rats received MPH (2.0 mg/kg) or saline during preadolescence (postnatal day 20-35). As adults, they were tested for behavioral reactivity to emotion-eliciting stimuli and natural and drug rewards, with or without prior fluoxetine treatment. Sucrose preference was tested with a two-bottle test and morphine reward with conditioned place preference. Stress sensitivity and anxiety-like behavior were assessed with the forced swim test and the elevated-plus maze, respectively. Results show that MPH-treated rats were significantly less responsive to sucrose and morphine rewards and more sensitive to stress- and anxiety-eliciting situations. These MPH-induced behavioral deficits were reversed by fluoxetine. For all tests, a single, acute injection of fluoxetine given 24 hours before had little or no effect, whereas seven days of injections was effective. The results highlight the need for further research to understand the effects of stimulants on the developing nervous system and the potential enduring effects resulting from early-life exposure. Bolanos, C.A., Willey, M.D., Maffeo, M.L., Powers, K.D., Kinka, D.W., Grausam, K.B., and Henderson, R.P. Antidepressant Treatment Can Normalize Adult Behavioral Deficits Induced by Early-life Exposure to Methylphenidate. Biological Psychiatry, September 2007 (Epub ahead of print).

Rats Maintained on a High-Fat Diet Show Decreased Acquisition of Cocaine Self-Administration

Previous studies have shown that nutritional status can alter the rewarding effects of psychostimulants and the acquisition of drug self-administration. In general, these studies indicate that food deprivation enhances, while satiation diminishes, drug reward and self-administration. The present study by Wellman and his colleagues compared the rate of acquisition of cocaine self-administration between rats fed on a regular chow-pellet diet (about 10% fat) versus a high-fat diet (35.9% fat) for 45 days prior to cocaine self-administration testing. Rats maintained on the chow-pellet diet slowly acquired cocaine self-administration such that, at the end of the 25 day testing period, only 3 out of 7 of them had met criterion (on days 5, 7 and 15, respectively). In contrast, only 2 of the 8 rats that had ingested the high-fat diet acquired self-administration, and they did so on later testing days (16 and 24) than the chow fed rats. This effect was not a result of dietary-induced obesity as only 2 of the rats on the high fat diet gained significantly more weight than the chow-fed rats. The results suggest that prolonged exposure to a high-fat diet diminishes the efficacy of cocaine reinforcement and adds to the growing body of literature on nutritional modulation of drug self-administration. Wellman, P.J., Nation, J.R., and Davis, K.W. Impairment of Acquisition of Cocaine Self-administration in Rats Maintained on a High-fat Diet. Pharmacol. Biochem. Behav. 88, pp. 89-93, 2007.

Rat Conflict Model More Closely Approximates Human Relapse

Animal models of human relapse employ a reinstatement paradigm with three experimental phases: First, drug self-administration is established, and then responding for drug is extinguished with saline infusions instead of the drug. Next, either a stimulus cue previously paired with drug self administration, a 'priming' dose of the drug, or a stressor is introduced. All three manipulations

reinstate responding for drug; in other words, produce drug-seeking behavior. This model has been criticized because human addicts rarely undergo forced extinction; rather, abstinence is self-imposed. Also, relapse to drug use is usually associated with negative consequences - that is, the return to drug taking is followed by adverse events. Recently, NIDA-funded investigator Dr. Abraham Zangen and Dr. Yavin Shaham from NIDA's IRP have proposed a conflict model of cue-induced relapse that may better mimic these aspects of human relapse. In their paradigm, rats are trained to press a lever for i.v. cocaine and when responding is stable an electrified grid is introduced. During this phase animals must cross the grid to gain access to the drug lever and eventually all animals develop self imposed abstinence. In phase three, a light cue previously paired with cocaine infusions is presented and animals are assessed for their willingness to cross the electrified grid and resume lever pressing - or to demonstrate drug seeking in the face of an adverse consequence (bar presses produce saline infusions in this phase). Surprisingly, in their study, 14 of 24 animals demonstrated drug seeking by crossing the electrified grid to press the lever, and some rats even crossed the barrier when placed in the operant chamber without the cue light illuminated. The most interesting finding was that there is great variability across animals, both in their willingness to cross the grid and in the number of operant responses made in the presence of the cue after crossing. Thus, this model may be valuable for investigating individual differences associated with the vulnerability to relapse under conditions that more closely approximate the human situation. Cooper, A., Barnea-Ygael, N., Levy, D., Shaham, Y., and Zangen, A. A Conflict Rat Model of Cue-induced Relapse to Cocaine Seeking. Psychopharmacology, 194, pp. 117-125, 2007.

Alternative Rewards Enhance Extinction in an Animal Model

When animals are trained to respond for natural or drug rewards in one environment (A), and extinction is carried out in an alternate environment (B), extinction does not reduce responding when animals are then placed back into environment A (an ABA procedure). The failure of extinction effects to transfer to the drug-taking environment, is reminiscent of extinction failure seen in therapeutic interventions with human addicts. When returning to the drug associated environment, the context may trigger relapse or it may serve as a setting that mediates the strength of drug-associated cues to elicit drug seeking. NIDA grantees Drs. David Kearns and Stanley Weiss conducted a study to determine if extinction transfer failure is due to the occasion setting properties of environment "A" (thus, a context renewal phenomenon), or due to learning a discrimination between A predicts 'drug' and B predicts 'no drug' (a simple operant discrimination). In their study, rats were trained in A to self-administer cocaine (coc) when a tone was present, but when the tone was off, responses were not reinforced with the drug. Then, in some the tone was presented alone in Context A until animals no longer responded to it. In others, the tone was presented alone in a new context - context B. All animals were tested for context renewal in the original environment (hence, AAA and ABA groups). As the researchers had predicted, ABA animals showed robust responding for coc when returned to A, whereas in AAA coc-seeking behavior had extinguished. Since animals in this study received discrimination training in phase one, they concluded that the "A" environment acts as an occasion setter to facilitate retrieval of the tone+drug association, triggering a reinstatement of drug seeking. Interestingly, additional animals were exposed to ABA conditions, but during extinction training in B they received food paired with the tone cue instead of coc. The tone+food pairing facilitated transfer of extinction effects to the A environment, whether food rewarded animals for not making an operant response when the tone was presented (that is, for not drug seeking in the presence of the cue), or if food was just delivered non-contingently with the tone presentation. Thus, it appears that the tone became associated with food reward and this new association interfered with the ability

of the drug-associated cue to elicit coc seeking. In conclusion, pairing an alternative reward with drug associated cues during extinction may facilitate transfer of extinction effects back to the original drug-taking environment. Kearns, D.N. and Weiss, S.J. Contextual Renewal of Cocaine Seeking in Rats and its Attenuation by the Conditioned Effects of an Alternative Reinforcer. Drug and Alcohol Dep. 90, pp. 193-202, 2007.

Cortisol Response to Stress Predicts Progression in Youth Smoking

Dr. Harriet de Wit and colleagues recently conducted a laboratory investigation to assess individual vulnerability associated with the progression from occasional to habitual smoking in 18-24 year-old college students. In this study the researchers assessed 44 students for subjective and physiological responses to an amphetamine (or placebo) challenge, and to a Trier Social Stress Test (TSST). All subjects were light smokers who reported smoking an average of 10 cigarettes per week and none were nicotine dependent. The design followed a double-blind, placebo-controlled protocol, with 20mg of oral amphetamine used for the drug challenge. The POMS and the ARCI were used to collect self-report data; heart rate was measured, and saliva cortisol (cort) was sampled. Amphetamine induced the expected increases on scales such as Vigor, Elation, Euphoria, Friendliness and Arousal, and also increased HR and cort. The TSST increased reports of Vigor and Anxiety, and also increased HR and cort. Peak increases in cort levels after stress and amphetamine were positively correlated. Thirty-one students were followed up 6 months after the laboratory sessions and questioned about their frequency of smoking. Peak increases in cort after acute, laboratory stress were significantly positively related to smoking progression. That is, subjects who increased the amount they smoked in six months had an approximate thirteen-fold greater increase in peak cort response on the TSST than those that did not increase. While the authors argue that these results are from a small sample and should be accepted as preliminary, they suggest that sensitivity to stress and escalation of smoking may be linked to a common neurobiological predisposition. Alternatively, individuals with greater stress reactivity may experience greater positive mood effects from smoking. de Wit, H., Vicini, L., Childs, E., Sayla, M.A., and Terner, J. Does Stress Reactivity or Response to Amphetamine Predict Smoking Progression in Young Adults? A Preliminary Study. Pharmacol. Biochem. Behav. 86, pp. 312-319, 2007.

A Conditioned Inhibitor Signaling Unavailability of Food Reward Decreases Cocaine-Seeking

Environmental stimuli associated with drugs of abuse act as conditioned excitors to induce craving and trigger drug-seeking behavior. Conversely, a conditioned inhibitor that signals the absence of a reinforcer exerts behavioral control opposite to that produced by drug-paired cues, and instead suppresses behavior. Researchers at American University, in collaboration with scientists at NIDA's IRP, have previously observed that introducing a cue signaling the absence of cocaine, when cocaine is being self-administered in the presence of a drug-paired cue, suppresses cocaine (coc) responding by greater than 90%. However, a conditioned inhibitor can only reduce behavior as long as the conditioned excitor (drug-paired cue) retains its strength to activate behavior. If drugs are no longer available (e.g., during abstinence) then the inhibitor loses its effect. In a new study by these investigators, a cue signaling "no food" was found to dramatically suppress responding in animals trained to self administer coc. In a complex experimental design, rats were first trained to associate food with a click or a tone. They also received discrimination training so that when the stimulus cue was turned off, food reward was not available. Then all animals were trained to self-administer i.v. coc and the food+click group now learned to associate tone+coc, whereas the food+tone group had

coc paired with the click. Again, discrimination training was conducted so that the absence of the reward-paired cue signaled unavailability of drug. Then both groups experienced a three component operant schedule in which animals had to respond appropriately during the click or tone to receive reward and a third component was an extinction component with no stimuli presented. Next all animals received training to establish a new stimulus as a conditioned inhibitor - a light was paired with the click that signaled food for one group of animals and coc for the other. Animals continued to respond appropriately for reward when the click or tone alone was present, but when the light+click compound stimulus was on, reinforcement was not available. In a subsequent test for conditioned inhibition, the inhibitor - the light - was now presented in compound stimulus with the tone and drug-seeking or food-seeking behavior was measured. During this test food or coc did not reinforce operant responses, but rats still made an average of 10-15 bar presses per minute (i.e., food- or drug-seeking responses). By contrast, when the uniquely paired light+tone combination was on, mean responses fell to less than one press per minute - representing a 94% and 87% response suppression for coc and food in the two groups (compared to tone alone). This result demonstrates that animals learned the light cue signaled "no food" - and thus it acquired properties of a conditioned inhibitor against the background of excitation induced by the food-associated click in cocaine-seeking animals. When then presented with the coc-associated tone, this inhibitor suppressed responding to receive drug. (A similar result was seen in food-seeking rats trained with food+tone). Cue-based extinction therapies have had limited success because of the strong control that drug related cues have to sustain the addict's behavior. These findings suggest that adding a conditioned inhibitor for alternate, non-drug rewards, to this context may increase treatment success. Weiss, S.J., Kearns, D.N., Christensen, C.J., Huntsberry, M.E., Schindler, C.W., and Panlilio, L.V. Reduction of Cocaine Seeking by a Food-based Inhibitor in Rats. Exper. Clin. Psychopharmacol. 15, pp. 359-367, 2007.

Drug Reinforcement is Enhanced by Social Stimuli

Many prior investigations have examined the interaction between social influences and the reinforcing properties of drugs of abuse. Reports from animal studies show that social isolation, or social subordination, is associated with an enhanced propensity to self-administer drugs such as cocaine or alcohol. In human subjects, subjective effects vary as a function of the social situation (alone or with peers) during testing. However, little is known about the effects of social stimuli, which are known to be inherently rewarding, on the reinforcing strength of drugs of abuse in the self-administration model. In the laboratory of Dr. Marilyn Carroll at the University of Minnesota, studies have been conducted to establish oral self-administration of PCP in rhesus monkeys. Dr. Carroll and colleagues have recently tested the effects of a nearby conspecific on PCP self administration in this model. Ten adult monkeys consumed 0.25 mg/ml PCP with water concurrently available, under fixed ratio (FR16) schedules. The test chamber could be fitted with a solid partition between two animal cages, or a grid that permitted access to a conspecific in the neighboring cage. After intake was stable with the solid partition in place, the grid wall was inserted for 14 days and when responding stabilized again, the solid partition was replaced. Salivary cortisol measures were taken during solid and grid partition phases. In the next phase of the experiment all animals were tested on progressive ratio (PR) schedules, (i.e., concurrent PRs for water and PCP), with increasing concentrations of the drug (0.125, 0.25, 0.5 and 1.0 mg/ml). Break points (BPs) were identified as the number of responses the animal was willing to make to receive drug at each of these concentrations. When observed under grid conditions monkeys vocalized (e.g., barking) and displayed interactive gesturing. Under these conditions, PCP intake was significantly greater than during the first, solid partition phase and remained significantly elevated even when the solid partition was replaced. Since water

intake also increased under grid conditions, it is possible that the social stimuli non-specifically enhanced consummatory behavior. However, on the PR schedule, mean BPs under grid conditions were significantly higher for all but the highest dose of PCP, with no change in BPs for water, suggesting that these social stimuli facilitate drug intake. Furthermore, while presence of the neighboring monkey was a novel stimulus, it does not appear that elevated intake can be attributed to introduction of a stressor, since cortisol levels were no different during solid versus grid partition conditions. Newman, J.L., Perry J.L., and Carroll, M.E. Social Stimuli Enhance Phencyclidine (PCP) Self-administration in Rhesus Monkeys. Pharmacol. Biochem. Behav. 87, pp. 280-288, 2007.

Sex Differences in THC's Effects on Spatial Learning in Adult and Adolescent Rats

In 2006 Dr. Scott Swartzwelder and colleagues at Duke University reported effects of 2.5, 5.0, and 10.0mg/kg THC on learning in male adolescent and adult rats in the Morris water maze (Cha et al., 2006). The researchers found that THC disrupts both spatial and non-spatial learning more powerfully in adolescent rats than in adults at all dose levels. Dr. Swartzwelder and his colleagues have now published results from three studies that extend findings of this initial report. In the first study, effects of 5.0 mg/kg THC on spatial learning in the Morris Water maze were studied in male and female adolescent and adult rats over 5 daily test sessions. In males, spatial learning was impaired in adolescents on all test days, but was not impaired on any of the test days in adults. Among females, adolescents exhibited impairment on all test days, but adults were impaired only during the first two sessions. Thus, THC impairment was more potent in adolescents than adults and more potent in adult females than adult males. To assess the effects of chronic THC on subsequent learning, in a second experiment, separate groups of male and female adolescent and adults rats were treated with 5.0 mg//kg THC for 21 days and tested 28 days later in the Morris Water maze. Chronic THC treatment did not produce learning deficits in any of the groups. The third experiment was a THC dose-response study (2.5, 5.0, and 10.0mg/kg THC) using adolescent and adult female rats, conducted to parallel the initial experiment in males (Cha et al., 2006). Each dose was tested for 5 days. Consistent with the earlier outcome in males, THC produced a dose-response impairment in spatial learning. Although there was no overall age effect on spatial learning, there were differences in the dose-response function between adolescents and adults, suggesting a greater dose sensitivity in adolescents. Additionally, assessment of spatial memory indicated impairment in adolescents but not adults. These outcomes have important implications for future research on THC and other abused drugs. Animal model research in drug abuse has largely been conducted on adult males. The results of the present study join a growing body of drug abuse research showing that outcomes observed in adult males do not always generalize to females and to adolescents, highlighting the limitations of research conducted with only adult male subjects. Cha, Y.M., Jones, K.H., Kuhn, C.M., Wilson, W.A., and Swartzwelder, H.S. Sex Differences in the Effects of Delta(9)-tetrahydrocannabinol on Spatial Learning in Adolescent and Adult Rats. Behavioral Pharmacol. 18, pp. 563-569, 2007.

Sex Chromosome Complement Regulates Habit Formation

Gonadal hormones can cause sex differences via their brain organization effects during development and via their activational effects in puberty and adulthood. Other sex differences, however, are not due to gonadal hormones, but rather the direct action of the chromosome complement. Recent development of the 'four core genotype' mouse model permits dissociation of gonadal sex and chromosomal sex by comparison of males and females that

are gonadally and chromosomally either congruent or incongruent. The two incongruent cases are (1) chromosomal XY males with deletion of the testis-determining Sry gene and are therefore gonadally female and (2) chromosomal XX females with insertion of the Sry gene and are therefore gonadally male. Dr. Jane Taylor and colleagues at Yale and UCLA have used this four core genotype mouse model to study the role of chromosomal sex versus gonadal sex on habit formation. In the first phase of their study, mice were trained to nose-poke in one of three apertures for a food pellet delivery. Following either moderate training (9 days) or extended training (15 days), food pellets were devalued in a conditioned taste aversion procedure in which food pellets were paired with injections of the emetic lithium chloride. The mice were then retested in the instrumental procedure. In past studies using this habit formation procedure, devaluation decreases instrumental performance prior to habit formation, but after habit formation, instrumental performance is unaffected by devaluation. Dr. Taylor and her colleagues found that XX mice that previously received moderate instrumental training, showed operant performance following devaluation that was insensitive to changes in reinforcer value, indicating formation of a habit. XY mice subjected to devaluation, however, exhibited poorer performance than those not subjected to devaluation of the reinforcer, indicating that XY mice had not yet acquired habit formation. This outcome was independent of gonadal phenotype and was independent of gonadectomy vs. sham-operated status, indicating that the effects did not depend on organizational or activational functions of gonadal hormones. Following extended instrumental training, XX mice exhibited better instrumental performance (more correct nose-pokes) than XY mice. After devaluation, XX and XY mice were equally insensitive to changes in reward value of the reinforcer, indicating that with extended training, all mice had developed an instrumental habit. The authors speculate that sex differences in habit formation, as determined by the sex chromosome complement, could have implications for studying and understanding sex differences in drug addiction. Quinn, J.J., Hitchcott, P.K., Umeda, E.A., Arnold, A.P. and Taylor, J.R. Sex Chromosome Complement Regulates Habit Formation. Nature Neurosci. 10, pp. 1398-1400, 2007.

Director's Report to the National Advisory Council on Drug Abuse - February, 2008

Research Findings - Behavioral and Brain Development Research

Prenatal Methamphetamine Use and Neonatal Neurobehavioral Outcome

Neurobehavioral effects of prenatal methamphetamine exposure were examined in this study conducted by Dr. Barry Lester and his colleagues from the Infant Development, Environment and Lifestyle (IDEAL) study. Of 13,808 subjects screened, 1632 were eligible and consented and 166 (n=74 exposed) were enrolled in a longitudinal follow-up. Exposure was determined by meconium assay and self-report with alcohol, marijuana, and tobacco present in both groups. The NICU Network Neurobehavioral Scale (NNNS) was administered within the first 5 days of life. Analyses conducted on NNNS summary scores included exposure group effects, heavy MA use effects, association with frequency of use by trimester, and dose-response relationships with amphetamine metabolites. After adjusting for covariates, exposure to MA was associated with increased physiological stress. Heavy MA use was related to lower arousal, more lethargy, and increased physiological stress. First trimester MA use was related to elevated stress abstinence. Third trimester use was related to poorer quality of movement. Higher level of amphetamine metabolites in meconium was associated with increased CNS stress. Prenatal MA exposure was associated with neurobehavioral patterns of decreased arousal, increased stress, and poor quality of movement. The dose-response relationships may represent neurotoxic effects from MA. Smith, L.M., Lagasse, L.L., Derauf, C., Grant, P., Shah, R., Arria, A., Huestis, M., Haning, W., Strauss, A., Grotta, S.D., Fallone, M., Liu, J., and Lester, B.M., Prenatal Methamphetamine Use and Neonatal Neurobehavioral Outcome. Neurotoxicology and Teratology. Oct 3, 2007 (e-pub ahead of print).

Vagal Tone as a Resilience Factor in Children with Prenatal Cocaine Exposure

Researchers from the Maternal Lifestyle Study examined vagal tone (VT) as a resilience factor for children with prenatal cocaine exposure (CE). Presence of CE and other prenatal drugs was summed with postnatal risks in infancy to yield a 15-item risk index and children were classified as high versus low risk. High-risk children had lower IQ scores, more problem behaviors, and lower ratings of adaptive behaviors than low-risk children. VT was assessed during an infant exam at 1 month and toy exploration at 36 months (217 CE, 333 non-CE). Children were classified as having consistently high, consistently low, or fluctuating VT at 1 and 36 months. A significant risk by VT-stability interaction indicated that for high-risk children, those with stable low VT had higher ratings of adaptive behaviors at 36 months. This finding is consistent with theory linking reduced VT during tasks to adaptive regulation and indicates that

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such regulatory functioning may serve as a protective factor in prenatal CE. Sheinkopf, S.J., Lagasse, L.L., Lester, B.M., Liu, J., Seifer, R., Bauer, C.R., Shankaran, S., Bada, H., and Das, A. Vagal Tone as a Resilience Factor in Children with Prenatal Cocaine Exposure. Developmental Psychopathology, 19(3), pp. 649-673, 2007.

Predictors of Neonatal Abstinence Syndrome Severity in Methadone-Exposed Newborns

Investigators at Johns Hopkins University examined potential predictors of Neonatal Abstinence Syndrome (NAS), which is made up of symptoms reflecting dysfunction in autonomic and central nervous systems. Although infants born to mothers who experienced methadone-maintenance during pregnancy frequently show evidence of NAS, the signs and symptoms of NAS vary widely among infants. This study attempted to investigate some possible reasons behind such variation, with a focus on maternal vagal tone, a measure that reflects autonomic nervous system homeostasis, stress vulnerability, and self-regulation. Specifically, the investigators examined whether vagal tone responsivity to methadone administration in pregnant women provides insight into the pathophysiology and expression of NAS in the newborn. The expectation was that newborns born to mothers who show greater autonomic dysregulation, as reflected by increased levels of vagal suppression relative to methadone maintenance, would exhibit more severe NAS. At 36 weeks of gestation, electrocardiogram monitoring was carried out for 50 methadone-maintained pregnant women, at the times of trough and peak maternal methadone levels. NAS expression was related to maternal vagal activity; maternal vagal tone suppression and activation were associated with NAS symptomatology and treatment. NAS expression was not related to histories of maternal substance use or methadone maintenance, or to psychotropic medication exposure. The authors discuss potential mechanisms for interpretation of their findings. Jansson, L.M., DiPietro, J.A., Elko, A., and Velez, M. Maternal Vagal Tone Change in Response to Methadone is Associated with Neonatal Abstinence Syndrome Severity in Exposed Neonates. Journal of Maternal, Fetal and Neonatal Medicine, 20(9), pp. 677-685, 2007.

Marijuana Use Motives and Social Anxiety among Marijuana-Using Young Adults

A link between social anxiety and marijuana use has been found in both clinical and college samples. The purpose of this study was to examine the associations between social anxiety and marijuana use motives, and marijuana use problems in 159 undergraduate students. The results indicated that social anxiety predicted both coping motives (i.e., to regulate negative affective states) and conformity motives (i.e., using marijuana to avoid social censure) even after controlling for a number of other relevant factors. Future studies need to identify the social situations in which socially anxious individuals desire to use marijuana to help them alleviate their anxiety. It would also be important to better understand why some socially anxious individuals use marijuana to regulate their emotions while others do not. This study has implications for the prevention and treatment of this high-risk population. Buckner, J., Bonn-Miller, M., Zvolensky, M., and Schmidt, N. Marijuana Use Motives and Social Anxiety among Marijuana-Using Young Adults. Addictive Behaviors, 32, pp. 2238-2252, 2007.

Neuropsychological Functioning in Adolescent Marijuana Users: Subtle Deficits Detectable after a Month of Abstinence

Marijuana is the most commonly used illicit substance in the adolescent population. Although previous studies have observed neuropsychological

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deficits in adolescents who abuse marijuana, these studies included subjects with comorbid psychiatric disorders which may have contributed to the observed deficits. The purpose of this study was to examine whether marijuana use or extent of marijuana use was associated with neuropsychological functioning in an adolescent sample aged 16 - 18. Subjects were excluded if independent psychiatric, medical and neurologic disorders were noted. The results indicated that subtle deficits in psychomotor speed, complex attention, planning and sequencing, and verbal story memory were evident in adolescent marijuana users even after 23 days of monitored abstinence. Decreased performance in these areas was also associated with increased frequency of lifetime marijuana use. Longitudinal studies are needed to address the long-term trajectory of cognitive and brain functioning in adolescents who use marijuana. Medina, K., Hanson, K., Schweinsburg, A., Cohen-Zion, M., Nagel, B., and Tapert, S. Neuropsychological Functioning in Adolescent Marijuana Users: Subtle Deficits Detectable after a Month of Abstinence. Journal of the International Neuropsychological Society, 13, pp. 807-820, 2007.

Resting Cerebral Blood Flow in Adolescents with In Utero Cocaine Exposure

The aim of this study was to explore effects of in utero cocaine exposure on resting cerebral activation patterns in the brains of adolescents. The investigators employed arterial spin labeling (ASL) perfusion functional MRI (fMRI) to measure resting cerebral blood flow (CBF) in two groups of adolescents, one group that had been exposed to cocaine prenatally (N = 25), and one not prenatally-exposed (N = 24). A priori regions of interest of frontal lobe and limbic structures were defined, including the cingulate cortex, caudate, insula, and amygdala. The occipital lobe and thalamus were included as the lower-order sensory processing regions for compassion with the frontal lobe. Perfusion fMRI was combined with optimized voxel-based morphometry, a quantitative morphometric analysis of structural MRI, to compare gray matter between the two groups. Relative to the comparison group, cocaine-exposed adolescents showed significantly reduced global CBF, seen mainly in posterior and inferior brain regions, including the occipital cortex and thalamus. After adjusting for global CBF, a significant increase in relative CBF in cocaine-exposed adolescents was found in anterior and superior brain regions, including the prefrontal, cingulate, insular, amygdala, and superior parietal cortex. The investigators conclude that in utero cocaine exposure may reduce global CBF, which may persist into adolescence. They also point out that the relative increase in CBF in anterior and superior brain regions in cocaine-exposed adolescents suggests that compensatory mechanisms for reduced global CBF may develop during neurodevelopment. Rao, H., Wang, J., Giannetta, J., et al. Altered Resting Cerebral Blood Flow in Adolescents with in Utero Cocaine Exposure Revealed by Perfusion Functional MRI. Pediatrics, 120(5), pp. e1245-1254, 2007.

Prenatal and Adolescent Exposure to Tobacco Smoke Modulates the Development of White Matter Microstructure

Smoking during pregnancy is related to elevated risks of cognitive and auditory processing deficits. Preclinical studies have revealed that disruption in neurodevelopment by exposure to nicotine is likely linked to the disruption of the trophic actions of acetylcholine at nicotinic acetylcholine receptors. This study utilized diffusion tensor anisotropy and anatomical magnetic resonance images to examine white matter microstructure in 67 adolescent smokers and nonsmokers with and without prenatal exposure to maternal smoking. Auditory attention was assessed in all subjects. Adolescents with prenatal and/or adolescent exposure demonstrated increases in regional white matter fractional anisotropy (FA) primarily in anterior cortical and subcortical regions. Increased FA of regions of the internal capsule that contain auditory thalamocortical and

corticofugal fibers was associated with adolescent smoking. Performance on the auditory performance task in smokers was positively correlated with FA of the posterior limb of the left internal capsule, but not in nonsmokers. The magnitude of tobacco exposure during adolescence was positively related to the FA of the genu of the corpus callosum further supporting the notion that the effects of nicotine on white matter maturation may be particularly significant during this developmental period. The results suggest that nicotine may disrupt the development of auditory corticofugal fibers which ultimately leads to reduced efficiency in the neurocircuitry that supports auditory processing. Jacobsen, L., Picciotto, M., Heath, C., Frost, S., Tsou, K., Dwan, R., Jackowski, M., Constable, R., and Menel, W. Prenatal and Adolescent Exposure to Tobacco Smoke Modulates the Development of White Matter Microstructure. The Journal of Neuroscience, 27(49) pp. 13491-13498, 2007.

Marijuana Use and HIV-Related Risk Factors

This study examined the role of early and current marijuana use as it relates to sexually transmitted infection (STI) risk in a sample of young women who had been pregnant teenagers. Pregnant adolescents (N= 279), ages 12-18, were recruited from an urban prenatal clinic as part of a study that was developed to evaluate the long-term effects of prenatal substance exposure. Six years later, they were asked about their substance use and sexual history. The association of early and late marijuana use to two HIV-related risk factors -- lifetime sexual partners and STIs --was examined, and then structural equation modeling (SEM) was used to illustrate the associations among marijuana use, number of sexual partners, and STIs. Bivariate analyses revealed a dose-response effect of early and current marijuana use on STIs in young adulthood. Early and current marijuana use also predicted a higher number of lifetime sexual partners. Using SEM, the effect of early marijuana use on STIs was mediated by lifetime number of sexual partners. African-American race, more externalizing problems, and a greater number of sexual partners were directly related to more STIs. Adolescent pregnancy, early marijuana use, mental health problems, and African-American race were significant risk factors for STIs in young adult women who had become mothers during adolescence. Pregnant teenage girls should be screened for early drug use and mental health problems, because they may benefit the most from the implementation of STI/HIV screening and skill-based STI and HIV prevention programs. DeGenna, N.M., Cornelius, M.D., and Cook, R.L. Marijuana Use and Sexually Transmitted Infections in Young Women Who Were Teenage Mothers. Women's Health Issues, 17(5), pp. 300-309, 2007.

Family Relationships and Sexual Activity among Hispanic Mid-Adolescents

Dr. Robles and her colleagues at the Universidad Central del Caribe examined the development of drug use and HIV/AIDS risk behaviors in a sample of 325 Hispanic 14 to 15-year old adolescents from a poor neighborhood in Puerto Rico. The study employed logistic regression analysis to identify variables associated with early sexual behavior. Adolescents whose parents reported poor communication and poor parent control were more likely to engage in early sexual activity than those peers who did not report this type of family relationship. Adolescents who reported poor parent bonding and lack of discipline were more likely to engage in early sexual relationships. Intervention and prevention programs need to be aware and address the role of family in early sexual activity in adolescence. Robles, R.R., Matos, T.D., Reyes, J.C., Colon, H.M., Negron, J., Calderon, J., Shepard, E.W. Correlates of Early Sexual Activity among Hispanic Children in Middle Adolescence. Puerto Rico Health Science Journal, 26(2), pp. 119-126, 2007.

Director's Report to the National Advisory Council on Drug Abuse - February, 2008

Research Findings - Clinical Neuroscience Research

Orbitofrontal Cortex Activation to the Words "No" and "Yes"

"No" and "Yes" are involved in conditioning to prohibit or encourage behavior and may therefore activate neuronal circuits involved with valence and emotional control. Functional MRI (fMRI) at 4 Tesla was used to measure regional brain activity while healthy normal participants listened to emphatic vocalizations of the words. "No" and "Yes" were associated with opposite brain-behavior responses. "No" was negatively valenced, produced slower response times, and evoked a negative signal in the right lateral orbitofrontal cortex (OFC). "Yes" was positively valenced, produced faster response times, and evoked a positive signal in a contiguous region of the OFC. Attribution of negative valence to "No" and trait anger control were associated with increased responsivity of the OFC to "No". These results indicate potential neuronal processes that may accompany admonitions to stop using drugs. Alia-Klein, N., Goldstein, R. Z., Tornasi, D., Zhang, L., Fagin-Jones, S., Telang, F., Wang, G-F., Folwer, J.S., and Volkow, N.D. What Is In A Word? No Versus Yes Differentially Engage the Lateral Orbitofrontal Cortex. Emotion, 7(3), pp. 649-659, 2007.

Resisting Craving during Cigarette Cue Exposure Entails Successful Recruitment of Cognitive Conflict-Monitoring Circuitry

In cigarette smokers, the most commonly reported areas of brain activation during visual cigarette cue exposure are the prefrontal, anterior cingulate, and visual cortices. Dr. Arthur Brody and colleagues at UCLA sought to determine changes in brain activity in response to cigarette cues when smokers actively resist craving. Forty-two tobacco-dependent smokers underwent functional magnetic resonance imaging, during which they were presented with videotaped cues. Three cue presentation conditions were tested: cigarette cues with subjects allowing themselves to crave (cigarette cue crave), cigarette cues with the instruction to resist craving (cigarette cue resist), and matched neutral cues. Activation was found in the cigarette cue resist (compared with the cigarette cue crave) condition in the left dorsal anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), and precuneus. Lower magnetic resonance signal for the cigarette cue resist condition was found in the cuneus bilaterally, left lateral occipital gyrus, and right postcentral gyrus. These relative activations and deactivations were more robust when the cigarette cue resist condition was compared with the neutral cue condition. These data provide evidence that suppressing craving during cigarette cue exposure involves activation of limbic (and related) brain regions and deactivation of primary sensory and motor cortices. Brody, A.L., Mandelkern, M.A., Olmstead, R.E., Jou J., Tiongson, E., Allen, V., Scheibal, D., London, E.D., Monterosso J.R., Tiffany S.T., Korb A., Gan, J.J., and Cohen, M.S.. Neural Substrates of Resisting

Craving During Cigarette Cue Exposure. Biol. Psychiatry, 62(6), pp. 642-651, 2007.

New Scale-Free Model For Motivation and Decision Making

Marc Potenza, Warren Bickel, and R. Andrew Chambers explored motivated behavior as a scale-free map in building a comprehensive translational theory of addiction. They reframed motivational and behavioral repertoires as link and nodal element sets, respectively, that comprise a scale-free structure. These sets are generated by semi-independent information-processing streams within cortical-striatal circuits that cooperatively provide decision-making and sequential processing functions necessary for traversing maps of motivational links connecting behavioral nodes. Dopamine modulation of cortical-striatal plasticity serves a central-hierarchical mechanism for survival-adaptive sculpting and development of motivational-behavioral repertoires by guiding a scale-free design. Potenza et al proposed that drug-induced dopamine activity promotes drug taking as a highly connected behavioral hub at the expense of natural-adaptive motivational links and behavioral nodes. Conceptualizing addiction as pathological alteration of scale-free motivational-behavioral repertoires unifies neurobiological, neurocomputational and behavioral research while addressing addiction vulnerability in adolescence and psychiatric illness. This model may inform integrative research in defining more effective prevention and treatment strategies for addiction. Chambers, R.A., Bickel, W.K., and Potenza, M.N. A Scale-Free Systems Theory of Motivation and Addiction. Neuroscience Biobehavior Review, 31(7), pp. 1017-1045, 2007.

Assessment of Asymptomatic Neurocognitive Impairment Adds Sensitivity, Specificity and Predictive Power to the Diagnosis of HIV Encephalitis

Asymptomatic neurocognitive impairment can be detectable according to recent developments in neurocognitive tasks. The present study examined whether early signs of neurocognitive dysfunction could be a valuable biomarker of disease progress in asymptomatic HIV+ individuals. Dr. Igor Grant and his group at the HIV Neurobehavioral Research Center (HNRC) compared neuropathological diagnosis of HIV encephalitis made at autopsy to antemortem neurocognitive diagnoses, resulting from HNRC criteria that assess asymptomatic neurocognitive impairment, to the original diagnostic criteria issued in 1991 by the American Academy of Neurology (AAN). Agreement between the two sets of definitional criteria was 79% regarding the classification of cases as either neurocognitively normal or impaired, and 54% with regard to specific neurocognitive diagnoses. When pathological evidence of HIV was taken as the external indicator of HIV-related brain involvement, 64% of cases were correctly classified by AAN criteria, compared to 72% by HNRC criteria. HNRC criteria had better positive predictive power (95% versus 88%), sensitivity (67% versus 56%), and specificity (92% versus 83%). Furthermore, several cases with HIV encephalitis were correctly identified by HNRC criteria for ANI but called normal by AAN criteria. These data suggest that assessment of asymptomatic neurocognitive impairment adds sensitivity, specificity and predictive power to the diagnosis of HIV encephalitis. In addition, it supports the concept that neuropathological changes may develop in individuals with sub-clinical neurocognitive dysfunctions. These results indicate that cognitive disturbances can reliably detect ongoing HIV brain infection without requiring declines in daily functioning, motor, or other behavioral abnormalities. Cherner, M., Cysique, L., Heaton, R., Marcotte, T., Ellis, R., Masliah, E., Grant, I. and HNRC Group. Neuropathologic Confirmation of Definitional Criteria for Human Immuno-deficiency Virus-associated Neurocognitive Disorders. J Neurovirol.,13(1), pp. 23-28, 2007.

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PET Study Reveals Minimal Gender Differences or Menstrual Cycle Effects on Nicotinic Acetylcholine Receptors

The effects of sex and hormones on brain chemistry and neurotransmission are not well-characterized, and are of increasing importance as evidence emerges of sex differences in behavioral symptoms and treatment response in neuropsychiatric disorders. The nicotinic acetylcholine receptor (nAChR) system has been implicated in a variety of psychiatric disorders, including tobacco smoking, for which there is strong evidence supporting sex differences in behaviors and response to smoking cessation treatments. Kelly Cosgrove, Julie Staley, and colleagues at Yale examined the availability of nAChR containing the ss2 subunit in healthy men and women nonsmokers, and the influence of menstrual phase among women. Regional brain activity was higher (39%-54%) in women than in men. When regional brain activity was normalized to total plasma parent to correct for individual differences in radiotracer metabolism (VT'), differences of 10%-16% were observed, with women greater than men. In contrast, when regional brain activity was normalized to free plasma parent (VT), there was less than a 4% difference by sex in regional brain ss2-nAChR availability. These sex differences in kBq/cm3 and VT' resulted from significantly higher levels of total plasma parent, free fraction (f1), and free plasma parent in women than in men nonsmokers. No differences in plasma measures or brain ss2-nAChR availability were observed across the menstrual cycle for any outcome measure. Overall, these findings demonstrate no significant difference in brain ss2-nAChR availability between men and women nonsmokers or across the menstrual cycle. Importantly, these findings demonstrate the need to control for sex differences in radiotracer metabolism and plasma protein binding. Cosgrove, K.P., Mitsis, E.M., Bois, F., Frohlich, E., Tamagnan, G.D., Krantzler, E., Perry, E., Maciejewski, P.K., Epperson, C.N., Allen, S., O'Malley S., Mazure, C,M,, Seibyl, J.P., van Dyck, C.H., and Staley, J.K. 123I-5-IA-85380 SPECT Imaging of Nicotinic Acetylcholine Receptor Availability in Nonsmokers: Effects of Sex and Menstrual Phase. J. Nucl. Med., 48(10), pp. 1633-1640, 2007.

No Change in MRS Measures in Moderate MDMA Users

High field strength proton MRS at 4.0 T was used to study absolute concentrations of occipital cortical NAA and MI in a cohort of moderate MDMA users (n = 9) versus non-MDMA using (n = 7) controls in order to resolve ambiguities in previous studies that used MRS at lower field strength. There were no statistical differences in absolute metabolite levels for NAA and MI in occipital cortex of MDMA users and controls. These findings are not supportive of MDMA-induced alterations in NAA or MI levels in this small sample of moderate MDMA users. Cowan, R.L., Bolo, N.R., Dietric, M., Haga, E., Lukas, S.E., and Renshaw, P.F. Psychiatry Research-Neuroimaging, 155(3), pp. 179-188, 2007.

Smoking Abstinence Effects on Selective Attention using the Stroop Task

Difficulty concentrating when abstinent from smoking may contribute to smoking cessation failures. This study compared smokers and nonsmokers on selective attention using the Stroop Test. In addition, the effects in smokers of overnight abstinence from smoking and of acute smoking on selective attention were also determined. Smokers participated after overnight abstinence and also within 1 hour of ad libitum smoking. Smokers each smoked a cigarette between test blocks on each day; nonsmokers did not. Smokers demonstrated longer response latencies for both congruent and incongruent stimuli after overnight when compared with brief abstinence, but no deficit specifically related to selective attention. Whereas nonsmokers showed no changes in

performance in the second test block, smoking between blocks reduced the Stroop effect when smokers were abstinent overnight. These data indicate that abstinence from smoking among nicotine-dependent individuals has deleterious effects on cognitive performance, but do not indicate that selective attention is adversely effected. Improvement in selective attention after terminating abstinence with one cigarette may also contribute to smokers' perceived enhanced ability to concentrate after smoking. Domier, C.P., Monterosso, J.R., Brody, A.L., Simon, S.L., Mendrek, A., Olmstead, R., et al. Effects of Cigarette Smoking and Abstinence on Stroop Task Performance. Psychopharmacology, 195(1), pp. 1-9, 2007.

Dissociation of MAO-A Genotype from MAO-A Brain Activity

A functional polymorphism in the promoter region of the monoamine oxidase A (MAO A) gene has two common alleles that are referred to as the high and low MAO A genotypes. The goal of this study was to determine whether there is an association between MAO A genotype and in vivo brain MAO A activity in healthy male subjects using PET ligand imaging. Brain MAO A activity was measured with positron emission tomography and [C-11]clorgyline in adult male nonsmokers genotyped for MAO A polymorphism. There was no significant difference in brain MAO A activity between the high (n = 26) and low (n = 12) MAO A genotypes. The lack of an association between the high and low MAO A genotype and brain MAO A activity suggests that this polymorphism by itself does not contribute to differences in brain MAO A activity in healthy adult male subjects. Fowler, J. S., Alia-Klein, N., Kriplani, A., Logan, J., Williams, B., Zhu, W., Craig, I.W., Telang, F, Goldstein, R., Volkow, N.D. Vaska, P., and Wang, G-J. Evidence that Brain MAO A Activity does not Correspond to MAO A Genotype in Healthy Male Subjects. Biological Psychiatry, 62(4), pp. 355-358, 2007.

Genetic Variants are Associated with Different Roles in Reinforcement Learning

A model that predicts dopamine receptor function differentially affects Go/NoGo performance was tested in healthy humans with different dopamine D1 and D2 gene variants. In particular, individuals with a variant of the DARPP-32 gene associated with the D1 receptor, which has been shown to strongly modulate striatal activity, favored responses in which a choice was made because of the positive reward valuation (as opposed to avoiding a choice because of negative valuation). By contrast, a variant of the DRD2 receptor facilitated avoiding a non-rewarded response. In the model, these striatal areas are hypothesized to be associated with acquisition of reinforced learning. An additional facet of the model involves the prefrontal cortex which hypothesizes that this area is responsible for maintaining reward information in memory for trial-to-trial evaluation. This was tested by variants of the COMT gene which are associated with prefrontal dopamine. It was found that the Val/Val homozygotes that have the lowest prefrontal cortex dopamine were the least responsive to the immediate effects of reward, thus supporting the model. Continued testing and refinement of the model will help establish a picture of cortical functions with regard to decision-making as well as providing a genetic basis for individual differences. Frank, M.J., Moustafa, A.A., Haughey, H.M., Curran, T., and Hutchison, K.E. Genetic Triple Dissociation Reveals Multiple Roles for Dopamine in Reinforcement Learning. Proceedings of the National Academy of Science, 104(41), pp. 16311-16316, 2007.

Cigarette Cues Activate Limbic Brain Regions

This study used arterial spin-labeled (ASL) perfusion fMRI, and newly developed and highly appetitive, explicit smoking stimuli, to examine neural

activity to cigarette cue-induced craving that strongly minimized contributions from pharmacological withdrawal. Twenty-one smokers (12 females) completed smoking and nonsmoking cue fMRI sessions. Craving self-reports were collected before and after each session. Blood flow (perfusion) in a priori-selected regions was greater during exposure to smoking stimuli compared to nonsmoking stimuli in ventral striatum, amygdala, orbitofrontal cortex, hippocampus, medial thalamus, and left insula ($p < 0.01$; corrected). Perfusion positively correlated with intensity of cigarette cue-induced craving in both the dorsolateral prefrontal cortex and posterior cingulate. This pattern of activation that includes the ventral striatum, a critical reward substrate, and the interconnected amygdala, cingulate and OFC, is consistent with decades of neural correlates of cue-induced craving for other drugs of abuse and conditioned drug responses in animals. Franklin, T.R., Wang, Z., Wang, J., Sciortino, N., Harper, D., Li, Y., Ehrman, R, Kampman, K, O'Brien, C.P., Detre, J.A., and Childress, A.R. Limbic Activation to Cigarette Smoking Cues Independent of Nicotine Withdrawal: A Perfusion fMRI Study. Neuropsychopharmacology, 32(11), pp. 2301-2309, 2007.

Cocaine Abuse and Cognitive Control

While hedonic and reward-related processes are central to drug use and dependence, impairment of cognitive processes may also make important contributions to addiction. In particular, attention is drawn to those processes involved in exercising control over behavior as drug dependence is characterized by risky, impulsive behavior. Functional neuroimaging implicates prefrontal deficits in cocaine dependence with an emerging picture of cocaine users having attentional biases towards drug-related stimuli, poor performance in laboratory tests of inhibitory control, and compromised monitoring and evaluation of their behavior. Combined, these deficits may contribute to the continuation of use in dependent individuals and may qualify as important targets for therapeutic interventions. Garavan, H., and Hester, R. The Role of Cognitive Control in Cocaine Dependence. Neuropsychology Review, 17(3), pp. 337-345, 2007.

Frontal-Occipital Interactions in Top-Down Attentional Control

Attention-dependent modulation of neural activity in visual association cortex (VAC) is thought to depend on top-down modulatory control signals emanating from the prefrontal cortex (PFC). Functional connectivity analysis was used to identify possible sources of these modulatory influences by examining how network interactions with VAC are influenced by attentional goals at the time of encoding. The results revealed a network of regions that exhibit strong positive correlations with a VAC seed during all task conditions, including foci in the left middle frontal gyrus (MFG). This PFC region is more correlated with the VAC seed when scenes were remembered and less correlated when scenes were ignored, relative to passive viewing. Moreover, the strength of MFG-VAC coupling correlates with the magnitude of attentional enhancement and suppression of VAC activity. Although these correlation analyses do not permit assessment of directionality, the findings suggest that PFC biases activity levels in VAC by adjusting the strength of functional coupling in accordance with stimulus relevance. These findings provide a basis for interpreting changes in frontal control of attention during presentation of drug-related stimuli that can elicit drug craving. Gazzaley, A., Rissman, J., Cooney, J., Rutman, A., Seibert, T., Clapp, W., D'Esposito, M. Functional Interactions between Prefrontal and Visual Association Cortex Contribute to Top-down Modulation of Visual Processing. Cerebral Cortex, 17, pp I125-I135, 2007.

Neuropsychological Effects of Opioid Use

Neurocognitive effects of acute and chronic opioid use suggest that the use of opiates has both acute and long-term effects on cognitive performance. Neuropsychological data indicate deficits in attention, concentration, recall, visuospatial skills and psychomotor speed with both acute and chronic opioid use. The long-term effects of opiate use appear to have the greatest impact on executive functions, including the ability to shift cognitive set and inhibit inappropriate response tendencies. Factors that contribute to addiction and recovery are discussed, as it is difficult to disentangle the effects of opiate use on cognitive performance from other factors that may affect neurobehavioral measures. Gruber, S.A., Silveri, M.M., and Yurgelun-Todd, D.A. Neuropsychological Consequences of Opiate Use. Neuropsychology Review, 17(3), pp. 299-315, 2007.

Analysis of Correlations of fMRI Activity across Participants

The analysis of correlations of fMRI technique takes advantage of similarities in the patterns of the hemodynamics between participants [i.e., interparticipant correlation (IPC)] to obtain the parsimony of the general linear model (GLM) without assuming a specific fMRI time course. The technique consists of calculating voxel-wise correlations between participants resulting in IPC maps, which indicate the activated regions the participants have in common. IPC analysis was applied to data collected from healthy controls in an auditory oddball task. As expected, the highest inter-participant correlations were detected in auditory cortical regions in the temporal lobes. In addition, areas that appear to be involved in the task were detected using IPC's but not the GLM regression. This technique, designed to have increased sensitivity to inter-subject correlations that are not necessarily task-related, may potentially be useful as a compliment to model-based approaches. Hejnar, M.R., Kiehl, K.A., and Calhoun, V.D. Interparticipant Correlations: A Model Free fMRI Analysis Technique. Human Brain Mapping, 28(9), pp. 860-867, 2007.

Cocaine Abusers Are Not Aware of Making Errors

Active cocaine abusers have a diminished neural response to errors, particularly in the anterior cingulate cortex thought critical to error processing. The inability to detect, or adjust performance following errors, has been linked to clinical symptoms including the loss of insight and perseverative behavior. Twenty-one active cocaine users (six female subjects, mean age 40.3) and 22 non-drug using adults (six female subjects, mean 39.9) participated in a study that used response inhibition tasks that required error awareness and performance adaptation. The results indicated that cocaine users had reduced awareness of committing errors as well as poorer inhibitory control. Cocaine abusers were also poorer at exerting inhibitory control on the trial immediately after failing to inhibit a response. However, post-error reaction times did not differ between groups. Thus, even though cocaine users demonstrated a diminished capacity for monitoring their behavior, they were able to perform post-error adjustment to processes not already suffering an underlying deficit. These difficulties are consistent with previous reports of cocaine-related hypoactivity in the neural system underlying cognitive control, and highlight the potential for cognitive dysfunction to manifest as behavioral deficits that likely contribute to the maintenance of drug dependence. Hester, R., Simoes-Franklin, C., and Garavan, H. Post-Error Behavior in Active Cocaine Users: Poor Awareness of Errors in the Presence of Intact Performance Adjustments. Neuropsychopharmacology, 32(9), pp. 1974-1984, 2007.

Cocaine Dependent Individuals Might Be More Susceptible to Infectious Disease

Irwin and associates at UCLA assessed the immune system in cocaine patients

over a 24-hour period. Cocaine-dependent volunteers showed a decreased capacity to express tumor necrosis factor (TNF)-_ and interleukin (IL)-6. The immune response was also blunted in response to a bacterial ligand. These observations were accompanied by sympathetic activity and vagal withdrawal. It was suggested that sympathovagal balance might be a novel strategy for partial amelioration of impairments. Irwin, M.R., Olmos, L., Wang, M., Valladares, E.D., Motivala, S.J., Fong, T., Newton, T., Butch, A., Olmstead, R., and Cole, S.W. Cocaine Dependence and Acute Cocaine Induce Decreases of Monocyte Proinflammatory Cytokine Expression across the Diurnal Period: Autonomic Mechanisms. The Journal of Pharmacology and Experimental Therapeutics, 320(2), pp. 507-515, 2007.

Synthesis of a PET ligand for Alpha 7 Nicotinic Receptors

(3E)-3-[(2,4-dimethoxy- phenyl)methylene]-3,4,5,6-tetrahydro-2,3'-bipyridi ne (GTS-21), is a partial alpha 7 nicotinic acetylcholine receptor agonist drug. GTS-21 was labeled in two different positions with carbon-11 ([2-methoxy-C-11]GTS-21 and [4-C-11]GTS-21) along with two corresponding demethylated metabolites ([2-methoxy-C-11]4-OH-GTS-21 and [4-rnethoxy-C-11]2-OH-GTS-21) for pharmacokinetic studies in baboons and mice with positron emission tomography (PET). The major findings are as follows: (a) extremely rapid uptake and clearance of [2-methoxy-C-11]GTS-21 from the brain, which may need to be considered in developing optimal dosing of GTS-21 for patients, and (b) significant brain uptake of 2-OH-GTS-21, suggesting that it might contribute to the therapeutic effects of GTS-21. This study illustrates the value of comparing different label positions and labeled metabolites to gain insight on the behavior of a central nervous system drug relevant to nicotine addiction and its metabolites in the brain, providing an important perspective on drug pharmacokinetics. Kim, S.W., Ding, Y., Alexoff, D., Patel, V., Logan, J., Lin, K., Shea, C.L., Muench, L., Xua, Y, Carter, P., King, P., Constanzo, J.R., Ciaccio, J.A., and Fowler, J.S. Synthesis and Positron Emission Tomography Studies of C-11-labeled Isotopomers and Metabolites of GTS-21, a Partial alpha-7 Nicotinic Cholinergic Agonist Drug. Nuclear Medicine and Biology, 34(5), pp. 541-551, 2007.

Brain Predictors of Financial Decisions

The balance between expected reward and risk are believed to drive financial decisions. It is now possible to use brain imaging techniques to visualize changes in neural activation before financial decisions are expressed. The results indicate that the ventral striatum plays a role in representation of expected reward, whereas the insula may play a more prominent role in the representation of expected risk. Accumulating evidence also suggests that antecedent neural activation in these regions can be used to predict upcoming financial decisions. These findings have implications for predicting choices and for building a physiologically-constrained theory of decision-making. Knutson, B., and Bossaerts, P. Neural Antecedents of Financial Decisions. Journal of Neuroscience, 27(31), pp. 8174-8177, 2007.

Groups Defined by Statistical Clustering Rather than Diagnosis Have High Heritability: Associated Genes Have the Highest LOD Scores

The H. Kranzler and J. Gelernter team recruited families and sib-pairs who abused one or more illicit drugs. Using an iterative algorithm they empirically formed clusters in an effort to define more homogeneous groups as phenotypes for genome wide analysis. While the clusters were segregated into groups that could be designated with differential names with respect to their drug use, they did not reflect the standard DSM diagnoses. Importantly, gene variants

associated with some of the clusters were stronger than for the DSM phenotypes such as Cocaine Dependence. Because psychiatric diagnoses are inclusive of individuals who may have a variety of symptomatology that may not have a similar underlying characteristic associated with a gene, analyses such as these may be helpful in determining genetic variability. Kranzler, H.R., Wilcox, M., Weiss, R.D., Brady, K., Hesselbrock, V., Rounsaville, B., Farrer, L., Gelernter, J. The Validity of Cocaine Dependence Subtypes. Addictive Behaviors, 33, pp. 41-53, 2008.

New Method of Analyzing Cocaine Effects with fMRI

Changes in BOLD fMRI signals in humans before, during and after the administration of a drug often result in a heterogeneous pattern of drug-induced hemodynamic responses in the brain. Exploratory techniques, including blind source separation, can be useful for BOLD data that contain patterns of cross-dependencies. Bayesian source separation (BSS) is a multivariate technique used to calculate the presence of unobserved signal sources in measured fMRI data, as well as the covariance between data voxels and between reference waveforms. Unlike conventional univariate regression analysis, BSS does not assume independence between voxel time series or source components. In this study, BOLD measurement of the acute effect of an intravenous dose of cocaine, a substance shown previously to engage multiple sites within the orbitofrontal cortex, was processed with BSS. The utility of BSS in pharmacological fMRI applications was demonstrated in multiple examples featuring single-ROI, multiple-ROI and whole-slice data. The flexibility of the BSS technique was shown by choosing different modeling strategies to form the prior reference functions, including approximating the pharmacokinetics of cocaine, interpolating simultaneously measured behavioral data and using observed BOLD responses from known subcortical afferents to the cortex of interest. Kufahl, P.R., Rowe, D.B., and Li, S. Processing the Acute Cocaine fMRI Response in Human Brain with Bayesian Source Separation. Digital Signal Processing, 17(5), pp. 965-978, 2007.

Emotional Memory Representation in the Brain

Neurobiological accounts of emotional memory have been derived largely from animal models investigating the encoding and retention of memories for events that signal threat. This literature has implicated the amygdala, a structure in the brain's temporal lobe, in the learning and consolidation of fear memories. Its role in fear conditioning has been confirmed, but the human amygdala also interacts with cortical regions to mediate other aspects of emotional memory. These include the encoding and consolidation of pleasant and unpleasant arousing events into long-term memory, the narrowing of focus on central emotional information, the retrieval of prior emotional events and contexts, and the subjective experience of recollection and emotional intensity during retrieval. Along with other mechanisms that do not involve the amygdala, these functions ensure that significant life events leave a lasting impression in memory. LaBar, K.S. Beyond Fear: Emotional Memory Mechanisms in the Human Brain. Current Directions in Psychological Science, 16(4), pp. 173-177, 2007.

Distinguished Memory Deficits Encourage Systemic Assessment of Neurocognitive Functions in HIV+ Individuals

Effective prevention of transmission of HIV from infected individuals to others relies upon continued preclusion of risk sexual behavior and adherence with medication regimens. It is desirable if the degree of impaired executive control functions mediated by prefrontal cortical systems is assessable in HIV+ individuals and drug abusers. In this study, Dr. Eileen Martin evaluated the

possibility of using current available cognitive tasks for different type of episodic memory to predict executive functions among HIV+ substance-dependent individuals and their relevance to "real-world" behaviors, such as future intention of risky decision-making or "remembering what one must do". The study found that compared with HIV-seronegative controls HIV-seropositive participants showed deficits in time-based but not event-based prospective memory. Performance of retrospective memory, but not working memory, correlated significantly with performance of time-based prospective memory. The preliminary study suggested poorer performance on the time-based prospective memory task, a significant predictor of self-reported risky sexual and injection practices. Martin, E.M., Nixon, H., Pitrak, D.L., Weddington, W., Rains, N.A., Nunnally, G., Grbesic, S., Gonzalez, R., Jacobus, J., and Bechara, A. Characteristics of Prospective Memory Deficits in HIV-seropositive Substance-dependent Individuals: Preliminary Observations. J. Clin. Exp. Neuropsychol. 29(5), pp. 496-504, 2007.

Expression of Genes in the Hippocampus that Regulate Extracellular Matrix Remodeling Differ in Cocaine Abusers

Mash and associates assessed gene expression in the hippocampi in postmortem brains of cocaine abusers and controls. The results demonstrated 151 gene transcripts that were up-regulated and 91 that were down-regulated. The gene with the largest up-regulation (two-fold) was RECK (reversion-inducing-cysteine-rich protein with kazal motifs) which is a membrane-anchored matrix metalloproteinase inhibitor that is implicated in the coordinated regulation of extracellular matrix integrity and angiogenesis. It is suggested that modified expression of this gene and others in the hippocampus by cocaine may contribute to the persistent memory of previous "highs" and thus contribute to relapse or prevent abstinence of cocaine use. Mash, D.C., French-Mullen, J., Adi, N., Qin, Y., Buck, A., and Pablo, J. Gene Expression in Human Hippocampus from Cocaine Abusers Identifies Genes which Regulate Extracellular Matrix Remodeling. PLos ONE 2(11), pp. e1187, 2007.

Abstinent Methamphetamine Users Show Reduced Striatal Dopamine Transporter Binding Potentials, Which Relate To Working Memory Deficits

It is not clear whether cognitive deficits and brain DAT reductions fully reverse with sustained abstinence or whether behavioral deficits in METH users are related to persistent dopamine (DA) deficits. Dean Wong and colleagues at Johns Hopkins further investigated potential persistent psychomotor deficits secondary to METH abuse, and their relationship to brain DAT availability, as measured using quantitative PET methods. Twenty-two abstinent METH users and 17 healthy non-METH using controls underwent psychometric testing to test the hypothesis that METH users would demonstrate selective deficits in neuropsychiatric domains known to involve DA neurons (e.g., working memory, executive function, motor function). METH users were found to have modest deficits in short-term memory, executive function, and manual dexterity. Exploratory correlational analyses revealed that deficits in memory, but not those in executive or motor function, were associated with decreases in striatal DAT BP. These results suggest a possible relationship between DAT BP and memory deficits in abstinent METH users, and lend support to the notion that METH produces lasting effects on central DA neurons in humans. McCann, U.D., Kuwabara, H., Kumar A., Palermo, M., Abbey, R., Brasic, J., Ye, W., Alexander, M., Dannals, R.F., Wong, D.F., and Ricaurte, G.A. Persistent Cognitive and Dopamine Transporter Deficits In Abstinent Methamphetamine Users. Synapse 62, pp. 91-100, 2008.

Dopamine DRD4 Receptor Polymorphism Predicts Limbic System

Activation in Response to Smoking Cues

A dopamine receptor 4 variable number tandem repeat (DRD4 VNTR) polymorphism has been related to reactivity to smoking cues among smokers, but the effect of this genetic variation on brain responses to smoking cues has not been evaluated. Francis McClernon and colleagues at Duke evaluated the relationship between carrying the DRD4 VNTR 7-repeat allele and transient functional magnetic resonance imaging (fMRI) responses to smoking cues among adult dependent cigarette smokers, who underwent fMRI scanning after a 2 hour abstinence. During scanning, they viewed visual smoking and control cues. A blood sample was assayed for the DRD4 VNTR polymorphism, and participants were categorized based on whether they carried one or two copies of the 7-repeat allele (DRD4 L, n = 7) or not (DRD4 S, n = 8). Smoking cues as compared to control cues elicited transient brain responses in right superior frontal gyrus (BA 8/9/10/32), left anterior cingulate gyrus (BA 32), and right cuneus (BA 19). Exposure to smoking cues resulted in greater activation of right superior frontal gyrus (BA 10) and right insula in DRD4 L compared to DRD4 S individuals. By contrast, exposure to smoking cues among DRD4 S individuals resulted in no significant increases in activation compared to DRD4 L individuals. These brain imaging results suggest that DRD4 VNTR polymorphism is related to transient brain responses to smoking cues in regions subserving executive and somatosensory processes. McClernon, F.J., Hutchison, K.E., Rose, J.E., and Kozink, R.V. DRD4 VNTR Polymorphism Is Associated With Transient fMRI-BOLD Responses To Smoking Cues. Psychopharmacology (Berl), 194(4), pp. 433-41, 2007.

Extinction-Based Treatment For Smoking Cessation Reduces Brain Responses To Smoking Cues in Amygdala

Francis McClernon and colleagues evaluated the effect of an extinction-based smoking cessation treatment on brain responses to smoking cues using functional magnetic resonance imaging (fMRI). Sixteen (n = 16) dependent smokers were scanned using fMRI at baseline, following 2-4 weeks of smoking RNC cigarettes while wearing a 21-mg nicotine patch, and 2-4 weeks following quitting smoking. During scanning, participants viewed smoking-related pictures (e.g. lit cigarette) and pictures of people engaged in everyday activities (e.g., using a stapler). Event-related responses to smoking and control cues were analyzed in regions of interest (ROIs) known to subserve reward, attention, motivation and emotion. The extinction-based treatment simultaneously attenuated responses to smoking cues in amygdala while potentiating responses to control cues. Exploratory analysis indicated that this pattern was also observed in the thalamus of future abstinent but not relapsing smokers. The results of this preliminary study suggest that an extinction-based treatment for smoking cessation alters brain responses to smoking and control cues in amygdala--a region previously associated with drug cue reactivity and extinction. McClernon, F.J., Hiott, F.B., Liu, J., Salley, A.N., Behm, F.M., and Rose, J.E. Selectively Reduced Responses To Smoking Cues In Amygdala Following Extinction-Based Smoking Cessation: Results of a Preliminary Functional Magnetic Resonance Imaging Study. Addiction Biology, 12(3-4), pp. 503-512, 2007.

Positive Arousing Distractors Impair Rapid Target Detection

Emotional stimuli tend to capture and hold attention more than non-emotional stimuli do. Aversive pictures have been found to impair perception of visual targets even after the emotional information has disappeared. The benefits of such interlinked emotion and attention systems have sometimes been discussed within an evolutionary framework, with a survival advantage attributed to early detection of threatening stimuli. However, consistent with

recent suggestions that attention is drawn to arousing stimuli regardless of whether they are positive or negative, the current investigation found that erotic distractors, generally rated as both pleasing and arousing, consistently elicited a transient "emotion-induced blindness" similar to that caused by aversive distractors. This effect persisted despite performance-based monetary incentives to ignore the distractors, and following attentional manipulations that reduced interference from aversive images. The findings indicate that positively arousing stimuli can spontaneously cause emotion-induced deficits in visual processing, just as aversive stimuli can. These results form a foundation for interpretation of how drug-related stimuli can capture attention and serve as distractors. Most, S.B., Smith, S.D., Cooter, A.B., Levy, B.N., and Zald, D.H. The Naked Truth: Positive, Arousing Distractors Impair Rapid Target Perception. Cognition and Emotion, 21(5), pp. 964-981, 2007.

Impaired Decision-Making Related to Homeostatic Processing

Decision-making consists of selecting an action from a set of available options. This results in an outcome that changes the state of the decision-maker. Therefore, decision-making is part of a homeostatic process. Individuals with psychiatric disorders show altered decision-making. They select options that are either non-optimal or non-homeostatic. These dysfunctional patterns of decision-making in individuals with psychiatric disorders may fundamentally relate to problems with homeostatic regulation. These may manifest themselves in (i) how the length of time between decisions and their outcomes influences subsequent decision-making, (ii) how gain and loss feedback are integrated to determine the optimal decision, (iii) how individuals adapt their decision strategies to match the specific context, or (iv) how seemingly maladaptive responses result from an attempt to establish an unstable homeostatic balance. Paulus, M.P. Decision-making Dysfunctions in Psychiatry - Altered Homeostatic Processing? Science, 318(5850), pp. 602-606, 2007.

Placebo Effects Are Due To Individual Differences in Reward Processing

Expectancies may contribute to placebo effects by impacting perceptions and biological processes. The role of the nucleus accumbens (NAC), a region centrally involved in the encoding of reward expectation, in the formation of placebo responses was examined using two types of brain imaging in healthy human participants. Increased dopamine (DA) release using PET ligand imaging was observed in the NAC during placebo administration and was related to its anticipated effects, perception-anticipation mismatches, and development of placebo effects. In additional fMRI studies, the expectation of monetary gain increased NAC synaptic activity in a manner proportional to placebo-induced DA release, anticipated effects, perception-anticipation differentials, and actual placebo effects. Individual variations in NAC response to reward expectation accounted for 28% of the variance in the formation of placebo analgesia. Scott, D.J., Stohler, C.S., Egnatuk, C.M., Wang, H., Koeppe, R.A., and Zubieta, J. Individual Differences in Reward Responding Explain Placebo-induced Expectations and Effects. Neuron, 55(2), pp 325-336, 2007.

Temporal Profile of Non-Pharmacological Release of Dopamine and Endogenous Opiates

The time-course of changes in binding potential was measured with [C-11]carfentanil and [C-11]raclopride during moderate levels of sustained pain as a nonpharmacological challenge. It was hypothesized that, contrary to pharmacological probes, the use of a more "physiological" stimulus would be associated with less persistent changes in the BP measures. This challenge induced robust reductions in mu-opioid and DA D2 Binding Potential (BP). The

pain challenge was associated with reductions in mu-opioid receptor BP in several cortical and subcortical regions. These did not persist in a subsequent scan. Similar results were obtained for DA D2 receptor BP, where the pain challenge induced significant reductions in the caudate nucleus. These data demonstrate that changes in receptor BP induced by a nonpharmacological challenge did not persist into subsequent scans. They further suggest differences in the effect of pharmacological and nonpharmacological probes on PET BP measures. These may reflect varying levels of change in receptor affinity, receptor internalization, and recycling depending on the type of challenge employed. Scott, D.J., Stohler, C.S., Koeppe, R.A., and Zubieta, J. Time-Course Of Change In [C-11]Carfentanil And [C-11]Raclopride Binding Potential After A Nonpharmacological Challenge. Synapse, 61(9), pp. 707-714, 2007.

Cocaine-Associated Brain Volume Changes in Cerebellum and Other Brain Regions

This study was conducted to explore differences in gray and white matter volume between cocaine-dependent and healthy comparison subjects using optimized voxel-based morphometry (VBM). Brain magnetic resonance imaging (MRI) and neuropsychological function tests were performed for 40 cocaine-dependent subjects (27 men) and 41 healthy age- and sex-matched comparison subjects (26 men). Whole brain MR images were compared between groups with statistical parametric mapping. The cocaine-dependent group had lower gray matter volumes (12%-16%; $p<0.05$ corrected) in bilateral premotor cortex (Brodmann area (BA) 6, 8), right orbitofrontal cortex (BA 10,), bilateral temporal cortex (BA 20, 38;), left thalamus (and bilateral cerebellum as well as lower right cerebellar white matter volume (10.0%). Duration of cocaine use negatively correlated with right and left cerebellar gray matter volumes ($r=-0.37$, $r=-0.39$, respectively). In cocaine-dependent subjects, lower cerebellar hemispheric gray and white matter volumes were correlated with deficits in executive function and decreased motor performance. This study reports that cocaine-dependent subjects have lower gray matter volumes in cerebellar hemispheres as well as in frontal, temporal cortex, and thalamus. The results suggest that the cerebellum may be vulnerable to cocaine-associated brain volume changes, and that cerebellar deficits may contribute to neuropsychological deficits and motor dysfunction frequently observed in cocaine-dependent subjects. Sim, M.E., Lyoo, I.K., Streeter, C.C., Covell, J., Sarid-Segal, O., Ciraulo, D.A., Kim, M.J., Kaufman, M.J., Yurgelun-Todd, D., and Renshaw, P.F. Cerebellar Gray Matter Volume Correlates With Duration Of Cocaine Use In Cocaine-Dependent Subjects. Neuropsychopharmacology, 32(10), pp. 2229-2237, 2007.

Brain Regions Involved in Stress and Cue- Induced Craving

Both stress- and drug-related cues are major factors contributing to drug relapse. Stress and cue-induced craving appear to engage overlapping neural circuits in corticostriatal limbic circuitry underlying both affective and reward processing. Taken as a whole the studies to date suggest medial prefrontal, anterior and posterior cingulate, striatal and posterior insula regions are most associated with relapse outcomes. Altered function in these brain regions is associated with stress-induced and drug cue-induced craving states and an increased susceptibility to relapse. Such alterations can serve as markers to identify relapse propensity and a more severe course of addiction. Efficacy of pharmacological and behavioral treatments that specifically target stress and cue-induced craving and arousal responses may also be assessed via alterations in these brain correlates. Sinha, R., and Li, C.S.R. Imaging Stress-And Cue-Induced Drug And Alcohol Craving: Association With Relapse And Clinical Implications. Drug and Alcohol Dependence, 26(1), 25-31, 2007.

Adults and Adolescents Use Different Brain Regions for Response Inhibition

This study identified age-related differences in the function of neural circuits that are associated with inhibitory behavioral performance across adolescent development. Adolescents differed from adults in the degree of network engagement, regional fronto-striatal-thalamic connectivity, and network dynamics. Functional and effective connectivity analyses of whole brain hemodynamic activity elicited during performance of a Go/No-Go task were used to identify functionally integrated neural networks and characterize their causal interactions. Three response inhibition circuits formed a hierarchical, inter-dependent system wherein thalamic modulation of input to premotor cortex by fronto-striatal regions led to response suppression. Steven, M.C., Kiehl, K. A., Pearlson, G.D., and Calhoun, V.D. Functional Neural Networks Underlying Response Inhibition In Adolescents and Adults. Behavioural Brain Research, 181(1), pp. 12-22, 2007.

Working Memory Neuronal Activity Patterns Are Disrupted in Cocaine Abusers

This study used fMRI to test the hypothesis that cognitive dysfunction during cocaine abstinence reflects in part impairment of cortical and subcortical regions modulated by dopamine. Brain activation during a verbal working memory task was studied in cocaine abusers and healthy controls (n=16). Compared to controls, cocaine abusers showed: (1) hypoactivation in the mesencephalon, where dopamine neurons are located, as well as the thalamus, a brain region involved in arousal; (2) larger deactivation in dopamine projection regions (putamen, anterior cingulate, parahippocampal gyrus, and amygdala); and (3) hyperactivation in cortical regions involved with attention (prefrontal and parietal cortices), which probably reflects increased attention and control processes as compensatory mechanisms. Furthermore, the working memory load activation was lower in the prefrontal and parietal cortices in cocaine abusers when compared with controls, which might reflect limited network capacity. These abnormalities were accentuated in the cocaine abusers with positive urines for cocaine at time of study (as compared to cocaine abusers with negative urines) suggesting that the deficits may reflect in part early cocaine abstinence. These findings provide evidence of impaired function of regions involved with executive control, attention and vigilance in cocaine abusers. This widespread neurofunctional disruption is likely to underlie the cognitive deficits during early cocaine abstinence and to reflect involvement of dopamine as well as other neurotransmitters. Tomasi, D., Goldstein, R. Z., Telang, F., Maloney, T., Alia-Klein, N., Caparelli, E. C., and Volkow, N.D. Widespread Disruption In Brain Activation Patterns To A Working Memory Task During Cocaine Abstinence. Brain Research, 1171, pp. 83-92, 2007.

Cocaine Impairs Attention by Disrupting Thalmo-Cortical Circuits

Functional magnetic resonance imaging (fMRI) and a sustained visuospatial attention task was used to assess the neuronal basis of visual attention network dysfunction in cocaine abusers (n = 14) compared to age-, gender-, and education-matched controls (n= 14). Compared with controls, cocaine abusers showed (1) hypoactivation of the thalamus, which may reflect noradrenergic and/or dopaminergic deficits; (2) hyperactivation in occipital and prefrontal cortices, which may reflect increased visual cortical processing to compensate for inefficient visual thalamic processing; and (3) larger deactivation of parietal and frontal regions possibly to support the larger hemodynamic supply to the hyperactivated brain regions. These findings provide evidence of abnormalities in thalamocortical responses in cocaine abusers that are likely to contribute to the impairments in sensory processing

and in attention. The development of therapies that diminish these thalamo-cortical deficits could improve the treatment of cocaine addiction. Tomasi, D., Goldstein, R.Z., Telang, F., Maloney, T., Alia-Klein, N., Caparelli, E.C., and Vokow, N.D. Thalamo-Cortical Dysfunction In Cocaine Abusers: Implications In Attention And Perception. Psychiatry Research-Neuroimaging, 155(3), pp. 189-201, 2007.

Brain Phosphorus Magnetic Resonance Spectroscopy Imaging of Sleep Homeostasis and Restoration in Drug Dependence

Numerous reports have documented a high occurrence of sleep difficulties in drug-dependent populations, prompting researchers to characterize sleep profiles and physiology in drug abusing populations. This mini-review examines studies indicating that drug-dependent populations exhibit alterations in sleep homeostatic and restoration processes in response to sleep deprivation. Sleep deprivation is a principal sleep research tool that results in marked physiological challenge, which provides a means to examine sleep homeostatic processes in response to extended wakefulness. A report from our laboratory demonstrated that following recovery sleep from sleep deprivation, brain high-energy phosphates particularly beta-nucleoside triphosphate (beta-NTP) are markedly increased as measured with phosphorus magnetic resonance spectroscopy (MRS). A more recent study examined the effects of sleep deprivation in opiate-dependent methadone-maintained (MM) subjects. The study demonstrated increases in brain beta-NTP following recovery sleep. Interestingly, these increases were of a markedly greater magnitude in MM subjects compared to control subjects. A similar study examined sleep deprivation in cocaine-dependent subjects demonstrating that cocaine-dependent subjects exhibit greater increases in brain beta-NTP following recovery sleep when compared to control subjects. The studies suggest that sleep deprivation in both MM subjects and cocaine-dependent subjects is characterized by greater changes in brain ATP levels than control subjects. Greater enhancements in brain ATP following recovery sleep may reflect a greater disruption to or impact of sleep deprivation in drug dependent subjects, whereby sleep restoration processes may be unable to properly regulate brain ATP and maintain brain high-energy equilibrium. These studies support the notion of a greater susceptibility to sleep loss in drug dependent populations. Additional sleep studies in drug abusing populations are needed, particularly those that examine potential differential effects of sleep deprivation. Trksak, G., Jensen, J., Renshaw, P., and Lukas, S. Brain Phosphorus Magnetic Resonance Spectroscopy Imaging of Sleep Homeostasis and Restoration in Drug Dependence. Scientific World Journal, 7, pp. 217-222, 2007.

Interaction of Drug Abuse and Anti-Social Personality Disorder on Impulsivity

The purpose of this investigation was to examine the influence of antisociality and extent of multidrug use on cognitive and motor impulsivity among substance-dependent individuals (SDIs) that used primarily cocaine and/or heroin in 100 currently abstinent male SDIs. Extent of multidrug use and degree of antisociality, assessed with the Socialization Scale of the California Psychological Inventory (So-CPI). Participants were classified into one of four groups: high antisocial/low multidrug use, high antisocial/high multidrug use, low antisocial/low multidrug use, and low antisocial/high multidrug use. The Iowa Gambling Task was used assess cognitive impulsivity and the Stroop Task to measure motor impulsivity. Contrary to expectations, antisociality was associated with more advantageous performance on the Iowa Gambling Task, independent of extent of multidrug use. In contrast, greater multidrug use was associated with general psychomotor slowing on the Stroop Task. Results suggest that a subclinical form of antisociality may have a paradoxically facilitating effect on decision-making and cognitive impulsivity among SDIs.

Vassileva, J., Gonzalez, R., Bechara, A., and Martin, E. Are All Drug Addicts Impulsive? Effects of Antisociality and Extent of Multidrug Use on Cognitive and Motor Impulsivity. Addict. Behav., 32(12), pp. 3071-3076, 2007.

Placebo Induced Reduction in Pain-Elicited Mu-Opioid Activity

Placebo-induced expectancies have been shown to decrease pain in a manner reversible by opioid antagonists, but little is known about the central brain mechanisms of opioid release during placebo treatment. This study examined placebo effects in pain by using PET with [C-11]carfentanil to assay regional mu-opioid receptor availability. Noxious thermal stimulation was applied at the same temperature for placebo and control conditions. These findings suggest that a mechanism of placebo analgesia is the potentiation of endogenous opioid responses to noxious stimuli. Placebo treatment affected endogenous opioid activity in a number of predicted mu-opioid receptor-rich regions that play central roles in pain and affect, including periaqueductal gray and nearby dorsal raphe and nucleus cuneiformis, amygdala, orbitofrontal cortex, insula, rostral anterior cingulate, and lateral prefrontal cortex. Some regions exhibited placebo-induced opioid activation specific to noxious heat, whereas others showed placebo-induced opioid reduction during warm stimulation in anticipation of pain. Opioid activity in many of these regions was correlated with placebo effects in reported pain. Connectivity analyses on individual differences in endogenous opioid system activity revealed that placebo treatment increased functional connectivity between the periaqueductal gray and rostral anterior cingulate, as hypothesized a priori, and also increased connectivity among a number of limbic and prefrontal regions, suggesting increased functional integration of opioid responses. Overall, the results suggest that endogenous opioid release in core affective brain regions is an integral part of the mechanism whereby expectancies regulate affective and nociceptive circuits. Wager, T., Scott, D., and Zubieta, J. Placebo Effects on Human Mu-Opioid Activity During Pain. PNAS. 104(26), pp. 1056-11061, 2007.

Support Vector fMRI Analysis

Comparisons were made between a machine learning algorithm, the support vector machine (SVM), and the random effect model for arterial spin labeling (ASL) perfusion fMRI analysis. Without any brain response modeling, SVM was used to extract a whole brain spatial discriminance map (SDM), representing the brain response difference between the contrasted experimental conditions. Population inference was then obtained through the random effect analysis (RFX) or permutation testing (PMU) on the individual subjects' SDMs. SDM RFX yielded lower false-positive rates in the null hypothesis test and higher detection sensitivity for synthetic activations with varying cluster size and activation strengths, compared to the univariate general linear model (GLM)-based RFX. For a sensory-motor ASL fMRI study, both SDM RFX and SDM PMU yielded similar activation patterns to GLM RFX and GLM PMU, respectively, but with higher t values and cluster extensions at the same significance level. Capitalizing on the absence of temporal noise correlation in ASL data, this study also incorporated PMU in the individual-level GLM and SVM analyses accompanied by group-level analysis through RFX or group-level PMU. Providing inferences on the probability of being activated or deactivated at each voxel, these individual-level PMU-based group analysis methods can be used to threshold the analysis results of GLM RFX, SDM RFX or SDM PMU. Wang, Z., Childress, A., Wang, J. and Detre, J. Support Vector Machine Learning-Based fMRI Data Group Analysis. Neuroimage, 36(4), pp. 1139-1151, 2007.

Brain Basis of Risky Decision-Making

A new measure of adaptive decision making under risk was used to examine whether damage to neural structures subserving emotion affects an individual's ability to make adaptive decisions differentially for gains and losses. The authors found that individuals with lesions to the amygdala, an area responsible for processing emotional responses, displayed impaired decision making when considering potential gains, but not when considering potential losses. In contrast, patients with damage to the ventromedial prefrontal cortex, an area responsible for integrating cognitive and emotional information, showed deficits in both domains. The authors argue that this dissociation provides evidence that adaptive decision making for risks involving potential losses may be more difficult to disrupt than adaptive decision making, for risks involving potential gains. This research further demonstrates the role of emotion in decision competence. Weller, J.A., Levin, I.P., Shiv, B., and Bechara, A. Neural Correlates of Adaptive Decision Making For Risky Gains and Losses. Psychological Science, 18(11), pp. 958-964, 2007.

Adjustment of Motor Behavior Following Reinforcement Involves Different Neural Systems

Performance of a reward-providing reaction time task during functional magnetic resonance imaging (fMRI) was used to investigate the adaptation of a simple motor response following four different outcomes (delivery versus omission and monetary gain versus loss). Activation in the thalamus and insula predicted adjustments of motor responses due to outcomes that were cued and delivered, whereas activation in the ventral striatum predicted such adjustments when outcomes were cued but omitted. Further, activation of OFC predicted improvement after all punishing outcomes, independent of whether they were omitted rewards or delivered punishments. Finally, activity in anterior cingulate predicted adjustment after delivered punishments and activity in dorsal striatum predicted adaptation after delivered rewards. These results provide evidence that different but somewhat overlapping circuits mediate the same behavioral adaptation when it is driven by different incentive outcomes. These findings form the foundation for investigating altered reinforcement processing by rewards and punishment incurred during substance abuse. Wrase, J., Kahnt, T., Schiagenhauf, F., Beck, A., Cohen, M.X., Knutson, B., and Heinz, A. Different Neural Systems Adjust Motor Behavior In Response To Reward And Punishment. Neuroimage, 36(4), pp. 1253-1262, 2007.

Director's Report to the National Advisory Council on Drug Abuse - February, 2008

Research Findings - Epidemiology and Etiology Research

Genetic and Environmental Influences on Drug Availability

This study used data from a study of twins to investigate the sources of individual differences in drug availability (DA). Subjects were 1788 adult males from the Mid-Atlantic Twin Registry who participated in a structured telephone interview that included retrospective assessments of DA (cigarette, alcohol, marijuana, cocaine and stimulants) between ages 8 and 25. The authors fitted a biometric dual change score (DCS) model, adapted for ordinal data, to model latent growth and estimate the genetic and environmental components of variance over time. They found that DA, despite being considered an environmental risk factor, is under both genetic and environmental control. For cigarette, alcohol, marijuana and cocaine availability, there was an overall increase in additive genetic variance and a decline in shared environmental variance over time. Non-shared environmental variance remained steady. Stimulant availability did not follow this pattern; rather, there was an upswing in shared environmental effects with increasing age. The authors conclude that the rise in additive genetic variance over time coincides with acceleration in the expression of individual differences, probably brought on by an increase in personal freedom and a reduction in social constraints. This work demonstrates the role of gene-environment correlations in understanding the influence of environmental factors on initiation of drug abuse, as individuals seek out certain environments based in part on genetic propensity. Gillespie, N., Kendler, K., Prescott, C., Aggen, S., Gardner, C., Jacobson, K., and Neale, M. Longitudinal Modeling of Genetic and Environmental Influences on Self-Reported Availability of Psychoactive Substances: Alcohol, Cigarettes, Marijuana, Cocaine and Stimulants. Psychol Med, 37(7), pp. 947-959, 2007.

A Twin Study of Peer Deviance

Peer-group deviance is strongly associated with externalizing behaviors. This study sought to clarify genetic and environmental contributions to peer-group deviance in twins from mid-childhood through early adulthood. Participants were members of male-male pairs from the population-based Virginia Twin Registry personally interviewed in 1998-2004 (n = 1802). Data were collected through retrospective assessments using a life-history calendar, on self-reported peer-group deviance at ages 8-11, 12-14, 15-17, 18-21, and 22-25 years. The results showed that mean and variance of peer-group deviance increased substantially with age. Genetic effects on peer-group deviance showed a strong and steady increase over time. Family environment generally declined in importance over time. Individual-specific environmental influences on peer-group deviance levels were stable in the first 3 age periods and then increased as most twins left home. When standardized, the heritability of peer-group deviance is approximately 30% at ages 8 to 11 years and rises to

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approximately 50% across the last 3 time periods. Both genes and shared environment contributed to individual differences in the developmental trajectory of peer-group deviance. However, while the correlation between childhood peer-group deviance levels and the subsequent slope of peer-group deviance over time resulting from genetic factors was positive, the same relationship resulting from shared environmental factors was negative. The authors concluded that as male twins mature and create their own social worlds genetic factors play an increasingly important role in their choice of peers, while shared environment becomes less influential. The individual-specific environment increases in importance when individuals leave home. Individuals who have deviant peers in childhood, as a result of genetic vs shared environmental influences, have distinct developmental trajectories. Understanding the risk factors for peer-group deviance will help clarify the etiology of a range of externalizing psychopathology. Kendler, K., Jacobson, K., Gardner, C., Gillespie, N., Aggen, S., and Prescott, C. Creating a Social World: A Developmental Twin Study of Peer-Group Deviance. Arch. Gen. Psych. 64(8), pp. 958-965, 2007.

The Relationship Between Lifetime Abuse and Suicidal Ideation in a Sample of Injection Drug Users

This study examined the relationship between lifetime abuse and suicidal ideation in a sample of 245 injection drug users who attended the Baltimore Needle Exchange Program and received a referral for opiate agonist therapy. Data were obtained from baseline interviews and HIV antibody tests. The sample mean age was 42.2 (SD = 8.1); 77% were African American; 69% were male. Overall, 27% reported thoughts of suicide in the last six months, and lifetime emotional, physical and sexual abuse was reported by 17%, 12% and 10%, respectively. In bivariate analyses, recent suicidal ideation was associated with emotional (odds ratio [OR] = 3.2; $p = 0.001$), physical (OR = 2.5; $p = 0.026$), and sexual abuse (OR = 5.0; $p < 0.001$). In multiple logistic regression models controlling for HIV status and Center for Epidemiological Studies Depression (CES-D) score, individuals who experienced emotional abuse were more than twice as likely to report recent suicidal ideation (adjusted odds ratio [AOR] = 2.6; $p = 0.011$); those who experienced sexual abuse were four times more likely to report suicidal ideation (AOR = 4.0; $p = 0.004$). These findings suggest that emotional and sexual abuse might be risk factors for suicidality among IDUs and also might suggest that suicide prevention should be an integral part of drug treatment for treatment-seeking IDUs. Lloyd, J., Ricketts, E., Havens, J., Cornelius, L., Bishai, D., Huettner, S., Latkin, C., and Strathdee, S. The Relationship Between Lifetime Abuse and Suicidal Ideation in a Sample of Injection Drug Users. J. Psychoactive Drugs, 39(2), pp. 159-166, 2007.

A Twin Study of Delinquent Peer Affiliation

This study used genetic epidemiologic approaches to evaluate whether the association between delinquent peer affiliation and conduct problems may occur because of shared genetic liability. Data came from 553 monozygotic and 558 dizygotic (same sex and opposite sex) twin pairs, over half female, aged 11 to 18 years, recruited from community based samples in Colorado, assessed through self-report for delinquent peer affiliation and conduct problems. The authors investigated whether genes contribute to both delinquent peer affiliation and the correlation between delinquent peer affiliations and conduct problems. Modeling found that delinquent peer affiliation was influenced by genetic, shared environmental and non-shared environmental factors; genetic factors also contributed to the correlation between delinquent peer affiliations and conduct problems, providing evidence for genotype-environment correlation. The magnitude of the genetic variance of conduct problems was contextually dependent on levels of delinquent peer affiliation and was greater

at higher levels of delinquent peer affiliation. Thus, this study adds to the growing literature showing that many putative environmental risks for drug abuse correlate with individuals "genotypes". Button, T., Corley, R., Rhee, S., Hewitt, J., Young, S., and Stallings, M. Delinquent Peer Affiliation and Conduct Problems: A Twin Study. J Abnorm. Psychol., 116(3), pp. 554-564, 2007.

ADHD Risk for Heavy Drinking and Alcohol Use Disorder is Age Specific

This study was designed to assess age specificity in the risk for heavy drinking and alcohol use disorder (AUD) among adolescents and young adults with Attention-Deficit/Hyperactivity Disorder (ADHD) diagnosed in childhood. Children diagnosed with ADHD (n=364 probands) were interviewed an average of 8 years later in the Pittsburgh ADHD Longitudinal Study, either as adolescents (11-17 years old) or as young adults (18-28 years of age). Demographically similar age-matched participants without ADHD were recruited as adolescents (n=120) or as adults (n=120) for comparison with the probands. Alcohol involvement was assessed comprehensively to include measures of heavy drinking that are standard in alcoholism research and prognostic of later alcohol-related problems. Results revealed age specificity in the association such that episodic heavy drinking (measured as 5+ drinks per occasion), drunkenness, DSM-IV AUD symptoms, and DSM-IV AUD were elevated among 15- to 17-year-old probands, but not among younger adolescents. Among young adults, drinking quantity and AUD were elevated among probands with antisocial personality disorder. Childhood predictors indexing antisocial behavior were also examined. Authors concluded that the age- specificity of these findings helps to explain prior inconsistencies across previous studies regarding risk for alcohol-related outcomes among children with ADHD. Molina, B., Pelham, W., Gnagy, E., Thompson, A., and Marshal, M. Attention-Deficit/ Hyperactivity Disorder Risk for Heavy Drinking and Alcohol Use Disorder Is Age Specific. Alcohol Clin. Exp. Res., 31(4), pp. 643-654, 2007.
Cocaine Use and Educational Achievement: Understanding a Changing Association Authors compared trends in cocaine use over the past 2 decades across levels of education in a population-based US sample of adults. Data from 1979-2002 NHSDA/NSDUH were analyzed to investigate cocaine use and educational achievement among adults 19-50 years old. Investigators found that significant inverse associations between educational achievement and cocaine use after 1990 were driven by dramatic decreases in persistent cocaine use among more highly educated adults, whereas persistent cocaine use remained relatively unchanged among those who did not finish high school. This emerging health disparity highlights the need for improved interventions that target persistent cocaine users with low educational achievement. Harder, V., and Chilcoat, H. Cocaine Use and Educational Achievement: Understanding a Changing Association over the Past 2 Decades. Am J Public Health, 97(10), pp. 1790-1793, 2007.

Conduct and Attentional Problems and Risk for Later SUDs

This paper examines the linkages between conduct problems and attentional problems in middle childhood and adolescence and later substance use, abuse and dependence in young adulthood. Data were gathered over the course of a 25-year longitudinal study of a 1977 birth cohort of 1265 New Zealand born children. These data included: (a) measures of conduct and attentional problems in middle childhood (7-9 years) and adolescence (14-16 years); (b) measures of substance use, abuse and dependence from 18-25 years; and (c) confounding social, family and related factors. Statistical modeling produced a consistent set of results showing: (i) conduct problems in childhood and adolescence were generally related to later substance use, abuse and dependence even after control for attentional problems and confounders; (ii) attentional problems were largely unrelated to later substance use, abuse and

dependence after control for conduct problems and confounders. The authors conclude that conduct problems in both middle childhood and adolescence are related to increased risks of longer-term substance use, abuse and dependence, and that any association between early attentional problems and later substance use, abuse and dependence is largely mediated via the association between conduct and attentional problems. This paper joins a growing literature on population-based samples studied longitudinally which finds that attentional problems in the absence of other disruptive behavior problems (including conduct disorder) does not confer increased risk for substance use problems. Fergusson, D., Horwood, L., and Ridder, E. Conduct and Attentional Problems in Childhood and Adolescence and Later Substance Use, Abuse and Dependence: Results of a 25-Year Longitudinal Study. Drug Alcohol Depend, 88 Suppl 1 (N/A), pp. S14-S26, 2007.

Family Study of Bipolar and Substance Use Disorders

This study follows up on previous findings that juvenile bipolar disorder (BPD) is a risk for substance use disorders (SUD), by examining the expression of both disorders in families of youth with BPD to evaluate the familial risk mechanism. Data were gathered from 108 adolescent BPD probands with 187 parents (34 with SUD and 58 parents) and 96 control probands with 177 parents using structured interviews. They compared the prevalence of BPD and SUD with Cox proportional hazards models with time to onset of BPD or SUD as the dependent variable and proband diagnosis (Control, BPD, or BPD+SUD) as the independent variable. The parents of the proband youth with BPD (without SUD) and BPD+SUD were more likely to develop BPD than the parents of control subjects [omnibus test chi2=10.18, p=.006]; no differences were found between the two bipolar groups. Parents of proband youth with BPD and with BPD+SUD were more likely than relatives of control subjects to develop SUD [omnibus test chi2=14.69, p<.001]; however, no differences between the parents of the two proband bipolar groups were found. Within the parents of proband youth with BPD+SUD, higher risk of SUD was found in parents with BPD than in those without BPD [chi2=8.39, p=.004], although the frequency of BPD was low in this group of parents. The authors conclude that bipolar disorder and SUD are prevalent in the first-degree relatives of adolescents with BPD, and that adults with BPD were more likely to manifest SUD with preliminary evidence of BPD and SUD co segregation. Wilens, T., Biederman, J., Adamson, J., Monuteaux, M., Henin, A., Sgambati, S., Santry, A., and Faraone, S. Association of Bipolar and Substance Use Disorders in Parents of Adolescents with Bipolar Disorder. Biol. Psychiatry, 62(2), pp. 129-134, 2007.

Prevalence of Illicit Use and Abuse of Prescription Stimulants, Alcohol, and Other Drugs among College Students: Relationship with Age at Initiation of Prescription Stimulants

This study examined associations between age at initiation of prescription stimulants and illicit use and abuse of prescription stimulants, alcohol, and other drugs among college students in the United States. Data were collected through a web-based survey of college students attending a large university. The web-based survey was sent to a random sample of 5389 undergraduate college students plus an additional 1,530 undergraduate college student's of various ethnic backgrounds over a 2-month period. Alcohol abuse was assessed by including a modified version of the Cut Down, Annoyance, Guilt, Eye-opener (CAGE) instrument. Drug use-related problems were assessed with a slightly modified version of the Drug Abuse Screening Test, short form (DAST-10). The final sample consisted of 4580 undergraduate students (66% response rate). For the analyses, five subgroups were created based on age at initiation of prescription stimulant use: no prescription stimulant use, grades kindergarten (K)-4, grades 5-8, grades 9-12, and college. Undergraduate students to whom stimulants were prescribed in grades K-4 reported similar rates of alcohol and

other drug use compared with that of the group that had no prescription stimulant use. For example, students who started prescription stimulants in grades K-4 were no more likely to report co-ingestion of alcohol and illicit prescription stimulants (odds ratio [OR] 1.4, 95% confidence interval [CI] 0.2-11.5, NS] than the group that had no prescription stimulant use. However, undergraduate students whose prescription stimulant use began in college had significantly higher rates of alcohol and other drug use. For example, students who started a prescription stimulant in college were almost 4 times as likely (OR 3.7, 95% CI 1.9-7.1, $p<0.001$) to report at least three positive indicators of drug abuse on the DAST-10 compared with the group that had no prescription stimulant use. These results indicate that initiation of prescription stimulants during childhood is not associated with increased future use of alcohol and other drugs. Kaloyanides, K., McCabe, S., Cranford, J., and Teter, C. Prevalence of Illicit Use and Abuse of Prescription Stimulants, Alcohol, and Other Drugs among College Students: Relationship with Age at Initiation of Prescription Stimulants. Pharmacotherapy, 27(5), pp. 666-674, 2007.

Methodological Issues in Assessing Cannabis Dependence in Community Surveys

The researchers probed issues relating to classification of drug dependence in epidemiologic studies with respect to cannabis dependence, making use of data from the cross-sectional United States National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a household survey of 43,093 adults aged 18 years and over. Specifically, they simulated a social impairment/ maladaptation ''gated '' assessment of cannabis dependence, and the end result was a very modest reduction in the estimated prevalence of cannabis dependence. This suggests that for every 10,000 general population survey respondents there would be no more than 12 cases of cannabis dependence without the above-referenced impairments/maladaptations. Patterns of association linking suspected background characteristics to the prevalence of cannabis dependence were not appreciably different when the ''gated '' and ''ungated '' approaches were applied. In summary, there are reasons to take the ungated approach in detailed research on cannabis use and dependence. Nevertheless, in panoramic mental health surveys, the inefficiency of an ''ungated '' approach must be balanced against the anticipated yield of cannabis dependence cases who lack social role impairments or socially maladaptive behaviors'. Degenhardt, L., Cheng, H., and Anthony, J. Assessing Cannabis Dependence in Community Surveys: Methodological Issues. Int. J. Methods Psychiatr. Res., 16(2), pp. 43-51, 2007.

Externalizing Symptoms Among Children of Alcoholic Parents: Entry Points for an Antisocial Pathway to Alcoholism

The authors examined heterogeneity in risk for externalizing symptoms in children of alcoholic parents (COA), as it may inform the search for entry points into an antisocial pathway to alcoholism. That is, they tested whether the number of alcoholic parents in a family, the comorbid subtype of parental alcoholism, and the gender of the child predicted trajectories of externalizing symptoms over the early life course, as assessed in high-risk samples of children of alcoholic parents and matched controls. Data from the Michigan Longitudinal Study provided 596 children from 338 families, and Adolescent/Adult Family Development Project 454 adolescents and their parents, both with COA and matched controls assessed over multiple waves. Through integrative analyses of these independent, longitudinal studies, they showed that children with either an antisocial alcoholic parent or 2 alcoholic parents were at greatest risk for externalizing symptoms. Moreover, children with a depressed alcoholic parent did not differ from those with an antisocial alcoholic parent in reported symptoms. These findings were generally consistent across mother, father, and adolescent reports of symptoms; child

gender and child age (ages 2-17); and the 2 independent studies examined. Multi-alcoholic and comorbid-alcoholic families may thus convey a genetic susceptibility to dysregulation along with environments that both exacerbate this susceptibility and provide few supports to offset it. Hussong, A., Wirth, R., Edwards, M., Curran, P., Chassin, L., and Zucker, R. Externalizing Symptoms Among Children of Alcoholic Parents: Entry Points for An Antisocial Pathway to Alcoholism. J.Abnorm. Psychol.,116, pp. 529-542, 2007.

Social Capital or Networks, Negotiations, and Norms? A Neighborhood Case Study

"Social capital" has been critiqued as distracting attention from inequalities and policies that produce ill health. Researchers examined another dimension often included in the concept of social capital--social network ties and their associated communication patterns. They present a case study of Bushwick, a community of 100,000 people in Brooklyn NY, to suggest that the network aspect of "social capital" is useful to understand the active, on-the-ground processes by which residents of some neighborhoods beset by poverty, racial/ethnic subordination, and internal divisions (that themselves arise from inequalities and state policies) work out ways to defend their own and others' safety and health. They use a combination of population-representative survey data for young adults; sexual network survey data; and ethnography to show that Bushwick residents (including drug users and dealers) have used social network ties, communication, and normative pressures to reduce the extent to which they are put at risk by the drug trade and by drug-use-related HIV/AIDS in spite of conflicting interests, disparate values, and widespread distrust both of other community members and of dominant social institutions. This was done by "intravention" health communications, development of protective norms, informal negotiations, and other forms of adjustments within and among various groups--but it occurred in the absence of trust or consensus in this community. The findings suggest both (1) that social network interpretations of "social capital" might be better conceptualized in dialectic terms as collective action to survive in a harsh social order, and (2) that the social capital theory emphasis on trust and consensus as important causal factors for lowering drug-related risks at the community level may be a romanticized and erroneous perspective. Friedman, S., Mateu-Gelabert, P., Curtis, R., Maslow, C., Bolyard, M., Sandoval, M., and Flom, P. Social Capital or Networks, Negotiations, and Norms? A Neighborhood Case Study. Am. J. Prev. Med., 32(6 Suppl), pp. S160-S170, 2007.

Marijuana Use Patterns Among African-American Middle-School Students: A Longitudinal Latent Class Regression Analysis

Authors sought to describe patterns of marijuana involvement during the middle-school years from the first chance to try marijuana down through the early stages of experiencing health and social problems from marijuana use in a sample of African-American adolescents. A total of 488 urban-dwelling African-American middle-school students were interviewed in sixth, seventh and eighth grades as part of a longitudinal field study. Longitudinal latent class models were used to identify subgroups (classes) of adolescents with similar patterns of marijuana involvement. Three classes were identified; little or no involvement (prevalence 85%, 71%, 55% in sixth, seventh and eighth grade, respectively), marijuana exposure opportunity (12%, 19% and 26%), and marijuana use and problems (2%, 9% and 19%). High levels of aggressive/ disruptive behavior exhibited as early as first grade and moderate to high levels of deviant peer affiliation were associated with an increased risk of marijuana exposure opportunities in middle-school. Moderate to high levels of aggressive/disruptive behavior and deviant peer affiliation, moderate to low levels of parent monitoring and high levels of perceived neighborhood disadvantage were associated with an increased risk of marijuana use and

problems. Significant interactions with grade provided evidence that the influences of parent monitoring and neighborhood disadvantage decrease through the middle-school years. Although not statistically significant, the magnitude of the effects of deviant peer affiliation on marijuana use and problems increased two-fold from sixth to eighth grade. These findings highlight the importance of marijuana exposure opportunities in the pathway to marijuana use and problems and the potential to intervene on behaviors exhibited as early as first grade. It also underscores the importance of developing interventions that are sensitive to the strong influence of parents at entry into middle-school and the shift to peer influences by the end of middle-school. Reboussin, B., Hubbard, S., and Ialongo, N. Marijuana Use Patterns Among African-American Middle-School Students: A Longitudinal Latent Class Regression Analysis. Drug Alcohol Depend., 90(1), pp. 12-24, 2007.

Direct and Indirect Associations of Neighborhood Disorder with Drug Use and High-Risk Sexual Partners

On a macrosocial level, neighborhood characteristics have been found to be associated with the prevalence of HIV and other blood borne and sexually transmitted infections. The current study used structural equation modeling to examine the relationship between neighborhood social and physical disorder and high-risk sexual partners. A cohort (N=838) recruited for an HIV prevention study of drug users in Baltimore, Maryland was interviewed about their neighborhood characteristics, drug use, depressive symptoms (using the Centers for Epidemiological Studies Depression Scale), and HIV/sexually transmitted infection risk behaviors of exchanging sex for money or drugs, having multiple sexual partners, and having partners who injected drugs or smoked crack cocaine. Data were analyzed in 2/2005, with models indicating statistically significant direct associations between neighborhood disorder and psychologic distress, neighborhood disorder and sexual risk behaviors, and neighborhood disorder and drug use. There were also significant indirect associations of neighborhood disorder on sexual risk behaviors. These results highlight the importance of viewing drug use, chronic stress, depression and hopelessness, and infectious diseases such as HIV and hepatitis C as interlinked epidemics that are fostered by neighborhood social and physical disorder. Neighborhood, network, and community level interventions are needed to address these intertwined public health issues. Latkin, C., Curry, A., Hua, W., and Davey, M. Direct and Indirect Associations of Neighborhood Disorder with Drug Use and High-Risk Sexual Partners. Am. J. Prev. Med., 32(6 Suppl), pp. S234-S241, 2007.

Neighborhood Socioeconomic Status, Personal Network Attributes, and Use of Heroin and Cocaine

Drug abuse is a significant public health problem and is associated with numerous negative health and social consequences. Examining the social context of drug use represents a burgeoning avenue of research in drug abuse. This study investigates the effects of neighborhood disadvantage and network factors on current heroin and cocaine use among a predominantly African-American adult sample residing in Baltimore City. It employs a cross-sectional, multilevel design using data from two sources: the SHIELD Study, a network-oriented HIV intervention in Baltimore City and the 1990 U.S. Decennial Census. The sample consisted of 1305 adults from 249 neighborhoods (census block groups) across Baltimore City. Multilevel logistic regression analysis was performed to examine personal network and neighborhood effects on current heroin and cocaine use. Neighborhood poverty was found to be significantly associated with current heroin and cocaine use (odds ratio [OR]=1.51, confidence interval [CI]=1.06-2.15). Social support (OR=0.80, CI=0.69-0.92) and having ties to employed people (OR=0.47, CI=0.24-0.92) were protective of current drug use, but did not buffer negative effects of neighborhood

poverty in the face of negative drug influences in the network (OR=8.62, CI=5.81-12.79). The contexts of neighborhoods and networks represent key determinants in understanding the social epidemiology of drug abuse. Network attributes have strong influences on drug use, and neighborhood poverty may increase odds of use. Further research is warranted to determine other aspects of neighborhood environments that may put individuals at risk for drug use and abuse. Williams, C., and Latkin, C. Neighborhood Socioeconomic Status, Personal Network Attributes, and Use of Heroin and Cocaine. Am J Prev Med, 32(6 Suppl), pp. S203-S210, 2007.

Methamphetamine Use and Risky Sexual Behaviors During Heterosexual Encounters

This study examined the association between event-level methamphetamine use and heterosexual risk behaviors. Data on 1213 heterosexual encounters were collected using audio-computer assisted self interviews from 703 injecting drug users in North Carolina. Data were obtained by asking participants a series of questions about the last time that they had sex. Although participants were interviewed at up to 3 time points, data were analyzed at the event level rather than as longitudinal because the interest was in the co-occurrence of methamphetamine use and sexual risk behaviors. Multivariate generalized estimating equations models were developed to examine the association between co-occurring methamphetamine use and each of 6 heterosexual risk behaviors. Methamphetamine was used in 7% of encounters. Methamphetamine use by either or both partners was associated with an increased likelihood of anal intercourse (odds ratio [OR] = 2.41, 95% confidence interval [CI] = 1.29-4.53), vaginal and anal intercourse (OR = 2.41, 95% CI = 1.22-4.77), and sex with a new partner (OR = 1.98, 95% CI = 1.09-3.61). In addition to these behaviors, methamphetamine use by both partners was also significantly associated with unprotected intercourse with a new partner (OR = 5.20, 95% CI = 2.09-12.93) and unprotected anal intercourse (OR = 4.63, 95% CI = 1.69-12.70). These findings underscore the influential role of methamphetamine use on increasing sexual risk-taking, especially when both partners are using it. Zule, W., Costenbader, E., Meyer, W., and Wechsberg, W. Methamphetamine Use and Risky Sexual Behaviors During Heterosexual Encounters. Sex Transm. Dis., 34(9), pp. 689-694, 2007.

Personality Disorders in Early Adolescence and the Development of Later Substance Use Disorders in the General Population

Assessments of personality disorder (PD) and conduct disorder (CD) in a random community sample at mean age 13 were employed to predict subsequent substance abuse disorder (SUD), trajectories of symptoms of abuse or dependence on alcohol, marijuana, or other illicit substances, and hazard of initiating marijuana use over the subsequent decade. Personality disorders and conduct disorder were associated with diagnoses and symptoms of SUDs in every model and their effects were independent of correlated family risks, participant sex, and other Axis I disorders. Specific elevated PD symptoms in early adolescence were also associated with differential trajectories of already initiated SUD symptoms as well as elevated risk for future onset of SUD symptoms. For several models the greatest of these effects were shown for borderline PD and for conduct disorder, the predecessor of adult antisocial PD. Passive-aggressive PD also showed independent elevation effects on substance use symptoms for alcohol and marijuana. Analyses over 30 years suggest that Cluster B PD (borderline, histrionic, narcissistic) are independent risks for development of SUD and warrant clinical attention. Cohen, P., Chen, H., Crawford, T., Brook, J., and Gordon, K. Personality Disorders in Early Adolescence and the Development of Later Substance Use Disorders in The General Population. Drug Alcohol Depend., 88 Suppl 1, pp. S71-S84, 2007.

Psychosocial Functioning after Adolescent SUD

The authors examined whether substance use disorder (SUD) before age 19 was associated with functioning at age 30. Participants (N = 773, about 60% female) came from a sample initially drawn randomly from representative high school samples in urban and rural western Oregon. They were assessed twice during adolescence at average ages of 16 and 17, and again at ages 24 and 30. The authors found that eight of 14 adult measures were associated with adolescent SUD: education, unemployment, income, risky sexual behavior, suicide attempt, coping, stressful life events, and global adjustment. After adolescent comorbidity and functioning and adult SUD were controlled for, education and unemployment remained associated with adolescent SUD diagnoses, and three variables emerged as significant: being a parent (significant only for participants without adult SUD), being currently married, and having decreased life satisfaction (significant only for participants with adult SUD). The authors do not postulate a causal relationship between adolescent SUD and these numerous functioning difficulties at age 30; some appear to be related to recurrent SUD, comorbid adolescent disorders, or functioning problems already evident in adolescence. Moreover, either pre-existing conditions or the neurotoxic effects of drugs in adolescence could contribute to the subsequent educational and employment problems observed. Nonetheless, further explication of these relationships may point to opportunities for intervention with substance-abusing adolescents and young adults. Rohde, P., Lewinsohn, P., Seeley, J., Klein, D., Andrews, J., and Small, J. Psychosocial Functioning of Adults Who Experienced Substance Use Disorders as Adolescents. Psychol. Addict. Behav., 21(2), pp. 155-164, 2007.

Developmental Trajectory Classes for SUD

This study sought to explicate factors underlying the tendency for neurobehavioral disinhibition to predict substance use disorders. Data were drawn from a longitudinal study of boys from ages 10-12 to 22 years studied by the Center for Education and Drug Abuse Research. Neurobehavior disinhibition, parental SUD, socioeconomic status, and affiliation with deviant peers were measured at baseline. Approval of socially non-normative behavior was measured at ages 10-12, 12-14, 16, and 19 years. Three trajectory classes culminating in substance use disorder (SUD) were discerned. Two high-risk trajectories, indicated by increasing approval of antisociality and progressive social maladjustment during adolescence (SUD rate = 72.7%) and stable high level of disturbance (SUD rate = 85%), were identified. Individual characteristics (neurobehavior disinhibition) in conjunction with contextual factors (low socioeconomic status, parental SUD, affiliation with deviant friends) promote approval of antisociality during adolescence and a high rate of SUD by young adulthood. Kirisci, L., Tarter, R., Mezzich, A., and Vanyukov, M. Developmental Trajectory Classes in Substance Use Disorder Etiology. Psychol. Addict. Behav. 21(3), pp. 287-296, 2007.

Self-Medication in Individuals with ADHD

Studies report increased rates of cigarette and substance use in youths with Attention-Deficit/Hyperactivity Disorder (ADHD), though the mechanism of risk remains unclear. The present study tests the hypothesis that ADHD individuals "self-medicate" with cigarettes and substances of abuse. As part of five- and ten-year case-control longitudinal family studies of ADHD, responses to the Drug Use Screening Inventory (DUSI) were examined for evidence of self-medication. DUSI data were obtained from 90 ADHD probands (58% male) and 96 control probands (52% male), all between ages 15 and 25. Thirty-six percent of subjects reported self-medication, 25% used to get high, and 39% had unknown motivation. No significant differences were found between ADHD

and controls in motivation. ADHD symptoms did not differ between self-medicators and subjects using to get high. DUSI problem scores were higher in ADHD (versus controls), those using to get high (versus self-medicators), and subjects using alcohol (versus other substances). More than one-third of adolescents and young adults endorsed using cigarettes and substances for self medication. The authors urge more studies to clarify the role of self-medication in substance use disorders. Wilens, T., Adamson, J., Sgambati, S., Whitley, J., Santry, A., Monuteaux, M., and Biederman, J. Do Individuals with ADHD Self-Medicate with Cigarettes and Substances of Abuse? Results from a Controlled Family Study of ADHD. Am. J. Addict., 16 Suppl 1, pp. 14-21, 2007.

State Anti-Tobacco Advertising and Smoking Outcomes by Gender and Race/Ethnicity

Investigators examined overall and gender- and racial/ethnic-specific relationships between exposure to state-sponsored anti-tobacco televised advertising and smoking-related outcomes among US middle and high school students using five years of cross-sectional nationally representative data. Nationally representative 8th, 10th, and 12th grade student sample data for 1999-2003 were merged with commercial ratings data on mean potential audience exposure to network and cable television anti-tobacco advertising across the 74 largest US designated market areas, resulting in a final sample size for analysis of 122,340. Associations between state-sponsored anti-tobacco televised advertising exposure and youth smoking-related beliefs and behaviors' were modeled while controlling for relevant individual and environmental factors as well as other televised tobacco-related advertising. Authors found higher potential for exposure to state anti-tobacco advertising within the previous four months was generally associated with decreasing odds of current smoking across groups. In addition, such exposure was related, to varying degrees, with decreased perceptions that most/all friends smoked, stronger five-year intentions not to smoke, and increased perceived harm of smoking. These relationships appeared possibly to be weaker for Asian students. The results from these analyses indicate that state anti-tobacco advertising significantly relates to beneficial outcomes -- especially regarding current smoking behaviour -- among US youth as a whole. Terry-McElrath, Y., Wakefield, M., Emery, S., Saffer, H., Szczypka, G., O 'Malley, P., Johnston, L., Chaloupka, F., and Flay, B. State Anti-tobacco Advertising and Smoking Outcomes by Gender and Race/ethnicity. Ethn. Health, 12(4), pp. 339-362, 2007.

Case Ascertainment of Alcohol Dependence in General Population Surveys

Similar to their report on case ascertainment of cannabis dependence, the authors focus this analysis on alcohol dependence, and issues surrounding methods of classification, making use of data from the cross-sectional US National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a household survey with 44,093 adult participants. NESARC alcohol dependence assessments were ''ungated '', but allowed simulation of a ''gated '' approach; the end result was a robust decrement in the estimated prevalence of this condition. Nonetheless, patterns of association linking suspected background characteristics to prevalence of alcohol dependence were not appreciably different when the gated and ungated estimates were contrasted. Authors concluded while there are reasons to take the ungated approach in detailed research on alcohol use and dependence, in panoramic mental health surveys the inefficiency of an ungated approach must be balanced against the anticipated yield of cases who have experienced alcohol dependence without alcohol related social role impairments or other maladaptation, particularly when the dependence syndromes without these consequences are sometimes thought to lack clinical significance. Degenhardt, L., Bohnert, K., and Anthony,

J. Case as Certainment of Alcohol Dependence in General Population Surveys: 'Gated ' Versus 'Ungated ' Approaches. Int. J. Methods Psychiatr. Res., 16(3), pp. 111-123, 2007.

Nationwide Increase in the Number of Hospitalizations for Illicit Injection Drug Use-Related Infective Endocarditis

Infective endocarditis is a potentially fatal consequence of illicit injection drug use. Researchers examined survey data and estimated that the number of hospitalizations for injection drug use-related infective endocarditis increased by 38%-66% in the United States between 2000-2001 and 2002-2003, a period during which the number of at-risk persons (i.e., injection drug users) remained stable. They interpret these findings to suggest that increasing methamphetamine use and/or drug injection frequency may have increased the incidence of infective endocarditis among active injection drug users. Cooper, H., Brady, J., Ciccarone, D., Tempalski, B., Gostnell, K., and Friedman, S. Nationwide Increase in the Number of Hospitalizations for Illicit Injection Drug Use-Related Infective Endocarditis. Clin. Infect. Dis., 45(9), pp. 1200-1203, 2007.

Perceptions of Financial Payment for Research Participation among African-American Drug Users in HIV Studies

Financial compensation for participating in research is controversial, especially when participants are recruited from economically disadvantaged and/or marginalized populations such as drug users. Little is known about these participants' own views regarding payment for research participation. The objective of the study was to elicit underserved minority drug users' views about monetary payments for participating in research. Semi-structured in-depth interviews about motivations for and perceptions of participation in research were conducted among 37 adult, economically disadvantaged African-American crack cocaine smokers. Participants were recruited from among those taking part in three HIV prevention studies. Interviews were conducted at one of 2 research field offices located in underserved minority neighborhoods in Houston, Texas. Interviews lasting 30-45 min were recorded, transcribed, coded, and analyzed for categories and themes using both conventional and directed qualitative content analysis. The study found that participants viewed monetary payment for research as essential to attract participation and desirable to provide optional income. Payment for research participation was perceived as one potential income source among others. Participants considered self-determination a prerogative for themselves and others. They rejected the notion of payment for participation as encouraging drug use or as inducing risk taking. Researchers should be aware of participants' views of their desires and capacity for autonomous decisions about financial compensation for research. Payment for research participation appears to be part of the "informal economy" that has been observed in underserved communities. Slomka, J., McCurdy, S., Ratliff, E., Timpson, S., and Williams, M. Perceptions of Financial Payment for Research Participation among African-American Drug Users in HIV Studies. J. Gen. Intern. Med., 22(10), pp. 1403-1409, 2007.

Gender Differences in Social Network Influence among Injection Drug Users: Perceived Norms and Needle Sharing

Whereas substantial research has linked perceived norms and HIV sexual risk behavior, less attention has been given to the relationship between perceived norms and injection drug practices. This study investigated the relationship between needle sharing and perceived norms in a sample of injection drug users. Data were collected through face-to-face interviews with 684 injectors from the STEP Into Action (STEP) project in Baltimore, Maryland. Logistic

regression was used to assess the associations between perceived norms (descriptive and injunctive norms) and needle sharing. Results were stratified by gender. Descriptive norms were significantly related to needle sharing among males (AOR = 1.58, 95%CI = 1.20-2.40) and females (AOR = 1.78; 95%CI = 1.24-2.55). Whereas injunctive norms were significantly associated with needle sharing among men (AOR = 1.30 95%CI = 1.05-1.61), this association was not significant among women (AOR = 0.99; 95%CI = 0.74-1.31). These findings suggest the utility of peer education interventions that promote norms regarding risk reduction among injection drug users. The data also provide support for gender-specific HIV prevention interventions. Davey-Rothwell, M., and Latkin, C. Gender Differences in Social Network Influence among Injection Drug Users: Perceived Norms and Needle Sharing. J. Urban Health, 84(5), pp. 691-703, 2007.

HCV Synthesis Project: Preliminary Analyses of HCV Prevalence in Relation to Age and Duration of Injection

Early acquisition of hepatitis C virus (HCV) infection appears to affect a substantial proportion of IDUs--between 20 percent and 90 percent. Analyzing the range of HCV prevalence estimates in new injectors may help identify factors that can be modified to reduce HCV transmission. The HCV Synthesis Project is a meta-analysis of studies of HCV epidemiology and prevention in drug users worldwide. In this preliminary analysis, researchers examined data from 127 studies of IDUs that reported HCV prevalence in relation to age or year since onset of drug injection, analyzing heterogeneity and calculating summary statistics where appropriate. Six studies reported gender-specific HCV prevalence rates among young or new injectors; the group mean prevalence was 47 percent for men and 44 percent for women (NS). Group mean age for HCV-negatives was 24.7 years (range 24-28) and 26.1 years (range 21-31) for HCV-positives (n=8 studies). Data were examined from 13 studies that compared HCV prevalence among young injectors to older injectors using 5-year age categories; substantial variation was present within these categories such that measures of central tendency were not calculated. Similarly, among studies reporting HCV prevalence among IDUs in relation to 1-year intervals of duration of injection (<1 year, <2 years, and <3 years), considerable variability was observed. Notably, there were studies in each category that reported prevalence of 70 percent or higher among recent-onset drug injectors. These findings confirm previous studies reporting high risk of acquiring HCV shortly after onset of injection; thus, HCV prevention programmes must emphasize methods to reach new injectors. Future research should (1) report data on time to infection in depth, (2) provide detailed information on study methodology, and (3) characterize the research setting with respect to underlying factors that affect injection practices and networks. This will permit synthesis of a greater number of studies and may lead to the identification of factors that impede HCV transmission. Hagan, H., Des Jarlais, D., Stern, R., Lelutiu-Weinberger, C., Scheinmann, R., Strauss, S., and Flom, P. HCV Synthesis Project: Preliminary Analyses of HCV Prevalence in Relation to Age and Duration of Injection. Int. J. Drug Policy, 18(5), pp. 341-351, 2007.

Developing the Diagnostic and Statistical Manual V: Statistics and Nosology

This report describes the developments resulting from a Launch and Methodology Conference hosted by the American Psychiatric Institute for Research and Education (APIRE) to discuss the role statistics might play in the eventual revision of the Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the Ninth Edition of the International Classification of Diseases (ICD9). The conference consisted of talks on specific topics by statisticians and epidemiologists from North America and Great Britain, followed by group discussion by experts in nosology and

psychopathology. Specific themes related to the future interaction between statisticians and nosologists in DSM-V development arose as a result of that meeting, such as (1) the nature of the statistician/nosologist interaction; (2) specific areas of concern in that interaction, and (3) the use of novel and complex statistical methods to challenge and inspire new avenues of thinking among nosologists. Both disciplines are recognized for their expertise and necessity in this process of attempting to accurately capture the nature of disorder, and respond to the needs and experience of clinicians and patients, and authors note that communication between nosologists and statisticians should start early and continue throughout the revision process. Kraemer, H., Shrout, P., and Rubio-Stipec, M. Developing The Diagnostic and Statistical Manual V: What Will. Soc. Psychiatry Psychiatr. Epidemiol., 42(4), pp. 259-267, 2007.

Rate of Methadone Use among Aboriginal Opioid Injection Drug Users

Previous studies have shown elevated rates of health-related harms among Aboriginal people who use injection drugs such as heroin. Methadone maintenance therapy is a potentially effective intervention to address the harms of heroin injection. This study assessed the rate of methadone use in a cohort of opioid injection drug users in Vancouver and investigated whether methadone use was associated with Aboriginal ethnic background. Using data collected as part of the Vancouver Injection Drug Users Study (May 1996-November 2005), researchers evaluated whether Aboriginal ethnic background was associated with methadone use using generalized estimating equations and Cox regression analysis. They compared methadone use among Aboriginal and non-Aboriginal injection drug users at the time of enrollment and during the follow-up period, and evaluated the time to first methadone use among people not using methadone at enrollment. During the study period, 1603 injection drug users (435 Aboriginal, 1168 non-Aboriginal) were recruited. At enrollment, 54 (12.4%) Aboriginal participants used methadone compared with 247 (21.2%) non-Aboriginal participants (odds ratio [OR] 0.53, 95% confidence interval [CI] 0.38-0.73, $p < 0.001$). Among the 1351 (84.3%) participants who used heroin, Aboriginal people were less likely to use methadone throughout the follow-up period (adjusted OR 0.60, 95% CI 0.45-0.81, $p < 0.001$). Among people using heroin but who were not taking methadone at enrollment, Aboriginal ethnic background was associated with increased time to first methadone use (adjusted relative hazard 0.60, 95% CI 0.49-0.74, $p < 0.001$). Methadone use was lower among Aboriginal than among non-Aboriginal injection drug users. Culturally appropriate interventions with full participation of the affected community are required to address this disparity. Wood, E., Montaner, J., Li, K., Barney, L., Tyndall, M., and Kerr, T. Rate of Methadone Use Among Aboriginal Opioid Injection Drug Users. CMAJ, 177(1), pp. 37-40, 2007.

Attention-Deficit Hyperactivity Disorder Moderates the Life Stress Pathway to Alcohol Problems in Children of Alcoholics

Parent alcoholism is a well-established risk factor for the development of pathological alcohol involvement in youth, and life stress is considered to be one of the central mechanisms of the parent alcoholism effect; however, little is known about the moderators of the life stress pathway. Attention-deficit hyperactivity disorder (ADHD) has also been shown to predict pathological alcohol involvement, however, little is known about whether or not ADHD interacts with parent alcoholism to increase offspring risk. The goals of this study were to examine stressful life events as mediators of the relationship between parent alcoholism and adolescent pathological alcohol involvement, and to examine whether or not this mediated pathway was stronger for adolescents with ADHD than for adolescents without ADHD. Participants were

142 adolescents with a childhood ADHD diagnosis (probands) and 100 demographically matched control adolescents without childhood ADHD. Probands, controls, and at least 1 parent were interviewed about drinking behavior; probands and controls were interviewed about negative life events. A moderated mediation paradigm was used to test the hypotheses using ordinary least squares regression. Results showed that the relationships between parent alcoholism and 2 of the stress variables ("family" stress and "peer" stress) were significant for probands only, and that stress in the probands mediated the parent alcoholism effect on offspring alcohol involvement. These results provide preliminary support for the hypothesis that offspring characteristics might moderate the life stress pathway to alcoholism, and indicate that ADHD may serve to facilitate the transmission of pathological alcohol use from parent to child. Marshal, M., Molina, B., Pelham, W., and Cheong, J. Attention-Deficit Hyperactivity Disorder Moderates the Life Stress Pathway to Alcohol Problems in Children of Alcoholics. Alcohol Clin. Exp. Res., 31(4), pp. 564-574, 2007.

Childhood Neurobehavior Disinhibition Amplifies the Risk of Substance Use Disorder: Interaction of Parental History and Prenatal Alcohol Exposure

Authors examined the influence of parental substance use disorder (SUD) and mother ''s alcohol consumption during pregnancy on neurobehavior disinhibition (ND) measured in 284 10- to 12-year-old boys. The extent to which ND predicted SUD outcome 7 to 9 years later was also determined. SUD was documented in each parent and as the outcome variable in their 19-year-old sons. Average daily alcohol consumption during the mother's pregnancy was recorded using a structured interview. ND was assessed using indicators of behavior under control, affect modulation and executive cognitive functions. Authors found paternal SUD and the interaction between maternal SUD and alcohol consumption during pregnancy predicted child's ND score. ND at 10 to 12 years of age was a significant predictor of SUD at age 19. Authors concluded that the disinhibitory disturbance associated with risk of SUD has both transmissible and teratogenic causes. Chapman, K., Tarter, R., Kirisci, L., and Cornelius, M. Childhood Neurobehavior Disinhibition Amplifies the Risk of Substance Use Disorder: Interaction of Parental History and Prenatal Alcohol Exposure. J. Dev. Behav. Pediatr., 28(3), pp. 219-224, 2007.

Modeling the Pathways Linking Childhood Hyperactivity and Substance Use Disorder in Young Adulthood

Authors modeled direct and mediated pathways linking childhood hyperactivity and substance use disorder (SUD). Boys (n = 112) were administered the revised Drug Use Screening Inventory at age 12-14 years and the Structured Clinical Interview for DSM-IV at age 22 years. Six newly derived scales having established heritability were conceptually organized into internalizing and externalizing pathways to SUD emanating from childhood hyperactivity. Authors found hyperactivity directly predicts SUD. Neuroticism, conduct problems, and their respective manifestations of social withdrawal and school problems mediated the association between hyperactivity and SUD. Hyperactivity also predicted neuroticism that, in turn, predicted low self-esteem leading to social withdrawal and SUD. These results indicate that hyperactivity is a diathesis for both internalizing and externalizing disturbances that, in turn, portend differential expression of psychosocial maladjustment presaging SUD. Tarter, R., Kirisci, L., Feske, U., and Vanyukov, M. Modeling the Pathways Linking Childhood Hyperactivity and Substance Use Disorder in Young Adulthood. Psychol. Addict. Behav., 21(2), pp. 266-271, 2007.

Impact of Prenatal Cocaine Exposure on Attention and Response Inhibition

Authors examined the influence of prenatal cocaine exposure on attention and response inhibition measured by continuous performance tests (CPTs) at ages 5 and 7 years. The baseline sample consisted of 253 cocaine-exposed and 223 non-cocaine-exposed children enrolled prospectively at birth and assessed comprehensively through age 7 years in the longitudinal Miami Prenatal Cocaine Study. This report includes a sub sample of 415 children (219 cocaine-exposed, 196 non-cocaine-exposed) who completed at least one CPT assessment at ages 5 and/or 7 years. Prenatal cocaine exposure was measured by maternal self-report and maternal and infant bioassays. Deficits in attention and response inhibition are estimated in relation to prenatal cocaine exposure using generalized estimating equations within the general linear model. Results indicate cocaine-associated increases in omission errors at ages 5 and 7 as well as increases in response times for target tasks (i.e., slower reaction times) and decreased consistency in performance at age 7. There were no demonstrable cocaine-associated deficits in commission errors. Estimates did not change markedly with statistical adjustment for selected prenatal and postnatal covariates. Evidence supports cocaine-associated deficits in attention processing through age 7 years. Accornero, V., Amado, A., Morrow, C., Xue, L., Anthony, J., and Bandstra, E. Impact of Prenatal Cocaine Exposure on Attention and Response Inhibition as Assessed by Continuous Performance Tests. J. Dev. Behav. Pediatr., 28(3), pp. 195-205, 2007.

Building Path Diagrams for Multilevel Models

The authors propose a path diagramming approach for multilevel models that seeks to provide a formal structure for deriving the underlying equations as well as provide a mechanism for clearly and efficiently communicating the model structure, assumptions, and empirical results. The authors begin with a description of the core components of their proposed diagramming system and establish tracing rules for the direct derivation of model equations, then demonstrate their approach using several published empirical multilevel applications. The authors conclude that these path diagrams can be expanded logically to incorporate cross-classified structures, multivariate models for multiple outcome variables, and multilevel models with mediating pathways as areas for future research. Curran, P., and Bauer, D. Building Path Diagrams for Multilevel Models. Psychol. Methods, 12(3), pp. 283-297, 2007.

Interval and Clinical Cohort Studies: Epidemiological Issues

Cohort studies based upon clinic populations and medical records are becoming more abundant due in part to an increasing trend toward electronic medical records and advancement in information technology. This design has been utilized in the HIV setting to great success and involves following individuals as they access medical care. These clinical cohort designs have not been compared to the classic interval cohort design in which individuals are followed at specified intervals that are unrelated to the participants' ongoing health care. The interval and clinical cohort designs are distinguished and the advantages and disadvantages inherent in each design are discussed. Lau, B., Gange, S., and Moore, R. Interval and Clinical Cohort Studies: Epidemiological Issues. AIDS Res. Hum. Retroviruses, 23(6), pp. 769-776, 2007.

Club Drug Use in Los Angeles among Young Men Who have Sex with Men

Little is known about young men who have sex with men and their use of club drugs and the risk factors associated with such use. A structured survey was administered in 2005 to 496 young men who were 18-22 years old (40% were 18-19 years old); self-identified as with a same-sex sexuality (83%), bisexual (16%), and/or had had sex with a man (97%); Caucasian (35%), African

American (24%), and Latino of Mexican descent (40%). Subjects were recruited from gay-identified venues in Los Angeles, California, using a venue-based probability sampling design. Descriptive statistics revealed a high prevalence of drug and club drug use. Regression analyses revealed risk factors associated with recent club drug use, including place of residence, religiosity, disclosure of sexuality to family, frequency of attendance at bars/clubs, and involvement in sexual exchange and street economy. Limitations and implications of this research are discussed. Kipke, M., Weiss, G., Ramirez, M., Dorey, F., Ritt-Olson, A., Iverson, E., and Ford, W. Club Drug Use in Los Angeles among Young Men Who have Sex with Men. Subst. Use Misuse, 42(11), pp. 1723-1743, 2007.

Impact of Social Network Characteristics on High-Risk Sexual Behaviors among Non-injection Drug Users

Sexually active non-injection drug users in New York City and their sexual partners or fellow drug users (N = 264) were recruited from 2002 to 2005, and associations between social network characteristics, sexual risk behaviors and sexual practices, and drug use were examined. Results suggest having a drug-centered social network, i.e., a network that includes a high proportion of individuals who provide, receive, or use drugs, increases the risk of engaging in high-risk sexual behaviors. The study's limitations are noted and longitudinal studies are needed to ascertain whether these associations are causal. Pilowsky, D., Hoover, D., Hadden, B., Fuller, C., Ompad, D., Andrews, H., de Leon, C., Hoepner, L., Xia, Q., and Latkin, C. Impact of Social Network Characteristics on High-Risk Sexual Behaviors among Non-injection Drug Users. Subst. Use Misuse, 42(11), pp. 1629-1649, 2007.

Harm Reduction Theory: Users' Culture, Micro-Social Indigenous Harm Reduction, and the Self-Organization and Outside-Organizing of Users' Groups

This paper discusses the user side of harm reduction, focusing to some extent on the early responses to the HIV/AIDS epidemic in each of four sets of localities-New York City, Rotterdam, Buenos Aires, and sites in Central Asia. Using available qualitative and quantitative information, researchers present a series of vignettes about user activities in four different localities regarding reducing drug-related harm. Some of these activities have been micro-social (small group) activities; others have been conducted by formal organizations of users that the users organized at their own initiative. In spite of the limitations of the methodology, the data suggest that users' activities have helped limit HIV spread. These activities are shaped by broader social contexts, such as the extent to which drug scenes are integrated with broader social networks and the way the political and economic systems impinge on drug users' lives. Drug users are active agents in their own individual networks, and potentially in helping to protect wider communities. Researchers and policy makers can work together to help develop ways to enable and support both micro-social and formally organized action by users. Friedman, S., deJong, W., Rossi, D., Touze, G., Rockwell, R., Des Jarlais, D., and Elovich, R. Harm Reduction Theory:Users' Culture, Micro-Social Indigenous Harm Reduction, and the Self-Organization and Outside-Organizing of Users' Groups. Int. J. Drug Policy, 18, pp. 107-117, 2007.

Three Types of Adherence to HIV Antiretroviral Therapy and their Association with AIDS Diagnosis, Medication Side-effects, Beliefs about Antiretroviral Therapy, and Beliefs about HIV Disease

One hundred and ninety-three adults with HIV taking antiretroviral therapy completed a questionnaire on demographics, health beliefs, medication side-

effects, and adherence to dose, schedule, and dietary instructions. Three health beliefs indices were identified: antiretroviral therapy (ART) benefits, ART adherence self-efficacy, and beliefs about future HIV-related health concerns. Patients who experienced medication side-effects reported strong beliefs that HIV infection would cause them future health problems or distrust in the benefits of ART. AIDS diagnosis obtained through medical records or medication side-effects were not related to any of the three types of adherence. Beliefs about future HIV-related health concerns were associated with suboptimal dose adherence. Beliefs about ART benefits were associated with suboptimal schedule and dietary instructions adherence. Older age and partner were protective factors of schedule adherence. Data suggest that health beliefs may vary across type of adherence and that adherence behaviours may be a coping strategy to adjust antiretroviral therapy to one's daily living. Schoennesson, L., Williams, M., Ross, M., Diamond, P., and Keel, B. Three Types of Adherence to HIV Antiretroviral Therapy and their Association with AIDS Diagnosis, Medication Side-effects, Beliefs about Antiretroviral Therapy, and Beliefs about HIV Disease. Int. J. STD AIDS, 18(6), pp. 369-373, 2007.

HIV-Related Communication and Perceived Norms: An Analysis of the Connection among Injection Drug Users

Although research has consistently shown a link between perceived norms and HIV risk behaviors, research examining interpersonal variables that may contribute to perceived norms is sparse. Verbal communication is an important mechanism for establishing, altering, and maintaining norms. In this study researchers assessed the association between HIV-related communication and perceived norms. Baseline data from 684 drug injectors enrolled in the STEP into Action (STEP) study were analyzed. Multivariate results revealed that injection drug users who talked to their drug partners about HIV were less likely to perceive that they engaged in risky injection behavior (beta = -1.53, SE = 0.29, $p < .001$). Exchanging sex for money or drugs (beta = 15.83, SE = 7.02, $p = .024$), going to a shooting gallery (beta = 17.03, SE = 6.79, $p = .013$), and having an IDU sex partner (beta = 15.34, SE = 6.58, $p = .020$) were associated with the belief that peers practiced risky drug behaviors. These findings may be used to develop peer education HIV prevention interventions for drug users. Davey-Rothwell, M., and Latkin, C. HIV-Related Communication and Perceived Norms: An Analysis of the Connection among Injection Drug Users. AIDS Educ. Prev., 19(4), pp. 298-309, 2007.

Injection Drug Users' Strategies to Manage Perceptions of Personal Risk: How do IDUs See HIV as Having Affected Them?

The U.S. public health community is in its 3rd decade of seeking to prevent and treat HIV/AIDS. Injection drug users (IDUs) are central to targeted HIV prevention interventions as approximately one third of new U.S. infections are attributable to injection drug use. Targeted behavior change efforts are often explicitly built upon the risk perception of targeted individuals. In this article, researchers consider the efficacy of behavior change based on IDUs' perceptions of elevated risk. Their qualitative analysis of 28 interviews with HIV negative IDUs' in inner city Baltimore suggests that participants did not see themselves as personally affected by HIV. Rather, respondents constructed accounts in which they differentiated themselves from the type of people who are so affected, thereby creating a less stigmatizing identity. These findings suggest that effective HIV prevention should explicitly acknowledge and address the stigmatized IDU identity, rather than assuming readiness for behavior change. Smith, K., Lillie, T., and Latkin, C. Injection Drug Users' Strategies to Manage Perceptions of Personal Risk: How Do IDUs See HIV as Having Affected Them? AIDS Educ. Prev., 19(3), pp. 245-257, 2007.

Nonmedical Use of Prescription Stimulants and Drug-Related Problems Among College Students

This college-based study compared nonmedical users of prescription stimulants to other types of drug users regarding drug use related problems. A Web survey was self-administered in 2005 by a probability sample of 3,639 full-time undergraduate students (68% response rate) at a large public Midwestern 4-year university in the United States. The survey consisted of measures to assess substance use and misuse, including a modified version of the Drug Abuse Screening Test (DAST-10). Nonmedical users of prescription stimulants were more likely than other drug users to report polydrug use. Nonmedical users of prescription stimulants had over four times greater odds than other drug users to experience three or more DAST-10 items in the past 12 months (AOR=4.61, 95% CI=3.28-6.48). Among nonmedical users of prescription stimulants, those who used prescription stimulants via intranasal and other non-oral routes of administration had greater odds than oral only users to experience three or more DAST-10 items in the past 12 months. The investigators conclude that study findings suggest that the majority of nonmedical users of prescription stimulants are polydrug users and should be screened for potential drug abuse or dependence, especially those who report non-oral routes of administration. McCabe, S., and Teter, C. Drug Use Related Problems Among Nonmedical Users of Prescription Stimulants: A Web-based Survey of College Students from a Midwestern University. Drug Alcohol Depend., 91(1), pp. 69-76, 2007.

Trends in Non-medical Use of Anabolic Steroids by U.S. College Students

This study assessed the prevalence, trends, and student- and college-level characteristics associated with the non-medical use of anabolic steroids (NMAS) among U.S. college students. Data were collected through self-administered mail surveys, from 15,282, 14,428, 13,953, and 10,904 randomly selected college students at the same 119 nationally representative colleges in 1993, 1997, 1999 and 2001, respectively. The prevalence of lifetime, past-year and past-month NMAS was 1% or less and generally did not change significantly between 1993 and 2001, with one exception: past-year NMAS increased significantly among men from 1993 (0.36%) to 2001 (0.90%). Multiple logistic regression analyses revealed that lifetime and past-year NMAS were associated with student-level characteristics such as being male and participation in intercollegiate athletics. Lifetime and past-year NMAS were also positively associated with several risky behaviors, including cigarette smoking, illicit drug use, drinking and driving, and DSM-IV alcohol use disorders. Nearly 7 out of every 10 lifetime non-medical users of anabolic steroids met past-year criteria for a DSM-IV alcohol use disorder. Although the overall prevalence of NMAS remained low between 1993 and 2001, findings suggest that continued monitoring is necessary because male student-athletes are at heightened risk for NMAS and this behavior is associated with a wide range of risky health behaviors. The characteristics associated with NMAS have important implications for future practice and research. McCabe, S., Brower, K., West, B., Nelson, T., and Wechsler, H. Trends in Non-medical Use of Anabolic Steroids by U.S. College Students: Results from Four National Surveys. Drug Alcohol Depend., 90(2-3), pp. 243-251, 2007.

Exploring Wine Shops as a Venue for HIV Prevention in Urban India

Addressing male heterosexual risk is a high priority for HIV prevention efforts in India. Particularly in urban India, which draws men for employment opportunities, these efforts are gaining momentum with a focus on

understanding possible risk facilitators such as alcohol use. However, little is known about venues where such efforts might be targeted. Researchers explored community-based alcohol outlets or "wine shops" in Chennai, India, as potential venues. They conducted ethnographic research with wine shop staff and clients to understand alcohol use and sexual behaviors and surveyed 118 wine shop patrons to quantify these risk behaviors and plan an appropriate intervention. Results show that wine shops are a venue where social and sexual networks converge; reports and observations of regular and heavy drinking were frequent. Over 50% of patrons surveyed reported three or more sexual partners in the past 3 months, and 71% of all patrons reported a history of exchanging sex for money. Condom use history was low overall but, in the adjusted analyses, was significantly higher (OR = 20.1) among those who reported that their most recent partner was a sex worker and lower (OR = 0.28) among those who reported they drank to feel disinhibited. The data suggest that wine shops may be an appropriate location to target men for HIV prevention interventions. The researchers include discussion of how these findings helped design such an intervention in Chennai. Sivaram, S., Johnson, S., Bentley, M., Srikrishnan, A., Latkin, C., Go, V., Solomon, S., and Celentano, D. Exploring Wine Shops as a Venue for HIV Prevention in Urban India . J. Urban Health, 84(4), pp. 563-576, 2007.

Initiation into Methamphetamine Use for Young Gay and Bisexual Men

Research over the past 10 years has suggested that methamphetamine use has become a significant problem and is associated with risky sexual behaviors among gay and bisexual men. In order to better understand initiation into methamphetamine use among gay and bisexual men, qualitative analyses were performed on a sample of young gay and bisexual men (ages 18-29) in New York City. Participants were recruited as part of a larger study which used time-space sampling to enroll club-going young adults who indicated recent club drug (ecstasy, ketamine, GHB, methamphetamine, cocaine, and/or LSD) use. The data for this paper are derived from the qualitative interviews of 54 gay and bisexual male methamphetamine users. At initiation (1) methamphetamine was used in a social, non-sexual setting for a majority of the participants; (2) participants expressed limited knowledge of methamphetamine; and (3) many participants used cocaine as a basis for comparison when describing various effects of the drug. These study findings have implications for prevention approaches. The understanding that at initiation methamphetamine was not solely used as a sexual enhancement for members of this community may enable health workers to more accurately target potential users when putting forth intervention efforts. The investigators recommend that future research should (1) aim to gain a better understanding of the role that methamphetamine plays in non-sexual contexts, particularly among gay and bisexual men who may not be part of the club "scene;" and, (2) explore the relationship between attitudes towards methamphetamine and other drugs, particularly cocaine, among gay and bisexual men. Parsons, J., Kelly, B., and Weiser, J. Initiation into Methamphetamine Use for Young Gay and Bisexual Men. Drug Alcohol Depend., 90(2-3), pp. 135-144, 2007.

Director's Report to the National Advisory Council on Drug Abuse - February, 2008

Research Findings - Prevention Research

Effects of a Nurse Visiting Program With African American Mothers and Infants On Age 9 Outcomes

This study examined the effect of prenatal and infancy home visits by nurses on mothers' fertility and children's functioning 7 years after the program ended at child age 2. A randomized, controlled trial in a public system of obstetric and pediatric care was conducted. A total of 743 primarily black women <29 weeks gestation, with previous live births and at least 2 socio-demographic risk characteristics (unmarried, <12 years of education, unemployed), were randomly assigned to receive nurse home visits or comparison services. Primary outcomes consisted of intervals between births of first and second children and number of children born per year; mothers' stability of relationships with partners and relationships with the biological father of the child; mothers' use of welfare, food stamps, and Medicaid; mothers' use of substances; mothers' arrests and incarcerations; and children's academic achievement, school conduct, and mental disorders. Secondary outcomes were the sequealae of subsequent pregnancies, women's employment, experience of domestic violence, and children's mortality. Nurse-visited women had longer intervals between births of first and second children, fewer cumulative subsequent births/year, and longer relationships with current partners. From birth through child age 9, nurse-visited women used welfare and food stamps for fewer months. Nurse-visited children born to mothers with low psychological resources, compared with control-group counterparts, had better grade-point averages and achievement test scores in math and reading in grades 1-3. Nurse-visited children, as a trend, were less likely to die from birth through age 9, an effect accounted for by deaths that were attributable to potentially preventable causes. By child age 9, the program reduced women's rates of subsequent births, increased the intervals between the births of first and second children, increased the stability of their relationships with partners, facilitated children's academic adjustment to elementary school, and seems to have reduced childhood mortality from preventable causes. Olds, D., Kitzman, H., Hanks, C., Cole, R., Anson, E., Sidora-Arcoleo, K. et al. Effects of Nurse Home Visiting on Maternal and Child Functioning: Age-9 Follow-up of a Randomized Trial. Pediatrics, 120(4), pp. e832-e845, 2007.

Long Term Follow up of Brief Intervention for Mandated College Students

It is known that brief interventions for mandated college students decrease alcohol use and/or related problems in the short term. However, none of the existing studies has followed students past 6 months. Therefore, this study compared the long-term efficacy of 2 brief substance use feedback interventions for mandated college students. The study followed up mandated

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students (n = 348) who were randomly assigned to either a brief motivational interview (BMI; n = 180) or a written feedback-only (WF; n = 168) intervention at 4 months and 15 months post intervention. Long-term follow-up data revealed that students, at the aggregate level, decreased their peak blood alcohol concentration (BAC) levels, number of drinks per week, and number of alcohol related problems at 15 months post intervention compared with their baseline levels. With the exception of peak BAC, the observed long-term reduction was mainly due to the positive change among students who received the BMI intervention. Students in the BMI intervention showed significantly lower levels of alcohol-related problems at 15 months than those in the WF intervention. The BMI intervention more effectively reduced within-individual alcohol-related problems during the initial 4 months, and more successfully curbed the subsequent increase in alcohol use frequency and number of drinks per week during the 11 months between the 2 follow-up assessments. These results suggest that brief substance use interventions reduce the riskiest type of alcohol use (e.g., peak BAC) among mandated college students over the long term, and that sleeper effects of in-person personal feedback interventions (PFIs) exist. In-person PFIs in the context of a motivational interview may be more efficacious in the long term than written feedback-only interventions for mandated students. Future studies comparing interventions for college students should extend follow-up for longer periods of time. White, H.R., Mun, E.Y., Pugh, L., and Morgan, T.J. Long-Term Effects of Brief Substance Use Interventions for Mandated College Students: Sleeper Effects of an In-Person Personal Feedback Intervention. Alcohol Clin. Exp. Res., 31(8), pp. 1380-1391, 2007.

Drug Testing Has Little Effect on Student Athletes' Drug Use

This study was designed to assess the effects of random drug and alcohol testing (DAT) among high school athletes. This was a 2-year prospective randomized controlled study of a single cohort among five intervention high schools with a DAT policy and six schools with a deferred policy, serially assessed by voluntary, confidential questionnaires. DAT school athletes were at risk for random testing during the full academic year. Positive test results were reported to parents or guardians, with mandatory counseling. Indices of illicit drug use, with and without alcohol use, were assessed at the beginning and end of each school year for the past month and prior year. Potential mediating variables were evaluated. Student-athletes from intervention and control schools did not differ in past 1-month use of illicit drug or a combination of drug and alcohol use at any of the four follow-up periods. At the end of the initial school year and after 2 full school years, student-athletes at DAT schools reported less drug use during the past year ($p < .01$) compared to athletes at the deferred policy schools. Combining past year drug and alcohol use together, student-athletes at DAT schools reported less use at the second and third follow-up assessments ($p < .05$). Paradoxically, DAT athletes across all assessments reported less athletic competence ($p < .001$), less belief authorities were opposed to drug use ($p < .01$), and indicated greater risk-taking ($p < .05$). At the final assessment, DAT athletes believed less in testing benefits ($p < .05$) and less that testing was a reason not to use drugs ($p < .01$). No DAT deterrent effects were evident for past month use during any of four follow-up periods. Prior-year drug use was reduced in two of four follow-up self-reports, and a combination of drug and alcohol use was reduced at two assessments as well. Overall, drug testing was accompanied by an increase in some risk factors for future substance use. More research is needed before DAT is considered an effective deterrent for school-based athletes. Goldberg, L., Elliot, D.L., MacKinnon, D.P., Moe, E.L., Kuehl, K.S., and Yoon, M. Outcomes of a Prospective Trial of Student-Athlete Drug Testing: The Student Athlete Testing Using Random Notification (SATURN) Study. J. Adolescent Health, 41 pp. 421-429, 2007.

Planned Meetings

Publications

Staff Highlights

Grantee Honors

Factors among Collaborative Community Teams that Influence Prevention Operations

This study examined the longitudinal predictors of quality of functioning of community prevention teams during the "operations" phase of team development. The 14 community teams were involved in a randomized-trial of a university-community partnership project, PROSPER, which implements evidence-based interventions intended to support positive youth development and reduce early substance use, as well as other problem behaviors. The study included a multi-informant approach to measurement of constructs, and included data from 137 team members, 59 human service agency directors and school administrators, 16 school principals, and 8 Prevention Coordinators (i.e. technical assistance providers). How community demographics and social capital, team level characteristics, and team member attributes and attitudes are related to local team functioning across an 18-month period was examined. Findings indicate that community demographics (poverty), social capital, team member attitudes towards prevention, and team members' views of the acceptability of teen alcohol use played a substantial role in predicting various indicators of the quality of team functioning 18 months later. Feinberg, M., Chilenski, S., Greenberg, M., Spoth, R., and Redmond, C. Community and Team Member Factors that Influence the Operations Phase of Local Prevention Teams: The PROSPER Project. Prev. Sci., 8(3), pp. 214-226, 2007.

Peer-led Prevention Programs Can Accelerate Positive or Negative Peer Influences

This study tested whether a social network tailored substance abuse prevention program can reduce substance use among high-risk adolescents without creating deviancy training (iatrogenic effects). A classroom randomized controlled trial comparing control classes with those receiving an evidence-based substance use prevention program [Towards No Drug Abuse (TND)] and TND Network, a peer-led interactive version of TND. Students (n = 541, mean age 16.3 years) in 75 classes from 14 alternative high schools completed surveys before and approximately 1 year after curriculum delivery. Past-month use of tobacco, alcohol, marijuana and cocaine were assessed. Overall, TND Network was effective in reducing substance use. However, the program effect interacted with peer influence and was effective mainly for students who had peer networks that did not use substances. Students with classroom friends who use substances were more likely to increase their use. These results demonstrate that a peer-led interactive substance abuse prevention program can accelerate peer influences. For students with a peer environment that supports non-use, the program was effective and reduced substance use. For students with a peer environment that supports substance use, an interactive program may have deleterious effects. Valente, T., Ritt-Olson, A., Stacy, A., Unger, J., Okamoto, J., and Sussman, S. Peer Acceleration: Effects of a Social Network Tailored Substance Abuse Prevention Program among High-Risk Adolescents. Addiction, 102(11), pp. 1804-1815, 2007.

An Acute Post-Sexual Assault Intervention to Prevent Drug Abuse

Sexual assault and rape routinely produce extreme distress and negative psychological reactions in victims. Further, past research suggests that victims are at increased risk of developing substance use or abuse post-rape. The post-rape forensic medical exam may itself exacerbate peritraumatic distress because it includes cues that may serve as reminders of the assault, thereby potentiating post-assault negative sequelae. To address these problems, a two-part video intervention was developed to take advantage of the existing sexual assault forensic exam infrastructure, and to specifically (a) minimize anxiety/discomfort during forensic examinations, thereby reducing risk of

future emotional problems, and (b) prevent increased substance use and abuse following sexual assault. Updated findings with a sample of 268 sexual assault victims participating in the forensic medical exam and completing one or more follow-up assessments at: (1) less than 3 months post-assault; (2) 3 to 6 months post-assault; or (3) 6 months or longer post-assault indicated that the video was associated with significantly lower frequency of marijuana use at each time point, among women who reported use prior to the assault. Resnick, H.S., Acierno, R., Amstadter, A. B., Self-Brown, S., and Kilpatrick, D.G. An Acute Post-Sexual Assault Intervention to Prevent Drug Abuse: Updated Findings. Addictive Behaviors, 32, pp. 2032-2045, 2007.

Randomized Controlled Evaluation of an Early Intervention to Prevent Post-Rape Psychopathology

A randomized between-group design was used to evaluate the efficacy of a video intervention to reduce post-traumatic stress disorder (PTSD) and other mental health problems, implemented prior to the forensic medical examination conducted within 72 h post-sexual assault. Participants were 140 female victims of sexual assault (68 video/72 non video) aged 15 years or older. Assessments were targeted for 6 weeks (Time 1) and 6 months (Time 2) post-assault. At Time 1, the intervention was associated with lower scores on measures of PTSD and depression among women with a prior rape history relative to scores among women with a prior rape history in the standard care condition. At Time 2, depression scores were also lower among those with a prior rape history who were in the video relative to the standard care condition. Small effects indicating higher PTSD and Beck Anxiety Inventory (BAI) scores among women without a prior rape history in the video condition were observed at Time 1. Accelerated longitudinal growth curve analysis indicated a video X prior rape history interaction for PTSD, yielding four patterns of symptom trajectory over time. Women with a prior rape history in the video condition generally maintained the lowest level of symptoms. Resnick, H., Acierno, R., Waldrop, A., King, L., King, D., Danielson, C., Ruggiero, K., and Kilpatrick, D. Randomized Controlled Evaluation of an Early Intervention to Prevent Post-Rape Psychopathology. Behav. Res. Ther., 45(10), pp. 2432-2447, 2007.

Clinical Trial of Bupropion for Smoking Prevention among Adolescents with ADHD

Since attention-deficit/hyperactivity disorder (ADHD) is a well-documented risk factor for smoking and bupropion has been shown to be effective for smoking cessation, the efficacy of bupropion was tested as a prophylactic agent for the prevention of smoking in children and adolescents with ADHD. A longitudinal, randomized, double-blind, placebo-controlled, parallel-group study was conducted of bupropion at a large, urban, outpatient medical center. Recruitment began in April 1999, and the last subject was followed until September 2004. Patients were nonsmoking youth, of both sexes, between 9 and 18 years of age, with DSM-IV ADHD. After random assignment to either bupropion or placebo, subjects were assessed weekly for 8 weeks, biweekly for 4 weeks, and monthly thereafter for up to 6.5 years (mean 12 months). Also, patients received treatment with psychostimulants for ADHD symptoms as needed. To assess smoking, an assay of cotinine in urine was used. Fifty-seven subjects (28 receiving bupropion and 29 receiving placebo) were randomly assigned and included in the analysis. No differences were found between the bupropion and placebo groups on demographic factors. About half of each group was treated with stimulants for ADHD. Statistical separation between bupropion and placebo in the rate of smoking initiation or continued smoking was not demonstrated. However, secondary post hoc analyses revealed that concurrent stimulant treatment was significantly associated with a lower rate of smoking onset (hazard ratio [HR] = 0.2, 95% CI = 0.08 to 0.89; z = -2.2, p =

.03) and a lower rate of continued smoking (HR = 0.3, 95% CI = 0.11 to 0.85; z = -2.3, p = .02). While bupropion was not associated with a lower rate of smoking in youth with ADHD, post hoc analyses suggest that stimulant treatment was. Future controlled studies should investigate the role of stimulants in the prevention of smoking in children and adolescents with ADHD. Monuteaux, M., Spencer, T., Faraone, S., Wilson, A., and Biederman, J. A Randomized, Placebo-Controlled Clinical Trial of Bupropion for the Prevention of Smoking in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder. J. Clin. Psychiatry, 68(7), pp. 1094-1101, 2007.

ALERT Plus Drug Prevention Curriculum Curbs Drinking and Drug Use Among At-Risk Ninth Grade Girls

In a recently published paper, Ellickson and colleagues found that the Project ALERT school-based drug prevention curriculum administered to youth in seventh and eight grade curbed alcohol misuse and tobacco and marijuana use among youth at the end of the eighth grade. The current research examined the effects among ninth-grade at-risk adolescents who participated in the trial. The current trial involved randomization of school clusters to three groups: the ALERT condition (intervened upon in 7th and 8th grade), the ALERT Plus conduction (received the ALERT condition intervention plus ninth-grade boosters), and the control group. Comparisons between at-risk girls in ALERT Plus schools and at-risk girls in control schools showed the program curbed weekly alcohol and marijuana use, at-risk drinking, alcohol use resulting in negative consequences, and attitudinal and perceptual factors conducive to drug use. Perceived social influences, ability to resist social influences, and beliefs about the consequences of drug use mediated the effects of the ALERT Plus program on drug use. No significant effects emerged for at-risk boys or at-risk adolescents in schools where the basic ALERT curriculum was delivered. Longshore, D., Ellickson, P., McCaffrey, D., and St. Clair, P. School-Based Drug Prevention among At-Risk Adolescents: Effects of ALERT Plus. Health Educ. Behav., 34(4), pp. 651-668, 2007.

Effects of Brief Family Intervention on Parenting Behavior and Mediation of Disruptive Behaviors in Preschoolers

Despite knowledge of early pathways to conduct problems, few preventive interventions are specifically designed to modify disruptive behavior in toddler hood. One potential prevention target is proactive and positive parenting, which is associated with reduced risk of conduct problems in preschoolers. This randomized trial with 120 low-income 2-year-old boys examined whether a brief family-centered intervention that reduces disruptive behavior also leads to increases in proactive and positive parenting. It also explored whether change in parenting predicts change in disruptive behavior. In the intervention group, proactive and positive parenting skills increased among parents of 3-year-olds. Change in proactive and positive parenting of 2- to 3-year-old toddlers correlated with change in child disruptive behavior, although the mediation effect of positive parenting was of only borderline significance. Findings suggest that even within a brief and multifaceted preventive intervention, change in proactive parenting skills contributes modestly but significantly to change in child problem behavior. Gardner, F., Shaw, D., Dishion, T., Burton, J., and Supplee, L. Randomized Prevention Trial for Early Conduct Problems: Effects on Proactive Parenting and Links to Toddler Disruptive Behavior. J. Fam. Psychol., 21(3), pp. 398-406, 2007.

Classroom Teachers Can Implement Evidence-based Prevention Programs with Fidelity

This paper presents the results of an effectiveness trial of Project Towards No

Drug Abuse [TND], in which the investigators compared program delivery by regular classroom teachers and program specialists within the same high schools. Within 18 schools that were randomly assigned to the program or control conditions, health classrooms were assigned to program delivery by teachers or (outside) specialists. Classroom sessions were observed by pairs of observers to assess three domains of implementation fidelity: adherence, classroom process, and perceived student acceptance of the program. Pre- and immediate posttest survey data were collected from 2331 students. Of the four composite indexes of implementation fidelity that were examined, only one (quality of delivery) showed a difference between specialists and teachers, with marginally higher ratings of specialists ($p < .10$). Both teachers and program specialists achieved effects on three of the five immediate outcome measures, including program-specific knowledge, addiction concern, and social self-control. Students' posttest ratings of the program overall and the quality of program delivery failed to reveal differences between the teacher- and specialist-led classrooms. These results suggest that motivated, trained classroom teachers can implement evidence-based prevention programs with fidelity and achieve immediate effects. Rohrbach, L.A., Dent, C.W., Skara, S., Sun, P., and Sussman, S. Fidelity of Implementation in Project Towards No Drug Abuse (TND): A Comparison of Classroom Teachers and Program Specialists. Prev. Sci., 8, pp. 125-132, 2007.

Positive Impact on Tobacco Use for Project MYTRI in India

The purpose of this study was to determine the intermediate results for Project MYTRI (Mobilizing Youth for Tobacco-Related Initiatives in India). Project MYTRI is a school-based, multiple component intervention designed to prevent and reduce many forms of tobacco use (chewing tobacco, cigarettes, and bidis) among youth in India. The intervention is based on effective models in the United States "translated" for use in this context. The intervention targets two cohorts of students who were in the 6th and 8th grade when the study started. Thirty-two schools in Delhi (north India) and Chennai (south India) were randomized to receive the intervention ($n = 16$) or serve as a delayed intervention control ($n = 16$). Students in these schools were surveyed before the intervention began and at an intermediate point, 1 year into this 2-year intervention ($n = 8,369$). A test of the changes in risk factors for tobacco use between the baseline and intermediate surveys revealed that, compared with the control, students in the intervention condition (a) had better knowledge about the health effects of tobacco; (b) believed that there were more negative social consequences to using tobacco; (c) had fewer reasons to use tobacco; (d) had more reasons not to use tobacco; (e) were less socially susceptible to chewing and smoking tobacco; (f) perceived fewer peers and adults around them smoked or chewed tobacco; (g) felt that tobacco use was not acceptable, especially among their peers; (h) were more confident in their ability to advocate for tobacco control; (i) were more knowledgeable about tobacco control policies; and (j) supported these policies, too. Fewer students in the intervention condition reported having intentions to smoke tobacco in the next year or chew tobacco when they reached college. Although no changes in actual tobacco use were observed at this stage of the study, the fact that a significant impact was made on important risk factors is promising and supports the theoretical model of change. Stigler, M., Perry, C., Arora, M., Shrivastav, R., Mathur, C., and Reddy, K. Intermediate Outcomes from Project MYTRI: Mobilizing Youth for Tobacco-Related Initiatives in India. Cancer Epidemiol. Biomarkers Prev., 16(6), pp. 1050-1056, 2007.

Risk Patterns of Tobacco Initiation in Indian Youth

Previous data from urban Indian students indicated that 6th graders reported more tobacco use than 8th graders. The current study examined underlying factors to understand this unexpected difference. Students in the 6th and 8th

grade (n = 11,642) from 32 private (high socioeconomic status) and government (low-mid SES) schools in two large cities in India (Delhi and Chennai) completed a cross sectional survey as the baseline evaluation tool for a group-randomized tobacco prevention intervention trial (Project MYTRI). Mixed-effects regression models were used to (1) examine the relationship between 15 psychosocial risk factors and current use of any tobacco, by grade; and (2) examine differences in psychosocial risk factors by grade. For students in both grades, almost all psychosocial factors were significantly related to tobacco use. Some of the strongest correlates included social susceptibility to and social norms about use. Exposure to tobacco advertising was a strong correlate of tobacco use for 6th graders, but not for 8th graders. Sixth graders scored lower than 8th graders on almost all factors, indicating higher risk. The data indicate that the 'risk profile' of these 6th graders makes them more vulnerable to begin using tobacco, as well as to outside influences that may encourage use. Stigler, M., Perry, C., Arora, M., and Reddy, K. Why Are Urban Indian 6th Graders Using More Tobacco Than 8th Graders? Findings from Project MYTRI. Tob. Control, 15 Suppl 1, pp. 54-60, 2006.

Self-Initiated Quitting of Cigarette Smoking Among High-Risk Youth

This paper provides a 5-year replication-extension of a previous 1-year follow-up study of the same sample of southern California alternative high school youth. Demographic, behavioral, psychosocial, and emerging adult function predictors of adolescent self-initiated smoking cessation were investigated. The baseline smokers varied from 14 to 19 years of age (mean age = 16.8 years, S.D. = 0.9). The sample was 59% male; 50% white, 37% Latino, 4% African American, 5% Asian, 2% Native American, and 2% other ethnicity. The retained sample size for analysis was 303 baseline cigarette smokers that were followed-up 5 years later. This analysis consisted of 51% of those 593 baseline cigarette smokers that previously had been examined at baseline and again at a 1-year follow-up (Sussman et al., 1998). The study compared the analysis sub sample on baseline measures to those of the full measured baseline sample, using a series of single sample t-tests or calculation of an approximate confidence interval for proportions with large samples. Quitters were more likely to be Latino (49% versus 34%), were less likely to be White (38% versus 52%), were slightly older (means=17.00 and 16.72 years, S.D. =0.89 and 0.93), were less acculturated, and were more likely to be holding down jobs. Regarding drug use related measures; quitters reported a lower level of cigarette smoking at baseline and intention to smoke cigarettes in the future at baseline. None of the perceived social variables discriminated between quitters and non-quitters. Based on these findings one may speculate that smoking cessation programs for adolescents should include counteraction of problem-prone attitudes, assistance with job aspirations and information about drug-free workplaces, motivation to quit strategies, and assistance with overcoming withdrawal symptoms. Sussman, S., and Dent, C.W. Five-Year Prospective Prediction of Self-Initiated Quitting of Cigarette Smoking of High-Risk Youth. Addict. Behav., 32, pp. 1094-1098, 2007.

Tests of Implicit Memory and Cognition Predict Marijuana Use Among High-Risk Adolescents

In this study, the authors compared indirect measures that attempt to quantify the level of marijuana associations among adolescents. They also evaluated whether these various methods overlap or tap different aspects of associative processes that may act in concert to influence marijuana use. Automatic drug-relevant associations were assessed in 121 at-risk youth in continuation high schools in California with the use of a word association index and computer-based, reaction time measures (i.e., Implicit Association Test [IAT] and Extrinsic Affective Simon Task [EAST]). Measures of working memory capacity,

sensation seeking, and explicit cognitions also were included in analyses as potential confounders. The word association index and the marijuana IAT excited D measure were significant predictors of marijuana use. The word association index accounted for more variance in marijuana use than did the IAT or EAST measures. Further, confirmatory factor analytic models of the indirect measures of marijuana use revealed a significant moderate correlation between the EAST Excitement and Word Association factors but no significant correlations between the Word Association and IAT factors. These findings suggest that there is some convergence among the different indirect measures, but these assessments also appear to tap different aspects of associative processes. The types of indirect measures evaluated in this work provide information about spontaneous cognitions related to substance use, capturing influences on behavior that are not evaluated with traditional explicit assessments of behavior. Findings from this work add to a growing body of research that implicates the importance of implicit associative processes in risk and health behaviors. Ames, S., Grenard, J., Thush, C., Sussman, S., Wiers, R., and Stacy, A. Comparison of Indirect Assessments of Association as Predictors of Marijuana use Among At-Risk Adolescents. Exp. Clin. Psychopharmacol., 15(2), pp. 204-218, 2007.

Effects of ONDCP Marijuana Initiative on High-Sensation-Seeking Adolescents

This study evaluated the effects of the Marijuana Initiative portion of the Office of National Drug Control Policy's National Youth Anti-Drug Media Campaign on high-sensation-seeking and low-sensation-seeking adolescents. Personal interviews were conducted via laptop computers with independent monthly random samples of 100 youths (ages 9 to 13) from the same age cohort in each of 2 moderate-sized communities (Fayette County Kentucky, and Knox County Tennessee) over 48 months (April 1999-March 2003) of the campaign, including the critical first 6 months of the 9-month initiative. The start of the initiative was treated as an "interruption" in time-series analyses of the combined community sample. The Marijuana Initiative reversed upward developmental trends in 30-day marijuana use among high-sensation-seeking adolescents ($P<.001$) and significantly reduced positive marijuana attitudes and beliefs in this at-risk population. Use of control substances was not affected. As expected, low-sensation-seeking adolescents had low marijuana-use levels, and the campaign had no detectable effects on them. Other analyses indicated that the initiative's dramatic depiction of negative consequences of marijuana use was principally responsible for its effects on high-sensation-seeking youths. Substance use prevention campaigns can be effective within an approach using dramatic negative-consequence messages targeted to high-sensation seekers. Palmgreen, P., Lorch, E.P., Stephenson, M.T., Hoyle, R.H., and Donohew, L. Effects of the Office of National Drug Control Policys' Marijuana Initiative Campaign on High-Sensation-Seeking Adolescents. Am. J. Public Health, 97(9), pp. 1644-1649, 2007.

Prevention Program Leader Characteristics Predict Program Outcomes

A previously published effectiveness study of Project ALERT delivered in schools by outside providers from Cooperative Extension found no positive effects for the adult or teen-assisted delivery of the curriculum despite high-quality implementation. Those findings and the likelihood that more outside providers will deliver evidence-based drug prevention programs in the future, led to this investigation of possible influences of leaders' personal characteristics on ALERT's program effects. Modeling techniques were utilized to determine the influence of leader characteristics on students' drug use. Students in classrooms with adult leaders who were more conscientious, sociable, or individuated were more likely to experience beneficial program effects.

Students in teen-assisted classrooms with teen leaders who were more sociable or, to a lesser extent, highly individuated, showed more positive effects. These findings suggest that significant program effects of ALERT implemented with outside providers may be achieved when utilizing providers with characteristics conducive to effective program delivery. St. Pierre, T., Osgood, D., Siennick, S., Kauh, T., and Burden, F. Project ALERT with Outside Leaders: What Leader Characteristics are Important for Success? Prev. Sci., 8(1), pp. 51-64, 2007.

Prospective Associations of Social Self-Control with Drug Use Among Youth from Regular and Alternative High Schools

This study examined the one year prospective associations between adolescent social self-control and drug outcomes (cigarette use, alcohol use, marijuana use, hard drug use, and problem drug use) among adolescents from regular and continuation high schools. In the authors' previous cross-sectional study, poor social self-control was found to be associated with higher drug use, controlling for 12 personality disorder categories. The aims of this study were to determine (a) whether lack of social self-control predicted drug use one year later, and (b) whether drug use at baseline predicted social self-control one year later. Subjects were 2081 older adolescents from 9 regular (N = 1529) and 9 continuation (alternative) (N = 552) high schools in the Los Angeles area. Data were collected at two time points in an interval of approximately 1 year. Past 30-day cigarette smoking, marijuana use, hard drug use, and problem drug use at baseline were found to predict lower social self-control at follow-up, controlling for baseline social self-control and demographic variables. The effect of problem drug use as a one-year predictor of social self-control was found to be moderated by school type (regular or continuation high school), such that the relationship was significant for continuation high school students only. Conversely, social self-control was found to predict past 30-day alcohol use, marijuana use, and problem drug use, controlling for baseline drug use and demographic variables. For alcohol use, marijuana use, and problem drug use outcomes, school type was not found to moderate the effects of social self-control, though an interaction effect was found regarding cigarette smoking. Social self-control was a significant predictor of cigarette use only at regular high school. The results indicate that social self-control and drug use share a reciprocal relationship. Lack of social self-control in adolescents seems to result in increased drug use, which in turn is likely to further decrease social self-control. Thus, it seems that social self-control is an alterable cognitive-behavioral attribute which can be improved through skill-based interventions in order to prevent drug use among adolescents. Policies aimed at preventing drug abuse among adolescents may benefit from institutionalizing social self-control skills training. Pokhrel, P., Sussman, S., Rohrbach, L., and Sun, P. Prospective Associations of Social Self-Control with Drug use Among Youth from Regular and Alternative High Schools. Subst. Abuse Treat. Prev. Policy, 2(1), pp. 22-29, 2007.

Development of Callous-Unemotional Traits and Antisocial Behavior in Children

Callous and unemotional (CU) traits have been linked to severe antisocial behavior in youth, but studies examining the etiology of CU traits are lacking. Based on prior research, it was hypothesized that childhood anxiety and parenting practices would interact to predict changes in CU traits over time. Hypotheses were tested using a sample of 120 moderate to highly aggressive fifth graders followed over a 1-year period. Although CU traits displayed moderate temporal stability and predicted increases in antisocial behavior, evidence suggested that these features were not immutable. Children exposed to lower levels of physical punishment showed decreases in CU traits over time, whereas higher levels of child-reported parental warmth and involvement predicted decreases in both CU traits and antisocial behavior over time. Lower

levels of anxiety were uniquely related to increased CU traits for children who described their primary caregiver as exhibiting low warmth and involvement. Pardini, D., Lochman, J., and Powell, N. The Development of Callous-Unemotional Traits and Antisocial Behavior in Children: Are There Shared and/or Unique Predictors? J. Clin. Child Adolesc. Psychol., 36(3), pp. 319-333, 2007.

Measuring and Valuing Time Costs in Prevention Interventions

The economic evaluation of psychosocial interventions is a growing area of research. Though time costs are central to the economist's understanding of social costs, these costs generally have been ignored by prevention scientists. This article highlights the need to measure such costs and then reviews the principles economists use in valuing time. It then considers the specific time costs that often arise in interventions designed to reduce behavior problems among children and youth. These include classroom time devoted to program activities, the time of parents or other caregivers, the time of teachers (outside of the classroom), and the time of volunteers. Consideration is give to the economic principles that govern how economists value these inputs and then apply these principles to data from an evaluation of a widely used intervention, the Incredible Years Program. Implications for public policy are discussed. Foster, E., Johnson-Shelton, D., and Taylor, T. Measuring Time Costs in Interventions Designed to Reduce Behavior Problems Among Children and Youth. Am. J. Community Psychol., 40(1-2), pp. 64-81, 2007.

Mediation of Effects of a Universal Prevention Program on Violent Behavior in Youth

The purpose of this investigation was to determine if the Aban Aya Youth Project, a culturally grounded intervention designed for low income African American youth, produced changes over time in core intervening variables and whether these variables mediated intervention effects on the development of youth violent behavior. The intervening variables of interest include communal value orientation (e.g., cooperating with others, keeping the neighborhood clean), empathy (items reflecting concern for others), and violence avoidance efficacy beliefs (certainty that one can keep from fighting). Fifth grade cohorts at 12 schools were randomly assigned to a classroom social development intervention, a school, family, and community intervention, or an attention control condition. Study participants were followed through eighth grade. Six hundred sixty-eight students (49% male) participated in the study. Mediation analyses suggested that compared to the control condition, both program conditions led to steeper increases over time in empathy which, in turn were related to reductions in the likelihood of violent behavior over time. There were no program effects on communal value orientation and violence avoidance efficacy beliefs. However, the investigators found that changes over time in violence avoidance efficacy were associated with reduced likelihood of violent behavior. Jagers, R., Morgan-Lopez, A., Howard, T., Browne, D., and Flay, B. Mediators of the Development and Prevention of Violent Behavior. Prev.Sci., 8, pp. 171-179, 2007.

Feasibility of Youth Purchase Attempts of Harmful Legal Products

Communities across the nation have become increasingly concerned about inhalant use and use of harmful legal products among youth because of increasing prevalence rates and deleterious health consequences from abusing these products. The increasing concern of communities about inhaling and ingesting legal products has been coupled with increasing awareness and concern about ability of youth to access and abuse a variety of other legal retail products. There are few examples of scientifically designed community

prevention projects that seek to reduce youth abuse of such legal products. This article describes a community prevention trial that is designed to reduce sales of inhalants and other harmful legal products to youth and demonstrates how the retailer component of the trial can be rigorously evaluated. Data on retailer surveys and youth purchase attempts confirm the feasibility of such data collection tools for component evaluation. Courser, M., Holder, H., Collins, D., Johnson, K., and Ogilvie, K. An Evaluation of Retail Outlets as Part of a Community Prevention Trial to Reduce Sales of Harmful Legal Products to Youth. Eval. Rev., 31(4), pp. 343-363, 2007.

Perceived Risks of Marijuana Use in Marijuana Users and Non-Users

The present study evaluates differences in risk perception related to marijuana use as a function of past use and, among those who report marijuana use, as a function of frequency of use and having experienced negative consequences of marijuana use. Participants were 725 incoming first year college students in a longitudinal study examining the efficacy of a marijuana prevention program and data used for this analysis were from the baseline survey. Participants were 57% female and 62% Caucasian, and 48% reported ever using marijuana. Analyses indicated that risk perception was greater among non-users of marijuana than for those who reported marijuana use (and, in turn, who were more likely to have actually experienced a drug-related consequence). Among marijuana users, risk perception was not influenced by the frequency of marijuana use nor was it influenced by the actual experience of a drug-related consequence. The findings suggest that for abstainers, perceived risk and the potential consequences of marijuana use may serve a protective role against the initiation of marijuana use. For those who use marijuana, intervention efforts utilizing motivation enhancement approaches could explore the discrepancy between perceived risks and actual experienced consequences. Kilmer, J., Hunt, S., Lee, C., and Neighbors, C. Marijuana Use, Risk Perception, and Consequences: Is Perceived Risk Congruent with Reality? Addict. Behav., 32, pp. 3026-3033, 2007.

Adolescent Friendship Interactions and Deviant vs. Normative Developmental Pathways

Interpersonal dynamics within friendships were observed in a sample of 120 (60 male, 60 female) ethnically diverse 16- and 17-year-old adolescents characterized as "persistently antisocial", "adolescent-onset", and normative. Group definitions were based on antisocial behavior scores from a survey of antisocial behavior and substance use developed by Dishion and Kavanagh and administered at four points in time to adolescents starting at age 11-12. Persistently antisocial adolescents were defined as those who had above average scores compared to those within their gender group and had greater than the median antisocial score at all assessment points. "Adolescent-onset" youth comprised participants whose antisocial behaviors increased from below the median in earlier waves of the survey to above the median in later waves. The normative group included participants with the lowest sum antisocial behavior scores of the group who also had below median antisocial behavior scores during all waves. Dyadic mutuality, i.e., talk that is mutually responsive, reciprocal, and harmonious, and deviant talk, i.e., inappropriate talk and talk about violating community or societal rules, were coded from videotaped friendship interactions. Persistently antisocial adolescents demonstrated lower levels of dyadic mutuality compared with adolescent-onset and normative adolescents. Persistently antisocial and adolescent-onset adolescents spent more time in deviant talk than did normative adolescents. Across groups, girls were rated as more mutual and coded less in deviant talk than boys. Furthermore, friendship dyads that engaged in high levels of deviant talk and were mutual in their interactions reported the highest rates of antisocial

behavior, Piehler, T., and Dishion, T. Interpersonal Dynamics within Adolescent Friendships: Dyadic Mutuality, Deviant Talk, and Patterns of Antisocial Behavior. Child Dev., 78(5), pp. 1611-1624, 2007.

Protective Factors Associated with Preadolescent Violence

This study explores the influences of communal values, empathy, violence avoidance self-efficacy beliefs, and classmates' fighting on violent behaviors among urban African American preadolescent boys and girls. As part of a larger intervention study, 644 low-income 5th grade students from 12 schools completed a baseline assessment that included the target constructs. Boys reported more violent behaviors, and lower levels of empathy and violence avoidance self-efficacy beliefs than girls. Path analyses revealed that, after controlling for classmates' fighting, violence avoidance self-efficacy beliefs were negatively associated with violent behavior. Communal values had a direct negative relationship with violence for boys, but not girls. Both communal values and empathy were associated with less violent behavior through positive relationships with violence avoidance self-efficacy beliefs. For girls, classmates' fighting had an indirect positive association with violent behavior through its negative relationship with violence avoidance self-efficacy beliefs. This research identifies protective factors that can potentially be harnessed to delay the onset and/or slow the growth of violent behaviors in youth. Jagers, R., Sydnor, K., Mouttapa, M., and Flay, B. Protective Factors Associated with Preadolescent Violence: Preliminary Work on a Cultural Model. Am. J. Community Psychol., 40(1-2), pp. 138-145, 2007.

Pediatric Health Care Providers Report Low Levels of Screening for Maternal Depression

Screening for maternal depression with appropriate intervention has been emphasized through pediatric guidelines, but engaging providers to implement such procedures remains challenging. This study examined self-reported practice in recognizing and treating maternal depression in 98 pediatric health care providers. Over 85% agreed that recognizing maternal depression was their responsibility, yet only half reported confidence in their ability to do so. Fewer than 10% reported asking mothers about depression or using a screening tool. Clear differences in practice, treatment, and perceived barriers by confidence level were found. Implications for practice, research, and training are discussed. Connelly, C., Baker, M., Hazen, A., and Mueggenborg, M. Pediatric Health Care Providers' Self-Reported Practices in Recognizing and Treating Maternal Depression. Pediatr. Nurs., 33(2), pp. 165-172, 2007.

Low Levels of Intimate Partner Violence Assessment by Child Welfare Services

The purpose of this study was to describe policy and practice with respect to the assessment of intimate partner violence in a sample of child welfare agencies located throughout the United States and to examine the relationship of contextual characteristics and assessment practices. Telephone interviews were conducted with key informants from child welfare agencies. A snowball interviewing strategy was used to identify the best informant in each agency. Almost all of the participating agencies conducted some assessment of intimate partner violence, with most reporting that the majority of screening or assessment occurred during investigation of referrals. However, only 43.1% reported that all of the families referred to the child welfare system were assessed for intimate partner violence, and 52.8% indicated they had a written policy pertaining to screening and assessment of the problem. There was little relationship between county or agency characteristics and assessment practices. Additional research is needed to determine factors that influence

assessment practices and to identify strategies to support and extend efforts to identify intimate partner violence and provide appropriate services for families in the child welfare system. Hazen, A.L., Connelly, C.D., Edleson, J., Kelleher, K., Landverk, J., Coben, J., Barth, R., McGeehan, J., Rolls, J., and Nuszukowski, M. Assessment of Intimate Partner Violence by Child Welfare Services. Children and Youth Services Review, 29 pp. 490-500, 2007.

Experience Seeking Correlates with Hippocampus Volume

Experience seekers continuously pursue novel environmental stimuli, a tendency linked to genetic variation in mesolimbic dopamine transmission. However, the neuroanatomical basis accompanying these genetic and neurochemical associations is unknown. Animal and human experimental results suggest a central role for the hippocampus in processing novel stimuli. This pilot study explored whether differences in human experience seeking are related to variations in hippocampal volume. High-resolution anatomic MR images were analyzed in 40 individuals who ranged from low through high on a validated experience seeking personality scale. Manual tracing analysis demonstrated positive correlation between right hippocampal volumes and scores on the experience seeking scale. A separate voxel-based morphometric analysis confirmed these results and localized the significant increase to the anterior portion of right hippocampal grey matter. The study tested and rejected the possibility that results were mediated by a personality trait related to, but distinct from, experience seeking. The present data provide the first direct evidence for a relationship between human experience seeking and brain structure. In addition, these results provide new ecologically relevant evidence for a link between right anterior hippocampus and novelty processing. Martin, S.B., Covell, D.J., Joseph, J.E., Chebrolu, H., Smith, C.D., Kelly, T.H., Jiang, Y., and Gold, B.T. Human Experience Seeking Correlates with Hippocampus Volume: Convergent Evidence from Manual Tracing and Voxel-Based Morphometry. Neuropsychologia, 45, pp. 2874-2881, 2007.

Gene-environment Contributions to Young Adult Sexual Partnering

There has been relatively little work completed to date on gene-environment contributions to human sexuality, especially molecular analyses examining the potential contributions of specific polymorphisms in conjunction with life experiences. Using Wave III data from 717 heterozygous young adult sibling pairs included in the National Longitudinal Study of Adolescent Health, this article examined the combined contributions of attendance at religious services and three genetic polymorphisms (in the dopamine D4 receptor [DRD4]), dopamine D2 receptor [DRD2]), and the serotonin transporter promoter [5HTT]) to sensation seeking, a personality construct related to sexual behavior, and the number of vaginal sex partners participants had in the year before interview. Data analyses used a mixed model approach to account for population stratification and correlated observations. DRD4 was unrelated to sensation seeking and to the number of sex partners in tests of both main effects and in interaction with religious attendance. Contrary to hypothesis, presence of the A1 DRD2 allele was associated with having had fewer sex partners in the past year. Associations between the 5HTT allele and sex partners varied by religious attendance, but again the patterns of associations were contrary to hypothesized relationships and were small in magnitude. These findings underscore the necessity of using more comprehensive multiple gene-multiple life experience approaches to investigations of complex behaviors such as sexual patterns. Halpern, C.T., Kaestle, C.E., Guo, G., Hallfors, D.D., and Hallfors, D.D. Gene-Environment Contributions to Young Adult Sexual Partnering. Arch. Sex Behav., 36(4), pp. 543-554, 2007.

Teens with Part-time Jobs More Likely to Smoke

This study investigated the links between working for pay and adolescent tobacco use to determine whether working for pay increases smoking risk. Analyses involved retrospective and prospective analyses using data from a representative cohort of 799 predominantly African American students in Baltimore, MD, who had been followed since the first grade. At the 10th year of follow-up, when the youths were aged 14 to 18 years, there was a positive relationship between the time they spent working for pay and current tobacco use. This relationship was attenuated somewhat after adjustment for potential selection effects. Adolescents who spent more than 10 hours per week working for pay also tended to initiate tobacco use earlier than did their peers. Among adolescents who had not yet used tobacco, those who started to work 1 year after assessment and those who worked over 2 consecutive assessments had an elevated risk of initiating use relative to adolescents who did not start working. In summary, there is a strong link between working for pay and adolescent tobacco use. Policymakers should monitor the conditions under which young people work to help minimize young workers' tobacco use and potential for initiating use. Ramchand, R., Ialongo, N.S., and Chilcoat, H.D. The Role of Working for Pay on Adolescent Tobacco Use. Am. J. Public Health, 97(11), pp. 1-7, 2007.

Rates of Substance Use Among Hispanic Youth in the US and Puerto Rico

This study examined patterns of progression in substance use among Hispanic youth 13 to 17 years of age from two longitudinally representative studies. Patterns of substance use among youth in Puerto Rico were examined using a longitudinal study (n=663) of adolescents living on the island. The National Longitudinal Study of Youth was used to examine patterns of substance use among Hispanics living in the United States (n=1445). Latent transition analysis was used to estimate the probability of membership in each stage of substance use and incidence of transitions between different substance use stages over time. Six stages best described the heterogeneity in substance use among youth in Puerto Rico. Five stages were sufficient to describe patterns of substance use among youth in the United States. Youth living in Puerto Rico reported lower rates of smoking and illicit drug use, but higher rates of alcohol use, when compared with rates among Hispanics in the United States. Similar patterns of substance use were identified for Hispanic youth living in the United States and youth living in Puerto Rico. Maldonado-Molina, M.M., Collins, L.M., Lanza, S.T., Prado, G., Ramirez, R., and Canino, G. Patterns of Substance use Onset among Hispanics in Puerto Rico and the United States. Addict. Behav., 32(10), pp. 2432-2437, 2007.

Water Pipe Smoking in Egypt: Misperceptions of Harm

This study investigated behavioral and sociodemographic factors associated with tobacco use among female university students patronizing water pipe cafes in Cairo, Egypt. Two groups of female university student smokers were interviewed (100 and 96 students from a public and a private university, respectively). The interviews took place in nine water pipe cafes near the two universities. A logistic regression model was developed to analyze the relationship between tobacco-related knowledge and beliefs and the choice between smoking water pipe or cigarettes. Among these smokers, 27% smoked cigarettes only, 37.8% smoked water pipe only, and 35.2% smoked both types of tobacco. Most of the water pipe smokers (74.1%) preferred this method because they believe it to be less harmful than smoking cigarettes. More than half of the subjects were encouraged to start smoking by other females (56.6%). Curiosity was a significant factor for initiation (OR = 2.8,

95% CI = 1.3-6.2, p<.01). The authors found no significant differences between water pipe and cigarette smokers regarding current age, age at initiation, quit attempts, knowledge about the hazards of smoking, wanting to be fashionable, or smoking with friends. About one in four (23.7%) attempted to quit, with health cited as a major reason. An urgent need exists for correction of the misperception among this study population that water pipe smoking is safe and less harmful than cigarette smoking. Labib, N., Radwan, G., Mikhail, N., Mohamed, M., Setouhy, M., Loffredo, C., and Israel, E. Comparison of Cigarette and Water Pipe Smoking among Female University Students in Egypt. Nicotine Tob. Res., 9(5), pp. 591-596, 2007.

Director's Report to the National Advisory Council on Drug Abuse - February, 2008

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

Sleeping On the Job Relates to Productivity in Employed Abstinent Methadone Maintained Cocaine Users

Drug abusers are at high risk for being terminated from both competitive and supported employment positions. This issue is important because gainful employment is essential for full integration into society. This study examined professional demeanor in fifty-three methadone maintained cocaine abusers who were participating in a unique Òtherapeutic workplaceÓ study in which cocaine abstinence was required for entry to training and employment as data entry operators. In the therapeutic workplace, professional demeanor was directly tied to training and payment opportunities. Staffs were instructed to record and provide written and standardized verbal corrections for all violations of professional demeanor including loud talking, vulgar language, unprofessional communication (such as threats or aggression towards staff or participants) sleeping on the job, or eating or drinking at a desk with an uncovered computer keyboard. If the behavior continued, sanctions including removal from the workplace for escalating time periods were implemented. Overall, the frequency of major disruptive behavior was low, but on average, each participant experienced close to 2 professional demeanor violations a week. Despite losing training opportunities and pay and advancement opportunities, sleeping was a serious problem for a number of participants. Sleeping was the main behavior related to training outcomes (typing achievement and accuracy) and hours worked. This study is important because it sheds light on behaviors drug abusers exhibit in workplaces which may increase their likelihood of termination. More research is needed on why sleeping violations for this population occurs at such high frequency and on ways to mitigate the effect of sleepiness on employed drug abusers attempting to maintain abstinence. Carpenedo, C., Needham, M., Knealing, T., Kolodner, K., Fingerhood, M., Wong, C.J., Silverman, K. Professional Demeanor of Chronically Unemployed Cocaine-Dependent Methadone Patients in a Therapeutic Workplace. Substance Use and Misuse, 42(7) pp. 1141-1159, 2007.

Directly Observed HIV Therapy Superior to Self-Administered Treatment

Adherence to antiretroviral therapy among HIV positive drug users is often poor. This study aimed to determine whether directly observed anti-retroviral therapy (DAART) administered under observation by workers from a mobile health van reduced surrogate HIV blood levels to low enough levels to show virologic and immunological improvements compared with standard (patient administered) therapy. Of the 141 people eligible for the trial, 62% were

randomized to the DAART condition and the remainder was randomized to standard therapy. At the end of the six months of treatment a significantly greater proportion of participants assigned to DAART showed the primary outcome of either a reduction in HIV-1 RNA level of > or = 1.0 log10 copies/mL or an HIV-1 RNA level < or = 400 copies/mL. This finding is significant because this is the first study to show DAARTÕs effectiveness among HIV+ drug users. More research is needed to determine the essential components of a successful DAART program, especially regarding how much social and medical support the program should provide to ensure participation. Altice, F., Maru, D., Bruce, R., Springer, S., and Friedland, G. Superiority of Directly Administered Therapy over Self-Administered Therapy for HIV-Infected Drug Users: A Prospective Randomized, Controlled Trial. Clinical Infectious Diseases, 45(6), pp. 770-778, 2007.

Behavioral Incentives Improve Outpatient Treatment Participation/Retention for Pregnant Drug Abusers

Treating pregnant drug abusers poses unique challenges; compared with non-pregnant drug users they leave treatment more often and their attendance is often unreliable. This study examined the utility of providing 2 weeks of vouchers exchangeable for goods and services on an escalating schedule to motivate participation in a program comprised of seven days of residential and thirty days of outpatient treatment. Ninety-one pregnant women were assigned to either a standard treatment condition (ST) or a voucher reinforcement condition (VR) in which vouchers were earned for treatment program attendance. Voucher values began at $5.00 and increased by $5.00 for each day the participant attended up to a maximum value of $70.00 for 2 weeks. If a participant missed a single session they forfeited their voucher that day. Participant voucher value reset to $5.00 if more than one session was missed. VR assignment did not impact early treatment dropout; one third of participants in both groups left treatment against medical advice (AMA). Among those who did not leave AMA, those assigned to VR attended more treatment days than those in ST. Additionally, those assigned to VR were more likely to attend treatment consistently (12-14 full days) as opposed to the typical pattern of attendance for ST (only 4 or 6 full days). When all participants were categorized as either consistent or inconsistent attenders, consistent early attendance predicted better attendance in the 30 days following the intervention. Within five days of the voucher treatment ending, no consistent early attenders dropped out of treatment. However, 25% of inconsistent treatment attenders dropped out during the five days post-intervention. These findings are significant for several reasons. First, although inpatient treatment participation was not differentially impacted by vouchers, the voucher program begun during the inpatient treatment period appeared to have an important effect on pregnant women making the transition to outpatient treatment. Additionally, critics contend that voucher effects do not last after the treatment ends but in this case the voucher effect was sustained post-treatment. More research is needed to determine what if any effect vouchers can have on pregnant women entering treatment to reduce dropout AMA rates Svikis, D., Silverman K, Haug, N., Stitzer, M., Keyser-Marcus, L. Behavioral Strategies to Improve Treatment Participation and Retention by Pregnant Drug-dependent Women. Substance Use Misuse, 42(10), pp. 1527-1535, 2007.

Abstinent Contingent Employment Training Plus Work Better Than Work Alone for Maintaining Cocaine Abstinence in Methadone-Maintained Cocaine and Opiate Users

In clinical trials with chronically unemployed drug users, SilvermanÕs abstinence contingent therapeutic workplace has produced very high rates of cocaine abstinence. Researchers hypothesize that at least two elements, access

Planned Meetings

Publications

Staff Highlights

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to desirable work training followed by relatively high pay employment (trainees learn and then get paid for computer data entry) or the requirement of abstinence from cocaine to gain admission to the workplace may be responsible for its effects. In this study, fifty-six recent cocaine users were assigned to twenty-six weeks of either entry to the workplace (work only WO) or the therapeutic workplace contingent on abstinence as measured by a urine sample test (TW). Although both groups attended the workplace at high rates during the baseline period when the abstinence contingency was not in place (> 80% of available days), suggesting that WO motivated attendance, those assigned to the TW produced 19% more cocaine metabolite free urine samples than WO participants. However, TW also reduced participation rates with TW participants attending only 39% of days and TW participants attending 71% of days. These findings are significant because they suggest that modifications to supported employment programs that require abstinence are likely to produce higher rates of cocaine abstinence than those that do not. Additionally many researchers have suggested that programs that ensure high rates of attendance by default will produce high rates of abstinence; however, this study clearly shows an intervention may be highly engaging but less effective than one that, because of an abstinence contingency, effectively bars participation when a participant has had a recent slip or relapse. More research is needed to determine if contingencies can be manipulated to maximize engagement while motivating drug abstinence. Silverman, K., Wong, C., Needham, M., Diemer, K, Knealing, T., Crone-Todd, D., Fingerhood, M., Nuzzo, P., Kolodner, K. A Randomized Trial of Employment-based Reinforcement of Cocaine Abstinence in Injection Drug Users. Journal of Applied Behavior Analysis, 40(3), pp. 387-410, 2007.

Costs of Therapeutic Workplace Treatment Intervention Lower than Intensive Outpatient Treatment

In clinical trials with chronically unemployed drug users, SilvermanÕs abstinence contingent therapeutic workplace has produced comparatively high rates of cocaine abstinence but like many contingency management interventions has been criticized because of its cost. Over a one year period, this study examined the costs of running the Therapeutic Workplace by systematically assessing all major components including personnel, client earnings, facilities, supplies, and equipment. On average, the cost for treating one methadone-maintained client who continued to use cocaine while in methadone treatment including the cost for methadone programming was $362.00 per week (in 2004 dollars) This is significant because these costs are substantially less than residential treatment, estimated to be $746.00 per week or intensive outpatient treatment estimated at $492.00 and they are less than $300.00 more than methadone maintenance (which generally fails to produce any cocaine abstinence in this group). Additionally these costs were calculated based on the training portion of the workplace where participants learn job skills. If the workplace treatment continued in the context of a business, the employee earning costs might be mitigated somewhat as wages earned by workers could offset by profit to the business from selling products or providing services. More research is needed on how to implement the Therapeutic Workplace especially in terms of establishing a profitable business model. Knealing, T. Roebuck, M.C, Wong, C., and Silverman, K. Economic Cost of the Therapeutic Workplace Intervention Added to Methadone Maintenance Treatment. Substance Abuse Treatment, 2007 (e-pub ahead of print).

Development of a Telephone-Based Intervention for Support Persons to Help Smokers Quit

Dr. Patten and colleagues at the Mayo Clinic in Rochester developed and pilot tested a novel approach to smoking cessation utilizing a support person as the agent of change. The support person was a non-smoker who wanted to assist a

smoker in quitting. This approach did not require the smoker to seek treatment. The support person was the sole recipient of the professional telephone-based intervention. Ten adult non-smoking females completed the treatment protocol, consisting of six 20-30 minute sessions and written materials. Feedback was obtained from 8 of the 10 participants and all 4 telephone counselors 1 week post- treatment (week 10). Results indicate that the telephone-based intervention was feasible and acceptable to participants. The intervention was refined based on participant and counselor feedback and will be tested in a randomized pilot trial. Patten, C.A., Petersen, L.R., Brockman, T.A., Gerber, T., Offord, K.P., Ebbert, J.O., Hughes, C.A., Decker, P.A., Beddow, C., Pyan, K., Quigg, S., and Boness, J. Development of a Telephone-based Intervention for Support Persons to Help Smokers Quit. Psychology, Health & Medicine, 12, pp. 1-12, 2007.

Bupropion and Cognitive-Behavioral Therapy for Smoking Cessation in Women

Dr. Schmitz and colleagues at the University of Texas Health Science Center at Houston conducted this study to examine the independent and interactive effects of medication (bupropion 300 mg/day vs. placebo) and psychotherapy (cognitive-behavioral therapy [CBT] vs. supportive therapy [ST]) in women in a two level factorial design. In addition to testing the hypothesis that bupropion with CBT would be the most effective of all the treatments, medication compliance and its role in the efficacy of bupropion was examined. Participants were 154 women who smoked more than 10 cigarettes/day. Compliance with study medication was assessed using Medication Event Monitoring Systems (MEMS) over 7 weeks of treatment. Psychological interventions were delivered in 60-min weekly group sessions. Longitudinal analysis of abstinence outcomes from end of treatment (EOT) through 12 months after treatment revealed a significant interaction of medication and therapy. Higher abstinence rates at EOT and 3, 6, 9, and 12-month follow-ups were observed when bupropion was delivered concurrently with CBT (44%, 24%, 30%, 23%, 17%) rather than with ST (18%, 1%, 8%, 5%, 2%). The bupropion-CBT combination, however, was not clearly superior to placebo, regardless of therapy assignment. Higher rates of medication compliance were positively predictive of abstinence, and this effect was most evident in the placebo condition. Findings provide only modest support for CBT as the preferred type of intensive therapy in conjunction with bupropion in women. Schmitz, J.M., Stotts, A.L., Mooney, M.E., DeLaune, K.A., and Moeller, F.G. Bupropion and Cognitive-Behavioral Therapy for Smoking Cessation in Women. Nicotine & Tobacco Research, 9, pp. 699-709, 2007.

Incremental Validity of Anxiety Sensitivity in Terms of Motivation to Quit, Reasons for Quitting, and Barriers to Quitting Among Community-Recruited Daily Smokers

Dr. Zvolensky and colleagues at the University of Vermont conducted the present investigation to examine the relationships between anxiety sensitivity and motivation to quit smoking, barriers to smoking cessation, and reasons for quitting smoking among 329 adult daily smokers. As expected, after covarying for the theoretically relevant variables of negative affectivity, gender, Axis I psychopathology, nonclinical panic attack history, number of cigarettes smoked per day, and current levels of alcohol consumption, it was found that anxiety sensitivity was significantly incrementally related to level of motivation to quit smoking as well as current barriers to quitting smoking. Partially consistent with the hypotheses, after accounting for the variance explained by other theoretically relevant variables, it was found that anxiety sensitivity was significantly associated with self-control reasons for quitting smoking (intrinsic factors) as well as immediate reinforcement and social influence reasons for quitting (extrinsic factors). These findings set the stage for additional research

targeted at disentangling the specific mechanisms that underlie these documented associations between anxiety sensitivity and smoking, and should help guide the future development for specialized intervention programs for smokers with anxiety vulnerabilities. Zvolensky, M.J., Vujanovic, A.A., Bonn Miller, M.O., Bernstein, A., Yartz, A.R., Gregor, K.L., McLeish, A.C., Marshall, E.C., and Gibson, L.E. Incremental Validity of Anxiety Sensitivity in Terms of Motivation to Quit, Reasons for Quitting, and Barriers to Quitting Among Community-recruited Daily Smokers. Nicotine & Tobacco Research, 9, pp. 965-975, 2007.

HIV-Positive Smokers Considering Quitting: Differences by Race/Ethnicity

Investigators at Brown Medical School conducted this study to better characterize smoking in HIV-positive individuals and to identify critical components of a targeted smoking cessation intervention for multiethnic HIV-positive smokers. Differences in baseline characteristics of 444 HIV-positive smokers were examined by race, and a multivariate linear regression model evaluated factors associated with nicotine dependence in an HIV-positive population, with a particular emphasis on race/ethnic differences. The results showed that low smoking self-efficacy and higher contemplation of quitting were predictive of greater nicotine dependence. An interaction between age and race was noted, with older Hispanic Americans less likely to be nicotine dependent. The authors concluded that efforts should be made to tailor smoking cessation intervention content to HIV-positive racial/ethnic minority groups. Lloyd-Richardson, E.E., Stanton, C.A., Papandonatos, G.D., Betancourt, R.M., Stein, M., Tashima, K., Morrow, K., and Niaura, R. HIV-positive Smokers Considering Quitting: Differences by Race/Ethnicity. American Journal of Health Behavior, 32(1), pp. 3-15, 2008.

Maintenance of Effects of Motivational Enhancement Therapy to Improve Risk Behaviors and HIV-related Health in a Randomized Controlled Trial of Youth Living with HIV

Dr. Naar-King and colleagues examined the maintenance of effects of Motivational Enhancement Therapy (MET) shown to improve risk behaviors and viral load in youth living with HIV (YLH) immediately posttreatment. Sixty-five youth (ages 16-25 years) were randomized to Healthy Choices or a waitlist control. Frequency of substance use, frequency of unprotected intercourse, and viral load were obtained at baseline, 3, and 6 months after study entry. The waitlist control then received intervention. An additional data collection was obtained at 9 months for follow-up of the original treatment. The results indicated that the treatment group had greater reductions in viral load and alcohol use from baseline to 6 months. These reductions appeared to be maintained at 9-month follow-up. Improvements in sexual risk were not evident. The authors concluded that MET showed significant promise in reducing substance use and in improving HIV-related health in YLH immediately posttreatment. These effects were maintained after treatment termination. Naar-King, S., Lam, P., Wang, B., Wright, K., Parson, J.T. and Frey, M.A. Maintenance of Effects of Motivational Enhancement Therapy to Improve Risk Behaviors and HIV-related Health in a Randomized Controlled Trial of Youth Living with HIV. Journal of Pediatric Psychology, 2007, (Epub ahead of print).

The 5AÕs vs. 3AÕs Plus Proactive Quitline Referral in Private Practice Dental Offices: Preliminary Results

Dr. Gordon and colleagues conducted this study to evaluate the relative efficacy to two dental office based interventions compared to usual care. One

intervention consisted of a combination of dental practitioner advice to quit and proactive telephone counseling (3AÕs), and the other arm consisted of a dental practitioner delivered intervention based on the 5AÕs of the Clinical Practice Guideline (5AÕs). Participants included 2177 tobacco using patients enrolled from 68 dental practices in Mississippi. The results showed that smokers in the two intervention conditions quit at a higher rate than those in the usual care. Although not significant, more patients in the 5AÕs condition quit than those in the 3AÕs. Of patients in the 3AÕs condition, 50% reported being asked by their dentist or hygienists about fax referral to the quitline, and 35% were referred. The authors concluded that there are both advantages and disadvantages to the use of quitlines as an adjunct to brief counseling provided by dental practitioners. Patients receiving quitline counseling quit at higher rates than those who did not; however, only a small percentage of patients received counseling from the quitline. Therefore, it appears that dental professionals may be most effective in helping their patients to quit by regularly providing the 5AÕs plus proactively referring only those patients who are highly motivated to a quitline for more intensive counseling. Gordon, J.S., Andrews, J.A., Crews, K.M., Payne, T.J. and Severson, H.H. The 5AÕs vs. 3AÕs Plus Proactive Quitline Referral in Private Practice Dental Offices: Preliminary Results. Tobacco Control, 16, pp. 285-288, 2007.

Behavioral Impulsivity Predicts Treatment Outcome in a Smoking Cessation Program for Adolescent Smokers

Dr. Krishnan-Sarin and colleagues examined the relationship between impulsivity and smoking cessation treatment response among adolescents. Thirty adolescent smokers participated in a high school smoking cessation program combining contingency management and cognitive behavioral therapy. Several measures of impulsivity were assessed at treatment onset. Sixteen participants (53%) were abstinent from smoking at completion of the four-week study. Behavioral measures of impulsivity predicted treatment outcome. Compared to abstinent adolescents, those not achieving abstinence discounted monetary rewards more on the discounting task and committed more commission errors on the Continuous Performance Task. These preliminary results suggest that specific behavioral measures of impulsivity may be associated with the ability to initiate and/or maintain abstinence from smoking among adolescent smokers. Krishnan-Sarin, S., Reynolds, B., Duhig, A.M., Smith, A., Liss, T., McFetridge, A., Cavallo, D.A., Carroll, K.M. and Potenza, M.N. Behavioral Impulsivity Predicts Treatment Outcome in a Smoking Cessation Program for Adolescent Smokers. Drug and Alcohol Dependence, 88, pp. 79-82, 2007.

Relationship Between Self-Reported Task Persistence and History of Quitting Smoking, Plans for Quitting Smoking, and Current Smoking Status in Adolescents

Dr. Steinberg and colleagues conducted this study to examine the relationship between task persistence and smoking in adolescents. In contrast to most studies of task persistence, which used behavioral measures, this study used a brief, 2-item, internally consistent, self-report measure. It was hypothesized that because quitting smoking involves persisting in an effortful behavior (i.e., resisting desire to smoke), individuals scoring higher in task persistence would be more likely to be motivated to quit smoking and to be successful in quitting. Results indicate that task persistence is greater among adolescent non-smokers as compared to adolescent current smokers, and those planning to quit smoking as compared to those with no plans to quit. Contrary to hypotheses, task persistence was not found to be related to prior successful attempts to quit smoking. The authors concluded that the brief self-report measure of task persistence differentiated between smokers and non-smokers, and between those planning on quitting smoking and those feeling ambivalent

or not planning on quitting. This study adds to the literature in that it shows that task persistence can be measured via self-report, can be evaluated in adolescents, and relates not just to smoking status, but also to motivation to quit smoking. Steinberg, M.L., Krejci, J.A., Collett, K., Brandon, T.H., Ziedonis, D.M. and Chen, K. Relationship Between Self-reported Task Persistence and History of Quitting Smoking, Plans for Quitting Smoking, and Current Smoking Status in Adolescents. Addictive Behaviors, 32, pp. 1451-1460, 2007.

Substantial Risk for Error in Random Drug Testing in Adolescent Substance Abuse Program

Dr. Sharon Levy and colleagues from Harvard Medical School and ChildrenÕs Hospital in Boston estimated the proportion of drug tests that are susceptible to interpretation errors in a random urine drug-testing program for adolescents. Secondary data analysis was conducted using a clinical database and chart review for 110 adolescents who participated in an outpatient substance abuse program. Of 710 urine drug tests, 40 negative tests were too dilute to interpret properly, and 45 of 217 positive tests resulted from prescription medication use for a total of 85 tests that were susceptible to error. Of 85 confirmatory laboratory reports reviewed, 43 were positive for oxycodone, but only 215 of these had produced a positive opiate screen. These findings suggest a substantial risk for error in interpreting laboratory testing for drugs in adolescent substance abuse programs. Levy, S., Sherritt, L., Vaughan, B. L., Germak, M., and Knight, J. R. Pediatrics, April, 119(4), pp. e843-e848, 2007.

Community Reinforcement Approach for Street-Living, Homeless Youth

Dr. Natasha Slesnick and colleagues from Ohio State University examined treatment outcomes for street living youth aged 14-22, randomly assigned to Community Reinforcement Approach (CRA) and treatment as usual (TAU). Findings suggest that compared to TAU, youth assigned to CRA reported significantly reduced substance use (by 37% vs. 17%), depression (by 40% vs. 23%), and increased social stability (by 58% vs. 13%). The results suggest that street living, homeless youth can be engaged in and respond positively to comprehensive treatment interventions. Slesnick, N., Prestopnik, J.L., Meyers, R.J., and Glassmann, M. Addictive Behaviors, 32, pp. 1237-1251, 2007.

Project CHAT: A Brief Motivational Intervention for High Risk Youth in Primary Care

Dr. Elizabeth DÕAmico and colleagues from RAND Corporation examined the feasibility of adapting a brief motivational intervention (MI) for high risk adolescents aged 12-18 years in a primary care (PC) setting. A pilot study of Project CHAT was conducted with adolescents and small feedback sessions were conducted with adolescents, parents and clinic staff. Findings from the small feedback sessions indicated that adolescents would feel comfortable talking about substance use, despite concerns expressed about this by clinic staff. Concerns regarding being judged by the PC provider were also expressed by parents and teens. Findings from the pilot study indicated that high risk adolescents were willing to disclose information regarding their substance use and willingness to change. The results suggest the feasibility of a brief MI for high risk adolescents in a primary care setting. Stern, S.A., Meredith, L.S., Gholson, J., Gore, P., and DÕAmico, E.J. Journal of Substance Abuse Treatment, 32, pp. 153-165, 2007.

Director's Report to the National Advisory Council on Drug Abuse - February, 2008

Research Findings - Research on Pharmacotherapies for Drug Abuse

Bupropion for Methamphetamine Dependence, Clinical Trial

Bupropion was tested for efficacy in increasing weeks of abstinence in methamphetamine-dependent patients, compared to placebo. This was a double-blind placebo-controlled study, with 12 weeks of treatment and a 30-day follow-up. Five outpatient substance abuse treatment clinics located west of the Mississippi participated in the study. One hundred and fifty-one treatment-seekers with DSM-IV diagnosis of methamphetamine dependence were consented and enrolled. Seventy-two participants were randomized to placebo and 79 to sustained-release bupropion 150 mg twice daily. Patients were asked to come to the clinic three times per week for assessments, urine drug screens, and 90-min group psychotherapy. The primary outcome was the change in proportion of participants having a methamphetamine-free week. Secondary outcomes included: urine for quantitative methamphetamine, self-report of methamphetamine use, subgroup analyses of balancing factors and comorbid conditions, addiction severity, craving, risk behaviors for HIV, and use of other substances. The generalized estimating equation regression analysis showed that, overall, the difference between bupropion and placebo groups in the probability of a non-use week over the 12-week treatment period was not statistically significant ($p<0.09$). Mixed model regression was used to allow adjustment for baseline factors in addition to those measured (site, gender, level of baseline use, and level of symptoms of depression). This subgroup analysis showed that bupropion had a significant effect compared to placebo, among male patients who had a lower level of methamphetamine use at baseline ($p<0.0001$). Comorbid depression and attention-deficit/ hyperactivity disorder did not change the outcome. These data suggest that bupropion, in combination with behavioral group therapy, was effective for increasing the number of weeks of abstinence in participants with low-to-moderate methamphetamine dependence, mainly male patients, regardless of their comorbid condition. Elkashef, A.M., Rawson, R.A., Anderson, A. L., Li, S.H., Holmes, T., Smith, E. V., Chiang, N., Kahn, R., Vocci, F., Ling, W., Pearce, V.J., McCann, M., Campbell, J., Gorodetzky, C., Haning, W., Carlton, B., Mawhinney, J., and Weis, D. Bupropion for the Treatment of Methamphetamine Dependence. Neuropsychopharmacology (advance online publication), 20 June 2007.

Combination Therapy with Pergolide and Ondansetron as a Potential Approach for Reducing Relapse in Abstinent Methamphetamine Abusers

The authors have shown in earlier studies that the serotonin 5-HT3 receptor antagonist ondansetron reduces cocaine self-administration and cocaine-

induced sensitization in rats if it is administered during cocaine withdrawal. The authors subsequently found that administration of the dopamine agonist pergolide followed by ondansetron, 3.5 h later, reversed cocaine sensitization and associated changes in NMDA and AMPA receptors. In their new study the authors tested this drug combination using a nose-poke task in 1) a methamphetamine sensitization model and 2) a reinstatement model following intravenous methamphetamine self-administration. They found that pergolide together with ondansetron administered on days 3-7 during methamphetamine withdrawal reversed methamphetamine-induced sensitization and attenuated reinstatement. Their hypothesis is that pergolide may evoke a methamphetamine-associated memory and that ondansetron disrupts its reconsolidation. These data support the hypothesis that combination treatment with pergolide plus ondansetron, two approved and clinically available human drugs, may hold potential as a therapeutic approach to reduce relapse in methamphetamine abusers. Davidson, C., Gopal, R., Ahn, C., Chen, Q., Mannelli, P., Patkar, A.A., Weese, G.D., Lee, T.H., and Ellinwood, E.H. Reduction in Methamphetamine Induced Sensitization and Reinstatement after Combined Pergolide plus Ondansetron Treatment during Withdrawal. Eur. J. Pharmacol., 565, pp. 113-118, 2007.

Treatment Retention for Buprenorphine Maintenance in "Real World"

The purpose of this study was to describe background characteristics, treatment process, outcomes and correlates of outcomes, for patients receiving buprenorphine maintenance in "real world" office-based settings in New York City. The study did not exclude patients with co-occurring psychiatric and non-opioid substance use disorders. A sample of six physicians completed anonymous chart abstraction forms for a total of 86 patients who began buprenorphine induction or who transferred to these practices during 2003-2005. The endpoint was the patient's current status or status at discharge from the index practice, presented in an intent-to-treat analysis. At the endpoint, 55% were retained in the index practice, 6% transferred to other buprenorphine practices, 7% transferred to other treatment, and 32% were lost to contact or out of any treatment, resulting in a total of 2/3 of patients remaining in an index practice or transferring to other treatment. Although co-occurring psychiatric disorders and polysubstance abuse at intake were common, these had no or minimal effect on study outcomes due to clinical attention for the disorders. Magura, S., Lee, S.J., Salsitz, E.A., Kolodny, A., Whitley, S.D., Taubes, T., Seewald, R., Joseph, H., Kayman, D.J., Fong, C., Marsch, L.A. and Rosenblum, A. Outcomes of Buprenorphine Maintenance in Office-Based Practice. J. Addict. Dis., 26(2), pp. 13-23, 2007.

Comparison of Heroin and Prescription Opioid Dependent Patients in Primary Care Office-Based Buprenorphine Treatment

Although prescription opioid dependence is increasing, treatment outcomes with office-based buprenorphine/naloxone among these patients remains to be described. This study compared demographic, clinical characteristics and treatment outcomes among 200 patients in a trial of primary care office-based buprenorphine/naloxone treatment, stratifying on those reporting exclusive heroin use (n = 124), heroin and prescription opioid use (n = 47), or only prescription opioid use (n = 29). Compared to heroin-only patients, prescription-opioid-only patients were younger, had fewer years of opioid use, less drug treatment history, more likely to be white, earned more income, and were less likely to have Hepatitis C antibodies. Prescription-opioid-only patients were more likely to complete treatment (59% vs. 30%), remained in treatment longer (21.0 vs. 14.2 weeks) and had a higher percent of opioid-negative urine samples than heroin-only patients (56.3% vs. 39.8%), all p values < .05. Patients who used both heroin and prescription opioids had outcomes that were

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intermediate between heroin-only and prescription-opioid-only patients. The study conclusion was that individuals dependent on prescription opioids have an improved treatment response to buprenorphine/naloxone maintenance in an office-based setting compared to those who exclusively or episodically use heroin. Moore, B.A., Fiellin, D.A., Barry, D.T., Sullivan, L.E., Chawarski, M.C., O'Connor, P.G. and Schottenfeld, R.S. Primary Care Office-Based Buprenorphine Treatment: Comparison of Heroin and Prescription Opioid Dependent Patients. J. Gen. Intern. Med., 22(4), pp. 527-30, 2007.

Intranasal Methamphetamine Produces Predictable Effects on Multiple Behavioral and Physiological Measures Before Peak Plasma Levels are Observed

This study investigated the acute effects of intranasal methamphetamine, the abuse of which has dramatically increased in the past decade. The effects of single-dose intranasal methamphetamine administration on a broad range of behavioral and physiological measures was examined in an inpatient, double-blind study in 11 non-treatment seeking methamphetamine abusers. During each session, one of four intranasal methamphetamine doses (0, 12, 25, and 50 mg/70 kg) was administered and methamphetamine plasma concentrations, cardiovascular, subjective, and psychomotor/cognitive performance effects were assessed before and after drug administration. Following drug administration, methamphetamine plasma concentrations systematically increased for 4h postdrug administration, then declined. Methamphetamine dose-dependently increased cardiovascular measures and positive subjective effects, with peaks occurring 5 - 15 minutes after drug administration, when plasma levels were still ascending. Cognitive performance on less complicated tasks was improved by all active methamphetamine doses, whereas performance on more complicated tasks was improved by intermediate (12 and 25 mg) doses. These results showed that intranasal methamphetamine produced predictable effects on multiple behavioral and physiological measures before peak plasma levels were observed. The dissociation between methamphetamine plasma concentrations and cardiovascular measures and positive subjective effects might have important implications for potential toxicity after repeated doses. Acute Physiological and Behavioral Effects of Intranasal Methamphetamine in Humans. Hart, C., Gunderson, E., Perez, A., Kirkpatrick, M., Thurmond, A., Comer, S., and Foltin, R. Neuropsychopharm., pp. 1-9 (2007) (advance online publication).

Effects of Intranasal Methamphetamine on Metacognition of Agency This study investigated the acute effects of intranasal methamphetamine on complex cognitive performance (a computerized task measuring metacognition of agency) in 10 non-treatment seeking methamphetamine abusers. In this four-session, within-participant, double-blind laboratory study, participants received one of four doses (0, 12, 25, or 50 mg/kg) and completed the metacognition of agency task. Following placebo, judgments of agency were greater under optimal task conditions compared with less than optimal task conditions. Relative to placebo, the 12 mg dose improved task performance, increased judgments of agency under the optimal condition, and decreased judgments of agency under the less than optimal condition. By contrast, the larger doses (25 and 50 mg) increased judgments of agency only under the optimal condition but disrupted performance under the less than optimal condition. These data show that a low intranasal methamphetamine dose enhanced judgments of agency and performance, while larger doses produced limited effects. Effects of Intranasal Methamphetamine on Metacognition of Agency. Kirkpatrick, M.G.,

Metcalfe, J., Greene, M.J., and Hart, C.L. Psychopharm. 2007 (e-pub ahead of print).

Difference in Attentional Bias Towards Cocaine Cues Between Treatment Seeking and Nontreatment Seeking Cocaine-Dependent Individuals

Cocaine-dependent individuals demonstrate attentional bias when measured by Stroop color-naming tasks that have been modified to include cocaine-related words. This study explored the relationship between attentional bias and the treatment-seeking status of cocaine-dependent individuals. The purpose of the study was to compare attentional bias towards cocaine-related verbal stimuli between treatment-seeking and nontreatment-seeking cocaine abusers. Performance on a Stroop task modified to include drug-related words was examined in 17 cocaine-dependent treatment-seeking male participants and 20 cocaine-dependent nontreatment-seeking male participants. Treatment seekers reported less experience with cocaine than nontreatment seekers but exhibited increased response latency and made more errors when identifying the colors of cocaine-related words, relative to neutral words ($p < .05$), whereas nontreatment seekers did not. The conclusions were that factors other than a high frequency of cocaine use may contribute to the difference in attentional bias towards cocaine cues between these subgroups of cocaine users. Attentional Bias Towards Cocaine-Related Stimuli: Relationship to Treatment-Seeking for Cocaine Dependence. Vadhan, N.P., Carpenter, K.M., Copersino, M.L., Hart, C.L., Foltin, R.W. and Nunes, E.V. Am. J. Drug and Alcohol Abuse, 33, pp. 727-736, 2007.

Quetiapine Treatment of Zolpidem Dependence

This is a case study of a 52-year old male with a lifelong history of substance use disorders who developed a dependence on zolpidem, and was successfully treated with quetiapine. The patient received a prescription for zolpidem 10 mg/day from his internist. Over a six-month period his use escalated to a minimum of 40 mg per day to a maximum of as much as 250 mg, which resulted in intoxication and amnesia. The patient was admitted to an inpatient detoxification unit and treated with clonazepam over a five-day period. After discharge, the patient experienced severe insomnia and craving for zolpidem. A trial of trazodone up to 200 mg QHS was initially effective, but the patient developed tolerance to the sedating effects. A trial of gabapentin followed, with initial efficacy, then a rapid development of tolerance. Quetiapine treatment was initiated at 50 mg QHS and titrated to higher doses as the patient developed tolerance to the sedating effects. The patient eventually stabilized at quetiapine 800 mg each night, with good hypnotic effects and no craving for zolpidem. Six months after detoxification from zolpidem, the patient has maintained abstinence from zolpidem and reports no craving. This case history suggests that, although zolpidem has relatively low abuse potential, patients with substance abuse histories may be at risk for abuse. In the case of zolpidem abuse or dependence, the use of another sedating agent with lower abuse potential should be considered. Quetiapine Treatment of Zolpidem Dependence. Mariani, J.J. and Levin, F.R. Am. J. on Addictions, 16, p. 426, 2007.

Comparison of Olanzapine to Risperidone in Substance-abusing Individuals with Schizophrenia

Drs. Akerele and Levin report the results of a 14-week double blind study that compared the efficacy of olanzapine to risperidone in reducing marijuana/cocaine craving and use in individuals with schizophrenia. The study consisted of three phases: a two-week assessment phase, a two-week cross-

taper phase onto olanzapine/risperidone, and a ten-week period of maintenance on olanzapine/risperidone. The proportion of cocaine-positive urines decreased over time for both groups with a trend for a greater reduction for the olanzapine group compared to risperidone group. In the last six weeks, marijuana craving was more likely for the risperidone group compared to the olanzapine group, although there was no group difference in the proportion of negative marijuana urines. The data suggest some potential for the utility of olanzapine for the treatment of cocaine dependence in individuals with schizophrenia. Akerele, E. and Levin, F.R. Comparison of Olanzapine to Risperidone in Substance-abusing Individuals with Schizophrenia. Am. J.Addict., 16, pp. 260-268, 2007.

Sustained-release Naltrexone: Novel Treatment for Opioid Dependence

At present, several different maintenance medications exist for treating opioid dependence, including methadone, buprenorphine and naltrexone. Of these, naltrexone is the only one that possesses no opioid agonist effects. Instead, naltrexone occupies opioid receptors and prevents or reverses the effects produced by opioid agonists. Despite its clear pharmacologic effectiveness, its clinical effectiveness in treating opioid dependence has been disappointing, primarily due to non-compliance with taking the medication. However, the recent availability of sustained-release formulations of naltrexone has renewed interest in this medication. The present paper describes the development of sustained-release naltrexone formulations and discusses the clinical issues associated with their use in treating opioid dependence. Comer, S.D., Sullivan, M.A., and Hulse, G.K. Sustained-release Naltrexone: Novel Treatment for Opioid Dependence. Expert. Opin. Investig. Drugs, 16, pp. 1285-1294, 2007.

Relevance of Rodent Models of Intravenous MDMA Self-administration to Human MDMA Consumption Patterns

Despite decades of research specifying harmful effects produced by 3,4-methylenedioxymethamphetamine (MDMA; a principal component of 'ecstasy' pills), young people (and adults) continue to use it. In an attempt to model human MDMA consumption patterns, preclinical investigators have sought to establish reliable patterns of intravenous MDMA self-administration in rodents. The objective of this report is to offer a critical review of published data that reveal MDMA self-administration in rodents. The data indicate that MDMA serves as a reinforcer in rodents, though the responses are not similar to those previously reported for psychostimulants (i.e., cocaine). Important differences between rodent models and human use patterns include frequency of dosing and dosage exposure, routes of administration, tolerance that develops to MDMA after repeated exposure, polydrug use in humans but not by rodents, limits on the repertoire of behaviors that can be exhibited by rodents undergoing IV self-administration procedures, and the question of neurotoxicity as it relates to models of self-administration. While MDMA is not as potent a reinforcer as other drugs of abuse, the fact remains that young people and adults continue to use the drug, and therefore, additional research is needed to determine why drugs with low reinforcing effects continue to be abused. De La, G.R., Fabrizio, K.R., and Gupta, A. Relevance of Rodent Models of Intravenous MDMA Self-administration to Human MDMA Consumption Patterns. Psychopharmacology, 189, pp. 425-434, 2007.

A 12-week Double-blind, Placebo-controlled Study of Bupropion SR Added to High-dose Dual Nicotine Replacement Therapy for Smoking Cessation or Reduction in Schizophrenia

The objective of this study was to examine whether there is a benefit of adding

bupropion SR to high-dose combination nicotine replacement therapy (NRT) and weekly group cognitive behavioral therapy (CBT) for smoking reduction or cessation in schizophrenia. Fifty-one adult smokers with schizophrenia were randomly assigned to a 12-week trial of bupropion SR 300 mg/d or placebo added to transdermal nicotine patch, nicotine polacrilex gum, and CBT. The treatment goal was smoking cessation. The primary outcome measure was biochemically confirmed 7-day point-prevalence of 50% -100% smoking reduction at week 12. Secondary outcomes were biochemically confirmed tobacco abstinence and change from baseline in expired air carbon monoxide (CO) and psychiatric symptoms. Subjects on bupropion + NRT had a greater rate of 50% to 100% smoking reduction at weeks 12 (60% vs. 31%; P=0.036) and 24, a lower expired air CO in the treatment and follow-up periods, (F=13.8; P< 0.001) and a greater continuous abstinence rate at week 8, before NRT taper, (52% vs. 19%; P=0.014). However, relapse rates in subjects on bupropion + dual NRT were 31% during NRT taper (weeks 8-12) and 77% at the 12-month follow-up. Abstinence rates did not differ by treatment group at weeks 12 (36% vs. 19%), 24 (20% vs. 8%), or 52 (12% vs. 8%). Because abstinence rates were high during treatment with combination pharmacotherapy and relapse rates were very high during taper and after discontinuation of treatment, study of longer term treatment with combination pharmacotherapy and CBT for sustained abstinence is warranted in those who attain initial abstinence with this intervention. Evins, A., Cather, C., Culhane, M., Birnbaum, A., Horowitz, J., Hsieh, E. et al. A 12-week Double-blind, Placebo-controlled Study of Bupropion SR Added to High-dose Dual Nicotine Replacement Therapy for Smoking Cessation or Reduction in Schizophrenia. J.Clin.Psychopharm., 27, pp. 380-386, 2007.

A Naturalistic Study of the Effects of Pharmacotherapy on Substance Use Disorders Among ADHD Adults

Studies of adults with attention deficit hyperactivity disorder (ADHD) show an elevated prevalence of substance use disorders (SUDs) and the substance abuse literature shows that ADHD is elevated in substance users. Some researchers postulate that stimulant treatment of ADHD increases the risk for SUD in ADHD patients but follow-up studies suggest treatment protects patients from subsequent SUDs. This report uses retrospective data to assess the impact of prior ADHD pharmacotherapy on SUDs in 206 ADHD adults (n=79 late-onset ADHD, n=127 full ADHD) grouped by lifetime history of ADHD treatment (no treatment, past treatment, current and past treatment). Structured Clinical Interview for DSM-IV (SCID) data were used to establish abuse and dependence, and Drug Use Screening Inventory (DUSI) responses were used to establish prevalence of use, preference for cigarettes, alcohol and drugs of abuse, complications from use, and motivation for use (get high, change mood, sleep better). No differences were found in the prevalence of cigarette smoking, alcohol or drug abuse or dependence, as well as no significant differences in 1-month prevalence of any use or use more than 20 times. No differences were found in complications of drug or alcohol use across groups. Subjects with current treatment rated getting high as a motivating factor significantly more frequently than subjects in the past treatment group; this result lost significance when the authors included ADHD diagnostic category. The results are consistent across substances and ADHD diagnoses, and support the hypothesis that pharmaco-therapy does not cause subsequent SUDs. Faraone, S.V., Biederman, J., Wilens, T.E., and Adamson, J. A Naturalistic Study of the Effects of Pharmacotherapy on Substance Use Disorders Among ADHD Adults. Psychol. Med., 37, pp. 1743-1752, 2007.

Sublingual Buprenorphine/Naloxone Precipitated Withdrawal in Subjects Maintained on Methadone

Buprenorphine is available in many countries for use as a sublingual medication

that is effective in the treatment of opioid dependence. When administered to opioid dependent persons, it can precipitate withdrawal under certain experimental and clinical conditions. Buprenorphine-related precipitated withdrawal is thought to occur due to its partial mu agonist effects. The risk of buprenorphine-precipitated withdrawal is increased as a function of three parameters: higher doses of buprenorphine, a shorter time interval between the exposure to the full agonist and buprenorphine administration (which may vary as a function of the half life of the full agonist), and higher levels of physical dependence. The purpose of this study was to examine the relationship between buprenorphine delivery and occurrence of buprenorphine-induced precipitated withdrawal in 16 subjects. Participants were adult male and female volunteers eligible for methadone maintenance treatment. Participants were initially stabilized as outpatients on methadone 100 mg/day for an average of 25 days. The findings have implications for the use of buprenorphine/naloxone. Specifically, findings suggest that patients with high levels of physical dependence, including those maintained on daily doses of methadone of up to 100mg, may receive repeated small doses of buprenorphine/naloxone and not experience significant precipitated withdrawal. The administration of repeated, small doses of buprenorphine/naloxone may by the optimal mechanism for transitioning patients with higher levels of opioid physical dependence onto sublingual buprenorphine/naloxone. Rosado, J., Walsh, S.L., Bigelow, G.E., and Strain, E.C., Sublingual Buprenorphine/Naloxone Preciptitated Withdrawal in Subjects Maintained on 100mg of Daily Methadone. Drug and Alcohol Dep., 90, pp. 261-269, 2007.

Buprenorphine and Norbuprenorphine in Hair of Pregnant Women and Their Infants after Controlled Buprenorphine Administration

Buprenorphine is under investigation as a pharmacotherapeutic agent for treating opioid dependence in pregnant women. The investigators hypothesized that there would be a relationship between the cumulative maternal dose of buprenorphine during pregnancy and the concentration of buprenorphine and norbuprenorphine in maternal and infant hair. This study examined buprenorphine and norbuprenorphine concentrations in hair obtained from 9 buprenorphine-maintained pregnant women and 4 of their infants. Specimens were analyzed by liquid chromatography-tandem mass spectrometry with limits of quantification of 3.0 pg/mg. All maternal hair specimens were washed with methylene chloride before analysis, and when sufficient amounts of maternal hair were available, specimens also were analyzed without washing. Infant hair specimens were not washed. Buprenorphine concentrations were significantly greater in unwashed hair than washed hair ($P = 0.031$). Norbuprenorphine concentrations were significantly greater than buprenorphine concentrations in both maternal ($P = 0.0097$) and infant hair ($P = 0.0033$). There were statistically significant associations between the cumulative maternal dose of buprenorphine administered and the concentrations of buprenorphine (washed, $P < 0.0001$; unwashed, $P = 0.0004$), norbuprenorphine (washed, $P < 0.0001$; unwashed, $P = 0.0005$), and buprenorphine plus norbuprenorphine (washed, $P < 0.0001$; unwashed, $P = 0.0005$) for both washed and unwashed maternal hair specimens. There was a significant positive association between concentrations of buprenorphine and norbuprenorphine in maternal hair (washed, $P < 0.0001$; unwashed, $P = 0.0003$), a trend for this association in infant hair ($P = 0.08$), and an association between buprenorphine concentrations in maternal unwashed hair and infant hair ($P = 0.0002$). The buprenorphine:norbuprenorphine ratio increased in distal segments. Buprenorphine treatment during gestation provides an opportunity for monitoring drug disposition in maternal and fetal tissues under controlled conditions. Goodwin, R.S., Wilkins, D.G., Averin, O., Choo, R.E., Schroeder, J.R., Jasinski, D.R. et al. Buprenorphine and Norbuprenorphine in Hair of Pregnant Women and Their Infants after Controlled Buprenorphine Administration. Clin. Chem. (e-pub ahead of print, 2007).

Behavioral Economic Analysis of Drug Preference Using Multiple Choice Procedure Data

The multiple choice procedure has been used to evaluate preference for psychoactive drugs, relative to money amounts (price), in human subjects. The present re-analysis shows that MCP data are compatible with behavioral economic analysis of drug choices. Demand curves were constructed from studies with intravenous fentanyl, intramuscular hydromorphone and oral methadone in opioid-dependent individuals; oral d-amphetamine, oral MDMA alone and during fluoxetine treatment, and smoked marijuana alone or following naltrexone pretreatment in recreational drug users. For each participant and dose, the MCP crossover point was converted into unit price (UP) by dividing the money value ($) by the drug dose (mg/70kg). At the crossover value, the dose ceases to function as a reinforcer, so "0" was entered for this and higher UPs to reflect lack of drug choice. At lower UPs, the dose functions as a reinforcer and "1" was entered to reflect drug choice. Data for UP vs. average percent choice were plotted in log-log space to generate demand functions. Rank of order of opioid inelasticity (slope of non-linear regression) was: fentanyl>hydromorphone (continuing heroin users)>methadone> hydromorphone (heroin abstainers). Rank order of psychostimulant inelasticity was d-amphetamine>MDMA>MDMA+fluoxetine. Smoked marijuana was more inelastic with high-dose naltrexone. These findings show this method translates individuals' drug preferences into estimates of population demand, which has the potential to yield insights into pharmacotherapy efficacy, abuse liability assessment, and individual differences in susceptibility to drug abuse. Greenwald, M.K. Behavioral Economic Analysis of Drug Preference Using Multiple Choice Procedure Data. Drug Alcohol Depend. (e-pub ahead of print, 2007).

Opioid Antagonism of Cannabinoid Effects: Differences between Marijuana Smokers and Nonmarijuana Smokers

The objective of this study was to test a lower, more opioid-selective dose of naltrexone (12 mg) in combination with THC. The influence of marijuana-use history and sex was also investigated. Naltrexone (0, 12 mg) was administered 30 min 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 (Study 1; n=22) and in nonmarijuana smoking (Study 2; n=21) men and women. The results show 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 shifted THC's effects in the opposite direction, enhancing the intoxicating effects of a low THC dose (2.5 mg) and decreasing 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. These data demonstrate that the interaction between opioid antagonists and cannabinoid agonists varies as a function of marijuana use history. Haney, M. Opioid Antagonism of Cannabinoid Effects: Differences between Marijuana Smokers and Nonmarijuana Smokers. Neuropsychopharmacology, 32, pp. 1391-1403, 2007.

Dronabinol and Marijuana in HIV-positive Marijuana Smokers: Caloric Intake, Mood, and Sleep

Individuals with HIV constitute the largest group using cannabinoids for medicinal reasons; yet, no studies have directly compared the tolerability and

efficacy of smoked marijuana and oral dronabinol maintenance in HIV-positive marijuana smokers. This placebo-controlled within-subjects study evaluated marijuana and dronabinol across a range of behaviors: eating topography, mood, cognitive performance, physiologic measures, and sleep. HIV-positive marijuana smokers (n = 10) completed 2 16-day inpatient phases. Each dronabinol (5 and 10 mg) and marijuana (2.0% and 3.9% Delta9-tetrahydrocannabinol [THC]) dose was administered 4 times daily for 4 days, but only 1 drug was active per day, thereby maintaining double-blind dosing. Four days of placebo washout separated each active cannabinoid condition. As compared with placebo, marijuana and dronabinol dose dependently increased daily caloric intake and body weight in HIV-positive marijuana smokers. All cannabinoid conditions produced significant intoxication, except for low-dose dronabinol (5 mg); the intoxication was rated positively (eg, "good drug effect") with little evidence of discomfort and no impairment of cognitive performance. Effects of marijuana and dronabinol were comparable, except that only marijuana (3.9% THC) improved ratings of sleep. These data suggest that for HIV-positive marijuana smokers, both dronabinol (at doses 8 times current recommendations) and marijuana were well tolerated and produced substantial and comparable increases in food intake. Haney, M., Gunderson, E.W., Rabkin, J., Hart, C.L., Vosburg, S.K., Comer, S.D. et al. Dronabinol and Marijuana in HIV-positive Marijuana Smokers. Caloric Intake, Mood, and Sleep. J. Acquir. Immune. Defic. Syndr., 45, pp. 545-554, 2007.

Similar Exposure to a Tobacco-specific Carcinogen in Smokeless Tobacco Users and Cigarette Smokers

Smokeless tobacco has been proposed as a reduced risk substitute for smoking, but no large studies have investigated exposure to the powerful carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in smokeless tobacco users versus smokers. The purpose of this study was to carry out such a comparison. Levels of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL), a biomarker of NNK exposure, and cotinine, a biomarker of nicotine exposure, were quantified in the urine of 420 smokers and 182 smokeless tobacco users who were participants in studies designed to reduce their use of these products. The measurements were taken at baseline, before intervention. Levels of total NNAL per milliliter of urine were significantly higher in smokeless tobacco users than in smokers ($P < 0.0001$). When adjusted for age and gender, levels of total NNAL per milligram of creatinine were also significantly higher in smokeless tobacco users than in smokers ($P < 0.001$). Levels of cotinine per milliliter of urine and per milligram of creatinine were significantly higher in smokeless tobacco users than in smokers ($P < 0.001$). These results show similar exposures to the potent tobacco-specific carcinogen NNK in smokeless tobacco users and smokers. These findings do not support the use of smokeless tobacco as a safe substitute for smoking. Hecht, S.S., Carmella, S.G., Murphy, S.E., Riley, W.T., Le, C., Luo, X. et al. Similar Exposure to a Tobacco-specific Carcinogen in Smokeless Tobacco Users and Cigarette Smokers. Cancer Epidemiol. Biomarkers Prev., 16, pp. 1567-1572, 2007.

Effects of Major Depressive Disorder and Attention-Deficit/Hyperactivity Disorder on the Outcome of Treatment for Cocaine Dependence

Co-occurring psychiatric disorders have been associated with poor prognosis among substance-dependent patients, but few studies have examined this association among patients with cocaine dependence (CD). The authors compared baseline characteristics and treatment outcome between cocaine-dependent patients with major depressive disorder (MDD; n = 66), those with attention-deficit/hyperactivity disorder (ADHD; n = 53), and those with CD without comorbid disorders (CD alone; n = 48) who had been randomized to

the placebo arms of clinical trials with venlafaxine, methylphenidate, and gabapentin, respectively. The three groups differed significantly in racial makeup, with more Caucasians and Hispanics among patients with MDD and those with ADHD but more African Americans among those with CD alone. The groups did not differ significantly in treatment retention, with retention rates ranging from 42% to 47%; neither did they differ in the rates of achieving 2 consecutive weeks of urinalysis-confirmed abstinence, with rates ranging from 40% to 50%. Using logistic regression for repeated measures with general estimating equations, modeling the likelihood of a cocaine-positive week over time in treatment, the authors found the diagnostic group to interact with the baseline level of cocaine use and time. Among cocaine-dependent patients who achieved abstinence at baseline, those with MDD and those with ADHD had better outcome over time as compared with patients with CD alone. However, among patients with cocaine-positive urine specimens at baseline, those with MDD and those with ADHD were associated with poor outcome as compared with patients with CD alone. The findings suggest that diagnosis and treatment of co-occurring disorders such as depression and ADHD may be important components of treatment planning for CD and that the baseline level of cocaine use should be included as a covariate in studies evaluating the impact of such treatment. Levin, F., Bisaga, A., Raby, W., Aharonovich, E., Rubin, E., Mariani, J. et al. Effects of Major Depressive Disorder and Attention-Deficit/Hyperactivity Disorder on the Outcome of Treatment for Cocaine Dependence. J. Subst. Abuse Treat (e-pub ahead of print, 2007).

Gender Differences with High-dose Naltrexone in the Patients with Co-occurring Cocaine and Alcohol Dependence

This is a randomized, double-blind, placebo-controlled clinical trial that evaluated the efficacy of a higher-than-typical daily dose of naltrexone (150 mg/day), taken for 12 weeks, in 164 patients (n = 116 men and n = 48 women) with co-occurring cocaine and alcohol dependence. Patients were stratified by gender and then randomly assigned to either naltrexone or placebo, and to either cognitive-behavioral therapy or a type of medical management. The two primary outcomes were cocaine use and alcohol use. Significant Gender x Medication interactions were found for cocaine use via urine drug screens (three way, with time) and self-reports (two way) for drug severity (two way) and alcohol use (two way). The type of psychosocial treatment did not affect outcomes. Thus, 150 mg/day naltrexone added to a psychosocial treatment resulted in reductions in cocaine and alcohol use and drug severity in men, compared to higher rates of cocaine and alcohol use and drug severity in women. Pettinati, H., Kampman, K., Lynch, K., Suh, J., Dackis, C., Oslin, D. et al. Gender Differences with High-dose Naltrexone in the Patients with Co-occurring Cocaine and Alcohol Dependence. J. Subst. Abuse Treat. (e-pub ahead of print, 2007).

Nicotine Replacement and Behavioral Therapy for Smoking Cessation in Pregnancy

This study examines whether adding nicotine replacement therapy (NRT) to cognitive-behavioral therapy (CBT) for pregnant smokers increases rates of smoking cessation. An open-label randomized trial (Baby Steps, n=181) of CBT-only versus CBT+NRT (choice of patch, gum, or lozenge; 1:2 randomization) was used. Data were collected from 2003 through 2005; analyses were conducted in 2006 and 2007. Outcomes were biochemically validated self-reported smoking status at 7 weeks post-randomization, 38 weeks gestation, and 3 months postpartum. Women in the CBT+NRT arm were almost three times more likely than women in the CBT-only arm to have biochemically validated cessation at both pregnancy time points (after 7 weeks: 24% vs 8%, p=0.02; at 38 weeks gestation: 18% vs 7%, p=0.04), but not at 3 months postpartum (20% vs 14%, p=0.55). Recruitment was

suspended early by an Independent Data and Safety Monitoring Board when an interim analysis found a higher rate of negative birth outcomes in the CBT+NRT arm than in the CBT-only arm. In the final analysis, the difference between the arms in rate of negative birth outcomes was 0.09 (p=0.26), when adjusted for previous history of preterm birth. The addition of NRT to CBT promoted smoking cessation in pregnant women. This effect did not persist postpartum. More data are needed to determine safety parameters and to confirm the efficacy of NRT use during pregnancy. Pollak, K.I., Oncken, C.A., Lipkus, I.M., Lyna, P., Swamy, G.K., Pletsch, P.K. et al. Nicotine Replacement and Behavioral Therapy for Smoking Cessation in Pregnancy. Am. J. Prev. Med., 33, pp. 297-305, 2007.

Progesterone Effects on Cocaine Use in Male Cocaine Users Maintained on Methadone: A Randomized, Double-blind, Pilot Study

Previously, the authors reported that progesterone treatment attenuated reports of cocaine-induced high in male and female cocaine users. In this pilot clinical trial, the authors tested the safety and efficacy of oral progesterone as a treatment for cocaine dependence in methadone-stabilized male cocaine users. This was a 10-week, randomized, double-blind, placebo-controlled trial. Forty-five male methadone-stabilized cocaine users were randomized to receive placebo (n=15) or progesterone (n=30) for 9 weeks. The progesterone dose was gradually increased from 100 mg to 300 mg twice daily by Week 4 and maintained through Week 10. Treatment retention for the clinical trial was 80%, without significant group differences (log rank=2.4, p=.12). Hierarchical linear modeling estimates of obtaining a cocaine positive urine result across 10 weeks showed a very slight reduction in cocaine use for the progesterone group (Z=-2.89, p<.004). The placebo group showed a slight increase in cocaine use from Week 1 to Week 10 (Z=2.72, p<.007). These slopes significantly differed from each other (Z=-3.83, p<.0001). Overall, the placebo group showed significantly lower probability of having a cocaine positive urine result at treatment's end (Weeks 9 and 10) compared with the progesterone group (0.60 vs. 0.73; U=4837, p<.04). These preliminary findings do not support the efficacy of progesterone in male cocaine users. The efficacy of progesterone in female cocaine users remains to be determined in future studies. Sofuoglu, M., Poling, J., Gonzalez, G., Gonsai, K., Oliveto, A., and Kosten, T.R. Progesterone Effects on Cocaine Use in Male Cocaine Users Maintained on Methadone: A Randomized, Double-blind, Pilot Study. Exp. Clin. Psychopharmacol., 15, pp. 453-460, 2007.

Modafinil and Nicotine Interactions in Abstinent Smokers

In this study, the authors examined the effects of a wakefulness-promoting medication, modafinil, alone and with the nicotine lozenge, on subjective, physiological and cognitive measures as well as on nicotine withdrawal in overnight abstinent cigarette smokers. Nineteen smokers, 13 male and 6 female, participated in a double-blind, placebo-controlled, crossover study. In each of three experimental sessions, subjects were treated orally with a single 200 mg or 400 mg dose of modafinil or placebo. Two hours and 10 min following the medication treatment, subjects received a single 2 mg nicotine lozenge. Both doses of modafinil alone increased the rating of elated-depressed on the Profile of Mood States (POMS) subscale in the direction of depressed and increased ratings of negative affect on the Positive and Negative Affect Schedule (PANAS). In contrast, the 200 mg modafinil dose combined with a 2 mg nicotine lozenge, increased the rating of energetic-tired in the direction of energetic on the POMS subscale. Modafinil attenuated self-reported rating of 'drug strength' in response to the nicotine lozenge. Modafinil, alone or in combination with the nicotine lozenge, did not affect tobacco withdrawal symptoms. There was an increase in baseline heart rate and systolic blood

pressure under modafinil treatment. In addition, modafinil speeded reaction times on a modified Stroop task. The clinical utility of modafinil for smoking cessation needs to be determined in future studies. Sofuoglu, M., Waters, A.J., and Mooney, M. Modafinil and Nicotine Interactions in Abstinent Smokers. Hum. Psychopharmacol. (e-pub ahead of print, 2007).

Management of Relapse in Naltrexone Maintenance for Heroin Dependence

This paper identifies critical determinants of lapses to opioid use during naltrexone maintenance. Time retained in treatment was examined as a function of whether lapses to opioid use occurred while adherent to naltrexone (blocked use), or after having missed naltrexone doses (unblocked). Participants (N=83) met DSM-IV criteria for opioid dependence and identified a significant other willing to participate in their treatment. Following inpatient detoxification, participants were enrolled in a 26-week outpatient course of therapy and naltrexone maintenance. Patients with unblocked use had a very high rate of dropout (10% retained at 6 months), dropout usually occurring within 2 weeks after unblocked use. Patients with only blocked use had less dropout (33% retained at 6 months). However, episodes of blocked use were often followed by unblocked use and dropout. During naltrexone maintenance for opioid dependence unblocked opioid use calls for immediate intervention, such as detoxification or switching to the partial agonist buprenorphine. Episodes of blocked use warrant increased clinical attention, such as direct observation of naltrexone ingestion, increased dose, or increased intensity of treatment contact. Maintenance on oral naltrexone is a fragile treatment because it is so easily undermined by episodes of opioid use while non-compliant. New long-acting injectable or implantable formulations of naltrexone may address this limitation and should be investigated for treatment of opioid dependence. Sullivan, M.A., Garawi, F., Bisaga, A., Comer, S.D., Carpenter, K., Raby, W. N. et al. Management of Relapse in Naltrexone Maintenance for Heroin Dependence. Drug Alcohol Depend., 91, pp. 289-292, 2007.

Neuronal Nicotinic Receptor Agonists for the Treatment of Attention-Deficit/Hyperactivity Disorder: Focus on Cognition

Attention deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed neurobehavioral disorder in children and adolescents, and in about half of these patients, significant symptomology continues into adulthood. Although impulsivity and hyperactivity are the most salient features of ADHD, cognitive deficits, particularly impairments in attention and executive function, are an important component, particularly in adolescents and adults, with over 90% of adults seeking treatment for ADHD manifesting cognitive dysfunction. Currently available medications treat the core ADHD symptoms but typically do not adequately address cognitive aspects of ADHD, underscoring the need for new therapeutics. Dopamine and norepinephrine are hypothesized to be particularly important in ADHD, but there is emerging evidence that cholinergic neurotransmission, particularly involving neuronal nicotinic acetylcholine receptors (nAChRs), may play a role in the pathophysiology of ADHD. Nicotine has demonstrated procognitive effects in both humans and experimental animals and has produced signals of efficacy in small proof-of-concept adult ADHD trials. Although adverse effects associated with nicotine preclude its development as a therapeutic, a number of novel nAChR agonists with improved safety/tolerability profiles have been discovered. Of these, ABT-418 and ABT-089 have both demonstrated signals of efficacy in adults with ADHD. Notably, tolerability issues that might be expected of a nAChR agonist, such as nausea and emesis, were not observed at efficacious doses of ABT-089. Further understanding of the effects of novel neuronal nAChR agonists on specific aspects of cognitive functioning in ADHD is required to assess the full potential of this approach. Wilens, T.E. and Decker, M.W. Neuronal Nicotinic Receptor

Agonists for the Treatment of Attention-Deficit/Hyperactivity Disorder: Focus on Cognition. Biochem. Pharmacol., 74, pp. 1212-1223, 2007.

When ADHD and Substance Use Disorders Intersect: Relationship and Treatment Implications

In this report, the authors describe the developmental relationship between ADHD and SUDs. ADHD alone and in combination with co-occurring psychopathology is a risk factor for the development of SUDs in adulthood. Conversely, approximately one fifth of adults with SUDs have ADHD. Pharmacotherapeutic treatment of ADHD in children reduces the risk for later cigarette smoking and SUDs in adulthood. In contrast, medication treatment alone of adults with ADHD and current SUD is inadequate for both ADHD and SUD. Stimulant diversion continues to be of concern, particularly in older adolescents and young adults. Wilens, T.E. and Fusillo, S. When ADHD and Substance Use Disorders Intersect: Relationship and Treatment Implications. Curr. Psychiatry Rep., 9, pp. 408-414, 2007.

The Novel Cannabinoid CB(1) Receptor Neutral Antagonist AM4113 Suppresses Food Intake and Food-Reinforced Behavior but Does not Induce Signs of Nausea in Rats

CB1 inverse agonists have been shown to suppress food intake, but they also appear to induce nausea and malaise. The present studies characterized the behavioral effects of AM4113, a CB1 neutral antagonist. AM4113 binds to CB1 receptors, but does not show inverse agonist properties (i.e. no effects on cyclic-AMP production). In tests of spontaneous locomotion and analgesia, AM4113 reversed the effects of the CB1 agonist AM411. It suppressed food-reinforced operant responding in rats on high-fat, high-carbohydrate, and lab chow diets in a dose-dependent manner. AM4113 did not induce conditioned gaping, which is a sign of nausea and food-related malaise in rats. Sink, K.S., McLaughlin, P.J., Wood, J.A., Brown, C., Fan, P., Vemuri, V.K., Pang, Y., Olzewska, T., Thakur, G.A., Makriyannis, A., Parker, L.A., Salamone, J.D. Neuropsychopharmacology, June 20, 2007 (e-pub ahead of print).

Antibody-Catalyzed Oxidation of Delta(9)- Tetrahydrocannabinol

Catalytic antibodies capable of oxidatively degrading the major psychoactive component of marijuana, Delta9-tetrahydrocannabinol (Delta9-THC), are presented. The antibodies generate reactive oxygen species from singlet oxygen (1O2*), using riboflavin (vitamin B2) and visible light as the 1O2* source. Cannabitriol was identified as the major degradation product of this reaction, demonstrating the ability of an antibody to catalyze a complex chemical transformation with therapeutic implications for treating marijuana abuse. Brogan, A.P., Eubanks, L.M., Koob, G.F., Dickerson, T.J., and Janda, K.D. J. Am. Chem. Soc. 129(12), pp. 3698-3702, 2007.

Effects of UMB24 and (+/-)-SM 21, Putative Sigma2-Preferring Antagonists, on Behavioral Toxic and Stimulant Effects of Cocaine in Mice

Earlier studies have demonstrated that antagonism of sigma1 receptors attenuates the convulsive, lethal, locomotor stimulatory and rewarding actions of cocaine in mice. In contrast, the contribution of sigma2 receptors is unclear because experimental tools to selectively target this subtype are unavailable. The authors characterized UMB24 (1-(2-phenethyl)-4-(2-pyridyl)-piperazine) and (+/-)-SM 21 (3alpha-tropanyl-2-(4-chorophenoxy)butyrate) in receptor binding and behavioral studies, which confirmed their preferential affinity for sigma2 over sigma1 receptors. In behavioral studies, pretreatment of mice

with these compounds significantly attenuated cocaine-induced convulsions and locomotor activity, but not lethality. Compared with saline, (+/-)-SM 21 produced no significant effects, but UMB24 had locomotor depressant actions. Together, the data suggest that sigma2 receptor antagonists have the potential to attenuate some of the behavioral effects of cocaine, and further development of more selective, high affinity ligands are warranted. Matsumoto, R.R., Pouw, B., Mack, A.L., Daniels, A., and Coop, A. Pharmacol. Biochem. Behav. 86(1), pp. 86-91, 2007.

Director's Report to the National Advisory Council on Drug Abuse - February, 2008

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

HIV/AIDS-Related

CD4+ T Cell-dependent Reduction in Hepatitis C Virus-specific Humoral Immune Responses after HIV Infection

Human immunodeficiency virus (HIV) infection adversely affects all stages of hepatitis C virus (HCV) infection, leading to increased rates of viral persistence, higher levels of HCV viremia, and accelerated progression of HCV-related liver disease. These disease interactions may result in part from impairment of B cell function, which is CD4(+) T cell dependent. To determine the effect of HIV infection on B cell function, authors compared HCV antibody levels and specificities in 29 HCV-infected persons before and after they acquired HIV and assessed the temporal correlation of these changes with overall CD4(+) T lymphocyte counts. The pre-HIV infection HCV antibody titer was a predictor of the subsequent titer for all antigens, and decreasing CD4(+) T cell numbers was strongly associated with a decrease in anti-HCV titers for several antigens. CD4(+) T cells counts of <500 cells/mm(3) were significantly associated with lower HCV antibody end-point titers. Higher HCV end-point titers were associated with fewer years from HIV infection and, for Core antigen, current drug use. The authors conclude that HCV-specific antibody production is impaired by HIV infection, and loss of antibody production depends on CD4(+) T cell depletion. However, the decrease in titers is less significant in those who continue to actively inject drugs. Netski, D.M., Mosbruger, T., Astemborski, J., Mehta, S., Thomas, D., and Cox, A. J. Infect. Dis. 195(6), pp. 857-863, 2007.

Hepatitis C Virus Infection is Associated with Insulin Resistance Among Older Adults with or at Risk of HIV Infection

The objectives of this research was to determine the associations of hepatitis C virus (HCV) infection with insulin resistance and abnormal glucose tolerance in a cohort of older adults with or at risk of HIV infection. A cross-sectional study of 267 HIV-infected and 179 at-risk-uninfected adults without a history of diabetes mellitus was employed. HCV antibody assays and RNA levels were performed to assess HCV status. Antiretroviral use, family history of diabetes, sedentary behavior, and sociodemographic data were obtained using standardized interviews. Fasting insulin levels and oral glucose tolerance tests were performed to assess two outcomes, the homeostasis model assessment of insulin resistance and abnormal glucose tolerance [impaired glucose tolerance (IGT) or diabetes]. Of 446 participants, 265 (59%) were HCV seropositive; of

these, 199 (75%) had detectable HCV-RNA levels. Insulin resistance was greater among HCV-seropositive compared with seronegative participants, adjusting for body mass index, Hispanic ethnicity, age greater than 55 years, sedentary behavior (watching television > 4h/day), HIV status, HAART, and protease inhibitor (PI) use. Ninety-eight participants (22%) had abnormal glucose tolerance (69 with IGT and 29 with diabetes). Among HIV-infected participants, 25% were on non-PI HAART and 52% were on PI HAART, but HAART and PI use were not associated with insulin resistance or abnormal glucose tolerance. Among obese participants, abnormal glucose tolerance was more common in HCV-seropositive than seronegative individuals, whereas among non-obese participants there was no association. The potential impact of HCV co-infection and obesity on glucose metabolism should be recognized in clinical care, and addressed in future research studies of HIV-infected individuals. Howard, A.A., Lo, Y., Floris-Moore, M., Klein, R.S., Fleischer, N., and Schoenbaum, E.E. AIDS. 21(5), pp. 633-641, 2007.

Body Image in Older Men With or At-risk for HIV Infection

Authors performed a cross-sectional analysis of factors associated with negative body image among 550 older men with or at-risk for HIV infection, including demographics, depression, illicit drug use, and antiretroviral therapy adherence. Overall, 31 per cent of participants reported negative body image, which was independently associated with increased BMI, self-rated fair/poor health, depression, and erectile dysfunction, but not HIV status. Screening for and treating depression, sexual dysfunction, and obesity in older men should be considered. Sharma, A., Howard, A.A., Klein, R.S., Schoenbaum, E.E., Buono, D., Webber, M.P. AIDS Care. 19(2), pp. 235-241, 2007.

Factors Affecting Reproductive Hormones in HIV-infected, Substance-using Middle-aged Women

The objective of this study was to determine whether reproductive hormone levels are affected by human immunodeficiency virus (HIV) and drug use. HIV-infected and uninfected women (N=429), median age 45, were interviewed on menstrual frequency, demographic and psychosocial characteristics, and drug use behaviors. Serum was obtained on cycle days 1 to 5 in women reporting regular menses. Premenopausal-, early menopausal, and late menopausal transition and postmenopausal stages were assigned based on menstrual history. Serum was assayed for follicle-stimulating hormone (FSH), estradiol (E2), luteinizing hormone (LH), prolactin, thyroid-stimulating hormone, and inhibin B. Body mass index, HIV serostatus, and CD4+ counts were measured. Factors associated with hormone concentrations were assessed using uni- and multivariable analyses. Hormone concentrations were compared within menstrual status categories using nonparametric comparisons of means. In this cross-sectional analysis, LH and FSH increased, and E2 and inhibin B were significantly lower in women of older age and more advanced menopausal status. Increased body mass index was strongly associated with decreased LH. Opiate use was significantly associated with lower inhibin B and E2 and increased prolactin. Poorer self-rated health was statistically significantly associated with lower LH and FSH, but increased education was associated with higher LH and FSH. Among HIV-seropositive women, opiate users had detectably lower FSH and LH than nonusers, and use of highly active antiretroviral therapy was significantly related to higher LH, FSH, and E2, whereas cocaine use was associated with lower E2. Authors conclude that age and menopausal status are strongly related to reproductive hormones. Body mass index and use of opiates, cocaine, and highly active antiretroviral therapy as well as educational attainment and perceived health can significantly modify reproductive hormones during the menopausal transition and need to be considered when interpreting hormone levels in middle-aged women. Santoro, N., Lo, Y., Moskaleva, G., Arnsten, J.H., Floris-Moore, M., Howard, A.A., Adel,

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G., Zeitlian, G., Schoenbaum, E.E. Menopause. 14(5), pp. 859-865, 2007.

Decreased Bone Mineral Density and Increased Fracture Risk in Aging Men With or At Risk for HIV Infection

Osteopenia has been described in HIV-infected persons, but most studies have not focused on aging men, have not included an HIV-negative comparison group with similar risks to those of the HIV-infected men, or lacked data on fracture rates. Authors analyzed bone mineral density (BMD) and incident fractures in 559 men who were >or= 49 years old with or at-risk for HIV, including 328 with and 231 without HIV infection. Median age was 55 years, 56% were black and 89% had used illicit drugs. In unadjusted analysis, BMD was lower in HIV-infected compared with HIV-uninfected men at the femoral neck (0.97 +/- 0.14 versus 1.00 +/- 0.15 g/cm; P < 0.05) and lumbar spine (1.17 +/- 0.20 versus 1.20 +/- 0.21 g/cm; P = 0.06); both differences were significant (P < 0.05) after adjusting for age, weight, race, testosterone level, and prednisone and illicit drug use. Non-black race and body weight were independently associated with BMD at both measurement sites and methadone therapy was independently associated with spine BMD. Among HIV-infected men, 87% had taken antiretrovirals and 74% had taken protease inhibitors, but their use was not associated with BMD. Among men who had at least one subsequent study visit (94%), incident fracture rates per 100 person-years differed among men with normal BMD, osteopenia and osteoporosis (1.4 versus 3.6 versus 6.5; P < 0.01). A 38% increase in fracture rate among HIV-infected men was not statistically significant. The authors conclude that HIV infection is independently associated with modestly reduced BMD in aging men, and decreased BMD is associated with increased fracture risk. Arnsten, J.H., Freeman, R., Howard, A.A., Floris-Moore, M., Lo, Y., and Klein, R.S. AIDS. 21(5), pp. 617-623, 2007.

Hepatitis C or Dual Infections of HIV and HCV Factors Affecting Serum Concentrations of Hepatitis C Virus (HCV) RNA in HCVgenotype 1-Infected Patients with Chronic Hepatitis

The serum concentration of hepatitis C virus (HCV) RNA is usually stable (4 to 8 log(10) IU/ml) in untreated patients with chronic hepatitis C. While this baseline HCV RNA concentration ([HCV RNA](BL)) is predictive of a sustained virologic response to treatment, its determinants are only partially identified. The authors therefore analyzed the baseline characteristics of 2,472 HCV genotype 1-infected patients to identify correlations with gender, age, race, weight, body mass index (BMI), HCV acquisition mode, HCV subtype, alanine aminotransferase concentration, or histopathologic changes in the liver. After separation of the data according to four [HCV RNA](BL) groups (< or =5.0, >5.0 to 5.6, >5.6 to 5.9, and >5.9 log(10) IU/ml), the authors determined that increasing [HCV RNA](BL) correlated (P < 0.05) with increasing proportions of patients who were male, >40 years of age, or heavier (a weight of >85 kg or a BMI of >27 kg/m(2)). Histologic activity index (HAI) data were available for 1,304 of these patients: increasing [HCV RNA](BL) correlated with higher fibrosis and necrosis-inflammation scores. As a continuous variable, [HCV RNA](BL) correlated with age, gender, weight (continuous or < or =85 versus >85 kg), BMI (continuous or < or =27 versus >27 kg/m(2)), subtype, fibrosis score, and necrosis-inflammation score; however, multiple-regression analysis yielded P values of <0.1 only for age, gender, BMI (< or =27 versus >27 kg/m(2)), and fibrosis score. While these findings are suggestive of a role for these factors in maintenance of the pretreatment state of HCV infection, the multiple-regression model accounted for only < or =4.6% of the [HCV RNA](BL) differences between individuals (R(2) = 0.046 for 1,304 patients with HAI scores; 0.043 for all 2,472 patients). Ticehurst, J., Hamzeh, F., Thomas, D. J. Clin. Microbiol. 45, pp. 2426-2433, 2007.

Liver Enzyme Flares and Occult Hepatitis B in Persons with Chronic Hepatitis C Infection

Occult hepatitis B (HBV) has been reported in numerous clinical settings, but it remains unclear whether occult HBV contributes to liver damage. Given that typical chronic HBV infections often have periodic flairs in viral replication and liver damage, the authors hypothesized that occult HBV may also have flares in viral replication that are associated with increased liver enzymes. Authors screened hepatitis B surface antigen negative injection drug users with untreated chronic hepatitis C viral (HCV) infection for unexplained ALT/AST flares. To further enrich for individuals with possible occult HBV flares, the authors studied those individuals whose flares were associated with IgM antibodies to hepatitis B core antigen. Serum samples were assayed for HBV DNA and serologies were performed in serum collected 6 months before, at the time, and 6 months after the flare. HCV RNA levels were also determined. Controls consisted of individuals who also had ALT/AST flares but who were negative for IgM antibodies to hepatitis B core antigen. Seven study cases and eight control cases were identified. HBV DNA was detectable during the enzyme flares in 7/7 study cases versus 3/8 controls, p=0.026. HBV DNA levels during the flare were low, averaging 1943 +/- 2341 copies/ml, but were higher in study cases versus controls, p=0.002. No change in HCV levels was associated with the flares. In this population at high risk for occult HBV, AST/ALT flares can be associated with detection of HBV DNA. These findings may link occult hepatitis B to liver injury. Kannangai, R., Vivekanandan, P., Netski, D., Mehta, S., Kirk, G.D., Thomas, D.L., Torbenson, M. J. Clin. Virol. 39(2), pp. 101-105, 2007.

Progression of Fibrosis during Chronic Hepatitis C is Associated with Rapid Virus Evolution

Hepatic fibrosis is the primary mediator of disease due to chronic infection with hepatitis C virus (HCV). HCV exists as a quasispecies in each infected individual, and longitudinal viral sequence changes may reveal viral dynamics and the selection pressures applied by the host immune system. Thus, the authors hypothesized that patterns of sequence change might reveal the immunopathogenesis of fibrosis progression. They tested this hypothesis by studying individuals enrolled in a prospective study of chronic HCV-related hepatic fibrosis with little or no fibrosis at first biopsy (stage 0 or 1) and a second planned liver biopsy sample obtained 4 years later. Serum was obtained from five individuals with fast progression (FP; defined as a >2-stage change between visits) and 10 carefully matched individuals with slow progression (SP; defined as a <2-stage change between visits). The authors sequenced multiple cloned hemigenomic cDNAs from each person spanning six genes (core through NS3). Phylogenetic analysis revealed temporal shifts in phylogenetic clustering over time, suggesting frequent quasispecies replacement rather than simple diversification. In addition, mixed infections were detected in three subjects, with coexistence in two subjects (one FP, one SP) of subtypes 1a and 1b throughout the 4-year biopsy interval. Subjects with FP had a higher rate of evolution than subjects with SP, with a preponderance of synonymous changes, suggesting purifying selection, except in hypervariable region 1, where positive selection pressure is frequently detected. Thus, in a small but carefully matched cohort the authors found evidence for rapid neutral evolution of HCV in persons with rapid progression of hepatic fibrosis, suggesting higher turnover of infected cells. Wang, X.H., Netski, D.M., Astemborski, J., Mehta, S.H., Torbenson, M.S., Thomas, D.L., and Ray, S.C. J. Virol. 81(12), pp. 6513-6522, 2007.

Evidence for a Functional RNA Element in the Hepatitis C Virus Core Gene

In the core protein-coding region of hepatitis C virus (HCV), evidence exists for both phylogenetically conserved RNA structures and a +1 alternative reading frame (ARF). To investigate its role in HCV infection, the authors introduced four stop codons into the ARF of a genotype 1a H77 molecular clone. The changes did not alter the core protein sequence, but were predicted to disrupt RNA secondary structures. An attenuated infection was established after inoculation of the mutant HCV RNA into an HCV naive chimpanzee. The acute infection was atypical with low peak viremia, minimal alanine aminotransferase elevation, and early virus control by a diverse adaptive immune response. Sequencing circulating virus revealed progressive reversions at the third and then fourth stop codon. In cell culture, RNA replication of a genome with four stop codons was severely impaired. In contrast, the revertant genome exhibited only a 5-fold reduction in replication. Genomes harboring only the first two stop codons replicated to WT levels. Similarly, reversions at stop codons 3 and 4, which improved replication, were selected with recombinant, infectious HCV in cell culture. The authors conclude that ARF-encoded proteins initiating at the polyprotein AUG are not essential for HCV replication in cell culture or in vivo. Rather, their results provide evidence for a functionally important RNA element in the ARF region. McMullan, L., Grakoui, A., Evans, M., et al. PNAS. 104(8), pp. 2879-2884, 2007.

Hepatitis C Infection is Associated with Lower Lipids and High-sensitivity C-reactive Protein in HIV-infected Men

Increased cardiovascular risk has been linked to HIV infection and combination antiretroviral therapy, but the impact of hepatitis C virus (HCV) status on indices of cardiovascular risk has not been routinely assessed in the HIV-infected population. The objective of this study was to analyze associations of HCV, HIV, and combination antiretroviral therapy with lipid levels and C-reactive protein (CRP) among older men. The authors measured fasting total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride, and high-sensitivity CRP serum levels in a cross-sectional study of 108 HIV-infected and 74 HIV-uninfected at-risk older men. One hundred ten men (60%) had detectable HCV RNA, with no difference by HIV status ($p = 0.25$). The majority (88%) of men with HCV infection had a history of injection drug use. Among all men, HCV infection was independently associated with lower total cholesterol ($p < 0.001$), LDL-C ($p < 0.001$), triglycerides ($p = 0.01$), and CRP ($p = 0.001$). Among HIV-infected men, HCV infection was associated with lower total cholesterol ($p < 0.001$), LDL-C ($p < 0.001$), and CRP ($p = 0.004$). HCV infection was associated with lower triglycerides among men on protease inhibitors (PI) ($p = 0.02$) and non-PI combination antiretroviral therapy ($p = 0.02$), but not among antiretroviral-naive men. These findings demonstrate an association of lower serum lipid and CRP levels with HCV infection and suggest that HCV status should be assessed as an important correlate of cardiovascular risk factors in studies of older men with or at risk for HIV. Floris-Moore, M., Howard, A.A., Lo, Y., Schoenbaum, E.E., Arnsten, J.H., and Klein, R.S. AIDS Patient Care STDS. 21(7), pp. 479-491, 2007.

Co-morbid Medical and Psychiatric Illness and Substance Abuse in HCV-infected and Uninfected Veterans

Comorbidities may affect the decision to treat chronic hepatitis C virus (HCV) infection. The authors undertook this study to determine the prevalence of these conditions in HCV-infected persons compared with HCV-uninfected controls. Demographic and comorbidity data were retrieved for HCV-infected and -uninfected subjects from the VA National Patient Care Database using ICD-9 codes. Logistic regression was used to determine the odds of comorbid conditions in the HCV-infected subjects. HCV-uninfected controls were

identified matched on age, race/ethnicity and sex. Authors identified 126,926 HCV-infected subjects and 126,926 controls. The HCV-infected subjects had a higher prevalence of diabetes, anemia, hypertension, chronic obstructive pulmonary disease (COPD)/asthma, cirrhosis, hepatitis B and cancer, but had a lower prevalence of coronary artery disease and stroke. The prevalence of all psychiatric comorbidities and substance abuse was higher in the HCV-infected subjects. In the HCV-infected persons, the odds of being diagnosed with congestive heart failure, diabetes, anemia, hypertension, OPD/asthma, cirrhosis, hepatitis B and cancer were higher, but lower for coronary artery disease and stroke. After adjusting for alcohol and drug abuse and dependence, the odds of psychiatric illness were not higher in the HCV-infected persons. The prevalence and patterns of comorbidities in HCV-infected veterans are different from those in HCV-uninfected controls. The association between HCV and psychiatric diagnoses is at least partly attributable to alcohol and drug abuse and dependence. These factors should be taken into account when evaluating patients for treatment and designing new intervention strategies. Butt, A., Khan, U., McGinnis, K. Et al. J. Viral Hepat.14, pp. 890-896, 2007.

Impact of Hepatitis C Virus Infection and Other Comorbidities on Survival in Patients on Dialysis

The impact of hepatitis C virus (HCV) and other comorbid conditions upon survival is not well quantified in patients on dialysis. The authors identified HCV-infected and uninfected persons in the USRDS using claims data in 1997-1998 and followed until September 22, 2002 or death. They used Gray's time-varying coefficients model to examine factors associated with survival. Subjects with a renal transplant were excluded. A total of 5,737 HCV-infected and 11,228 HCV-uninfected persons were identified. HCV-infected subjects were younger (mean age 57.8 vs 65.3 years), more likely to be male (57.6%vs 49.6%) and black (54.0%vs 36.4%). They were more likely to have a diagnosis of drug (16.5%vs 4.6%) and alcohol use (14.0%vs 3.1%), and to be human immunodeficiency virus (HIV) co-infected (7.4%vs 1.8%) (all comparisons, $P < 0.0005$). In an adjusted Gray's time-varying coefficient model, HCV was associated with an increased risk of mortality ($P < 0.0005$). The hazards were highest at the time of HCV diagnosis and decreased to a stable level 2 years after diagnosis. Other factors associated with increased risk of mortality were ($P < 0.0005$ unless stated) HIV coinfection; diagnosis of drug use ($P = 0.001$); coronary artery disease ($P = 0.006$); stroke; diabetes as the primary cause for renal failure; peripheral vascular disease; depression and presence of anemia. HCV was associated with higher risk of death in patients on dialysis, even after adjusting for concurrent comorbidities. The risk was highest at the time of HCV diagnosis and stabilized over time. Clinical trials of HCV screening and treatment to reduce mortality in this population are warranted. Butt, A.A., Skanderson, M., McGinnis, K.A., Ahuja, T., Bryce, C.L., Barnato, A.E., and Chang, C.C. J. Viral Hepat. 14(10), pp. 688-696, 2007.

Biochemical and Virologic Parameters in Patients Co-infected with Hepatitis C and HIV Versus Patients with Hepatitis C Mono-infection

Previous studies of patients with hepatitis C virus (HCV) infection looking at the effect of human immunodeficiency virus (HIV) co-infection on biochemical parameters and HCV RNA level have shown conflicting results. Accurate characterization of the effect of HIV is important for evaluation and treatment of HCV in coinfected persons. Authors studied 315 HCV mono-infected and 75 HCV-HIV co-infected subjects to determine the effect of HIV on biochemical parameters and HCV RNA and to determine the predictors of elevated serum alanine aminotransferase (ALT) levels and HCV RNA levels. The co-infected subjects were more likely to be African-American (55% vs 26%, $P<0.0005$),

have used injection drugs (68% vs 60%, P = 0.02), have detectable HCV RNA (84% vs 70.5%, P=0.018), have HCV RNA levels >6 log10 IU/mL (60% vs 38%, P=0.001), and have lower mean serum ALT levels (50.4 IU/mL vs 73.7 IU/mL, P=0.006). In multivariable analyses, the following factors predicted an ALT level >50 IU/mL: log10 HCV RNA (OR, 1.15; 95% CI, 1.00 to 1.32); HIV co-infection (OR, 0.48; 95% CI, 0.25-0.89); and having ever been treated for HCV (OR, 1.92; 95% CI, 1.16 to 3.18). The only significant predictor of HCV RNA level >6 log10 IU/mL was HIV co-infection (OR, 2.75; 95% CI, 1.46-5.15). Significant predictors of having a detectable HCV RNA level were female sex (OR, 3.81; 95% CI, 1.18-12.25); HIV co-infection (2.45; 95% CI, 1.14-5.26); and ever being treated for HCV (OR, 1.96; 95% CI, 1.10 to 3.48). HCV-HIV co-infected persons have higher HCV RNA levels but lower serum ALT levels than HCV mono-infected patients. Criteria for performing liver biopsy and treating HCV infection in co-infected patients may need to be revisited. Butt, A., Tsevat, J., Ahmad, J., et al., Am.J.Med.Sci. 333, pp. 271-275, 2007.

Two-step Tuberculin Skin Testing in Drug Users

To assess the utility of booster testing and to identify factors associated with a positive booster test, two-step tuberculin testing was performed in drug users recruited from methadone treatment. Participants also received a standardized interview on demographics and testing for HIV and CD4+ lymphocyte count. Of 619 enrollees completing the protocol, 174 (28%) had a positive PPD and 24 of the remaining 445 (5%) had a positive booster test. On multivariate analysis, boosting was associated with older age (adjusted odds ratio [ORadj] 2.38/decade, 95% confidence interval [CI] 1.34-4.22), history of using crack cocaine (ORadj 2.61, 95% CI 1.10-6.18) and a history of working as a home health aide (ORadj 4.23, 95% CI 1.39-12.86). Two-step tuberculin skin testing increased the proportion of participants with latent tuberculosis infection from 22% to 25%. Given the effectiveness of chemoprophylaxis, booster testing should be considered when drug users are screened for tuberculosis infection. Swaminathan, S., Schoenbaum, E., Klein, R. et al. J. Addict. Dis. 26(2), pp. 71-79, 2007.

Director's Report to the National Advisory Council on Drug Abuse - February, 2008

Research Findings - Services Research

Interim Methadone Maintenance Superior to Waitlisting in Enrollment, Retention, and Opaite Use

This study compares interim methadone maintenance (IM) to sample not offered methadone. Both groups were waitlisted for opiate treatment program (OTP) enrollment. As defined by US federal regulations, IM provides observed methadone dosing and emergency counseling only for a maximum of 120 days. Three hundred and nineteen individuals enrolled on an OTP waiting list were randomly assigned on a 3:2 basis to either IM or waiting list control. Outcomes were measured at OTP entry (or at 4 months from baseline for those who did not enter treatment), and 6 months thereafter. At the second follow-up, 129 (64.8%) of the IM participants reported being enrolled in an OTP, versus 33 (27.5%) of the controls, $p < .001$. Significant treatment condition_time interaction effects occurred for heroin and cocaine use (both p's $< .001$) and the ASI Legal composite score ($p < .001$). Moreover, a significant difference occurred between conditions at the second follow-up for heroin-positive drug tests (interim 48.1% versus control 72.3%, $p = .001$) but not for cocaine-positive drug tests. At 10 months after study enrollment, there are sustained benefits of IM as compared to waiting list in terms of increased treatment entry and reduced heroin use and criminal behavior. Schwartz, R.P., Jaffe, J.H., Highfield, D.A., Callaman, J.M., and O'Grady, K.E. A Randomized Controlled Trial of Interim Methadone Maintenance: 10-Month follow-up. Drug Alcohol Depend., 86 pp. 30-36, 2007.

Concurrent Drug and Alcohol Use in National Sample

This study estimates the prevalence, assesses predictors and evaluates factors associated with concurrent and simultaneous use of drugs and alcohol in the United States population. Using data from the 2000 National Alcohol Survey (n=7612), respondents were asked if they used specific drugs in the last 12 months. Current drinkers who reported using each type of drug were asked if they used alcohol and the drug at the same time. Approximately 10% reported using marijuana in the last 12 months (concurrent use); 7% reported drinking alcohol and using marijuana at the same time (simultaneous use). Approximately 5% of current drinkers reported using drugs other than marijuana in the last 12 months; 1.7% reported drinking alcohol and using drugs other than marijuana at the same time. Being younger, having less than a high school education, not having a regular partner and having heavier drinking patterns were associated with using alcohol and marijuana simultaneously. Simultaneous use of marijuana and alcohol as well as other drugs and alcohol were significantly related to social consequences, alcohol dependence, and depression. These results mirror clinical populations in which increasingly younger clients report use of alcohol and drugs and need

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treatment for both. Midanik, L., Tam, T., and Weisner, C. Concurrent and Simultaneous Drug and Alcohol Use: Results of the 2000 National Alcohol Survey. Drug Alcohol Depend., 90(1), pp. 72-80, 2007.

Prescription Opiate Misuse

Prescription opiate misuse is a major public health issue, especially in rural areas. The purpose of this analysis was to examine trends in prescription opiate misuse over time in a cohort of community-based rural probationers. Participants (N=800), recruited over a four-year period, were divided into cohorts according to the year in which they were interviewed. Prescription opiate misuse increased significantly between 2001 and 2004 ($p<0.001$). After adjustment for changes in demographic characteristics of the cohorts, misuse of prescription opiates was still significantly greater in 2004 compared with 2001. These data suggest changes in drug use patterns among community-based rural probationers from street to prescription drugs. Implications of the findings are discussed. Havens, J., Oser, C., and Leukefeld, C. Increasing Prevalence of Prescription Opiate Misuse Over Time Among Rural Probationers. J. Opioid Manag., 3, pp. 107-111, 2007.

Increase in the Prevalence of Prescription Drug Use Disorders in the United States

The purpose of this study was to examine changes in the prevalence of non-medical prescription drug use and DSM-IV non-medical prescription abuse and dependence in the United States between 1991-1992 and 2001-2002. The authors compared the prevalence of past-year non-medical prescription drug use and drug use disorders in the total sample and among lifetime non-medical users in two large national surveys conducted 10 years apart (NLAES and NESARC). From 1991-1992 to 2001-2002, the prevalence of DSM-IV non-medical prescription drug use increased by 53%, from 1.5% to 2.3% ($p<0.001$), and the prevalence of drug use disorders increased by 67% from 0.3% to 0.5% ($p<0.001$). The conditional prevalence of a disorder among users increased numerically from 19.9% to 23.6%, but this increase was not statistically significant ($p=0.15$). The authors concluded that there have been substantial increases in the prevalence of prescription drug non-medical use and prescription drug use disorders in the United States. Given the clinical utility of prescription drugs, they noted that urgent action is needed to find approaches that balance the need for access to these medications among those who need them, against their potential for abuse and dependence in subgroups of vulnerable individuals. Blanco, C., Alderson, D., Ogburn, E., Grant, B., Nunes, E., Hatzenbuehler, M., and Hasin, D. Changes In the Prevalence of Non-Medical Prescription Drug Use and Drug Use Disorders in the United States: 1991-1992 and 2001-2002. Drug Alcohol Depend., 90(2-3), pp. 252-260, 2007.

A Randomized Clinical Trial of Methadone Maintenance for Prisoners: Results at 1-Month Post-Release

Despite its effectiveness, methadone maintenance is rarely provided in American correctional facilities. This study is the first randomized clinical trial in the US to examine the effectiveness of methadone maintenance treatment provided to prisoners with pre-incarceration heroin addiction. A three-group randomized controlled trial was conducted between September 2003 and June 2005. Two hundred eleven Baltimore pre-release inmates who were heroin dependent during the year prior to incarceration were enrolled in this study. Participants were randomly assigned to the following: counseling only: counseling in prison, with passive referral to treatment upon release (n=70); counseling+transfer: counseling in prison with transfer to methadone maintenance treatment upon release (n=70); and counseling+methadone:

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methadone maintenance and counseling in prison, continued in a community-based methadone maintenance program upon release (n=71). Two hundred participants were located for follow-up interviews and included in the current analysis. The percentages of participants in each condition that entered community-based treatment were, respectively, counseling only 7.8%, counseling+transfer 50.0%, and counseling+methadone 68.6%, p<.05. All pairwise comparisons were statistically significant (all ps<.05). The percentage of participants in each condition that tested positive for opioids at 1-month post-release were, respectively, counseling only 62.9%, counseling+transfer 41.0%, and counseling+methadone 27.6%, p<.05, with the counseling only group significantly more likely to test positive than the counseling+methadone group. Methadone maintenance initiated prior to or immediately after release from prison appears to have beneficial short-term impact on community treatment entry and heroin use. This intervention may be able to fill an urgent treatment need for prisoners with heroin addiction histories. Kinlock, T., Gordon, M., Schwartz, R., O'Grady, K., Fitzgerald, T., and Wilson, M. A Randomized Clinical Trial of Methadone Maintenance for Prisoners: Results at 1-Month Post-Release. Drug Alcohol Depend., 91, pp. 220-227, 2007.

HIV Treatment: A Simulation Model

In recent studies, subjects who had achieved suppression of the human immunodeficiency virus (HIV) RNA level while receiving an initial 3-drug antiretroviral regimen successfully maintained suppression while receiving treatment with a "boosted" protease inhibitor (PI) alone. The long-term outcomes of this treatment simplification strategy were projected to inform the design of a proposed multi-center, randomized clinical trial. Published studies were used to estimate the efficacy, adverse effects, and cost of a sequence of HIV drug regimens for the simplification strategy, compared with those outcomes for the current standard-of-care (SOC) strategy. Using a published simulation model of HIV disease, researchers projected life expectancy, discounted quality-adjusted life expectancy (QALE), and discounted lifetime medical costs for each strategy. Results showed that subjects who have not developed PI-resistant HIV infection at the time of failure of the simplification regimen have a greater life expectancy (27.9 vs. 27.1 years) and QALE (14.9 vs. 14.7 years), compared with SOC subjects, because they receive an additional line of therapy without negative consequences for future treatment options. The QALE for the simplification strategy remains higher than that for the SOC, unless a large proportion of patients experiencing virologic failure while receiving the simplification regimen develop PI resistance. Depending on the probability of simplification regimen failure, the advantage is maintained even if HIV develops PI resistance in 42%-70% of subjects. Projected lifetime costs are $26,500-$72,400 per person lower for the simplification strategy than for the SOC strategy. An HIV treatment simplification strategy involving use of a boosted PI alone may lead to longer survival overall at lower cost, compared with the SOC combination therapy, because the simplification strategy potentially adds an additional line of therapy. The risk of emergence of PI resistance during treatment with a simplified regimen is a critical determinant of the viability of this strategy. Schackman, B., Scott, C., Sax, P., Losina, E., Wilkin, T., McKinnon, J., Swindells, S., Weinstein, M., and Freedberg, K. Potential Risks and Benefits of HIV Treatment Simplification: A Simulation Model of a Proposed Clinical Trial. Clin. Infect. Dis., 45(8), pp. 1062-1070, 2007.

DAART Superior to Self-Administered Therapy for HIV+ Drug Users

Directly administered antiretroviral therapy (DAART) is one approach to improve treatment adherence among human immunodeficiency virus (HIV)-infected drug users. In this randomized, controlled trial (ClinicalTrials.gov

identifier, NCT00367172), the biological outcomes of a 6-month community intervention of DAART were compared with those of self-administered therapy among HIV-infected drug users. Patients randomized to receive DAART received supervised therapy 5 days per week from workers in a mobile health care van. The primary outcome, using an intention-to-treat approach, was the proportion of patients achieving either a reduction in HIV-1 RNA level of > or = 1.0 log10 copies/mL or an HIV-1 RNA level < or = 400 copies/mL at 6 months. Secondary outcomes included the mean change from baseline in HIV-1 RNA level and CD4+ T lymphocyte count. Of the 141 patients who met the entry criteria, 88 were randomized to receive DAART, and 53 were randomized to receive self-administered therapy; 74 (84%) of 88 of the patients randomized to receive DAART accepted the intervention. Of the 74 patients who initiated DAART, 51 (69%) completed the full 6-month intervention. At the end of 6 months, a significantly greater proportion of the DAART group achieved the primary outcome (70.5% vs. 54.7; P=.02). Additionally, compared with patients receiving self-administered therapy, patients receiving DAART demonstrated a significantly greater mean reduction in HIV-1 RNA level (-1.16 log10 copies/mL vs. -0.29 log10 copies/mL; P=.03) and mean increase in CD4+ T lymphocyte count (+58.8 cells/microL vs. -24.0 cells/microL; P=.002). This randomized, controlled trial was, to the authors' knowledge, the first to demonstrate the effectiveness of DAART at improving 6-month virologic outcomes among drug users. These results suggest that DAART should be more widely available in HIV treatment programs that target drug users who have poor adherence to treatment. Altice, F., Maru, D., Bruce, R., Springer, S., and Friedland, G. Superiority of Directly Administered Antiretroviral Therapy Over Self-Administered Therapy Among HIV-infected Drug Users: A Prospective, Randomized, Controlled Trial. Clin. Infect. Dis., 45(6), pp. 770-778, 2007.

HIV Treatment Access for IDUs in Ukraine

Injection drug use (IDU) accounts for 70 percent of HIV cases in Ukraine. Until buprenorphine maintenance therapy (BMT) was introduced, few effective strategies aimed at achieving reduction in illicit drug use were available as a conduit to anti-retroviral therapy (ARV) among IDUs. In October 2005, BMT was scaled-up using Global Fund resources in six regions within Ukraine. Entry criteria included opioid dependence, HIV-1 seropositivity, age >or=18 years and reported interest in BMT. All sites included a multidisciplinary team. To date, 207 patients have been initiated on BMT. The existing infrastructure allows for further scale-up of and administration of BMT and the possibility of co-administration with ARV. The process for prescription and administration of buprenorphine and ARV is at times cumbersome and constrained by current regulations. More IDU need BMT to improve overall health outcomes. Central to expanding access will be legislative changes to existing drug policy. Moreover, the cost of buprenorphine is prohibitively expensive. Sustainable substitution therapy in Ukraine requires lower negotiated prices for buprenorphine, the addition of methadone, or both to the existing formulary for HIV+ drug users. Bruce, R., Dvoryak, S., Sylla, L., Altice, F. HIV Treatment Access and Scale-Up for Delivery of Opiate Substitution Therapy with Buprenorphine for IDUs in Ukraine: Programme Description and Policy Implications. Int. J. Drug Policy,18, pp. 326-328, 2007.

HIV/AIDS, TB and Drug Treatment Services

Injection drug use (IDU) plays a critical role in the HIV epidemic in several countries throughout the world. In these countries, injection drug users are at significant risk for both HIV and tuberculosis, and active IDU negatively impacts treatment access, adherence and retention. Comprehensive strategies are therefore needed to effectively deliver preventive, diagnostic and curative services to these complex patient populations. The researchers propose that

developing co-located integrated care delivery systems should become the focus of national programmes as they continue to scale-up access to antiretroviral medications for drug users. Existing data suggest that such a programme will expand services for each of these diseases; increase detection of tuberculosis (TB) and HIV; improve medication adherence; increase entry into substance use treatment; decrease the likelihood of adverse drug events; and improve the effectiveness of prevention interventions. Key aspects of integration programmes include: co-location of services convenient to the patient; provision of effective substance use treatment, including pharmacotherapies; cross-training of generalist and specialist care providers; and provision of enhanced monitoring of drug-drug interactions and adverse side effects. Central to implementing this agenda will be fostering the political will to fund infrastructure and service delivery, expanding street-level outreach to IDUs, and training community health workers capable of cost effectively delivering these services. Sylla, L., Bruce, R., Kamarulzaman, A., and Altice, F. Integration and Co-Location of HIV/AIDS, Tuberculosis and Drug Treatment Services. Int. J. Drug Policy, 18(4), pp. 306-312, 2007.

Specialized Prisons and Services Results From a National Survey

The National Criminal Justice Treatment Practices Survey conducted a national survey of correctional and community-corrections institutions, to describe the types of services provided, as part of the National Criminal Justice Drug Abuse Treatment Studies (CJDATS). Responses from wardens or administrators of adult correctional institutions were examined to describe services provided by three types of prisons: those that serve a cross-section of offenders, those that specialize in serving offenders with special psychosocial and medical needs, and those that specialize in serving legal status or gender specific populations. These data present a current snapshot of the types of specialized prisons, services available, and the proportions of offenders who access these services. Nationally about 12% of prisons are considered specialized, and these institutions were over-sampled. About half of the surveyed prisons were considered specialized and this group was divided into service-oriented (psychosocial: substance abuse, mental health and medical) and more functional population specialization (other) related to structural and process aspects of incarceration (e.g., reception, parole violators, youth, females, and work release). Most prisons report a surprising overall number and types of services (including assessment and treatment services) offered, ranging from requisite medical to faith-based or spiritual services. But, many of the services available are inadequate (e.g, most prisons report conducting mental health assessments and COD assessments, but about 40% do not use a standardized tool). Prisons report offering assessments (TB and mental health) and physical health services to the majority of inmates. Yet, fewer than half of offenders received counseling (mental health, COD, family, and domestic violence) and job placement, services that are considered critical to reentering offenders. Specialized facilities tend to offer more services than generic prisons. Prisons that specialize in psychosocial needs tend to offer more HIV counseling, HCV screening, social skills training, anger management, and cognitive skills development than other prisons. The survey addressed networking and integration of services using an integration scale examining different operational practices to collaborate services with other organizations or with community correctional partners (e.g., parole, probation, etc.). Specialized facilities focused on psychosocial need showed most integration (M=4.94) (out of 11), compared to other prisons (M=1.18), or generic facilities (3.84), suggesting that psychosocial facilities make greater efforts to coordinate services between prison and community treatment services. Cropsey, K.L., Wexler, H.K., Taxman, F.S., Melnick, G., and Young, D.W. Specialized Prisons and Services Results from a National Survey. The Prison Journal, 87(1), pp. 1-28, 2007.

Validating of the Organizational Readiness for Change Scale

This study examined the convergent validity and concurrent validity of the Organizational Readiness for Change (ORC; Lehman, W.E.K., Greener, J.M., and Simpson, D.D. Assessing Organizational Readiness for Change. Journal of Substance Abuse Treatment 22, pp. 197-210, 2002) scale among practitioners who treat adolescents. Within the context of a larger study, the authors administered the ORC scale and measures of practitioner attitudes toward evidence-based practices as well as treatment manuals to a heterogeneous sample of 543 community-based therapists in the state mental health and substance abuse treatment sectors. Using a contextual random-effects regression model, the association between ORC scale domains and measures of practitioner characteristics and attitudes were examined at both therapist and agency levels. The results support the convergent validity and concurrent validity of several domains. Namely, the domains focusing on motivational readiness and training needs were associated with higher appeal and openness to innovations. Those on program resources and climate were less related, however. Discussion focuses on the utility of the ORC scale in helping evaluate the needs of programs considering the adoption of evidence-based practices. Henggeler, S.W., Saldana, L., Chapman, J.E., and Rowland, M.D. The Organizational Readiness for Change Scale in Adolescent Programs: Criterion Validity. J. Subst. Abuse Treat., 32(2), pp. 121-131, 2007.

Institutionalization Confounds Results Unless the Correct Model for Correction is Applied

Drug treatment clients are at high risk for institutionalization, i.e., spending a day or more in a controlled environment where their freedom to use drugs, commit crimes, or engage in risky behavior may be circumscribed. Some longitudinal studies ignore institutionalization at follow-up, thus outcome measures and treatment effect estimates conflate treatment effects on institutionalization with effects on many of the outcomes of interest. Causal modeling is used as a framework for evaluating the four standard approaches for addressing the institutionalization confound to illustrate the effects of each approach using a case study comparing drug use outcomes of 1,256 youths who enter either residential or outpatient treatment modalities. Common methods provide biased estimates of the treatment effect except under improbable assumptions. Common methods for estimating treatment effects in the presence of institutionalization during the evaluation were not found to be robust to violations of the assumptions. Depending on which model is used, the same data show significant positive or negative results. Thus, institutionalization is likely to confound treatment effect estimates in studies on populations like those in ATM. McCaffrey, D.F., Morral, A.R., Ridgeway, G., and Griffin, B. Interpreting Treatment Effects When Cases Are Institutionalized. Drug Alcohol Depend., 89(2-3), pp. 126-138, 2007.

Licensing/Accreditation Improve Quality of Substance Abuse Treatment

Licensing and accreditation are widely used to improve and convey organizational quality. The objective of this study was to provide substance abuse treatment stakeholders with better evidence about how well licensing and accreditation actually correlate with staffing and treatment practices. Regressions using data from national surveys of outpatient substance abuse treatment facilities indicated that no form of licensing or accreditation was associated with better staff-to-client ratios or with one important aspect of comprehensive treatment-the percentage of clients receiving routine medical care. There were several positive associations between licensing/accreditation and other aspects of treatment comprehensiveness. Three categories of

licensure/accreditation were also positively associated with use of after-treatment plans. Post hoc analyses revealed that accreditation was associated with units' organizational contexts and referral sources as well as the nature of the competitive environment. Licensing/accreditation may reveal as much about units' institutional environments as about the quality of treatment provided. Wells, R., Lemak, C., Alexander, J., Nahra, T., Ye, Y., and Campbell, C. Do Licensing and Accreditation Matter in Outpatient Substance Abuse Treatment Programs? J. Subst. Abuse Treat., 33(1), pp. 43-50, 2007.

Hepatitis C Care

Since 2002, clinicians have been encouraged to offer chronic hepatitis C virus (HCV) treatment to patients with injection drug use histories. Researchers conducted 69 baseline and 35 follow-up interviews between September 2002 and November 2004 with HCV patients who were treatment-naive and receiving regular medical care at an HIV or methadone clinic in New York City at baseline. Of the 31 patients reinterviewed, 20 (65%) were offered treatment but only 2 (7%) were treated. Reasons for failure to be reinterviewed were loss to follow-up at the original site of care (30), death (6), and refusal to be reinterviewed (2). Whereas offers of HCV treatment may be increasing, there is a need to improve continuity of care, patient-provider communication, and patient education regarding HCV treatment options for treatment rates to improve. Schackman, B., Teixeira, P., and Beeder, A. Offers of Hepatitis C Care Do Not Lead to Treatment. J. Urban Health, 84(3), pp. 455-458, 2007.

Violence and HIV Risk Among Incarcerated Women

The association between history of violence and risk for HIV infection among incarcerated women was examined. Specifically, physical violence and rape were considered as they relate to unprotected sex with male primary and non primary (male or female) sexual partners among a sample of HIV negative female inmates (n = 1,588) housed in Connecticut's sole correctional facility for women between November 1994 and October 1996. A supplement to the mandatory Connecticut Department of Correction Inmate Medical Screening/Health History was used to collect information on each woman's background, history of violence, and unprotected sex practices. Multivariate logistic regression was used to determine the associations between violence and unprotected sex by partner type. Experiencing any violence was found to be significantly associated with increased odds of unprotected sex with one's primary partner, even after controlling for race, history of sex work, drug use, employment status, and having other non primary partners. Of particular importance was having a history of physical violence. History of violence was not significantly associated with unprotected sex with non primary partners. These findings demonstrate the considerable vulnerability of incarcerated women to violence and suggest that this history is associated with increased unprotected sex practices, especially with male primary partners. HIV prevention interventions among women should take experiences of violence into account. Conversely, violence prevention and interventions aimed at coping with violence can be a part of the HIV prevention agenda for incarcerated women. Future longitudinal research can confirm the relationships of violence to HIV risk in women. Ravi, A., Blankenship, K., and Altice, F. The Association Between History of Violence and HIV Risk: A Cross-Sectional Study of HIV-Negative Incarcerated Women in Connecticut. Womens Health Issues, 17(4), pp. 210-216, 2007.

Persistent Pain is Associated with Substance Use After Detoxification: a Prospective Cohort Analysis

This study investigated whether persistent pain is associated with increased

odds of substance use after detoxification. The data analyzed was from a prospective cohort of individuals enrolled in a randomized controlled trial (RCT) to improve linkage with primary medical care. The study occurred in an urban residential detoxification program; where adults (n = 397) enrolled in the RCT with heroin, alcohol or cocaine as a substance of choice and at least one follow-up interview. The key independent variable was pain status: persistent pain (moderate to very severe pain at all available interviews), no pain (mild pain or less at all available interviews) and intermittent pain (all others). There were four outcomes of interest: self-reported use of any substance; heroin/opioid use; heavy alcohol use; and cocaine use 24 months after detoxification. Multivariable logistic regression controlled for several covariates including demographics, physical/sexual abuse, depressive symptoms, and duration of follow-up and addiction severity at study entry. The authors found that pain in detoxification patients was common; 16% had persistent pain and 54% had intermittent pain. Persistent pain was associated with an increased odds for use of any substance [adjusted odds ratio (AOR) 4.2, 95% confidence interval (CI) 1.9-9.3], heroin/opioid use (AOR 5.4, 95% CI 2.1-13.8) and heavy alcohol use (AOR 2.2, 95% CI 1.0-4.5) at the 24-month follow-up. A statistically non-significant increase in the odds of cocaine use (AOR 2.0, 95% CI 0.9-4.6) was also observed. From this study, it is shown that among individuals leaving residential detoxification, chronic pain is a common problem and is associated independently with long-term substance use after detoxification. Addressing pain as a treatable chronic condition among adults receiving detoxification presents a potential opportunity to improve long-term clinical outcomes and warrants further intervention research. Larson, M., Paasche-Orlow, M., Cheng, D., Lloyd-Travaglini, C., Saitz, R., and Samet, J. Persistent Pain is Associated with Substance Use After Detoxification: A Prospective Cohort Analysis. Addiction, 102(5), pp. 752-760, 2007.

Strategies for Identifying Drug Use in Private Health Plan Populations Not Widely Disseminated

This study, based on a nationally-representative survey of 368 private health plans representing 767 insurance products conducted in 2003, analyzed screening practices specific to mental health, alcohol abuse, and drug abuse. Just over 8% of products verify specific primary care practitioner screening for alcohol (8.2%) and drug (8.3%) compared with 34.4% that verify mental health screening. In addition, 33.% of products distributed guidelines for treating for alcohol or drug abuse problems, compared with 78.0% that do so for depression. These differences may reflect assumptions about prevalence in this population and/or employers concerns about costs associated with each disorder. Garnick, D.W., Horgan, C.M., Merrick, E.L., and Merrick, A.H. Identification and Treatment of Mental and Substance Use Conditions: Health Plan Strategies. Med. Care, 45 pp. 1060-1067, 2007.

The Deleterious Effects of Changing Treatment Providers for In-Prison Therapeutic Communities

Corrections officials frequently use private contractors to operate in-prison, therapeutic community (TC) treatment programs. However, the recurrent competitive bidding process inherent in state agencies contracting for services sometimes results in a treatment-provider change. Few studies have focused on whether this change leads to better or worse treatment motivation and engagement for clients and how it might be evaluated. Using data collected during the larger Criminal Justice Drug Abuse Treatment Studies Performance Indicators for Corrections study, quantitative assessments of client functioning were made at two points in time. Changing to new treatment providers in three in-prison TC treatment facilities caused significant disruptions, leading to decreased client-counselor rapport and peer support as well as lower levels of treatment readiness, participation, and satisfaction of clients. Qualitative client

and staff interviews provided further insight relevant for correctional administrators and treatment providers who may be considering similar changes. General recommendations for provider transition planning are offered. Saum, C.A., O'Connell, D.J., Martin, S.S., Hiller, M.H., Bacon, G.A., and Simpson, D.D. Tempest in a TC: Changing Treatment Providers for In-Prison Therapeutic Communities. Criminal Justice and Behavior, 34(9), pp. 1168-1178, 2007.

Organizations With the Most Need for Improvement are Most Likely to Engage in Change Activities

This study examined the characteristics of 42 community-based treatment units in a single state in the Southwest. Data were obtained from 284 counselors. Findings showed that treatment programs with expressed higher needs for improvement were 1.3 times more likely to engage in change activities. Treatment programs in which staff perceived pressures for change were 57% more likely to engage in change activities, and those perceiving staffing shortages were 86% more likely to engage in change. Organizational climate also played a role in change, raising the likelihood of engaging in change activities 93% for lower staff cohesion, 83% for lower communication, 143% for higher job stress, and 80% for limited openness to change. Furthermore, organizations with greater staff consensus (i.e., smaller standard deviations) on ratings of organizational climate were also more an average of 85% more likely to engage in change. Courtney, K.O., Joe, G.W., Rowan-Szal, G.A., and Simpson, D.D. Using Organizational Assessment as a Tool for Program Change. J. Subst. Abuse Treat., 33(2), pp. 131-137, 2007.

Training to Adopt Evidence Based Practices Changes Therapeutic Behaviors

Training assessment data collected at two time points from substance abuse treatment counselors who participated in training on dual diagnosis and another on therapeutic alliance (N=253) were examined to determine the impact of training to adopt new evidence-based practices. Customized evaluations were collected to assess counselor perceptions of training quality, relevance, and resources in relation to its use during the 6 months after the conference. Higher ratings for relevance of training concepts and materials to service the needs of clients, desire to have additional training, and level of program support were related to greater trial use during the follow-up period ($R=.55$ and $.42$; $p<.001$). Primary resource-related and procedural barriers cited by the counselors included lack of time and redundancy with existing practices. Bartholomew, N.G., Joe, G.W., Rowan-Szal, G.A., and Simpson, D.D. Counselor Assessments of Training and Adoption Barriers. J. Subst. Abuse Treat., 33(2), pp. 193-199, 2007.

Providers with Positive Organizational Climates are Most Likely to Adopt Innovations that Improve Patient Care

The process of innovation adoption was investigated using longitudinal records collected from a statewide network of almost 59 treatment programs over a 2-year period. Program-level measures of innovation adoption were defined by averaged counselor ratings of program training needs and readiness, organizational functioning, quality of a workshop training conference, and adoption indicators at follow-up. Findings showed that staff attitudes about training needs and past experience with training (job relevant/not relevant) are predictive of their subsequent ratings of training quality and progress in adopting innovations a year later. Organizational climate (clarity of mission, cohesion, openness to change) is also positively related to innovation adoption ($p<.05$). In programs that lack an open atmosphere for adopting new ideas, it

was found that counselor trial usage is likely to be attenuated (r=-.33; p<.05). Most important was evidence that innovation adoption based on training for improving treatment engagement was significantly related to client self-reports of improved treatment participation (r=.50; p<.01) and rapport (r=.35; p<.35) recorded several months later. Simpson, D.D., Joe, G.W., and Rowan-Szal, G.A. Linking The Elements of Change: Program and Client Responses To Innovation. J. Subst. Abuse Treat., 33(2), pp. 201-209, 2007.

Efficacy of Bupropion Alone and in Combination with Nicotine Gum

In this double-blind, placebo-controlled smoking cessation treatment study, 608 participants were randomly assigned to receive active bupropion and active 4-mg gum (AA, n = 228), active bupropion and placebo gum (AP, n = 224), or placebo bupropion and placebo gum (PP, n = 156). Relative to the PP group, the AA and AP groups were each significantly more likely to be abstinent at 1 week, end of treatment, and 6 months but not at 12 months post quit. After the first week post quit there were no differences in abstinence rates between the AA and AP groups. The authors found no significant individual difference variables that moderated outcome beyond 1 week post quit. Piper, M., Federman, E., McCarthy, D., Bolt, D., Smith, S., Fiore, M., and Baker, T. Efficacy of Bupropion Alone and in Combination With Nicotine Gum. Nicotine Tob. Res., 9(9), pp. 947-954, 2007.

Rural-Urban Differences in Prescription Opiate Misuse

The prevalence of prescription opiate misuse among 2 cohorts of felony probationers (N = 1525) were compared. Multiple logistic regression was utilized to determine the independent correlates of prescription opiate misuse among rural (n = 782) and urban (n = 743) probationers participating in an HIV-intervention study. After adjustment for differences in demographic and drug use characteristics, rural participants were almost five times more likely than their urban counterparts to have misused prescription opiates. The prevalence of prescription opiate misuse was significantly higher among the rural probationers; however, given the paucity of illicit opiates and relatively recent emergence of prescription opiates in rural areas, rural substance abuse treatment may be ill-prepared to treat prescription opiate misuse. Havens, J., Oser, C., Leukefeld, C., Webster, J., Martin, S., O 'Connell, D., Surratt, H., and Inciardi, J. Differences in Prevalence of Prescription Opiate Misuse Among Rural and Urban Probationers. Am. J. Drug Alcohol Abuse, 33(2), pp. 309-317, 2007.

Gender Differences in Housing Patterns and Homelessness

Homeless individuals experience high rates of morbidity and mortality, yet many homeless studies include small percentages of female participants. The authors therefore sought to determine correlates of homelessness separately for men and women in a sample of individuals visiting free food programs. Between August 2003 and April 2004, 324 individuals were recruited from San Francisco free food programs and interviewed regarding housing, sociodemographics, health, drug use, sex trade, and incarceration. Over one-half of women and almost three-fourths of men reported homelessness in the prior year. Among women, white race, younger age, not living with minor children, engaging in sex trade and recent incarceration were strongly associated with homelessness; however, only incarceration maintained the strong association in adjusted analysis (OR = 7.16, CI = 3.83-13.4). Among men, heavy alcohol use, drug use, years spent living in San Francisco and monthly income were strongly associated with homelessness; however, only years living in San Francisco (OR = 0.28, CI = 0.19-0.42) and monthly income maintained strong association in adjusted analysis (OR = 0.27, CI = 0.13-

0.57). Housing patterns and the strongest correlates of homelessness among individuals visiting free food programs differ by sex. These results suggest the need to characterize homelessness and develop effective homeless interventions separately for men and women. Riley, E., Weiser, S., Sorensen, J., Dilworth, S., Cohen, J., and Neilands, T. Housing Patterns and Correlates of Homelessness Differ by Gender Among Individuals Using San Francisco Free Food Programs. J. Urban Health, 84(3), pp. 415-422, 2007.

Probability of Cost-effectiveness Depends on the Value Attached to the Outcome

Cost-effectiveness analysis compares the incremental costs of interventions to achieve an incremental improvement in a given outcome. As such, unless the outcome has an inherent value, or has been assigned one by society, cost-effectiveness ratios in and of themselves may not provide adequate guidance for allocation decisions. In addition, given that incremental cost-effectiveness ratios are computed from sample data, there is an inherent variability in the estimates. The authors calculated the incremental cost-effectiveness ratios of four treatments drug abuse counseling (TAU), motivational enhancement therapy plus cognitive behavioral training (MET/CBT), TAU + Contingency Management (CM) and MET/CBT + CM on the Longest Duration Abstinent (LDA) during treatment, the relative effectiveness of which were studied under a NIDA grant analyzing 136 marijuana-dependent young adults. They then conducted a bootstrap analysis and constructed an acceptability curve to arrive at the probability that each intervention would be deemed most cost-effective at different dollar values of an extra week of LDA. The findings show that the optimal intervention depends on how much society values an extra week of LDA. For example, if society valued (or were willing to pay) $250 for an extra week LDA then MET/CBT would have the highest probability of being the optimal choice. If society were willing to pay $1,000, MET/CBT would still be the optimal choice, but at $3,000 MET/CBT + CM, the most expensive intervention, would be optimal. Research is needed to determine society's value of standard drug abuse outcomes. Olmstead, T., Sindelar, J., Easton, C., and Carroll, K. The Cost-Effectiveness of Four Treatments for Marijuana Dependence. Addiction, 102(9), pp. 1443-1453, 2007.

Communication, Staff Cohesiveness, Clarity of Mission, and Work Stress are Key Components in the Organizational Dynamics of Counselors in Their Workplace

This study examined drug counselor perceptions of their programs and their skills in relation to their attitudes about innovations training and its utilization. Latent profile analysis of measures on organizational climate and staff attributes for 1047 counselors from 345 programs defined three categories of counselors: isolated, integrated, and exceptional. All had generally positive views of their professional skills, although the isolated group scored lower on scales representing professional growth and influence on peers. They were less positive about the "climate" of programs in which they worked and were higher on stress. Program resources predicted the counselor groups with the isolated having more limited resources. Counselor categorizations also differed in terms of workshop training experiences, with the isolated group of counselors reporting significantly less exposure, satisfaction, and program-wide use of workshop training. The results emphasize the importance of considering communication, staff cohesiveness, clarity of mission, and work stress as key components in the organizational dynamics of counselors in their workplace. Joe, G., Broome, K., Simpson, D., and Rowan-Szal, G. Counselor Perceptions of Organizational Factors and Innovations Training Experiences. J. Subst. Abuse Treat., 33(2), pp. 171-182, 2007.

Interim Methadone Maintenance was Equally Effective for Both Intravenous and Intranasal Heroin Addicts

This study compared the characteristics of intravenous (i.v.) and intranasal (i.n.) heroin users seeking methadone treatment, and examined their response to treatment. Participants consisted of 319 heroin-dependent adults assigned randomly to receive interim methadone treatment or to a waiting list control on a 3:2 basis. Interim methadone treatment consisted of providing an adequate and stable dose of methadone, but no psychosocial services, to heroin-dependent adults for up to 120 days while they awaited an opening for comprehensive methadone treatment. At baseline, over 60% of participants were i.n. users and had been for an average of over 12 years; i.v. users, compared to i.n. users, were more likely to have ever used cocaine, to have used cocaine in the past 30 days, to have more medical complications and to report more income generated from criminal behavior. Both i.v. and i.n. users reduced their self-reported days of heroin use, cocaine use and days of criminal activity in response to interim methadone treatment. Thus interim treatment is effective for both groups. Highfield, D., Schwartz, R., Jaffe, J., and O 'Grady, K. Intravenous and Intranasal Heroin-Dependent Treatment-Seekers: Characteristics and Treatment Outcome. Addiction, 102(11), pp. 1816-1823, 2007.

Pilot Study Shows that a Brief, Didactic and Experiential Course can Improve Physician Knowledge and Attitudes about AA

Implementation of a brief, didactic and experiential educational intervention about AA was evaluated for its impact on physician knowledge and attitudes, using a before-after repeated measures study design. Thirty-six first-year internal medicine resident physicians received an educational intervention, which consisted of a 45-minute lecture about AA, a visit to an AA meeting, and a 30-minute debriefing session the next day. Residents' knowledge and attitudes were assessed by a brief written anonymous survey before and after the educational intervention. Residents reported increases in self-perceived knowledge about AA and had more favorable attitudes towards AA after the intervention (average $p<.001$). Pilot study shows that a brief, didactic and experiential course can improve physician knowledge and attitudes about AA, and holds promise for improving physician interface with this commonly used intervention. Rose, A.J., Stein, M.R., Arnsten, J.H., and Saitz, R. Teaching Internal Medicine Resident Physicaians About Alcoholics Anonymous: A Pilot Study of an Educational Intervention. Subst. Abuse, 27(3), pp. 5-11, 2006.

Cultural Competence among Healthcare Providers

Mandates for culturally competent substance abuse and mental health services call for behavioral health providers to recognize and engage cultural issues. These efforts to incorporate culture typically focus on client culture, but provider views of culture can also influence the provision of services. Analysis of 42 semi-structured interviews with behavioral health providers suggests that culture is considered by many to be an obstacle to help seeking and treatment of substance-abusing youth. Although some providers do not highlight cultural issues, others conceptualize culture in terms of (a) generalized Hispanic cultural attributes, (b) male-dominant gender roles, and (c) the culture of poverty. Recommendations for provider training on cultural issues focus on ways they might critically consider their ideas about culture. Quintero, G., Lilliott, E., and Willging, C. Substance Abuse Treatment Provider Views of "Culture": Implications for Behavioral Health Care in Rural Settings. Qual. Health Res., 17(9), pp. 1256-1267, 2007.

Violence Against Homeless Women

Research on violence against homeless women has focused mainly on individual rather than community-level risk factors. Using an ecological conceptual framework, the researchers estimated the independent association of community characteristics with sexual and physical assault in a probability sample of 974 homeless women. Participants were interviewed at 66 assistance programs in Los Angeles County, California in 1997. Individual responses were linked to community-level data from land use files and the U.S. Census by the facility ZIP codes. Multivariate logistic regression analysis showed that women using service providers in closer proximity to Skid Row had higher odds of physical assault (OR=1.48; 95% CI=1.03, 2.14). A number of individual characteristics were also associated with violent victimization. To reduce violence against homeless women, ensuring the safety of locations for shelters and other assistance programs should be a planning priority for local housing authorities. Heslin, K., Robinson, P., Baker, R., and Gelberg, L. Community Characteristics and Violence Against Homeless Women in Los Angeles County. J. Health Care Poor Underserved, 18(1), pp. 203-218, 2007.

Recovery More Than Total Abstinence: An Ongoing Process of Growth, Self-Change, and Reclaiming the Self

Combining quantitative and qualitative analyses, this study examines recovery definitions and experiences among persons who self-identify as "in recovery." The author addresses two questions: (a) Does recovery require total abstinence from all drugs and alcohol?, and (b) Is recovery defined solely in terms of substance use or does it extend to other areas of functioning as well? Inner-city residents with resolved dependence to crack or heroin were interviewed yearly three times (N = 289) in the study. Most individuals defined recovery as total abstinence. However, the authors commented that recovery goes well beyond abstinence; it is experienced as an ongoing process of growth, self-change, and reclaiming the self. Implications for clinical and assessment practice are discussed, including the need to effect paradigmatic shifts from pathology to wellness and from acute to continuing models. Laudet, A. What Does Recovery Mean To You? Lessons from the Recovery Experience for Research & Practice. J.Subst.Abuse Treat. 33, pp. 243-256, 2007.

Gender-specific Substance Abuse Treatment for Women Promotes Continuity of Care

Research has stressed the value of providing specialized services to women and suggests the importance of treatment duration. This quasiexperimental retrospective study reports on the continuity of care for women with children who were admitted to long-term residential substance abuse treatment. Women were admitted to 7 agencies offering specialized, women's only treatment (SP, n = 747) or to 9 agencies that provided standard mixed-gender treatment (ST, n = 823). Client and treatment data were gathered from administrative sources. Women in SP programs (37%) were more likely than those in ST programs (14%) to continue care. Multivariate analyses revealed that SP clients who completed treatment with longer stays were most likely to continue care. The findings show that specialized treatment for women promotes continuing care and demonstrate the importance of treatment completion. Claus, R.E., Kissin, W., Krupski, A., Campbell, K., and Stark, K. Does Gender-Specific Substance Abuse Treatment for Woman Promote Continuity of Care. J. Subst. Abuse Treat., 32, pp. 29-39, 2007.

Individual and System Factors Influence Waiting Time for Addiction Treatment

The authors of this study assessed waiting time preceding clinical assessment at a centralized intake unit and during the period after the assessment but

before treatment entry. The analysis included 577 substance abusers who were enrolled in a large clinical trial of two brief treatment interventions in a midsize metropolitan area in Ohio. Bivariate analyses identified individual and system factors that influenced pre-assessment and post-assessment waiting time, as well as total wait to treatment services. Multivariate analyses demonstrated that longer wait time for an assessment is influenced by being court referred, less belief in having a substance abuse problem, and less desire for change. A shorter wait to actually enter treatment is predicted by having a case manager, being more ready for treatment, and having less severe employment and alcohol problems. The different influences present during the two waiting periods suggest that assessment and treatment programs need to implement system changes and entry enhancement interventions that are specific to the needs of substance abusers at each waiting period. Carr, C.J., Jiangmin, X.U., Redko, C., Lane, T., and Rapp, R. Individual and System Influences on Waiting Time for Substance Abuse Treatment. J. Subst. Abuse Treat., May 16, 2007 (e-pub ahead of print).

Children Are Important Sources of Social Support for Women in Addiction Treatment

The authors examined the status of children and the types of support available from children as reported by women in substance abuse treatment. Their findings indicate that children are viewed as sources of social support to women in addiction treatment. Children were viewed as providing as much sobriety support to respondents as that provided by adult network members. In addition, both children living with the respondent and children in the care of others were viewed as providers of specific types of social support. These study findings indicate that treatment providers need to be aware of the extent to which women clients may rely on support from children. Focusing only on adult relationships misses the fact that children may be a strong source of support for women in treatment, particularly for women in residential treatment, where the need for support may be greater. Tracy, E., and Martin, T. Children's Roles in The Social Networks of Women in Substance Abuse Treatment. J. Subst. Abuse Treat., 32(1), pp. 81-88, 2007.

Older Women Have Better Long-Term Addiction Treatment Outcomes Than Older Men

This study examined participants at seven-year follow-up to assess long-term outcomes of older women (n = 25) and men (n = 59) ages 55 and over in an outpatient addiction program. It measured demographic characteristics, alcohol and drug use, psychiatric symptoms, Addiction Severity Index, treatment length, and outcomes. At seven years, 76.0% of women reported abstinence in the prior 30 days versus 54.2% of men ($p = 0.05$). Logistic regression analysis revealed that longer treatment stay predicted abstinence. Findings indicate that older women have better long-term addiction outcome than older men, but treatment length is more significant than gender in predicting outcome. Satre, D., Blow, F., Chi, F., and Weisner, C. Gender Differences in Seven-year Alcohol and Drug Treatment Outcomes Among Older Adults. Am. J. Addict., 16(3), pp. 216-221, 2007.

Measuring Offender Attributes and Engagement in Treatment Using the Client Evaluation of Self and Treatment

Monitoring drug abuse treatment delivery and progress requires the use of reliable and valid instruments to measure client motivation, psychosocial and cognitive functioning, and other treatment process dynamics. As part of the Criminal Justice Drug Abuse Treatment Studies (CJDATS) protocol to examine client performance indicators for corrections-based treatment populations, this

study examined psychometric properties of the 108-item TCU Criminal Justice Client Evaluation of Self and Treatment (CJ CEST), which is composed of 15 scales across 3 major domains. Treatment Motivation includes scales on desire for help; treatment readiness; treatment needs; and pressures for treatment. Psychosocial Functioning includes scales on depression; anxiety; self-esteem; decision-making; hostility; and risk-taking. Treatment Engagement includes scales on treatment participation; treatment satisfaction; counseling rapport; peer support; and social support. The sample included 3,266 offenders from 26 corrections-based treatment programs located in 6 states. Overall, the client assessment demonstrated good reliabilities at individual and program levels, and in test-retest administrations. Additionally, evidence for construct validity was favorable, based on confirmatory factor analyses. All but 4 scales had conventionally acceptable fit indices; the remaining 4 scales (desire for help; treatment readiness; decision making; risk taking) had acceptable GFIs, but other indices indicated possible multidimensionality. Multilevel analyses were used to examine program level variation, after controlling for client-level attributes (e.g., age, race, time in treatment). Over 20% of treatment readiness and counseling rapport was at the program level, but only 5-7% of offender anxiety and hostility. Differences were also found between male-only and female-only programs (all but 3 programs). Women were more motivated and involved in their treatment, and had stronger social support systems. Finally, bivariate correlations were examined between CJ CEST scales and criminal thinking scales (using the CTU Criminal Thinking Scales), after removing program differences. Less criminal thinking was found with higher overall motivation, psycosocial functioning, and engagement. In conclusion, the CJ CEST is a brief yet comprehensive instrument that effectively and efficiently measures client needs and functioning at intake. It also is appropriate for use during treatment to monitor client progress over time. Garner, B.R., Garner, K.K., Flynn, M.P., Morey, J.T., and Simpson, D.D. Measuring Offender Attributes and Engagement in Treatment Using the Client Evaluation of Self and Treatment. Criminal Justice & Behavior, 34(9), pp. 1113-1130, 2007.

Several Treatment Components Not Associated with Crime and Employment Outcomes of Substance Abuse Treatment

This study examines the associations between various components of treatment services and post-treatment employment and crime using data from 960 adults in outpatient non-methadone clinics from the 1992-1995 National Treatment Improvement Evaluation Study. Using principal components analysis to create treatment service factors based on both patient self-reports and treatment record extracts to minimize the effects of measurement error, the authors include measures of five treatment components - logistical services (including job training and employment counseling), medical services, parent training and counseling, and two life skills training factors - in addition to variables such as the number of individual and group counseling sessions and pre-treatment employment and criminal involvement, in multivariate models to estimate the relationship between services and post-treatment employment and crime. The overall effects of services measured in this way were generally insignificant. The authors conclude that either service is unrelated to these outcomes or that they are not measuring the key aspects of service provision that may be important. Dunlap, L., Zarkin, G., Lennox, R., and Bray, J. Do Treatment Services for Drug Users in Outpatient Drug-free Treatment Programs Affect Employment and Crime? Subst. Use Misuse, 42(7), pp. 1161-1185, 2007.

Research Agenda for Employee Assistance Programs

Research suggests that employee assistance programs (EAPs) yield improved clinical and work outcomes and are cost-effective. However, much of that literature is old and of poor scientific quality, and it pre-dates the move to

provision of these services by managed behavioral healthcare organizations. It also covers EAP models that are very different from the broad-based provision of services common today. This comment summarizes the salient issues and sets an agenda for further research on EAPs. Levy Merrick, E., Volpe-Vartanian, J., Horgan, C., and McCann, B. Alcohol & Drug Abuse: Revisiting Employee Assistance Programs and Substance Use Problems in the Workplace: Key Issues and a Research Agenda. Psychiatr. Serv., 58(10), pp. 1262-1264, 2007.

Self-rated Health and its Determinants Among Adults in Syria: a Model From the Middle East

Self-rated health (SRH) has been widely used to research health inequalities in developed western societies, but few such studies are available in developing countries. Similar to many Arab societies, little research has been conducted in Syria on the health status of its citizens, particularly in regards to SRH. This Study aims to investigate and compare determinants of SRH in adult men and women in Aleppo, Syria. The authors performed a cross-sectional survey of adults 18 to 65 years old residing in Aleppo, Syria (2,500,000 inhabitants) in 2004. The study involved 2038 household representatives (45.2% men, age range 18-65 years, response rate 86%). SRH was categorized as excellent, normal, and poor. Odds ratios for poor and normal SRH, compared to excellent, were calculated separately for men and women using logistic regression. It was found that women were more likely than men to describe their health as poor. Men and women were more likely to report poor SRH if they were older, reported two or more chronic health problems, or had high self perceived functional disability. Important gender-specific determinants of poor SRH included being married, low socioeconomic status, and not having social support for women, and smoking with low physical activity for men. The authors conclude that women were more likely than men to describe their health as poor. The link with age and pre-existing chronic conditions seems universal and likely reflects natural aging process. Determinants of SRH differed between men and women, possibly highlighting underlying cultural norms and gender roles in the society. Understanding the local context of SRH and its determinants within the prevailing culture will be important to tailor intervention programs aimed at improving health of the Syrian and similar Arab societies. Asfar, T., Ahmad, B., Rastam, S., Mulloli, T., Ward, K., and Maziak, W. Self-Rated Health and its Determinants Among Adults in Syria: A Model From the Middle East. BMC Public Health, 7, pp. 177-186, 2007.

Organizational Climates Affect Patient Outcomes

Counselor ratings of the organizational climates (N=531) of 163 clinics taken during training sessions at three regional Addiction Technology Transfer Centers across the country showed positive relationships with patient ratings (N=3,475) of counselor rapport ($R^2=.19$; $p<.05$) and treatment satisfaction ($R^2=.27$; $p<.001$). Most measures of client engagement in treatment (rapport, satisfaction, and participation) were shown to be significantly correlated with staff member perceptions of organizational functioning (17 of 23; $p<.05$). In particular, these programs had fewer agency needs and more favorable ratings for their resources, staff attributes, and climate. These findings help establish a link between clinic organizational climate and patient engagement in treatment. Greener, J.M., Joe, G.W., Simpson, D.D., Rowan-Szal, G.A., and Lehman, W.E. Influence of Organizational Functioning On Client Engagement in Treatment. J. Subst. Abuse Treat., 33(2), pp. 139-147, 2007.

Organizational Characteristics (Accreditaiton, Size, Treatment Approach) Significantly Predict Patient Engagement in Treatment

This study explored client and program differences in engagement in treatment

using data from a nationwide set of 94 outpatient drug-free treatment programs in a hierarchical linear model analysis. The results show that elements of program context, including structural features (e.g., smaller size and Joint Commission on the Accreditation of Healthcare Organizations/Commission on Accreditation of Rehabilitation Facilities accreditation; R=.40 to.65; p<.01)) and staff's perceptions of personal efficacy, organizational climate (R=.40; p<.01), and communal workplace practices (R=.40; p<.01), relate to better overall client engagement (R=.40; p<.01). These findings add further evidence that treatment providers should also address the workplace environment for staff as part of quality improvement efforts. Broome, K.M., Flynn, P.M., Knight, D.K., and Simpson, D.D. Program Structure, Staff Perceptions, and Client Engagement in Treatment. J. Subst. Abuse Treat., 33(2), pp. 149-158, 2007.

Measuring Offender Progress in Treatment Using The Client Assessment Inventory

The accurate and reliable assessment of client psychological and cognitive change during correctional substance abuse treatment has gained increasing importance during the past decade as criminal justice systems seek to evaluate and understand those treatment elements associated with long-term change. The 103-item Client Assessment Inventory (CAI) is a self-report instrument for measuring client change during treatment, using 14 subscales across four cognitive and behavioral domains. The Developmental dimension includes subscales on maturity; responsibility; and values. The Socialization dimension includes subscales on drug/criminal lifestyle; maintaining images; work attitude; and social skills. The Psychological dimension includes subscales on cognitive skills; emotional skills; and self-esteem/self-efficacy. The program participation dimension includes subscales on philosophy/understands program rules; engagement; attachment/investment; and role model. The reliability and internal consistency of the CAI, as adapted for use in criminal justice settings, were examined with data gathered from 1,170 offenders. The research addressed the utility of the CAI for different subpopulations of offenders (e.g., race/ethnicity, gender) across a variety of correctional treatment settings. Total CIA demonstrated high reliability (alpha = .96). Subscale alphas ranged from .42 to .90; with work attitudes and maintaining image demonstrating low unidimensionality (alphas = .42 and .53). Female clients were significantly higher on 9 of 14 subscales, after controlling for ethnicity, treatment program, and treatment retention. A sub-sample (n=165) were retested after 1 week. Total CAI test-retest reliability was Kappa = .68; subscale Kappa's ranged from .31 to .54.Validity of the instrument was evaluated using time in treatment at CAI administration, which ranged from 2 weeks to 15 mos. Longer time in treatment was associated with significantly higher scores on 13 of 14 scales. Overall, the data support the use of the CAI as a consistent, reliable, and easily administered instrument for measuring client performance and progress in treatment in both therapeutic community (TC) and non-TC correctional treatment settings. Sacks, J.Y., McKendrick, K., and Kressel, D. Measuring Offender Progress in Treatment Using The Client Assessment Inventory. Criminal Justice and Behavior, 64(9), pp. 1131-1142, 2007.

A Model for Implementing Evidence-based Practices

A model for the study of implementing evidence-based practices in addiction treatment clinics is presented. Data from over 800 treatment programs nationwide served as the basis for an implementation model based on the TCU organizational readiness for change (ORC) survey. The ORC represents a standardized assessment of organizational functioning that describes environments, settings, and staffing, and the findings from incumbent perspectives are interpreted in the context of a stage-based approach to program changes. Basically the model moves from planning and preparation, to

training, adoption activities by leaders to overcome resistance to change, followed by implementation activities, culminating in evaluation of practice improvement. Simpson, D.D., and Flynn, P.M. Moving Innovation into Treatment: A Stage-Based Approach to Program Change. J. Subst. Abuse Treat., 33(2), pp. 111-120, 2007.

Gender Differences in Treatment Engagement Among a Sample Of Incarcerated Substance Abusers

This article examines gender differences in treatment engagement, psychosocial variables, and criminal thinking among a sample of male and female substance abusers (N = 2,774) enrolled in 20 prison-based treatment programs in five different states as part of the National Institute on Drug Abuse-funded Criminal Justice Drug Abuse Treatment Studies cooperative agreement. Results indicate that inmates in female treatment programs report more psychosocial dysfunction, less criminal thinking, and higher engagement than in male facilities, and there is a more negative relationship between psychosocial variables and treatment engagement (compared to male programs). Only one subscale of criminal thinking had a significant gender interaction, with males having a significantly stronger relationship between cold-heartedness and low treatment engagement. Implications for treatment interventions with a gender-specific focus are discussed. Staton-Tindall, M., Garner, B.R., Morey, J.S., Leukefeld, C., Krietemeyer, J., Saum, C.A., and Oser, C.B. Gender Differences in Treatment Engagement Among a Sample Of Incarcerated Substance Abusers. Criminal Justice and Behavior, 34(9), pp. 1143-1156, 2007.

An Assessment of Criminal Thinking Among Incarcerated Youths in Three States

The Texas Christian University Criminal Thinking Scales (CTS) instrument has been shown to predict outcomes for institutionalized adult offenders. This article examines responses among male (n = 151) and female (n = 52) incarcerated adolescents, and they were compared to norms for incarcerated adult offenders. The results indicated that the adolescent sample had higher scores on four scales (Entitlement, Justification, Personal Irresponsibility, and Power of Orientation) but not on Criminal Rationalization. Scores did not differ by gender or ethnicity of respondents. The results provide convergent validity indicating that the scores for adolescents were correlated with prior history of criminal behavior, substance use, family dysfunction, and Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition diagnoses of conduct disorder and oppositional defiant disorder. Thus, the CTS may provide useful diagnostic information to help identify youth with a constellation of problem behaviors that predict poor outcomes following incarceration. It also may prove helpful in accounting for individual variations in response to treatment for incarcerated adolescents who receive treatment during reentry back into the community. Dembo, R., Turner, C. W., and Jainchill, N. An Assessment of Criminal Thinking Among Incarcerated Youths in Three States. Criminal Justice and Behavior, 34(9), pp. 1157-1167, 2007.

Psychometrics of the Inmate Prerelease Assessment for Reentry Planning

The Inmate Prerelease Assessment (IPASS) was developed specifically as a measure of post release risk for prison-based treatment graduates. By taking into account historical drug use and criminal activity of inmates as well as their performance during prison-based treatment, the IPASS provides a "priority" score indicating the relative need for more (versus less) intensive treatment services on release. The present study used data from offenders paroling from

prisons in a southwest (N = 127) and Midwest (N = 75) state to examine the psychometric properties of the IPASS subscales. With regard to construct validity, psychometric properties ranged from good to excellent. The IPASS scales also showed strong internal consistency, with coefficient alphas greater than .80 for the Texas Christian University Drug Screen, Client Evaluation of Treatment, and Counselor Evaluation of Client scales. Further research will explore alternatives on how the Client and Counselor scales are optimally incorporated into the IPASS priority score and will examine the score in relation to aftercare participation and post release outcomes. Farabee, D., Knight, K., Garner, B.R., and Calhoun, S. The Inmate Prerelease Assessment for Reentry Planning. Criminal Justice and Behavior, 34(9), pp. 1188-1197, 2007.

A Validation Study of the Co-Occurring Disorders Screening Instrument For Mental Disorders Developed Under the Criminal Justice Drug Abues Treatment Studies

Three standardized screening instruments--the Global Appraisal of Individual Needs Short Screener, the Mini-International Neuropsychiatric Interview-Modified, and the Mental Health Screening Form (MHSF)--were compared to two shorter instruments, the 6-item Co-Occurring Disorders Screening Instrument for Mental Disorders (CODSI-MD) and the 3-item CODSI for Severe Mental Disorders (CODSI-SMD) for use with offenders in prison substance abuse treatment programs, which was developed as part of the Criminal Justice Drug Abuse Treatment Studies (CJDATS). Results showed that the CODSI screening instruments were comparable to the longer instruments in overall accuracy and that all of the instruments performed reasonably well. The CODSI instruments showed sufficient value to justify their use in prison substance abuse treatment programs and to warrant validation testing in other criminal justice populations and settings. Sacks, S., Melnick, G., Coen, C., Banks, S., Friedmann, P.D., Grella, C., Knight, K., and Zlotnick, C. CJDATS Co-Occurring Disorders Screening Instrument For Mental Disorders: A Validation Study. Criminal Justice and Behavior, 34(9), pp. 1198-1215, 2007.

Screening, Assessment, and Referral Practices in Adult Correctional Settings: A National Perspective

The use of screening and assessment tools to gauge substance abuse disorders and the risk for recidivism are two widely recommended practices. A national survey of adult prisons, jails, and community correctional agencies was conducted to examine the practices used to place offenders in appropriate treatment services. Study findings indicate that 58.2% of the surveyed respondents report the use of a standardized substance abuse-screening tool, and that 34.2% use an actuarial risk tool. The provision of higher intensity treatment programs, the use of standardized risk tools, and the provision of more community referral services were all independently associated with the use of a standardized substance abuse-screening tool. Because practices vary considerably, agencies desiring to improve correctional programming should consider different dissemination, implementation, and technology transfer strategies. Taxman, F. S., Cropsey, K.L., Young, D.W., and Wexler, H. Screening, Assessment, and Referral Practices in Adult Correctional Settings: A National Perspective. Criminal Justice and Behavior, 34(9), pp. 1216-1234, 2007.

Case Managment of Substance Abuse Patients Can Lower Costs of Mental and Physical Healthcare

This study examines the relationship between specific dimensions of case management and the utilization of health and ancillary social services in outpatient substance abuse treatment. Results were from the 2005 National

Drug Abuse Treatment System Survey, a random national telephone survey of 552 addiction treatment provider organizations conducted by the Universities of Michigan and Chicago. In general, results suggest that more active case management during the referral process and providing case management both on-site and off-site are most consistent with predictions of greater use of health ($p<.05$) and ancillary social services ($p<.05$) by substance abuse clients. However, these effects are specific to general health care and mental health services. Case management had no significant effect on use of social services or aftercare plans. Alexander, J., Pollack, H., Nahra, T., Wells, R., and Lemak, C. Case Management and Client Access to Health and Social Services in Outpatient Substance Abuse Treatment. J. Behav. Health Serv. Res., 34(3), pp. 221-236, 2007.

Oxford House: Deaf-Affirmative Support For Substance Abuse Recovery

Previous research indicates that Oxford House, a network of resident-run recovery homes, serves a diverse group of individuals in recovery. The present study found no significant differences between deaf and hearing men living in Oxford House in terms of sense of community and abstinence self-efficacy. However, unlike most of the hearing participants, none of the Deaf Oxford House members were able to achieve full employment. The study's findings indicate that Oxford House may be a promising option for individuals seeking recovery from substance abuse. However, as Oxford House members must be self-supporting, Oxford Houses designed for the Deaf community will need to accommodate to employment problems facing recovery deaf addicts. Leonard, J.A., Alvarez, J., Adebanjo, A.M., Davidson, M.K., and Davis, M.I. Oxford House: Deaf-Affirmative Support for Substance Abuse Recovery. Project Muse Scholarly Journals Online, 151(4), pp. 418-422, 2006.

Application of Gelberg-Andersen Behavioral Model

The Gelberg-Andersen Behavioral Model for Vulnerable Populations was applied to predict health services utilization (HSU) in 875 homeless US women. Structural models assessed the impact of predisposing (demographics, psychological distress, alcohol/drug problems, and homelessness severity), enabling (health insurance, source of care, barriers) and need (illness) variables on HSU (preventive care, outpatient visits, and hospitalizations). Homelessness severity predicted illness, barriers and less insurance. Distress predicted more barriers, illness and less outpatient HSU. Drug problems predicted hospitalizations. Barriers predicted more illness and less outpatient HSU. Health and homelessness indicators were worse for White women. Better housing, access to care and insurance would encourage appropriate HSU. Stein, J., Andersen, R., and Gelberg, L. Applying the Gelberg-Andersen Behavioral Model for Vulnerable Populations to Health Services Utilization in Homeless Women. J. Health Psychol., 12(5), pp. 791-804, 2007.

It is More Than the Money: Adolescents with Substance Use Problems Have Many Reasons for Participating in Research

The authors of this paper examined reasons why adolescents with substance use problems continued to participate in follow-up interviews. The sample consisted of 145 adolescents between the ages of 12 and 18, who completed an outcome study following outpatient treatment for substance use. Participants were asked to report on 18 possible reasons for continued participation. Adolescents' top reason for continued participation was financial compensation; however, a high percentage of adolescents responded favorably to several other attitudinal questions concerning their follow-up participation, suggesting that the adolescents had a primarily positive view of their research

experience and that reasons for research participation are multidimensional. Reasons other than financial compensation that were reported include fulfillment of a commitment, wanting to help others, and the perception that the research was important and credible. Garner, B.R., Passetti, L.L., Orndorff, M.G., and Godley, S.H. Reasons for and Attitudes Toward Follow-Up Research Participation Among Adolescents Enrolled in an Outpatient Substance Abuse Treatment Program. J. of Child and Adol. Subst. Abuse, 164, pp. 45-58, 2007.

Crack Cocaine Trajectories Among Users In a Midwestern American City

Although crack cocaine first appeared in cities in the United States in the mid-1980s, little is known about its use over long periods of time. This study identified crack cocaine user groups on the basis of long-term trajectories. Following a natural history approach, data were collected periodically from 1996 to 2005. Group-based modeling assessed the probability of a crack smoker becoming abstinent during the observation period. A targeted sampling plan guided the recruitment of a community sample of crack cocaine users in Dayton, Ohio. Crack smokers (n = 430) 18 years or older whose urine tested positive for cocaine metabolites at the baseline interview. Interviewer-administered and audio computer self-administered, structured questionnaires were used to collect data on a range of variables, including frequency of crack use. Abstinence was defined as not having used crack for at least 6 consecutive months during the study. Three trajectory-based groups were identified: (1) No Change, characterized by a very low probability of abstinence; (2) Some Change, characterized by a low to moderate probability of abstinence; and (3) Dramatic Change, characterized by a high probability of abstinence. African Americans and men were significantly less likely to become abstinent. For the majority of the people (63.6%), crack use was uninterrupted by extended periods of abstinence during the study. Crack cocaine use that persists for a decade or longer may well be the norm for a large proportion of people who have experience with the drug. Falck, R., Wang, J., and Carlson, R. Crack Cocaine Trajectories Among Users In a Midwestern American City. Addiction, 102(9), pp. 1421-1431, 2007.

Director's Report to the National Advisory Council on Drug Abuse - February, 2008

Clinical Trials Network Research

Abstinence-Based Incentives in Methadone Maintenance: Interaction with Intake Stimulant Test Results

Baseline drug use detected in urine toxicology has been shown to predict drug abuse treatment outcome, including response to contingency management interventions with drug abstinence as their target. This study examined the association between baseline urine test result and treatment outcome in stabilized methadone maintenance patients with ongoing stimulant use to determine whether abstinence incentives were differentially effective in those testing stimulant negative versus positive at study entry. Participants were 386 methadone-maintained patients who took part in a National Drug Abuse Treatment Clinical Trials Network multisite study aimed at reducing stimulant abuse during treatment (J.M. Peirce et al., 2006). At study intake, 24% of participants tested stimulant negative and 76% tested positive. Those testing negative at entry submitted 82% negative urines during the study versus 36% for those testing positive at entry (odds ratio [OR] = 8.67; confidence interval [CI] = 5.81-12.94). Compared with those receiving usual care, the addition of abstinence incentives resulted in a significant increase in stimulant-negative urine samples submitted during the study both for those testing negative at study entry (OR = 2.27; CI = 1.13-4.75) and for those testing positive (OR = 1.84; CI = 1.25-2.71). These findings suggest that abstinence incentives have significant clinical benefits independent of initial drug use severity among methadone maintenance patients with ongoing stimulant drug use. Stitzer, M.L., Peirce, J., Petry, N.M., Kirby, K., Roll, J., Krasnansky, J., Cohen, A., Blaine, J., Vandrey, R., Kolodner, K., Li, R. APA Exp. Clin. Psychopharmacol. 15(4), pp. 344-350, 2007.

Implementation of a Smoking Cessation Treatment Study at Substance Abuse Rehabilitation Programs: Smoking Behavior and Treatment Feasibility Across Varied Community-based Outpatient Programs

Cigarette smoking is widely prevalent among individuals in treatment for drug or alcohol dependence; however, the treatment of nicotine addiction in this population has numerous obstacles at both programmatic and patient levels. Despite these difficulties, recent studies have demonstrated moderate success in implementing smoking cessation treatment in drug rehabilitation programs. The National Drug Abuse Treatment Clinical Trials Network sponsored a smoking cessation study in 13 community-based outpatient substance abuse rehabilitation programs across the country. The study evaluated the effectiveness of smoking cessation treatment provided as an adjunct to substance abuse treatment-as-usual. This report summarizes the practical and clinical experiences encountered at each of the study sites with regard to

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implementing the smoking cessation treatment intervention. Smoking behavior of the treatment clientele was assessed by anonymous survey at each site. In addition, sites were systematically characterized by using program review and assessment tools completed by the respective staff and program directors at the site. Survey and recruitment data indicated that cigarette smoking is more prevalent and that smoking cessation treatment is more feasible, in methadone maintenance treatment programs. Other factors associated with smoking behavior and with the recruitment of drug- and alcohol-dependent individuals into the smoking cessation treatment study are described. Reid, M.S., Fallon, B., Sonne, S., Nunes, E.V., Lima, J., Jiang, H., Tyson, C., Hiott, R., Arfken, C., Bohs, R., Orr, D., Muir, J., Pihlgren, E., Loree, A., Fuller, B.E., Giordano, L., Robinson, J., Rotrosen, J. J Addict. Med. 1(3), pp. 154-160, September 2007.

A Feasibility Study of a Web Based Performance Improvement System for Substance Abuse Treatment Providers

Authors report here on the feasibility of implementing a semiautomated performance improvement system-Patient Feedback (PF)-that enables real-time monitoring of patient ratings of therapeutic alliance, treatment satisfaction, and drug/alcohol use in outpatient substance abuse treatment clinics. The study was conducted in six clinics within the National Institute on Drug Abuse Clinical Trials Network. It involved a total of 39 clinicians and 6 clinic supervisors. Throughout the course of the study (consisting of five phases: training period [4 weeks], baseline [4 weeks], intervention [12 weeks], postintervention assessment [4 weeks], sustainability [1 year]), there was an overall collection rate of 75.5% of the clinic patient census. In general, the clinicians in these clinics had very positive treatment satisfaction and alliance ratings throughout the study. However, one clinic had worse drug use scores at baseline than other participating clinics and showed a decrease in self-reported drug use at postintervention. Although the implementation of the PF system proved to be feasible in actual clinical settings, further modifications of the PF system are needed to enhance any potential clinical usefulness. Forman, R., Crits-Christoph, P., Kaynak, O., Worley, M., Hantula, D.A., Kulaga, A., Rotrosen, J., Chu, M., Gallop, R., Potter, J., Muchowski, P., Brower, K., Strobbe, S., Magruder, K., Chellis, A.H., Clodfelter, T., and Cawley, M. J. Subst. Abuse Treat. 33(4), pp. 363-371, December 2007. (e-pub May 11, 2007).

Telephone Enhancement of Long-term Engagement (TELE) in Continuing Care for Substance Abuse Treatment: A NIDA Clinical Trials Network (CTN) Study

The TELE study examined the feasibility and potential efficacy of phone calls to patients after discharge from short- term inpatient and residential substance abuse treatment programs to encourage compliance with continuing care plans. After review of their continuing care plans, 339 patients from four programs were randomized either to receive calls or to have no planned contact. Ninety-two percent of patients randomized to receive calls received at least one call. No difference was found between groups in self-reported attendance at one or more outpatient counseling sessions after discharge ($p = .89$). When program records of all participants were examined, those receiving calls had a greater likelihood of documented attendance (48%) than those not called (37%). Results were not statistically significant ($p < .003$) because of the Hochberg correction for multiple tests. While the phone calls were feasible, the lack of clear evidence of efficacy of the calls suggests the need for further investigation of the role of telephone intervention to encourage compliance and improve outcomes. Hubbard, R.L., Leimberger, J.D., Haynes, L., Patkar, A.A., Holter, J., Liepman, M.R., Lucas, K., Tyson, B., Day, T., Thorpe, E.A., Faulkner, B., and Hasson, A. Am. J. Addict. 16, pp. 495-502, 2007.

Planned Meetings

Publications

Staff Highlights

Grantee Honors

Treatment Programs in the National Drug Abuse Treatment Clinical Trials Network

Drug abuse treatment programs and university-based research centers collaborate to test emerging therapies for alcohol and drug disorders in the National Drug Abuse Treatment Clinical Trials Network (CTN). Programs participating in the CTN completed Organizational Surveys (n=106 of 112; 95% response rate) and Treatment Unit Surveys (n=348 of 384; 91% response rate) to describe the levels of care, ancillary services, patient demographics, patient drug use and co-occurring conditions. Analyses describe the corporations participating in the CTN and provide an exploratory assessment of variation in treatment philosophies. A diversity of treatment centers participate in the CTN; not for profit organizations with a primary mission of treating alcohol and drug disorders dominate. Compared to National Survey of Substance Abuse Treatment Services (N-SSATS), programs located in medical settings are over-represented and centers that are mental health clinics are under-represented. Outpatient, methadone, long-term residential and inpatient treatment units differed on patients served and services provided. Larger programs with higher counselor caseloads in residential settings reported more social model characteristics. Programs with higher social model scores were more likely to offer self-help meetings, vocational services and specialized services for women. Conversely, programs with accreditation had less social model influence. The CTN is an ambitious effort to engage community-based treatment organizations into research and more fully integrate research and practice. McCarty, D., Fuller, B., Kaskutas, L.A., Wendt, W.W., Nunes, E.V., Miller, M., Forman, R., Magruder, K.M., Arfken, C., Copersino, M., Floyd, A., Sindelar, J., and Edmundson, E. Drug Alcohol Depend. 92(1-3), pp. 200-207, January 1, 2008. (e-pub September 17, 2007).

Prize-based Contingency Management in MMT Programs Estimated to Cost $141 for Each 1 Week Increase in LDA

Data on 388 participants in the National Drug Abuse Treatment Clinical Trials Network Motivational Incentives for Enhanced Drug Abuse Recovery (MIEDAR) study were used to examine the cost-effectiveness of prize-based contingency management in six methadone programs. Compared to usual care, the incremental cost of using prize-based CM to lengthen the longest duration abstinent (LDA) by 1 week was $141 [95% confidence interval (CI), $105-$193]. The incremental cost to obtain an additional stimulant-negative urine sample was $70 (95% CI, $53-$117). These incremental costs were lower than those computed for non-methadone programs in a related study, but the difference was due to less overall abstinence among MMT clients compared with other clients. In either case, whether the additional cost is worthwhile depends on the value placed on the outcomes produced. Sindelar, J., Olmstead, T., and Peirce, J. Cost-Effectiveness of Prize-Based Contingency Management in Methadone Maintenance Treatment Programs. Addiction, 102(9), pp. 1463-1471, 2007.

Director's Report to the National Advisory Council on Drug Abuse - February, 2008

Research Findings - International Research

Publications by Former NIDA INVEST Drug Abuse Research Fellows

Former NIDA INVEST Drug Abuse Research Fellows

AMPA Receptor Antagonists Reverse Effects of Extended Habit Training on Signaled Food Approach Responding in Rats
INVEST Fellow: Anton Bespalov, Russia, 1994-1995
Dopamine D1 receptor stimulation is critically involved in early appetitive phases of learning in various behavioral paradigms. However, extended habit training was previously shown to reduce the ability of dopamine D1 receptor antagonists such as R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SCH-23390) to disrupt behavioral performance. The present study aimed to evaluate whether coadministration of glutamate alpha-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) receptor antagonists restores sensitivity to acute blockade of D1 receptors. Adult male Wistar rats were presented with 45-mg food pellets delivered to the food tray, which was immediately preceded by a 400-ms tone (2.8 kHz, 78 dB). During each training and test session, there were 28 food-tone presentations with an average intertrial interval of 70 s, and each head entry into the food tray was recorded. Drug tests were conducted on either day 3 or 9 of the training using independent groups of animals. The main dependent variable was the number of trials during which no head-entry response was made during the 10-s period immediately after the food delivery. Longer training duration enhanced the resistance of the signaled food approach behavior to extinction and to disrupting effects of supplementary food ration. Similarly, acute administration of SCH-23390 (0.04-0.16 mg/kg) dose-dependently reduced the number of omitted trials when given before the test session on day 3 but much less so when injected on day 9. AMPA receptor antagonists, NBQX (10 mg/kg) or GYKI-52466 (3-10 mg/kg), had no effects on their own but significantly enhanced the disrupting effects of SCH-23390 (0.08 and 0.16 mg/kg) when given on day 9 but not on day 3 of the training. These results indicate that AMPA receptor blockade restores sensitivity to appetitive behavior-disrupting effects of SCH-23390 in subjects exposed to extended training protocol. Bespalov, A.Y., Harich, S., Jongen-Relo, A.L., van Gaalen, M.M., and Gross, G. Psychopharmacology (Berl). July 19, 2007 (e-pub ahead of print).

Delay of First Treatment of Mental and Substance Use Disorders in Mexico
INVEST Fellow: Guilherme Borges, Mexico, 1997-1998
Authors studied failure and delay in making initial treatment contact after the first onset of a mental or substance use disorder in Mexico as a first step to understanding barriers to providing effective treatment in Mexico. Data were from the Mexican National Comorbidity Survey (2001-2002), a representative,

face-to-face household survey of urban residents aged 18 to 65 years. The age of onset for disorders was compared with the age of first professional treatment contact for each lifetime disorder (as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition). Many people with lifetime disorders eventually made treatment contact, although the proportions varied for mood (69.9%), anxiety (53.2%), and substance use (22.1%) disorders. Delays were long: 10 years for substance use disorders, 14 years for mood disorders, and 30 years for anxiety disorders. Failure and delay in making initial treatment contact were associated with earlier ages of disorder onset and being in older cohorts. The authors conclude that failure to make prompt initial treatment contact is an important reason explaining why there are unmet needs for mental health care in Mexico. Meeting these needs will likely require expansion and optimal allocation of resources as well as other interventions. Borges, G., Wang, P.S., Medina-Mora, M.E., Lara, C., and Chiu, W.T. Am. J. Public Health. July 31, 2007 (e-pub ahead of print).

Prevalence and Socio-demographic Correlates of Drug Use Among Adolescents: Results from the Mexican Adolescent Mental Health Survey

The aims of the study were to estimate the life-time and 12-month prevalence of illicit drug use among Mexican adolescents, the age of onset of first drug use and the socio-demographic correlates. A multi-stage probability survey of adolescents aged 12-17 years residing in the Mexico City Metropolitan Area was carried out in 2005. Adolescents were administered the computer-assisted adolescent version of the World Mental Health Composite International Diagnostic Interview by trained lay interviewers in their homes. The response rate was 71% (n = 3005). Descriptive and logistic regression analyses were performed considering the multi-stage and weighted sample design of the survey. Of the adolescents, 5.2% have ever tried illicit drugs, 2.9% in the last 12 months. The most frequently used drugs are marijuana, followed by tranquilizers/ stimulants. The median age of first use is 14 years. Correlates of life-time drug use are older age, having dropped out of school, parental drug problems, low religiosity and low parental monitoring. The authors conclude that while drug use among Mexican adolescents is lower than among adolescents from other developed countries, its increasing prevalence with age and the narrowing male/female ratio calls for firm public health actions, particularly prevention strategies. Benjet, C., Borges, G., Medina-Mora, M.E., Fleiz, C., Blanco, J., Zambrano, J., Rojas, E., Ramirez, M. Addiction. 102(8), pp. 1261-1268, 2007.

Subcutaneous, Intrathecal and Periaqueductal Grey Administration of Asimadoline and ICI-204448 Reduces Tactile Allodynia in the Rat

INVEST Fellow: Silvia Cruz, Mexico, 1996-1997

The purpose of this study was to assess the possible antiallodynic effect of asimadoline ([N-methyl-N-[1S)-1-phenyl)-2-(13S))-3-hydroxypyrrolidine-1-yl)-ethyl]-2,2-diphenylacetamide HCl]) and ICI-20448 ([2-[3-(1-(3,4-Dichlorophenyl-N-methylacetamido)-2-pyrrolidinoethyl)-phenoxy]acetic acid HCl]), two peripheral selective kappa opioid receptor agonists, after subcutaneous, spinal and periaqueductal grey administration to neuropathic rats. Twelve days after spinal nerve ligation tactile allodynia was observed, along with an increase in kappa opioid receptor mRNA expression in dorsal root ganglion and dorsal horn spinal cord. A non-significant increase in periaqueductal grey was also seen. Subcutaneous (s.c.) administration of asimadoline and ICI-204448 (1-30 mg/kg) dose-dependently reduced tactile allodynia. This effect was partially blocked by s.c., but not intrathecal, naloxone. Moreover, intrathecal administration of asimadoline or ICI-204448 (1-30 mug) reduced tactile allodynia in a dose-dependent manner and this effect was completely blocked by intrathecal naloxone. Microinjection of both kappa opioid receptor agonists (3-30 mug) into periaqueductal grey also produced a naloxone-sensitive antiallodynic effect in rats. These results indicate that systemic, intrathecal and periaqueductal grey administration of

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asimadoline and ICI-204448 reduces tactile allodynia. This effect may be a consequence of an increase in kappa opioid receptor mRNA expression in dorsal root ganglion, dorsal horn spinal cord and, to some extent, in periaqueductal grey. Finally, these data suggest that these drugs could be useful to treat neuropathic pain in human beings. Caram-Salas, N.L., Reyes-Garcia, G., Bartoszyk, G.D., Araiza-Saldana, C.I., Ambriz-Tututi, M., Rocha-Gonzalez, H.I., Arreola-Espino, R., Cruz, S.L., and Granados-Soto, V. Eur. J. Pharmacol. June 29, 2007 (Epub ahead of print).

Pharmacological Actions of NGB 2904, a Selective Dopamine D(3) Receptor Antagonist, in Animal Models of Drug Addiction

INVEST Fellow: Zhengxiong Xi, China, 1995-1996

As a continuation of the authors' work with SB-277011A, they have examined the effects of another highly elective dopamine (DA) D3 receptor antagonist, N-(4-[4-{2,3-dichlorophenyl}-1-piperazinyl]butyl)-2-fluorenylcarboxamide (NGB 2904), in animal models of addiction. Their results indicate that by systemic administration, NGB 2904 inhibits intravenous cocaine self-administration maintained under a progressive-ratio (PR) reinforcement schedule, cocaine- or cocaine cue-induced reinstatement of cocaine-seeking behavior, and cocaine- or other addictive drug-enhanced brain stimulation reward (BSR). The action of NGB 2904 on PR cocaine self-administration was long-lasting (1-2 days) after a single injection, supporting its potential use in treatment of cocaine addiction. The effects of NGB 2904 in the BSR paradigm were dose-dependent for both NGB 2904 and cocaine; that is, only lower doses of NGB 2904 were effective, and their putative antiaddiction effect could be overcome by increasing the doses of cocaine or other addictive drugs. A dopamine-dependent mechanism is proposed to explain the effects of NGB 2904 on cocaine's actions in these animal models of drug addiction. The data reviewed in this paper suggest that NGB 2904 or other D3-selective antagonists may have potential in controlling motivation for drug-taking behavior or relapse to drug-seeking behavior, but may have a limited role in antagonizing the acute rewarding effects produced by cocaine or other addictive drugs. In addition, NGB 2904 may also act as a useful tool to study the role of D3 receptors in drug addiction. Xi, Z.X., and Gardner, E.L. CNS Drug Rev. 13(2), pp. 240-259, 2007.

Effects of mGlu1 Receptor Blockade on Working Memory, Time Estimation, and Impulsivity in Rats

INVEST Fellow: Anton Bespalov, Russia, 1994-1995

Metabotropic glutamate 1 (mGlu1) receptor antagonists were reported to induce cognitive deficits in several animal models using aversive learning procedures. The present study aimed to further characterize behavioral effects of mGlu1 receptor antagonists using appetitively motivated tasks that evaluate working memory, timing, and impulsivity functions. Separate groups of adult male Wistar rats were trained to perform four food-reinforced operant tasks: delayed non-matching to position (DNMTP), differential reinforcement of low rates of responding 18 s (DRL 18-s), signal duration discrimination (2-s vs 8-s bisection), and tolerance to delay of reward. Before the tests, rats were pretreated with (3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methanesulfonate (EMQMCM; 2.5-10 mg/kg, i.p.; JNJ16567083). In DNMTP task, EMQMCM produced delay-dependent increases in performance accuracy so that, at 10 mg/kg dose level, percentage of correct lever choices was enhanced at 8- and 16-s delays. In DRL task, at all three tested doses, response rates were higher, and reinforcement rates were lower than under control conditions. In signal duration discrimination tasks, EMQMCM did not have any specific effects on temporal control. In tolerance to delay of reward, EMQMCM (5 and 10 mg/kg) facilitated choice of the lever associated with large reward at longer delay levels. The authors conclude that blockade of mGlu1 receptors improves working memory and reduces impulsive choice at the doses that have no effects on time perception but appear to facilitate impulsive action. Sukhotina, I.A., Dravolina, O.A., Novitskaya, Y., Zvartau, E.E., Danysz, W., and Bespalov, A.Y. Psychopharmacology (Berl). October 2, 2007 (e-pub

ahead of print).

The Effect of Migration to the United States on Substance Use Disorders Among Returned Mexican Migrants and Families of Migrants
INVEST Fellow: Guilherme Borges, Mexico, 1997-1998
Authors examined the association between substance use disorders and migration to the United States in a nationally representative sample of the Mexican population. They used the World Mental Health version of the Composite International Diagnostic Interview to conduct structured, computer-assisted, face-to-face interviews with a cross-sectional sample of household residents aged 18 to 65 years who lived in Mexico in cities with a population of at least 2,500 people in 2001 and 2002. The response rate was 76.6%, with 5,826 respondents interviewed. Respondents who had migrated to the United States and respondents who had family members who migrated in the United States were more likely to have used alcohol, marijuana, or cocaine at least once in their lifetime; to develop a substance use disorder; and to have a current (in the past 12 months) substance use disorder than were other Mexicans. Authors conclude that international migration appears to play a large role in transforming substance use norms and pathology in Mexico. Future studies should examine how networks extending over international boundaries influence substance use. Borges, G., Medina-Mora, M.E., Breslau, J., and Aguilar-Gaxiola, S. Am. J. Public Health. 97(10), pp. 1847-1851, 2007. e-pub August 29, 2007.

Use of Mental Health Services for Anxiety, Mood, and Substance Disorders in 17 Countries in the WHO World Mental Health Surveys
INVEST Fellow: Guilherme Borges, Mexico, 1997-1998
Mental disorders are major causes of disability worldwide, including in the low-income and middle-income countries least able to bear such burdens. Authors describe mental health care in 17 countries participating in the WHO world mental health (WMH) survey initiative and examine unmet needs for treatment. Face-to-face household surveys were undertaken with 84,850 community adult respondents in low-income or middle-income (Colombia, Lebanon, Mexico, Nigeria, China, South Africa, Ukraine) and high-income countries (Belgium, France, Germany, Israel, Italy, Japan, Netherlands, New Zealand, Spain, USA). Prevalence and severity of mental disorders over 12 months, and mental health service use, were assessed with the WMH composite international diagnostic interview. Logistic regression analysis was used to study sociodemographic predictors of receiving any 12-month services. The number of respondents using any 12-month mental health services (57 [2%; Nigeria] to 1477 [18%; USA]) was generally lower in developing than in developed countries, and the proportion receiving services tended to correspond to countries' percentages of gross domestic product spent on health care. Although seriousness of disorder was related to service use, only five (11%; China) to 46 (61%; Belgium) of patients with severe disorders received any care in the previous year. General medical sectors were the largest sources of mental health services. For respondents initiating treatments, 152 (70%; Germany) to 129 (95%; Italy) received any follow-up care, and one (10%; Nigeria) to 113 (42%; France) received treatments meeting minimum standards for adequacy. Patients who were male, married, less-educated, and at the extremes of age or income were treated less. Unmet needs for mental health treatment are pervasive and especially concerning in less-developed countries. Alleviation of these unmet needs will require expansion and optimum allocation of treatment resources. Wang, P.S., Aguilar-Gaxiola, S., Alonso, J., Angermeyer, M.C., Borges, G., Bromet, E.J., Bruffaerts, R., de Girolamo, G., de Graaf, R., Gureje, O., Haro, J.M., Karam, E.G., Kessler, R.C., Kovess, V., Lane, M.C., Lee, S., Levinson, D., Ono, Y., Petukhova, M., Posada-Villa, J., Seedat, S., and Wells, J.E. Lancet. 370(9590), pp. 841-850, 2007.

NMDA Receptor Surface Trafficking and Synaptic Subunit Composition are Developmentally Regulated by the Extracellular Matrix Protein

Reelin

INVEST Fellow: Olivier Manzoni, France, 1997-1998

During postnatal development, changes in the subunit composition of glutamate receptors of the NMDA subtype (NMDARs) are key to the refinement of excitatory synapses. Hypotheses for maturation of synaptic NMDARs include regulation of their expression levels, membrane targeting, and surface movements. In addition, several members of extracellular matrix (ECM) proteins such as Reelin are involved in synaptic plasticity. However, it is not known whether and how ECM proteins regulate synaptic NMDAR maturation. To probe the participation of NMDARs to synaptic currents and NMDARs surface dynamics, the authors used electrophysiological recordings and single-particle tracking in cultured hippocampal neurons. Their results show that, during maturation, Reelin orchestrates the regulation of subunit composition of synaptic NMDARs and controls the surface mobility of NR2B subunits. During postnatal maturation, we observed a marked decrease of NR1/NR2B receptor participation to NMDAR-mediated synaptic currents concomitant with the accumulation of Reelin at active synapses. Blockade of the function of Reelin prevented the maturation-dependent reduction in NR1/NR2B-mediated synaptic currents. The reduction of NR1/NR2B receptors was not inhibited by blocking synaptic activity but required beta1-containing integrin receptors. Single-particle tracking showed that inhibition of Reelin decreased the surface mobility of native NR2B-containing NMDARs, whereas their synaptic dwell time increased. Conversely, recombinant Reelin dramatically reduced NR2B-mediated synaptic currents and the time spent by NR2B subunits within synapses. These data reveal a new mode of control of synaptic NMDAR assembly at postnatal hippocampal synapses and an unprecedented role of ECM proteins in regulating glutamate receptor surface diffusion. Groc, L., Choquet, D., Stephenson, F.A., Verrier, D., Manzoni, O.J., and Chavis, P. J. Neurosci. 27(38), pp. 10165-10175, 2007.

Molecular Components and Functions of the Endocannabinoid System in Mouse Prefrontal Cortex

INVEST Fellow: Olivier Manzoni, France, 1997-1998

BACKGROUND: Cannabinoids have deleterious effects on prefrontal cortex (PFC)-mediated functions and multiple evidences link the endogenous cannabinoid (endocannabinoid) system, cannabis use and schizophrenia, a disease in which PFC functions are altered. Nonetheless, the molecular composition and the physiological functions of the endocannabinoid system in the PFC are unknown. Here, using electron microscopy authors found that key proteins involved in endocannabinoid signaling are expressed in layers v/vi of the mouse prelimbic area of the PFC: presynaptic cannabinoid CB1 receptors (CB1R) faced postsynaptic mGluR5 while diacylglycerol lipase alpha (DGL-alpha), the enzyme generating the endocannabinoid 2-arachidonoyl-glycerol (2-AG) was expressed in the same dendritic processes as mGluR5. Activation of presynaptic CB1R strongly inhibited evoked excitatory post-synaptic currents. Prolonged synaptic stimulation at 10Hz induced a profound long-term depression (LTD) of layers V/VI excitatory inputs. The endocannabinoid -LTD was presynaptically expressed and depended on the activation of postsynaptic mGluR5, phospholipase C and a rise in postsynaptic Ca(2+) as predicted from the localization of the different components of the endocannabinoid system. Blocking the degradation of 2-AG (with URB 602) but not of anandamide (with URB 597) converted subthreshold tetanus to LTD-inducing ones. Moreover, inhibiting the synthesis of 2-AG with Tetrahydrolipstatin, blocked endocannabinoid-mediated LTD. All together, these data show that 2-AG mediates LTD at these synapses. These data show that the endocannabinoid -retrograde signaling plays a prominent role in long-term synaptic plasticity at the excitatory synapses of the PFC. Alterations of endocannabinoid -mediated synaptic plasticity may participate in the etiology of PFC-related pathologies. Lafourcade, M., Elezgarai, I., Mato, S., Bakiri, Y., Grandes, P., and Manzoni, O.J. PLoS ONE. 2(1), pp. e709, 2007.

KCNMB1 Genotype Influences Response to Verapamil SR and Adverse Outcomes in the INternational VErapamil SR/Trandolapril STudy (INVEST)

INVEST Fellow: Danxin Wang, China, 1996-1997

Authors sought to determine whether polymorphisms in the large-conductance calcium and voltage-dependent potassium (BK) channel beta1 subunit gene, KCNMB1, are associated with blood pressure response to verapamil SR or adverse outcomes in the GENEtic substudy of the INternational VErapamil SR/trandolapril STudy (INVEST-GENES). KCNMB1 is involved in calcium sensitivity and hypertension. The association between variability in KCNMB1 and calcium antagonist response, however, has not been assessed. Genetic samples were collected from 5,979 patients in INVEST. Blood pressure response to verapamil SR and time to achieve blood pressure control was assessed in relation to Glu65Lys and Val110Leu genotypes. The primary outcome (all cause mortality, nonfatal myocardial infarction or nonfatal stroke) was compared between genotype groups, and interaction with verapamil SR therapy was assessed. Systolic blood pressure response to verapamil SR did not differ by KCNMB1 genotype. Lys65 variant carriers, however, achieved blood pressure control earlier than Glu65Glu individuals [1.47 (interquartile ratio 2.77) versus 2.83 (interquartile ratio 4.17) months, P=0.01] and were less likely to require multiple drugs at the time of blood pressure control (adjusted odds ratio 0.43, 95% confidence interval 0.19-0.95). Leu110 variant carriers had a reduced risk of primary outcome (hazard ratio 0.68, 95% confidence interval 0.47-0.998). Subgroup analysis revealed this finding to be more pronounced in verapamil SR-assigned patients (hazard ratio 0.587, 95% confidence interval 0.33-1.04) compared with atenolol-assigned patients (hazard ratio 0.946, 95% confidence interval 0.56-1.59). No difference was seen in the occurrence of the primary outcome compared by codon 65 genotype. These findings suggest that KCNMB1 genotype influences responsiveness to verapamil SR and risk of adverse cardiovascular outcomes. Beitelshees, A.L., Gong, Y., Wang, D., Schork, N.J., Cooper-Dehoff, R.M., Langaee, T.Y., Shriver, M.D., Sadee, W., Knot, H.J., Pepine, C.J., and Johnson, J.A; INVEST Investigators. Pharmacogenet. Genomics. 17(9), pp. 719-729, 2007.

Levo-tetrahydropalmatine Inhibits Cocaine's Rewarding Effects: Experiments with Self-administration and Brain-stimulation Reward in Rats

INVEST Fellow: Zhengxiong Xi, China, 1995-1996

It was recently reported that levo-tetrahydropalmatine (l-THP), a dopamine (DA) D(1) and D(2) receptor antagonist purified from the Chinese herb Stephanie, appears to be effective in attenuating cocaine self-administration, cocaine-triggered reinstatement and cocaine-induced conditioned place preference in preclinical animal models. The present study was designed to contrast l-THP's effects on cocaine self-administration under fixed-ratio (FR) and progressive-ratio (PR) reinforcement, and to study l-THP's effects on cocaine-enhanced brain stimulation reward (BSR). Systemic administration of l-THP produced dose-dependent, biphasic effects, i.e., low-to-moderate doses (1, 3, 10mg/kg) increased, while a high dose (20mg/kg) inhibited cocaine self-administration behavior under FR2 reinforcement. The increased cocaine self-administration is likely a compensatory response to a reduction in cocaine's rewarding effects, because the same low doses of l-THP dose-dependently attenuated cocaine self-administration under PR reinforcement and also attenuated cocaine-enhanced BSR. These attenuations of PR cocaine self-administration and cocaine-enhanced BSR are unlikely due to l-THP-induced sedation or locomotor inhibition, because only 10mg/kg, but not 1-3mg/kg, of l-THP inhibited locomotion, sucrose self-administration and asymptotic operant performance in the BSR paradigm. In vivo microdialysis demonstrated that l-THP slightly elevates extracellular nucleus accumbens DA by itself, but dose-dependently potentiates cocaine-augmented DA, suggesting that a postsynaptic, rather than presynaptic, DA receptor antagonism underlies l-

THP's actions on cocaine reward. Together, the present data, combined with previous findings, support the potential use of l-THP for treatment of cocaine addiction. Xi, Z.X., Yang, Z., Li, S.J., Li, X., Dillon, C., Peng, X.Q., Spiller, K., and Gardner, E.L. Neuropharmacology. 53(6), pp. 771-782, 2007. e-pub August 15, 2007.

Cannabinoid CB1 Receptor Antagonists Attenuate Cocaine's Rewarding Effects: Experiments with Self-Administration and Brain-Stimulation Reward in Rats

INVEST Fellow: Zhengxiong Xi, China, 1995-1996

Previous studies suggest that cannabinoid CB1 receptors do not appear to be involved in cocaine's rewarding effects, as assessed by the use of SR141716A, a prototypic CB1 receptor antagonist and CB1-knockout mice. In the present study, the authors found that blockade of CB1 receptors by AM 251 (1-10 mg/kg), a novel CB1 receptor antagonist, dose-dependently lowered (by 30-70%) the break point for cocaine self-administration under a progressive-ratio (PR) reinforcement schedule in rats. The same doses of SR141716 (freebase form) maximally lowered the break point by 35%, which did not reach statistical significance. Neither AM 251 nor SR141716 altered cocaine self-administration under a fixed-ratio (FR2) reinforcement schedule. AM 251 (0.1-3 mg/kg) also significantly and dose-dependently inhibited (by 25-90%) cocaine-enhanced brain stimulation reward (BSR), while SR141716 attenuated cocaine's BSR-enhancing effect only at 3 mg/kg (by 40%). When the dose was increased to 10 or 20 mg/kg, both AM 251 and SR141716 became less effective, with AM 251 only partially inhibiting cocaine-enhanced BSR and PR cocaine self-administration, and SR141716 having no effect. AM 251 alone, at all doses tested, had no effect on BSR, while high doses of SR141716 alone significantly inhibited BSR. These data suggest that blockade of CB1 receptors by relatively low doses of AM 251 dose-dependently inhibits cocaine's rewarding effects, whereas SR141716 is largely ineffective, as assessed by both PR cocaine self-administration and BSR. Thus, AM 251 or other more potent CB1 receptor antagonists deserve further study as potentially effective anti-cocaine medications. Xi, Z.X., Spiller, K., Pak, A.C., Gilbert, J., Dillon, C., Li, X., Peng, X.Q., and Gardner, E.L. Neuropsychopharmacology. August 29, 2007 (e-pub ahead of print).

Gender Differences in the Relationship Between Alcohol and Violent Injury: An Analysis of Cross-national Emergency Department Data

INVEST Fellow: Guilherme Borges, Mexico, 1997-1998

The objectives of the present study were twofold: (1) to determine whether gender differences exist in the roles of drinking in the event (i.e., self-reported drinking before the injury and estimated blood alcohol concentration [BAC] captured after injury) and drinking pattern (i.e., heavy episodic drinking) in explaining violent versus nonviolent injuries and (2) to assess whether these gender differences vary by country. Emergency department data were analyzed from 30 hospitals in 15 countries, as part of the Emergency Room Collaborative Alcohol Analysis Project and the World Health Organization Collaborative Study of Alcohol and Injuries. Interaction effects between gender and alcohol were tested in the prediction of violent versus nonviolent injury for each country. The bivariate analyses revealed significantly larger effects of drinking-in-the-event variables for men than for women in three countries (i.e., 6 hours before the injury in Argentina and having a positive BAC in Belarus and Spain). In the multivariate analyses, restricted to countries with sufficient sample sizes (i.e., Mexico, South Africa, and the United States), no significant gender differences were found between the drinking-in-the-event variables and violent injury. In the bivariate and multivariate analyses, a significant interaction effect between gender and heavy episodic drinking was found in the United States, indicating that heavy episodic drinking predicted violent injury for women but not for men. Although the results are preliminary, treatment and prevention programs may need to target both genders equally or perhaps even focus more on heavy-drinking women, particularly in the United States. Wells, S., Thompson,

J.M., Cherpitel, C., Macdonald, S., Marais, S., and Borges, G. J. Stud. Alcohol Drugs. 68(6), pp. 824-833, 2007.

Comorbidity for Alcohol Use Disorders and Drug Use in Mexican-origin Groups: Comparison of Data from National Alcohol Surveys in the U.S. and Mexico

INVEST Fellow: Guilherme Borges, Mexico, 1997-1998

The comorbidity, separately, of alcohol dependence and consequences of drinking with illicit drug use is compared between Mexicans and Mexicans Americans, using data from the 1995 and 2000 U.S. National Alcohol Surveys (n = 830) and the 1998 Mexico National Household Survey on Addictions (n = 3313). Among drinkers, comorbidity was significantly more prevalent among Mexican Americans than among Mexicans and was positively associated with level of acculturation among Mexican Americans. Although data may not be generalizable, they are important for a better understanding of cultural influences on the development of comorbid substance abuse conditions among Mexicans immigrating to the United States and their substance abuse treatment needs. Cherpitel, C.J., Robertson, M., Ye, Y., Borges, G., Bautista, C.F., Lown, A., Greenfield, T., and Bond, J. Subst. Use Misuse 42(11), pp. 1685-1703, 2007.

Effects of Nitric Oxide Synthase Inhibitors in Attenuating Nicotine Withdrawal in Rats

INVEST Fellow: Raka Jain, India, 1996-1997

This study evaluates the effects of three nitric oxide synthase (NOS) inhibitors (L-NNA, L-NAME, L-NMMA) in attenuating the precipitated nicotine withdrawal syndrome in rats. Male albino Wistar rats were made dependent on nicotine by subcutaneous infusion of nicotine (9.0 mg/kg/day) via a 7 day osmotic pump, whereas control rats received saline via osmotic pumps. Test doses of each NOS inhibitor were administered 30 min prior to mecamylamine (1 mg/kg) challenge in control and test rats on the 7th day. Somatic signs of withdrawal were scored for 15 min by using the global Gellert-Holtzman rating scale followed by a measurement of motor activity. A comparison of NOS inhibitors treated rats with the mecamylamine-precipitated nicotine rats showed that at highest dose L-NNA appears to produce a more complete attenuation of all aspects of withdrawal syndrome. On the other hand, L-NAME appears to do so both at moderate and highest doses. This could be due to an incomplete reversal of some signs of withdrawals by L-NMMA. However, motor activity increased in nicotine dependent rats with the administration of NOS inhibitors. This study demonstrates that NO plays an important role in the expression of behavioral signs of nicotine withdrawal syndrome and suggests a potential use of NOS inhibitors as an aid in tobacco smoking cessation. Jain, R., Mukherjee, K., and Mohan, D. Pharmacol. Biochem. Behav. October 22, 2007 (e-pub ahead of print).

Painful Purinergic Receptors

INVEST Fellow: Steven McGaraughty, Canada, 1995-1996

Multiple P2 receptor-mediated mechanisms exist by which ATP can alter nociceptive sensitivity following tissue injury. Evidence from a variety of experimental strategies including genetic disruption studies and the development of selective antagonists has indicated that the activation of P2X receptor subtypes, including P2X3, P2X2/3, P2X4 and P2X7, and P2Y (e.g. P2Y2) receptors can modulate pain. For example, administration of a selective P2X3 antagonist, A-317491, has been shown to effectively block both hyperalgesia and allodynia in different animal models of pathological pain. Intrathecally delivered antisense oligonucleotides targeting P2X4 receptors decrease tactile allodynia following nerve injury. Selective antagonists for the P2X7 receptor also reduce sensitization in animal models of inflammatory and neuropathic pain providing evidence that purinergic glial-neural interactions are important modulators of noxious sensory neurotransmission. Additionally, activation of P2Y2 receptors leads to sensitization of polymodal TRPV1

receptors. Thus, ATP acting at multiple purinergic receptors, either directly on neurons (e.g. P2X3, P2X2/3 and P2Y receptors) or indirectly through neural-gial cell interactions (P2X4 and P2X7 receptors), alters nociceptive sensitivity. The development of selective antagonists for some of these P2 receptors has greatly aided investigations into the nociceptive role of ATP. This perspective highlights some of the recent advances to identify selective P2 receptor ligands, which has enhanced the investigation of ATP-related modulation of pain sensitivity. Donnelly-Roberts, D., McGaraughty, S., Shieh, C.C., Honore, P., and Jarvis, M.F. J. Pharmacol. Exp. Ther. November 27, 2007 (e-pub ahead of print).

Physical Design Analysis and Mainstream Smoke Constituent Yields of the New Potential Reduced Exposure Product, Marlboro UltraSmooth

INVEST Fellow: Vaughan Rees, Australia, 1999-2000

Potential reduced exposure products (PREPs) purport to lower toxicant emissions, but without clinical and long-term health outcome data, claims for reduced harm status of PREPs depend heavily on standard machine yield smoke constituent data. Two prototypes of the new carbon-filtered PREP Marlboro UltraSmooth (MUS) were investigated using both standard (FTC/ISO) and intensive (Health Canada) machine methods to measure gas/vapor- and particulate-phase smoke constituents. Basic physical design characteristics that may influence smoke constituent yields, such as ventilation, pressure drop (resistance to draw), quantity of tobacco, and quantity and type of carbon, were measured. The possible presence of added chemical flavorant compounds was investigated using gas chromatography-mass spectroscopy. MUS prototypes were found to have several key differences in physical design compared with a conventional cigarette, including higher ventilation, lower draw resistance, and in the case of the Salt Lake City prototype, the use of vitreous carbon beads and the presence of chemical flavorants on both the beads and an embedded filter fiber. When tested under the standard regimen, gas-phase constituents of MUS prototypes were reduced compared with a conventional low-yield cigarette. However, far smaller reductions in gas-phase constituents were observed under the intensive regimen, suggesting that the carbon technology used in MUS is less effective when smoked under more intensive conditions. Particulate-phase constituents were not reduced by the carbon filter under either machine-smoking regimen. The data suggest that MUS has been designed to reduce toxic yields while preserving consumer appeal. However, MUS is less effective in reducing toxic smoke constituents when smoked under intensive conditions. Rees, V.W., Wayne, G.F., Thomas, B.F., and Connolly, G.N. Nicotine Tob. Res. 9(11), pp. 1197-1206, 2007.

Internal Tobacco Industry Research on Olfactory and Trigeminal Nerve Response to Nicotine and Other Smoke Components

INVEST Fellow: Vaughan Rees, Australia, 1999-2000

Evidence has shown that factors other than the central pharmacological effects of nicotine are important in promoting smoking behavior. One such non-nicotine effect includes sensory stimulation, which may promote smoking by developing learned associations with nicotine's rewarding effects, or by constituting a rewarding experience independent of nicotine. The present study used internal tobacco industry documents to examine industry efforts to understand and manipulate stimulation of the sensory nerves by tobacco smoke, and the influence of sensory stimulation on smoker behavior. Research focused on sensory nerves of the head and neck, including the olfactory nerve, which carries flavor and odor, and the trigeminal nerve, which carries irritant information. The tobacco industry maintained a systematic research program designed to elucidate an understanding of responses of sensory nerves to nicotine and other components of tobacco smoke, and attempted to develop nicotine-like compounds that would enhance sensory responses in smokers. Industry research appeared intended to aid in the development of new products with greater consumer appeal. The potential influence of sensory response in enhancing nicotine dependence through an associative mechanism

was acknowledged by the tobacco industry, but evidence for research in this area was limited. These findings add to evidence of industry manipulation of sensory factors to enhance smoking behavior and may have implications for development of more effective treatment strategies, including more "acceptable" nicotine replacement therapies. Megerdichian, C.L., Rees, V.W., Ferris, Wayne G., and Connolly, G.N. Nicotine Tob. Res. 9(11), pp. 1119-1129, 2007.

Long-term Synaptic Plasticity in the Spinal Dorsal Horn and its Modulation by Electroacupuncture in Rats with Neuropathic Pain

INVEST Fellow: You Wan, China, 1998-1999

The authors previous study has reported that electroacupuncture (EA) at low frequency of 2 Hz had greater and more prolonged analgesic effects on mechanical allodynia and thermal hyperalgesia than that EA at high frequency of 100 Hz in rats with neuropathic pain. However, how EA at different frequencies produces distinct analgesic effects on neuropathic pain is unclear. Neuronal plastic changes in spinal cord might contribute to the development and maintenance of neuropathic pain. In the present study, the authors investigated changes of spinal synaptic plasticity in the development of neuropathic pain and its modulation by EA in rats with neuropathic pain. Field potentials of spinal dorsal horn neurons were recorded extracellularly in sham-operated rats and in rats with spinal nerve ligation (SNL). They found for the first time that the threshold for inducing long-term potentiation (LTP) of C-fiber-evoked potentials in dorsal horn was significantly lower in SNL rats than that in sham-operated rats. The threshold for evoking the C-fiber-evoked field potentials was also significantly lower, and the amplitude of the field potentials was higher in SNL rats as compared with those in the control rats. EA at low frequency of 2 Hz applied on acupoints ST 36 and SP 6, which was effective in treatment of neuropathic pain, induced long-term depression (LTD) of the C-fiber-evoked potentials in SNL rats. This effect could be blocked by N-methyl-d-aspartic acid (NMDA) receptor antagonist MK-801 and by opioid receptor antagonist naloxone. In contrast, EA at high frequency of 100 Hz, which was not effective in treatment of neuropathic pain, induced LTP in SNL rats but LTD in sham-operated rats. Unlike the 2 Hz EA-induced LTD in SNL rats, the 100 Hz EA-induced LTD in sham-operated rats was dependent on the endogenous GABAergic and serotonergic inhibitory system. Results from the present study suggest that (1) hyperexcitability in the spinal nociceptive synaptic transmission may occur after nerve injury, which may contribute to the development of neuropathic pain; (2) EA at low or high frequency has a different effect on modulating spinal synaptic plasticities in rats with neuropathic pain. The different modulation on spinal LTD or LTP by low- or high-frequency EA may be a potential mechanism of different analgesic effects of EA on neuropathic pain. LTD of synaptic strength in the spinal dorsal horn in SNL rats may contribute to the long-lasting analgesic effects of EA at 2 Hz. Xing, G.G., Liu, F.Y., Qu, X.X., Han, J.S., and Wan, Y. Exp. Neurol. 208(2), pp. 323-332, 2007. e-pub September 12, 2007.

The Selective Dopamine D(3) Receptor Antagonists SB-277011A and NGB 2904 and the Putative Partial D(3) Receptor Agonist BP-897 Attenuate Methamphetamine-enhanced Brain Stimulation Reward in Rats

INVEST Fellow: Zhengxiong Xi, China, 1995-1996

The authors have previously reported that selective antagonism of brain D(3) receptors by SB-277011A or NGB 2904 significantly attenuates cocaine- or nicotine-enhanced brain stimulation reward (BSR). In the present study, the authors investigated whether the selective D(3) receptor antagonists SB-277011A and NGB 2904 and the putative partial D(3) agonist BP-897 similarly reduce methamphetamine (METH)-enhanced BSR. Rats were trained to respond for rewarding electrical self-stimulation of the medial forebrain bundle. To assess the degree of drug-induced changes in BSR, a rate-frequency curve shift paradigm was used to measure brain-reward threshold (theta (0)). METH

(0.1-0.65 mg/kg, i.p.) dose-dependently lowered (approximately 10-50%) BSR thresholds, producing an enhancement of BSR. Pretreatment with SB-277011A (12 mg/kg, but not 24 mg/kg, i.p.) significantly attenuated METH-enhanced BSR. NGB 2904 (0.1-1.0 mg/kg, but not 10 mg/kg) also attenuated METH-enhanced BSR. SB-277011A or NGB 2904 alone, at the doses tested, had no effect on BSR. Pretreatment with BP-897 (0.1-5 mg/kg) dose-dependently attenuated METH-enhanced BSR. However, when the dose was increased to 10 mg/kg, BP-897 shifted the stimulation-response curve to the right (inhibited BSR itself) in the presence or absence of METH. Selective antagonism of D(3) receptors by SB-277011A or NGB 2904 attenuates METH-enhanced BSR in rats, while the METH-enhanced BSR attenuation produced by BP-897 may involve both D(3) and non-D(3) receptors. These findings support a potential use of selective D(3) receptor antagonists for the treatment of METH addiction. Spiller, K., Xi, Z.X., Peng, X.Q., Newman, A.H., Ashby, C.R. Jr., Heidbreder, C., Gaal, J., and Gardner, E.L. Psychopharmacology (Berl). November 6, 2007 (e-pub ahead of print).

Age and Gender Effects on Olanzapine and Risperidone Plasma Concentrations in Children and Adolescents

INVEST Fellow: Gerald Zernig, Austria, 1993-1994

Risperidone and olanzapine are second-generation antipsychotics that are increasingly used in child and adolescent psychiatry. So far, little is known about plasma concentrations and concentration-to-dose (C/D) ratios of these agents in children and adolescents compared to adults. This study investigated whether age and gender influence risperidone and olanzapine plasma concentration by determining risperidone and olanzapine plasma levels by tandem mass spectrometry in 162 Caucasian patients (98 risperidone and 64 olanzapine). For risperidone and 9-hydroxyrisperidone, the C(total)/D ratio was almost identical in both age groups (10-18 and 19-45 years, respectively). In the younger age group, females exhibited significantly higher total plasma levels than males while receiving similar doses of risperidone. For olanzapine, in adolescents significantly higher C/D ratios were detected by an average of 43% (after adjustment for weight: 34%) compared to adults. This study demonstrates an age effect for olanzapine but not for risperidone resulting in higher olanzapine plasma levels in younger patients. For risperidone, the authors found a gender effect as female adolescent patients had significantly higher risperidone plasma concentrations than male adolescent patients. Future prospective studies are necessary to clarify whether the prescribed dosage should be different in young and older patients. Aichhorn, W., Marksteiner, J., Walch, T., Zernig, G., Hinterhuber, H., Stuppaeck, C., and Kemmler, G. J. Child Adolesc. Psychopharmacol. 17(5), pp. 665-674, 2007.

Study on the Association between Vaginal Douching and Sexually Transmitted Diseases among Female Sex Workers in a County of Yunnan Province

INVEST Fellow: Lan Zhang, China, 2004-2005

The objective of the present study was to explore the epidemic characteristics of vaginal douching, human immunodeficiency virus (HIV) and other sexually transmitted diseases(STD) among female sex workers (FSWs) in Yunnan province. FSWs were recruited to be investigated on their demographic data, drug abuse and sexual behavior, HIV/AIDS knowledge and procreation health status. Venous blood were collected to test for HIV, herpes simplex virus 2 (HSV-2) and syphilis while urine specimen was for morphine, cervical secretion for Gonorrhoea and Chlamydia trachomatis, and vaginal secretion for Trichomonas. A total number of 833 blood specimen were collected, in which 84 specimen were confirmed to be HIV positive with a prevalence rate of 10.1%. The prevalence rates of syphilis and HSV-2 were 8.2% and 68.4% respectively. 832 vaginal and cervical secretion specimen were collected with the prevalence rates of Gonorrhoea, Chlamydia trachomatis and Trichomonas were 11.5%, 28.2% and 11.9% respectively. In multivariate logistic analysis, the factors associated with vaginal douching were: being Han nationality,

locations of sex work at middle/high level, ever heard of HIV/AIDS, emerged hypogastric pain last year, the number of sex work location > or =4. Vaginal douching was shown a risk factor for HIV and some STD. Wang, H.B., Wang, N., Ma, J.G., Wang, G.X., Chang, D.F., Ding, G.W., Xu, J.J., Zhang, G.L., Dong, R.L., Zhang, L., Wu, Z.L., and Zheng, X.W. Zhonghua Liu Xing Bing Xue Za Zhi. 28(6), pp. 558-561, 2007. [Article in Chinese]

Publications by Former NIDA Hubert H. Humphrey Fellows

Personality Traits and Sensitivity to Pain in Male Chronic Opioid Addicts
HHH Fellow: Eli Lawental, Israel, 1993-1994
Previous evidence concerning pain mechanisms, long-term opioids use, and personality traits evolve the possibility that pain perception and opioid abuse are two related phenomena and there is a need to take into account the specific personality traits as well, in examining the relationships among them. Opioid addicts (OAs) have been shown to exhibit different personality traits and pain perception as compared with healthy subjects. The aim of the present study was to examine the relations between personality traits and pain perception among in-treatment OAs in comparison with controls. Participants (54 OAs, 59 controls), all males, were exposed to the cold pressor test and were evaluated for latency of pain onset (seconds); pain intensity (0-100 visual analogue scale [VAS)]); and pain tolerance (time for hand withdrawal). Personality traits were evaluated using Cloninger's Tridimensional Personality Questionnaire, TPQ; harm avoidance, HA; reward dependence, RD; novelty seeking, NS. In comparison with controls, OAs exhibited longer latencies, lower VAS scores, and shorter tolerance, and significantly higher NS, bigher HA, and lower RD. Control group, but not OAs, showed a significant positive correlation between HA and VAS ($r = 0.31$, $p = 0.02$) and significant negative correlation between HA and tolerance ($r = - 0.29$, $p = 0.03$). It is concluded that in contrast to healthy population, personality traits, as measured by the TPQ, do not predict pain perception in OAs. Eisenberg, E., Cohen, D., Lawental, E., and Pud, D. J. Opioid Manag. 3(4), pp. 225-230, 2007.

The Effect of Clozapine on Neuroimaging Findings in Schizophrenia
HHH Fellow: Berna Ulug, Turkey, 1995-1996
Functional and structural neuroimaging help us to compare the brains of schizophrenic patients and controls, moreover they let us observe the changes with treatment. Longitudinal studies comparing patients with typical and atypical antipsychotics have been useful in understanding the effects of these antipsychotic medications on brain function. In general, atypical antipsychotics are suggested to have greater normalizing effects on brain function than typicals, although the results are controversial. In particular, clozapine appears to act more selectively than typical antipsychotics on the prefrontal region, an area of special relevance in higher cognitive functions and schizophrenia. The study of anatomic and functional brain variables associated with clozapine response in schizophrenia may help to identify patients who are most likely to benefit from clozapine treatment. The authors investigated the effect of clozapine on regional cerebral blood flow and (1)H MRS findings and studied their relationship with treatment response. Clozapine increased frontal/basal ganglia perfusion ratio in treatment-responders. In addition, NAA/Cre ratio has increased and Cho/Cre has decreased in dorsolateral prefrontal cortex after 8 weeks of clozapine treatment. The results of the study will be discussed in the light of current literature. These findings can contribute to better understanding of mechanism of action of clozapine. Ertugrul, A., and Ulu_, B. Psychiatr. Danub. 19(4), pp. 367-369, 2007.

HIV Treatment Access and Scale-up for Delivery of Opiate Substitution Therapy with Buprenorphine for IDUs in Ukraine--programme Description and Policy Implications
HHH Fellow: Sergiy Dvoryak, Ukraine, 1999-2000
Injection drug use (IDU) accounts for 70 percent of HIV cases in Ukraine. Until

buprenorphine maintenance therapy (BMT) was introduced, few effective strategies aimed at achieving reduction in illicit drug use were available as a conduit to anti-retroviral therapy (ARV) among IDUs. In October 2005, BMT was scaled-up using Global Fund resources in six regions within Ukraine. Entry criteria included opioid dependence, HIV-1 seropositivity, age >or=18 years and reported interest in BMT. All sites included a multidisciplinary team. To date, 207 patients have been initiated on BMT. The existing infrastructure allows for further scale-up of and administration of BMT and the possibility of co-administration with ARV. The process for prescription and administration of buprenorphine and ARV is at times cumbersome and constrained by current regulations. More IDU need BMT to improve overall health outcomes. Central to expanding access will be legislative changes to existing drug policy. Moreover, the cost of buprenorphine is prohibitively expensive. Sustainable substitution therapy in Ukraine requires lower negotiated prices for buprenorphine, the addition of methadone, or both to the existing formulary for HIV+ drug users. Bruce, R.D., Dvoryak, S, Sylla, L., and Altice, F.L. Int. J. Drug Policy. 18(4), pp. 326-328, 2007. e-pub February 5, 2007.

Using Thought Mapping and Structured Stories to Decrease HIV Risk Behaviors among Cocaine Injectors and Crack Smokers in the South of Brazil

HHH Fellow: Flavio Pechansky, Brazil, 1993-1994

The objectves of this study were to compare changes in AIDS knowledge and risk behaviors among Brazilian cocaine users in an intervention trial. 119 participants were randomly assigned to either a standard or a standard plus "thought mapping" intervention, and re-interviewed 2 and 8 weeks after intake using standardized data collection instruments. Intervention effects were examined using generalized estimated equation model. Significant increases in AIDS knowledge and condom use were observed in the experimental group, as well as significant changes in the subscores for sexual and drug risks. The experimental intervention was less successful in decreasing mean days of cocaine use when compared to the standard. Although not robust, the findings nevertheless suggest that components of the experimental thought-mapping model might be useful in combination with other approaches. Pechansky, F., Bassani, D.G., von Diemen, L., Kessler, F., Leukefeld, C.G., Surratt, H.L., Inciardi, J.A., and Martin, S.S. Rev. Bras. Psiquiatr. 29(3), pp. 233-240, 2007. e-pub September 18, 2007.

Alcohol and Drug Use Among University Students: Gender Differences

HHH Fellows: Arthur Guerra de Andrade, Brazil, 1991-1992, and Vladimir Stempliuk, Brazil, 2003-2004

This study compared the pattern of alcohol, legal and illegal drugs use among students of the Universidade de Sao Paulo (Brazil) in 1996 and 2001. Samples of 2.564 (1996) and 2.837 (2001) students answered a questionnaire proposed by the World Health Organization, which characterizes the consumption of alcohol, legal and illegal drugs in lifetime, in the last 12 months and in the last 30 days. Men showed a significant increase in lifetime use of tobacco (44.8% to 50.9%), marijuana (33.7% to 39.5%) and hallucinogens (6.6% to 14.1%) between 1996 and 2001. No significant change was observed among women between 1996 and 2001 in tranquilizer use. Concerning the consumption reported in the last 12 months, both genders displayed significant increases in the consumption of marijuana (22.3% to 27.1% for men and 12.9% to 16.9% for women), amphetamines (1.9% to 5.0% for men and 3.4% to 5.6% for women), and inhalants (9.8% to 15.7% for men and 5.4% to 10.6% for women). The greatest gender difference was observed in consumption reported in the last 30 days with significant increases in male use of tobacco (19.6% to 23.5%), marijuana (15.8% to 20.5%), amphetamines (1.1% to 3.2%), and inhalants (4.0% to 7.9%). Substance use reported in the last 30 days remained stable among women between the 2 surveys. Rates of substance use among university students increased. These gender differences in substance consumption should be taken into account in the development of preventive

and treatment strategies for undergraduate university students. Wagner, G.A., Stempliuk, Vde A., Zilberman, M.L, Barroso, L.P., and de Andrade, A.G. Rev. Bras. Psiquiatr. 29(2), pp. 123-129, 2007.

Gender Differences in Sex Risk Behaviors Among Ukraine Injection Drug Users

HHH Fellow: Sergiy Dvoryak, Ukraine, 1999-2000

The objective of this study was to assess gender differences in drug and sex risk behaviors and evaluate predictors of HIV-related sex risk behaviors among heterosexual injection drug users (IDUs) in Ukraine. Street-recruited IDUs from Kiev, Odessa, and Makeevka/ Donesk, Ukraine. From June 2004 through November 2006, outreach workers recruited 1557 IDUs, including 526 from Kiev, 494 from Odessa, and 537 from Makeevka/Donesk. Participants were administered a standardized computer-assisted interview assessing HIV-related drug and sex risk behaviors, self-efficacy for practicing safe sex, and HIV knowledge. Overall, 80% of the participants were sexually active in the 30-day period before their interview. They also engaged in high-risk sex behaviors during this brief 30-day window: 53% reported anal or vaginal sex without a condom, 27% had sex with more than 1 partner, 41% had an IDU sex partner, and 37% had an HIV-positive sex partner or a partner whose HIV status they did not know. Overall, women were at higher risk than men and were more likely to have been told they were HIV-positive. The extremely high HIV prevalence rate in Ukraine and in this cohort, combined with their recent high-risk sex behaviors, forecasts not only a continuance of the epidemic in the region but an escalation. Booth, R.E., Lehman, W.E., Brewster, J.T., Sinitsyna, L., and Dvoryak, S. J. Acquir. Immune Defic. Syndr. July 19, 2007 (e-pub ahead of print).

Adaptation and Construct Validation of the Barratt Impulsiveness Scale (BIS 11) to Brazilian Portuguese for Use in Adolescents

HHH Fellow: Flavio Pechansky, Brazil, 1993-1994

Impulsivity is associated with different psychiatric disorders. The Barratt Impulsiveness Scale version 11 is one of the scales mostly used to measure impulsivity and it does not have a validated version for Brazilian Portuguese. The objective of this study is to adapt and conduct the construct validation of the Barratt Impulsiveness Scale version 11 for adolescents. The scale was translated and adapted into Portuguese and then back-translated into English. The psychometric proprieties, factor analysis and construct validity were evaluated in two samples: 18 bilingual undergraduate medical students and 464 male adolescents between 15 and 20 years old from a well-delimited geographical area in the city of Canoas, southern Brazil. The adolescent sample had a mean age of 17.3 +/- 1.7 years. Intra-class correlation coefficient achieved a value of 0.90, and internal consistency had a of 0.62. Factor analysis did not identify the 3 factors of the original scale. Impulsivity scores from the Barratt Impulsiveness Scale version 11 had a correlation with scores for attention deficit/hyperactive disorder and oppositional defiant disorder and with number of symptoms of conduct disorder, suggesting an appropriate construct validity of the scale. Even considering some limitations in the Portuguese version, Barratt Impulsiveness Scale version 11 can be used in male adolescents and should be tested in other populations. von Diemen, L., Szobot, C.M., Kessler, F., and Pechansky, F. Rev. Bras. Psiquiatr. 29(2), pp. 153-156, 2007.

Brain Injury Markers (S100B and NSE) in Chronic Cocaine Dependents

Studies have shown signs of brain damage caused by different mechanisms in cocaine users. The serum neuron specific enolase and S100B protein are considered specific biochemical markers of neuronal and glial cell injury. This study aimed at comparing blood levels of S100B and NSE in chronic cocaine users and in volunteers who did not use cocaine or other illicit drugs. Twenty subjects dependent on cocaine but not on alcohol or marijuana, and 20 non-substance using controls were recruited. Subjects were selected by consecutive

and non-probabilistic sampling. Neuron specific enolase and S100B levels were determined by luminescence assay. Cocaine users had significantly higher scores than controls in all psychiatric dimensions of the SCL-90 and had cognitive deficits in the subtest cubes of WAIS and the word span. Mean serum S100B level was 0.09 +/- 0.04 microg/l among cocaine users and 0.08 +/- 0.04 microg/l among controls. Mean serum neuron specific enolase level was 9.7 +/- 3.5 ng/l among cocaine users and 8.3 +/- 2.6 ng/l among controls. In this first study using these specific brain damage markers in cocaine users, serum levels of S100B and neuron specific enolase were not statistically different between cocaine dependent subjects and controls. Kessler, F.H., Woody, G., Portela, L.V., Tort, A.B., De Boni, R., Peuker, A.C., Genro, V., von Diemen, L., de Souza, D.O., and Pechansky, F. Rev. Bras. Psiquiatr. 29(2), pp. 134-139, 2007.

Director's Report to the National Advisory Council on Drug Abuse - February, 2008

Research Findings - Intramural Research

Biomedical Informatics Section, Administrative Management Branch

A Clinical Recruiting Management System for Complex Multi-Site Clinical Trials Using Qualification Decision Support Systems
A clinical recruiting management system implementing a qualification decision support systems was developed to increase the efficiency of screening and evaluation of participants during a recruiting process whereby recruiting for various protocols are conducted at multiple sites by different groups with process interdependencies. This system is seamlessly integrated into the authors' enterprise-scale Human Research Information System (HuRIS), encompassing research participants' electronic health records (EHR), with real-time access to the clinical trial data. Vahabzadeh, M., Lin, J.-L., Mezghanni, M., Contoreggi, C., and Leff, M. Proc. AMIA Annual Symposium on Biomedical and Health Informatics: From Foundations to Applications to Policy (AMIA 2007), pp. 1141, 2007.

Office of the Scientific Director

EEG Absolute Power during Extended Cocaine Abstinence
Cocaine causes acute changes in the human EEG, such as increased beta activity, but few studies have evaluated longitudinal changes in EEG during extended cocaine abstinence. Such changes may be relevant for assessing the neurophysiological effects of cocaine use and risk of relapse. This study evaluated EEG absolute power in 6 frequency bands in 20 adult chronic cocaine users during 3 months of monitored abstinence on a closed clinical research ward. The first EEG was recorded 0-7 weeks after their last cocaine use. Compared to non-drug using, healthy controls, the first EEG in the 8 cocaine users who had last used within 2 weeks showed decreased absolute power in most frequency bands in the left frontal brain region. During extended cocaine abstinence, absolute power among all 20 subjects increased in the beta1 frequency band in the left temporal region and in the delta frequency band in the right temporal region. These findings suggest that chronic cocaine use is associated with EEG changes that may reflect persisting brain electrophysiological abnormalities during cocaine abstinence. Levin K.H., Herning R.I., Better W.E., Epstein DH, Cadet J-L., and Gorelick D.A. Journal of Addiction Medicine, 1, pp. 139-144, 2007.

Neural Protection and Regeneration Section, Molecular Neuropsychiatry Branch

Tropism and Toxicity of Adeno-associated Viral Vector Serotypes 1, 2, 5, 6, 7, 8, and 9 in Rat Neurons and Glia *in vitro*

Planned Meetings

Publications

Staff Highlights

Grantee Honors

Recombinant adeno-associated viral (rAAV) vectors are frequently used for gene delivery to the central nervous system and are capable of transducing neurons and glia in vitro. In this study, seven serotypes of a rAAV vector expressing green fluorescent protein (GFP) were characterized for tropism and toxicity in primary cortical cells derived from embryonic rat brain. At 2 days after transduction, serotypes 1 and 5 through 8 expressed GFP predominately in glia, but by 6 days post-transduction expression was neuronal except for AAV5. AAV2 and 9 produced minimal GFP expression. Using cell viability assays, toxicity was observed at higher multiplicities of infection (MOI) for all serotypes except AAV2 and 9. The toxicity of AAV1 and 5-8 affected mostly glia as indicated by a loss of glial-marker immunoreactivity. A frameshift mutation in the GFP gene reduced overall toxicity for serotypes 1, 5 and 6, but not 7 and 8 suggesting that the toxicity was not solely due to the overexpression of GFP. Collectively, a differential tropism and toxicity was observed among the AAV serotypes on primary cortical cultures with an overall preferential glial transduction and toxicity. Howard, D.B., Powers, K., Wang, Y., and Harvey, B.K. Virology November 20, 2007 [Epub ahead of print].

Development and Plasticity Section, Cellular Neurobiology Research Branch

An Immortalized Rat Ventral Mesencephalic Cell Line, RTC4, is Protective in a Rodent Model of Stroke

One therapeutic approach to stroke is the transplantation of cells capable of trophic support, reinnervation, and/or regeneration. Previously, IRP researchers have described the use of novel truncated isoforms of SV40 large T antigen to generate unique cell lines from several primary rodent tissue types. Here the authors describe the generation of two cell lines, RTC3 and RTC4, derived from primary mesencephalic tissue using a fragment of mutant T antigen, T155c (cDNA) expressed from the RSV promoter. Both lines expressed the glial markers vimentin and S100beta, but not the neuronal markers NeuN, MAP2, or beta-III-tubulin. A screen for secreted trophic factors revealed substantially elevated levels of platelet-derived growth factor (PDGF) in RTC4, but not RTC3 cells. When transplanted into rat cortex, RTC4 cells survived for at least 22 days and expressed PDGF. Because PDGF has been reported to reduce ischemic injury, the authors examined the protective functions of RTC4 cells in an animal model of stroke. RTC4 or RTC3 cells, or vehicle, were injected into rat cortex 15-20 min prior to a 60-min middle cerebral artery ligation. Forty-eight hours later, animals were sacrificed and the stroke volume was assessed by triphenyl-tetrazolium chloride (TTC) staining. Compared to vehicle or RTC3 cells, transplanted RTC4 cells significantly reduced stroke volume. Overall, the authors generated a cell line with glial properties that produces PDGF and reduces ischemic injury in a rat model of stroke. Harvey, B.K., Chen, J., Schoen, C.J., Lee, C.T., Howard, D.B., Dillon-Carter, O., Coggiano, M., Freed, W.J., Wang, Y., Hoffer, B.J., and Sanchez, J.F. Cell Transplantation, 16(5), pp. 483-491, 2007.

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

Sigma-1 Receptor Chaperones at the ER-Mitochondrion Interface Regulate Ca(2+) Signaling and Cell Survival

Communication between the endoplasmic reticulum (ER) and mitochondrion is important for bioenergetics and cellular survival. The ER supplies Ca(2+) directly to mitochondria via inositol 1,4,5-trisphosphate receptors (IP3Rs) at close contacts between the two organelles referred to as mitochondrion-associated ER membrane (MAM). IRP scientists found here that the ER protein sigma-1 receptor (Sig-1R), which is implicated in neuroprotection, carcinogenesis, and neuroplasticity, is a Ca(2+)-sensitive and ligand-operated

receptor chaperone at MAM. Normally, Sig-1Rs form a complex at MAM with another chaperone, BiP. Upon ER Ca(2+) depletion or via ligand stimulation, Sig-1Rs dissociate from BiP, leading to a prolonged Ca(2+) signaling into mitochondria via IP3Rs. Sig-1Rs can translocate under chronic ER stress. Increasing Sig-1Rs in cells counteracts ER stress response, whereas decreasing them enhances apoptosis. These results reveal that the orchestrated ER chaperone machinery at MAM, by sensing ER Ca(2+) concentrations, regulates ER-mitochondrial interorganellar Ca(2+) signaling and cell survival. Hayashi, T. and Su, T.P. Cell, 131(3), pp. 596-610, 2007.

Proteomics Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

A Snapshot of Tissue Glycerolipids

The lipid membrane is the portal to the cell and its first line of defense against the outside world. Its plasticity, diversity and powers of accommodation in a myriad of environments, mirrored by the varied make up of the cells it protects, are unparalleled. Glycerophospholipids are one of its major components. In cell membranes the extracellular layer is mainly made up of positively charged glycolipids, while the intracellular one's main components are negatively charged. Advances in mass spectrometry have allowed the direct probing of tissues, and thus a direct approach to probing membranes make up was developed. Until recently most studies have focused on proteins. An overview of the use of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOFMS) for the direct analysis of phospholipids in various tissues is presented. Molecular ions corresponding to phosphatidlycholines, sphingomyelin, phosphatidylethanolamines, phosphatidylserines, phosphatidylinositols and sulfatides were mapped. Woods, A.S., Wang, H.Y., and Jackson, S.N. Current Pharmaceutical Design, 13(32), pp. 3344-3356, 2007.

A Stargardt Disease-3 Mutation in the Mouse Elovl4 Gene Causes Retinal Deficiency of C32-C36 Acyl Phosphatidlycholines

Stargardt disease-3 (STGD3) is a juvenile dominant macular degeneration caused by mutations in elongase of very long chain fatty acid-4. All identified mutations produce a truncated protein which lacks a motif for protein retention in endoplasmic reticulum, the site of fatty acid synthesis. In these studies of Stgd3-knockin mice carrying a human pathogenic mutation, IRP investigators examined two potential pathogenic mechanisms: truncated protein-induced cellular stress and lipid product deficiency. Analysis of mutant retinas detected no cellular stress but demonstrated selective deficiency of C32-C36 acyl phosphatidylcholines. The authors conclude that this deficit leads to the human STGD3 pathology. McMahon, A., Jackson, S.N., Woods, A.S., and Kedzierski, W. FEBS Letters, 581(28), pp. 5459-5463, 2007.

Adenosine Receptor Heteromers and their Integrative Role in Striatal Function

By analyzing the functional role of adenosine receptor heteromers, IRP scientists review a series of new concepts that should modify our classical views of neurotransmission in the central nervous system (CNS). Neurotransmitter receptors cannot be considered as single functional units anymore. Heteromerization of neurotransmitter receptors confers functional entities that possess different biochemical characteristics with respect to the individual components of the heteromer. Some of these characteristics can be used as a "biochemical fingerprint" to identify neurotransmitter receptor heteromers in the CNS. This is exemplified by changes in binding characteristics that are dependent on coactivation of the receptor units of different adenosine receptor heteromers. Neurotransmitter receptor heteromers can act as "processors" of computations that modulate cell signaling, sometimes critically involved in the control of pre- and postsynaptic

neurotransmission. For instance, the adenosine A1-A2A receptor heteromer acts as a concentration-dependent switch that controls striatal glutamatergic neurotransmission. Neurotransmitter receptor heteromers play a particularly important integrative role in the "local module" (the minimal portion of one or more neurons and/or one or more glial cells that operates as an independent integrative unit), where they act as processors mediating computations that convey information from diverse volume-transmitted signals. For instance, the adenosine A2A-dopamine D2 receptor heteromers work as integrators of two different neurotransmitters in the striatal spine module. Ferre, S., Ciruela, F., Quiroz, C., Lujan, R., Popoli, P., Cunha, R.A., Agnati, L.F., Fuxe, K., Woods, A.S., Lluis, C., and Franco, R. Scientific World Journal, 7, pp. 74-85, 2007.

Functional Relevance of Neurotransmitter Receptor Heteromers in the Central Nervous System

The existence of neurotransmitter receptor heteromers is becoming broadly accepted and their functional significance is being revealed. Heteromerization of neurotransmitter receptors produces functional entities that possess different biochemical characteristics with respect to the individual components of the heteromer. Neurotransmitter receptor heteromers can function as processors of computations that modulate cell signaling. Thus, the quantitative or qualitative aspects of the signaling generated by stimulation of any of the individual receptor units in the heteromer are different from those obtained during coactivation. Furthermore, recent studies demonstrate that some neurotransmitter receptor heteromers can exert an effect as processors of computations that directly modulate both pre- and postsynaptic neurotransmission. This is illustrated by the analysis of striatal receptor heteromers that control striatal glutamatergic neurotransmission. Ferre, S., Ciruela, F., Woods, A.S., Lluis, C., and Franco, R. Trends in Neuroscience, 30(9), pp. 440-446, 2007.

Electrophysiology Unit, Cellular Neurophysiology Section

The Endocannabinoid Anandamide Inhibits the Function of Alpha4beta2 Nicotinic Acetylcholine Receptors

The effects of the endocannabinoid anandamide (arachidonylethanolamide, AEA) on the function of alpha4beta2 nicotinic acetylcholine receptors (nAChR) stably expressed in SH-EP1 cells were investigated using the whole-cell patch-clamp technique. In the concentration range of 200 nM to 2 microM, AEA significantly reduced the maximal amplitudes and increased the desensitization of acetylcholine (ACh)-induced currents. The effects of AEA could be neither replicated by the exogenous cannabinoid Delta(9)-tetrahydrocannabinol (1 microM) nor reversed by the selective CB1 receptor antagonist 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide (SR-141716A) (1 microM). The actions of AEA were apparent when applied extracellularly but not during intracellular dialysis. Furthermore, the effects of AEA ACh currents were not altered by the calcium chelator 1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid. The onset and washout of the AEA effects required several minutes (10-30 min), but the latter was significantly decreased in the presence of lipid-free bovine serum albumin (BSA). Moreover, BSA alone increased peak ACh current amplitudes and diminished desensitization rates in naive cells, suggesting a tonic modulation of alpha4beta2 nAChR function by an endogenous AEA-like lipid. Further analysis of AEA effects on alpha4beta2 nAChR-mediated currents, using a two-stage desensitization model, indicated that the first forward rate constant leading to desensitization, k(1), increased nearly 30-fold as a linear function of the AEA concentration. In contrast, the observation that the other three rate constants were unaltered by AEA suggested that AEA raised the energy of the activated state. These results indicate that AEA directly inhibits the function of alpha4beta2 nAChRs in a CB1 receptor-independent manner. Spivak, C.E., Lupica, C.R., and Oz, M. Molecular Pharmacology, 72(4), pp. 1024-1032, 2007.

Medicinal Chemistry Section, Medications Discovery Research Branch

Novel Dopamine D3 Receptor Ligands: Potential Substance Abuse Therapeutic Agents

Dopamine D3 receptor antagonists and partial agonists have been shown to modulate drug-seeking effects induced by cocaine and other abused substances. IRP scientists have recently discovered a potent and selective dopamine D3 receptor antagonist, PG01037, and related analogues that are currently being evaluated in animal models of drug addiction. In these studies, a discrepancy between in vitro binding affinity, in vivo occupancy and behavioral potency has been observed. The purpose of this study was to examine 1) modifications of the 2-pyridylphenyl moiety of PG01037 and 2) incorporate hydroxyl, acetyl and cyclopropyl substitutions on the butyl amide linking-chain systematically coupled with 2-fluorenylamide or 2-pyridylphenyl amide and 2-methoxy or 2,3-dichloro-substituted phenylpiperazines to measure impact on binding affinity, D2/D3 selectivity, lipophilicity and function. In general, these modifications were well tolerated at the human dopamine D3 (hD3) receptor (Ki=1-5 nM) as measured in competition binding assays. Several analogues showed >100-fold selectivity for dopamine D3 over D2 and D4 receptors. In addition, while all the derivatives with an olefinic linker were antagonists, in quinpirole-stimulated mitogenesis at hD3 receptors, several of the hydroxy-butyl-linked analogues showed partial agonist activity. Finally, several structural modifications reduced lipophilicities while retaining the desired binding profile. These compounds will provide novel tools with which to further elucidate the role of dopamine D3 receptors in drug abuse, in vivo, and may serve as leads for therapeutic agents for the treatment of addiction. Grundt, P., Prevatt, K.M., Cao, J., Taylor, J., Floresca, C.Z., Choi, J.-K., Jenkins, B.G., Luedtke, R.R., and Newman, A.H. Journal of Medicinal Chemistry, 50, pp. 4135-4146, 2007.

Clinical Psychopharmacology Section, Chemical Biology Research Branch

Chronic Fenfluramine Administration Increases Plasma Serotonin (5-HT) to Non-Toxic Levels

Large elevations in blood serotonin (5-HT) can produce valvular heart disease in humans and laboratory animals. Accordingly, one prevailing hypothesis (i.e., the "5-HT hypothesis") suggests 5-HT transporter substrates like fenfluramine increase the risk for valvular heart disease by elevating plasma 5-HT, secondary to the release of 5-HT from platelets. The main purpose of this study was to determine if chronic administration of fenfluramine increases plasma 5-HT to concentrations that are associated with the development of valvular heart disease. To the best of the study authors' knowledge, this is the first study to address this issue using an in vivo microdialysis method that measures plasma 5-HT in non-hypoxic rats. They examined the effects of chronic (+/-)-fenfluramine and fluoxetine on plasma levels of 5-HT and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in blood samples from conscious catheterized rats. Plasma indoles were measured by HPLC-ECD in dialysates of whole blood. Baseline plasma 5-HT was < 1.0 nM. Chronic fenfluramine (14-day minipump infusion) produced small increases in baseline plasma 5-HT (~2-to-4-fold), while chronic fluoxetine had no effect. Chronic fenfluramine and fluoxetine markedly decreased whole blood 5-HT, and reduced the ability of acute fenfluramine to evoke 5-HT release. Elevations in baseline plasma 5-HT produced by chronic fenfluramine are far below M levels necessary to produce valvular heart disease. Furthermore, chronic fenfluramine reduces the ability of acute fenfluramine to increase plasma 5-HT, suggesting the "5-HT hypothesis" can not explain the increased risk of valvular heart disease in patients treated with fenfluramine. Zolkowska, D., Baumann, M.H.,

and Rothman, R.B. J.Pharmacol.Exp.Ther. Nov. 21, 2007 (e-pub ahead of print).

Dopamine Transport Inhibitors Based on GBR12909 and Benztropine as Potential Medications to Treat Cocaine Addiction
The discovery and development of medications to treat addiction and notably, cocaine addiction, have been frustrated by both the complexity of the disorder and the lack of target validation in human subjects. The dopamine transporter has historically been a primary target for cocaine abuse medication development, but addictive liability and other confounds of such inhibitors of dopamine uptake have limited clinical evaluation and validation. Herein IRP researchers describe efforts to develop analogues of the dopamine uptake inhibitors GBR 12909 and benztropine that show promising profiles in animal models of cocaine abuse that contrast to that of cocaine. Their unique pharmacological profiles have provided important insights into the reinforcing actions of cocaine and the authors propose that clinical investigation of novel dopamine uptake inhibitors will facilitate the discovery of cocaine-abuse medications. Rothman, R.B., Baumann, M.H., Prisinzano, T.E., and Newman, A.H. Biochemical Pharmacology August 9, 2007 (e-pub ahead of print).

Behavioral Neuroscience Section, Behavioral Neuroscience Research Branch

A Role for Conditioned Ventral Tegmental Glutamate Release in Cocaine Seeking
Initiation of cocaine self-administration in rats was associated with release of glutamate in the ventral tegmental area (VTA). The glutamate release was transient, despite continued cocaine intake. Similar glutamate release was seen in rats earning, for the first time, unexpected saline rather than expected cocaine. VTA glutamate release was not seen in similarly trained rats earning saline instead of cocaine for the 13th time. VTA glutamate release was also seen in similarly trained rats that received yoked rather than earned cocaine injections on test day. VTA glutamate release was not seen in a group of rats that had never earned cocaine but had received yoked injections during the training period. Glutamate release was also not seen in a group of rats that received yoked injections but had no previous experience with cocaine. VTA GABA levels did not fluctuate during any aspect of cocaine seeking. Blockade of VTA glutamate receptors appeared to attenuate the rewarding effects of intravenous cocaine injections and blocked almost completely the conditioned responding normally seen during extinction trials. These findings indicate that VTA glutamate release is a conditioned response dependent on an associative process and is not a simple consequence of previous cocaine exposure. The findings implicate glutamate as at least one of the sources of VTA signals from reward-associated environmental stimuli. You, Z.B., Wang, B., Zitzman, D., Azari, S., and Wise, R.A. Journal of Neuroscience, 27, pp. 10546-10555, 2007.

Dopamine Reward Circuitry: Two Projection Systems from the Ventral Midbrain to the Nucleus Accumbens-Olfactory Tubercle Complex
Anatomical and functional refinements of the mesolimbic dopamine system of the rat are discussed. Present experiments suggest that dopaminergic neurons localized in the posteromedial ventral tegmental area (VTA) and central linear nucleus raphe selectively project to the ventromedial striatum (medial olfactory tubercle and medial nucleus accumbens shell), whereas the anteromedial VTA has few if any projections to the ventral striatum, and the lateral VTA largely projects to the ventrolateral striatum (accumbens core, lateral shell and lateral tubercle). These findings complement the recent behavioral findings that cocaine and amphetamine are more rewarding when administered into the ventromedial striatum than into the ventrolateral striatum. Drugs such as nicotine and opiates are more rewarding when administered into the posterior VTA or the central linear nucleus than into the anterior VTA. A review of the

literature suggests that (1) the midbrain has corresponding zones for the accumbens core and medial shell; (2) the striatal portion of the olfactory tubercle is a ventral extension of the nucleus accumbens shell; and (3) a model of two dopamine projection systems from the ventral midbrain to the ventral striatum is useful for understanding reward function. The medial projection system is important in the regulation of arousal characterized by affect and drive and plays a different role in goal-directed learning than the lateral projection system, as described in the variation-selection hypothesis of striatal functional organization. Ikemoto, S. Brain Research Reviews, 56, pp. 27-78, 2007.

Neurobiology of Relapse Section, Behavioral Neuroscience Research Branch

Differential Effects of Blockade of Dopamine D1-family Receptors in Nucleus Accumbens Core or Shell on Reinstatement of Heroin-Seeking Induced by Contextual and Discrete Cues

In humans, exposure to environmental contexts previously associated with heroin intake can provoke drug relapse, but the neuronal mechanisms mediating this relapse are unknown. Using a drug relapse model, IRP scientists found previously that re-exposing rats to heroin-associated contexts, after extinction of drug-reinforced responding in different contexts, reinstates heroin seeking. This effect is attenuated by inhibition of glutamate transmission in the ventral tegmental area and medial accumbens shell, components of the mesolimbic dopamine system. Here, these investigators explored the role of dopamine of the accumbens in context-induced reinstatement by using the D1-family receptor antagonist SCH 23390 [R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride]. Rats were trained to self-administer heroin for 12 d; drug infusions were paired with a discrete tone-light cue. Subsequently, the heroin-reinforced 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. When tested in the original drug self-administration context, systemic and medial or lateral accumbens shell SCH 23390 injections attenuated context-induced reinstatement of heroin seeking, whereas accumbens core SCH 23390 injections were ineffective. In contrast, core but not lateral or medial shell SCH 23390 injections attenuated discrete-cue-induced reinstatement in a non-drug context after extinction of lever presses without this cue. Results indicate that activation of medial and lateral accumbens shell D1-family dopamine receptors mediate context-induced reinstatement of heroin seeking and provide the first demonstration for a role of lateral shell dopamine in conditioned drug effects. Results also demonstrate novel dissociable roles of accumbens core and shell in context- versus discrete-cue-induced reinstatement of heroin seeking. Bossert, J.M., Poles, G.C., Wihbey, K.A., Koya, E. and Shaham, Y. Journal of Neuroscience, 27, pp. 12655-12663, 2007.

Peptide YY3-36 Decreases Reinstatement of High-fat Food Seeking During Dieting in a Rat Relapse Model

A major problem in treating obesity is high rates of relapse to maladaptive food-taking habits during dieting. This relapse is often provoked by acute re-exposure to palatable food, food-associated cues, or stress. IRP researchers used a reinstatement model, commonly used to study relapse to abused drugs, to explore the effect of peptide YY3-36 (PYY3-36) on reinstatement of high-fat (35%, 45 mg pellets) food seeking induced by acute exposure to the pellets (pellet priming), a cue previously associated with pellet delivery (pellet cue), or yohimbine (2 mg/kg, a pharmacological stressor). Rats were placed on a restricted diet (16 g of chow per day) and lever-pressed for the pellets for 9-12 sessions (6 h/d, every 48 h); pellet delivery was paired with a tone-light cue. They were then given 10-20 extinction sessions wherein lever presses were not

reinforced with the pellets and subsequently tested for reinstatement of food seeking. Systemic PYY3-36 injections (100-200 micro g/kg) decreased pellet priming- and pellet cue-induced reinstatement of food seeking but not yohimbine-induced reinstatement. Arcuate nucleus (Arc) injections of PYY3-36 (0.4 microg per side) decreased pellet priming-induced reinstatement. The attenuation of pellet priming-induced reinstatement by systemic PYY3-36 was reversed by systemic (2 mg/kg) but not Arc (0.5 microg per side) injections of the Y2 receptor antagonist BIIE0246. Arc PYY3-36 injections did not decrease pellet cue-induced reinstatement. Finally, systemic PYY3-36 injections had minimal effects on ongoing food self-administration or heroin priming- or heroin cue-induced reinstatement of heroin seeking. These data identify an effect of systemic PYY3-36 on relapse to food seeking that is independent of Y2 receptor activation in Arc and suggest that PYY3-36 should be considered for the treatment of relapse to maladaptive food-taking habits during dieting. Ghitza, U.E., Nair, S.G., Golden, S.A., Gray, S.M., Uejima, J.L., Bossert, J.M., and Shaham, Y. Journal of Neuroscience, 27, pp. 11522-11532, 2007.

Repeated Amphetamine Administration Outside the Home Cage Enhances Drug-induced Fos Expression in Rat Nucleus Accumbens

Induction of the immediate early gene protein product Fos has been used extensively to assess neural activation in the striatum after repeated amphetamine administration to rats in their home cages. However, this technique has not been used to examine striatal activation after repeated administration outside the home cage, an environment where repeated drug administration produces more robust psychomotor sensitization. IRP scientists determined the dose-response relationship for amphetamine-induced psychomotor activity and Fos expression in nucleus accumbens and caudate-putamen 1 week after repeated administration of amphetamine or saline in locomotor activity chambers. Repeated administration of amphetamine enhanced amphetamine-induced locomotor activity and stereotypy and Fos expression in nucleus accumbens, but not in caudate-putamen. In comparison, levels of Fos expression induced by 1mg/kg amphetamine were not altered in nucleus accumbens or caudate-putamen by repeated amphetamine administration in the home cage. Double-labeling of Fos protein and enkephalin mRNA indicates that Fos is expressed in approximately equal numbers of enkephalin-negative and enkephalin-positive neurons in nucleus accumbens and caudate-putamen following injections outside the home cage. Furthermore, repeated amphetamine administration increased drug-induced Fos expression in enkephalin-positive, but not enkephalin-negative, neurons in nucleus accumbens. The authors conclude that repeated amphetamine administration outside the home cage recruits the activation of enkephalin-containing nucleus accumbens neurons during sensitized amphetamine-induced psychomotor activity. Mattson, B.J., Crombag, H.S., Mitchell, T., Simmons, D.E., Kreuter, J.D., Morales, M. and Hope, B.T. Behavioural Brain Research, 185, pp. 88-98, 2007.

In Vivo Electrophysiology Unit, Behavioral Neuroscience Research Branch

I.V. Cocaine Induces Rapid, Transient Excitation of Striatal Neurons via its Action on Peripheral Neural Elements: Single-cell, Iontophoretic Study in Awake and Anesthetized Rats

Cocaine's (COC) direct interaction with the dopamine (DA) transporter is usually considered the most important action underlying the psychomotor stimulant and reinforcing effects of this drug. However, some physiological, behavioral and psycho-emotional effects of COC are very rapid and brief and they remain intact during DA receptor blockade, suggesting possible involvement of peripheral non-DA neural mechanisms. To assess this issue, single-unit recording with microiontophoresis was used to examine changes in impulse activity of dorsal and ventral striatal neurons to i.v. COC (0.25-0.5

mg/kg) in the same rats under two conditions: awake with DA receptor blockade and anesthetized with urethane. In the awake preparation approximately 70% striatal neurons showed rapid and transient (latency approximately 6 s, duration approximately 15 s) COC-induced excitations. These effects were stronger in ventral than dorsal striatum. During anesthesia, these phasic effects were fully blocked and COC slowly decreased neuronal discharge rate. Cocaine-methiodide (COC-M), a derivative that cannot cross the blood-brain barrier, also caused phasic excitations in the awake, but not anesthetized condition. In contrast to regular COC, COC-M had no tonic effect on discharge rate in either preparation. Most striatal neurons that were phasically excited by both COC forms also showed short-latency excitations during tail-touch and tail-pinch in the awake preparation, an effect strongly attenuated during anesthesia. Finally, most striatal neurons that in awake conditions were phasically excited by somato-sensory stimuli and COC salts were also excited by iontophoretic glutamate (GLU). Although striatal neurons were sensitive to GLU in both preparations, the response magnitude at the same GLU current was higher in awake than anesthetized conditions. These data suggest that in awake animals, i.v. COC, like somato-sensory stimuli, transiently excites striatal neurons via its action on peripheral neural elements and rapid neural transmission. While the nature of these neuronal elements needs to be clarified using other analytical techniques, they might involve voltage-gated K(+) and Na(+) channels, which have a high affinity for COC and are located on terminals of visceral sensory nerves that densely innervate peripheral vessels. Therefore, along with direct action on specific brain substrates, central excitatory effects of COC may occur via indirect action, involving afferents of visceral sensory nerves and rapid neural transmission. By providing a rapid sensory signal and triggering transient neural activation, such a peripherally triggered action might play a crucial role in the sensory effects of COC, thus contributing to learning and development of drug-taking behavior. Kiyatkin, E.A. and Brown, P.L. Neuroscience, 148, pp. 978-995, 2007.

Brain Edema and Breakdown of the Blood-brain Barrier during Methamphetamine Intoxication: Critical Role of Brain Hyperthermia

To clarify the role of brain temperature in permeability of the blood-brain barrier (BBB), rats were injected with methamphetamine (METH 9 mg/kg) at normal (23 degrees C) and warm (29 degrees C) environmental conditions and internal temperatures were monitored both centrally (nucleus accumbens, NAcc) and peripherally (skin and nonlocomotor muscle). Once NAcc temperatures peaked or reached 41.5 degrees C (a level suggesting possible lethality), animals were administered Evans blue dye (protein tracer that does not normally cross the BBB), rapidly anaesthetized, perfused and had their brains removed. All METH-treated animals showed brain and body hyperthermia associated with relative skin hypothermia, suggesting metabolic activation coupled with peripheral vasoconstriction. While METH-induced NAcc temperature elevation varied from 37.60 to 42.46 degrees C (or 1.2-5.1 degrees C above baseline), it was stronger at 29 degrees C (+4.13 degrees C) than 23 degrees C (+2.31 degrees C). Relative to control, METH-treated animals had significantly higher brain levels of water, Na(+), K(+) and Cl(-), suggesting brain edema, and intense immunostaining for albumin, indicating breakdown of the BBB. METH-treated animals also showed strong immunoreactivity for glial fibrillary acidic protein (GFAP), possibly suggesting acute abnormality or damage of astrocytes. METH-induced changes in brain water, albumin and GFAP correlated linearly with NAcc temperature (r = 0.93, 0.98 and 0.98, respectively), suggesting a key role of brain hyperthermia in BBB permeability, development of brain edema and subsequent functional and structural neural abnormalities. Therefore, along with a direct destructive action on neural cells and functions, brain hyperthermia, via breakdown of the BBB, may be crucial for both decompensation of brain functions and cell injury following acute METH intoxication, possibly contributing to neurodegeneration resulting from chronic drug use. Kiyatkin, E.A., Brown, P.L., and Sharma, H.S. European Journal of Neuroscience, 26, pp. 1242-1253, 2007.

Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch

Endocannabinoid System Involvement in Brain Reward Processes Related to Drug Abuse

Cannabis is the most commonly abused illegal drug in the world and its main psychoactive ingredient, delta-9-tetrahydrocannabinol (THC), produces rewarding effects in humans and non-human primates. Over the last several decades, an endogenous system comprised of cannabinoid receptors, endogenous ligands for these receptors and enzymes responsible for the synthesis and degradation of these endogenous cannabinoid ligands has been discovered and partly characterized. Experimental findings strongly suggest a major involvement of the endocannabinoid system in general brain reward functions and drug abuse. First, natural and synthetic cannabinoids and endocannabinoids can produce rewarding effects in humans and laboratory animals. Second, activation or blockade of the endogenous cannabinoid system has been shown to modulate the rewarding effects of non-cannabinoid psychoactive drugs. Third, most abused drugs alter brain levels of endocannabinoids in the brain. In addition to reward functions, the endocannabinoid cannabinoid system appears to be involved in the ability of drugs and drug-related cues to reinstate drug-seeking behavior in animal models of relapse. Altogether, evidence points to the endocannabinoid system as a promising target for the development of medications for the treatment of drug abuse. Solinas, M., Yasar, S. and Goldberg, S.R. Pharmacological Research, 56, pp. 393-405, 2007.

A Stimulus-control Account of Regulated Drug Intake in Rats

Patterns of drug self-administration are often highly regular, with a consistent pause after each self-injection. This pausing might occur because the animal has learned that additional injections are not reinforcing once the drug effect has reached a certain level, possibly due to the reinforcement system reaching full capacity. Thus, interoceptive effects of the drug might function as a discriminative stimulus, signaling when additional drug will be reinforcing and when it will not. This hypothetical stimulus control aspect of drug self-administration was emulated using a schedule of food reinforcement. Rats' nose-poke responses produced food only when a cue light was present. No drug was administered at any time. However, the state of the light stimulus was determined by calculating what the whole-body drug level would have been if each response in the session had produced a drug injection. The light was only presented while this virtual drug level was below a specific threshold. A range of doses of cocaine and remifentanil were emulated using parameters based on previous self-administration experiments. Response patterns were highly regular, dose-dependent, and remarkably similar to actual drug self-administration. This similarity suggests that the emulation schedule may provide a reasonable model of the contingencies inherent in drug reinforcement. Thus, these results support a stimulus control account of regulated drug intake in which rats learn to discriminate when the level of drug effect has fallen to a point where another self-injection will be reinforcing. Panlilio L.V., Thorndike, E.B. and Schindler, C.W. Psychopharmacology (Berl), October 24, 2007 (e-pub ahead of print).

Differential Involvement of Dopamine Receptors in Conditioned Suppression Induced by Cocaine

Cocaine-paired stimuli can suppress food-reinforced operant behavior in rats, providing an animal model of conditioned drug effects. To study the neuropharmacological basis of this phenomenon, IRP researchers examined the effects of various dopamine receptor antagonists on the acquisition and expression of cocaine-induced conditioned suppression in rats. Superimposed on an ongoing baseline of food-reinforced operant responding, a stimulus was paired with response-independent cocaine (3.0 mg/kg, i.v.) during each of 8

training sessions. To study acquisition, independent groups of rats were given saline, the dopamine D(1)-like receptor antagonist R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SCH 23390) (0.001-0.03 mg/kg, i.p.), or the dopamine D(2)-like receptor antagonist eticlopride (0.001-0.03 mg/kg, i.p.) prior to each training session. To study expression, independent groups of rats were trained first, then given saline, SCH 23390, eticlopride, or N-[4-(4-(2-methoxyphenyl) piperazinyl)butyl]-2-naphthamide (BP 897) (a dopamine D(3) partial receptor agonist; 0.1-1.0 mg/kg, i.p.) before test sessions in which the stimulus was presented without cocaine. Pre-treatment with either SCH 23390 or eticlopride during acquisition reduced the direct suppressant effects of cocaine, but conditioning was blocked only in rats that were treated with SCH 23390 during acquisition training. Expression of conditioning was attenuated only by eticlopride. Thus, dopamine at least partially mediates both the acquisition and expression of cocaine-induced conditioned suppression, with activation of dopamine D(1)- and D(2)-like receptors underlying these respective processes. Grakalic, I., Panlilio, L.V., Thorndike, E.B., and Schindler, C.W. European Journal of Pharmacology, 573, pp. 116-123, 2007.

Self-administration of Drugs in Animals and Humans as a Model and an Investigative Tool

The aim of this research was to review briefly the methods, assumptions, models, accomplishments, drawbacks and future directions of research using drug self-administration in animals and humans. The use of drug self-administration to study addiction is based on the assumption that drugs reinforce the behavior that results in their delivery. A wide range of drug self-administration techniques have been developed to model specific aspects of addiction. These techniques are highly amenable to being combined with a wide variety of neuroscience techniques. The identification of drug use as behavior that is reinforced by drugs has contributed greatly to the understanding and treatment of addiction. As part of a program of pre-clinical research that also involves screening with a variety of simpler behavioral techniques, drug self-administration procedures can provide an important last step in testing potential treatments for addiction. There is currently a concerted effort to develop self-administration procedures that model the extreme nature of the behavior engendered by addiction. As advances continue to be made in neuroscience techniques, self-administration should continue to provide a means of applying these techniques within a sophisticated and valid model of human drug addiction. Panlilio, L. and Goldberg, S.R. Addiction, 102, pp. 1863-1870, 2007.

Adenosine A1-A2A Receptor Heteromers: New Targets for Caffeine in the Brain

The contribution of blockade of adenosine A1 and A2A receptor to the psychostimulant effects of caffeine is still a matter of debate. When analyzing motor activity in rats, acutely administered caffeine shows a profile of a non-selective adenosine receptor antagonist, although with preferential A1 receptor antagonism. On the other hand, tolerance to the effects of A1 receptor blockade seems to be mostly responsible for the tolerance to the motor-activating effects of caffeine, while the residual motor-activating effects of caffeine in tolerant individuals seem to involve A2A receptor blockade. These behavioral studies correlate with in vivo microdialysis experiments that suggest that A1 receptor-mediated modulation of striatal glutamate release is involved in the psychostimulant effects of caffeine. Experiments in transfected cells demonstrate the ability of A1 receptors to heteromerize with A2A receptors and the A1-A2A receptor heteromer can be biochemically identified in the striatum, in striatal glutamatergic terminals. The striatal A1-A2A receptor heteromer provides a "concentration-dependent switch" mechanism by which low and high concentrations of synaptic adenosine produce the opposite effects on glutamate release. The analysis of the function of A1-A2A receptor heteromers during chronic treatment with caffeine gives new clues about the well-known

phenomenon of tolerance to the psychostimulant effects of caffeine. Ferre, S., Ciruela, F., Borycz, J., Solinas, M., Quarta, D., Antoniou, K., Quiroz, C., Justinova, Z., Lluis, C., Franco, R. and Goldberg, S.R. Front Bioscience, 13, pp. 2391-2399, 2008.

The Endogenous Cannabinoid Anandamide has Effects on Motivation and Anxiety that are Revealed by Fatty Acid Amide Hydrolase (FAAH) Inhibition

Converging evidence suggests that the endocannabinoid system is an important constituent of neuronal substrates involved in brain reward processes and emotional responses to stress. Here, IRP researchers evaluated motivational effects of intravenously administered anandamide, an endogenous ligand for cannabinoid CB1-receptors, in Sprague-Dawley rats, using a place-conditioning procedure in which drugs abused by humans generally produce conditioned place preferences (reward). Anandamide (0.03-3mg/kg intravenous) produced neither conditioned place preferences nor aversions. However, when rats were pre-treated with the fatty acid amide hydrolase (FAAH) inhibitor URB597 (cyclohexyl carbamic acid 3'-carbamoyl-3-yl ester; 0.3mg/kg intraperitoneal), which blocks anandamide's metabolic degradation, anandamide produced dose-related conditioned place aversions. In contrast, URB597 alone showed no motivational effects. Like URB597 plus anandamide, the synthetic CB1-receptor ligand WIN 55,212-2 (50-300mug/kg, intravenous) produced dose-related conditioned place aversions. When anxiety-related effects of anandamide and URB597 were evaluated in a light/dark box, both a low anandamide dose (0.3mg/kg) and URB597 (0.1 and 0.3mg/kg) produced anxiolytic effects when given alone, but produced anxiogenic effects when combined. A higher dose of anandamide (3mg/kg) produced anxiogenic effects and depressed locomotor activity when given alone and these effects were potentiated after URB597 treatment. Finally, anxiogenic effects of anandamide plus URB597 and development of place aversions with URB597 plus anandamide were prevented by the CB1-receptor antagonist AM251 (3mg/kg intraperitoneal). Thus, additive interactions between the effects of anandamide on brain reward processes and on anxiety may account for its aversive effects when intravenously administered during FAAH inhibition with URB597. Scherma, M., Medalie, J., Fratta, W., Vadivel, S. K., Makriyannis, A., Piomelli, D., Mikics, E., Haller, J., Yasar, S., Tanda, G. and Goldberg, S. R. Neuropharmacology, August 19, 2007 (e-pub ahead of print).

Effects of Kappa Opioid Agonists Alone and in Combination with Cocaine on Heart Rate and Blood Pressure in Conscious Squirrel Monkeys

As kappa agonists have been proposed as treatments for cocaine abuse, the cardiovascular effects of the kappa opioid receptor agonists ethylketocyclazocine (EKC) and enadoline were investigated in conscious squirrel monkeys. Both EKC and enadoline increased heart rate with little effect on blood pressure. This effect appeared to be specific for kappa receptors as the mu opioid agonist morphine did not mimic the effects of the kappa agonists. The opioid antagonist naltrexone, at a dose of 1.0 mg/kg, blocked the effect of EKC. An action at both central and peripheral receptors may be responsible for the heart rate increase following kappa agonist treatment. The ganglionic blocker chlorisondamine partially antagonized the effect of EKC on heart rate, suggesting central involvement, while the peripherally-acting agonist ICI 204,448 ((+/-)-1-[2,3- (Dihydro-7-methyl-1H-inden-4-yl)oxy]-3-[(1-methylethyl)amino]-2-butanol hydrochloride) also increased heart rate, supporting a peripheral site of action. When given in combination with cocaine, EKC produced effects that were sub-additive, suggesting that the kappa agonists may be used safely as cocaine abuse treatments. Schindler, C.W., Graczyk, Z., Gilman, J.P., Negus, S.S., Bergman, J., Mello, N.K. and Goldberg, S.R. European Journal Pharmacology, 576, pp. 107-113, 2007.

Validation of an Extracerebral Reference Region Approach for the

Quantification of Brain Nicotinic Acetylcholine Receptors in Squirrel Monkeys with PET and 2-18F-flour-A-85380

The aim of the present study was to explore the applicability of an extracerebral reference region for the quantification of cerebral receptors with PET. Male squirrel monkeys underwent quantitative PET studies of cerebral nicotinic acetylcholine receptors (nAChRs) with 2-(18)F-fluoro-A-85380 (2-FA). Data from dynamic PET scans were analyzed with various compartment- and non-compartment-based models, including a simplified reference tissue model (SRTM). Nondisplaceable volume-of-distribution (VDnd) values were determined in regions of interest after the blockade of 2-FA-specific binding by nicotine infusion. Binding potential values, estimated with the cerebellum and muscle as reference regions, were compared and the reproducibility of measurements was determined. One- and 2-tissue-compartment modeling and linear graphic analysis provided similar total volume-of-distribution (VD(T)) values for each studied region. VD(T) values were high in the thalamus, intermediate in the cortex and midbrain, and low in the cerebellum and muscle, consistent with the distribution pattern of nAChR containing alpha(4) and beta(2) receptor subunits (alpha(4)beta(2)*). The administration of nicotine at 2 mg/kg/d via an osmotic pump resulted in a nearly complete saturation of 2-FA-specific binding and led to very small changes in volumes of distribution in the cerebellum and muscle (-9% +/- 4% [mean +/- SEM] and 0% +/- 6%, respectively), suggesting limited specific binding of the radioligand in these areas. VD(T) measured in muscle in 15 monkeys was reasonably constant (3.0 +/- 0.2, with a coefficient of variation of 8%). VDnd in studied brain regions exceeded VD(T) in muscles by a factor of 1.3. With this factor and with muscle as a reference region, BP* values calculated for studied brain regions with the SRTM were in good agreement with those obtained with the cerebellum as a reference region. Significant correlations were observed between BP* values estimated with these 2 approaches. The reproducibilities of BP* measurements obtained with the 2 methods were comparable, with coefficients of variation of less than 11% and 13% for the thalamus and the cortex, respectively. These results suggest that the accurate quantification of nAChRs can be performed with 2-FA and a reference region outside the brain, providing a novel approach for the quantification of brain receptors when no suitable cerebral reference region is available. LeFoll, B., Chefer, S.I., Kimes, A.S., Shumway, D., Goldberg, S.R., Stein, E.A. and Mukhin, A.G. Journal Nuclear Medicine, 48, pp. 1492-1500, 2007.

G-protein-coupled Receptor Heteromers: Function and Ligand Pharmacology

Almost all existing models for G-protein-coupled receptors (GPCRs) are based on the occurrence of monomers. Recent studies show that many GPCRs are dimers. Therefore for some receptors dimers and not monomers are the main species interacting with hormones/neurotransmitters/drugs. There are reasons for equivocal interpretations of the data fitting to receptor dimers assuming they are monomers. Fitting data using a dimer-based model gives not only the equilibrium dissociation constants for high and low affinity binding to receptor dimers but also a 'cooperativity index' that reflects the molecular communication between monomers within the dimer. The dimer cooperativity index (D(C)) is a valuable tool that enables to interpret and quantify, for instance, the effect of allosteric regulators. For different receptors heteromerization confers a specific functional property for the receptor heteromer that can be considered as a 'dimer fingerprint'. The occurrence of heteromers with different pharmacological and signalling properties opens a complete new field to search for novel drug targets useful to combat a variety of diseases and potentially with fewer side effects. Antagonists, which are quite common marketed drugs targeting GPCRs, display variable affinities when a given receptor is expressed with different heteromeric partners. This fact should be taken into account in the development of new drugs. Franco, R., Casado, V., Cortes, A., Mallol, J., Ciruela, F., Ferre, S., Lluis, C. and Canela, E.I. British Journal Pharmacology, November 26, 2007 (e-pub ahead of print).

Reduction of Cocaine Seeking by a Food-based Inhibitor in Rats
Environmental stimuli can exert a powerful influence over drug seeking and taking. For example, previous experiments found that combining multiple drug-related stimuli tripled drug seeking and doubled drug intake (L.V. Panlilio, S.J. Weiss, & C.W. Schindler, 1996, 2000), whereas a signal for the absence of cocaine (i.e., a drug-related inhibitor) dramatically reduced cocaine seeking in rats by over 90% (D.N. Kearns, S.J. Weiss, C.W. Schindler, & L.V. Panlilio, 2005). In the present experiment, a signal for the absence of food created through the A+/AB- conditioned inhibition paradigm also suppressed responding for cocaine by approximately 90%. Symmetrically, a signal for the absence of cocaine (i.e., a cocaine-based inhibitor) suppressed food seeking to a similar degree. These findings, consistent with the appetitive-aversive interaction theory of motivation, suggest that using inhibitors based on non-drug appetitive reinforcers might be a practical method of reducing drug seeking in human drug abusers and should be seriously considered for clinical test and application. Weiss, S.J., Kearns, D.N., Christensen, C.J., Huntsberry, M.E., Schindler, C.W. and Panlilio, L.V. Experimental Clinical Psychopharmacology, 15, pp. 359-367, 2007.

Adenosine Receptor Heteromers and their Integrative Role in Striatal Function
By analyzing the functional role of adenosine receptor heteromers, IRP scientists review a series of new concepts that should modify our classical views of neurotransmission in the central nervous system (CNS). Neurotransmitter receptors cannot be considered as single functional units anymore. Heteromerization of neurotransmitter receptors confers functional entities that possess different biochemical characteristics with respect to the individual components of the heteromer. Some of these characteristics can be used as a "biochemical fingerprint" to identify neurotransmitter receptor heteromers in the CNS. This is exemplified by changes in binding characteristics that are dependent on coactivation of the receptor units of different adenosine receptor heteromers. Neurotransmitter receptor heteromers can act as "processors" of computations that modulate cell signaling, sometimes critically involved in the control of pre- and postsynaptic neurotransmission. For instance, the adenosine A1-A2A receptor heteromer acts as a concentration-dependent switch that controls striatal glutamatergic neurotransmission. Neurotransmitter receptor heteromers play a particularly important integrative role in the "local module" (the minimal portion of one or more neurons and/or one or more glial cells that operates as an independent integrative unit), where they act as processors mediating computations that convey information from diverse volume-transmitted signals. For instance, the adenosine A2A-dopamine D2 receptor heteromers work as integrators of two different neurotransmitters in the striatal spine module. Ferre, S., Ciruela, F., Quiroz, C., Lujan, R., Popoli, P. Cunha, R. A., Agnati, L.F., Fuxe, K., Woods, A.S., Lluis, C. and Franco, R. Scientific World Journal, 2, pp. 74-85, 2007.

Basic Concepts in G-protein-coupled Receptor Homo- and Heterodimerization
Until recently, heptahelical G-protein-coupled receptors (GPCRs) were considered to be expressed as monomers on the cell surface of neuronal and non-neuronal cells. It is now becoming evident that this view must be overtly changed since these receptors can form homodimers, heterodimers, and higher-order oligomers on the plasma membrane. Here IRP researchers discuss some of the basics and some new concepts of receptor homo- and heteromerization. Dimers-oligomers modify pharmacology, trafficking, and signaling of receptors. First of all, GPCR dimers must be considered as the main molecules that are targeted by neurotransmitters or by drugs. Thus, binding data must be fitted to dimer-based models. In these models, it is considered that the conformational changes transmitted within the dimer molecule lead to cooperativity. Cooperativity must be taken into account in the binding of

agonists-antagonists-drugs and also in the binding of the so-called allosteric modulators. Cooperativity results from the intramolecular cross-talk in the homodimer. As an intramolecular cross-talk in the heterodimer, the binding of one neurotransmitter to one receptor often affects the binding of the second neurotransmitter to the partner receptor. Coactivation of the two receptors in a heterodimer can change completely the signaling pathway triggered by the neurotransmitter as well as the trafficking of the receptors. Heterodimer-specific drugs or dual drugs able to activate the two receptors in the heterodimer simultaneously emerge as novel and promising drugs for a variety of central nervous system (CNS) therapeutic applications. Franco, R., Casado, V., Cortes, A., Ferrada, C., Mallol, J., Woods, A., Lluis, C., Canela, E.I. and Ferre, S. Scientific World Journal, 7, pp. 48-57, 2007.

Old and New Ways to Calculate the Affinity of Agonists and Antagonists Interacting with G-protein-coupled Monomeric and Dimeric Receptors: The Receptor-dimer Cooperativity Index

Almost all existing models that explain heptahelical G-protein-coupled receptor (GPCR) operation are based on the occurrence of monomeric receptor species. However, an increasing number of studies show that many G-protein-coupled heptahelical membrane receptors (HMR) are expressed in the plasma membrane as dimers. IRP investigators here review the approaches for fitting ligand binding data that are based on the existence of receptor monomers and also the new ones based on the existence of receptor dimers. The reasons for equivocal interpretations of the fitting of data to receptor dimers, assuming they are monomers, are also discussed. A recently devised model for receptor dimers provides a new approach for fitting data that eventually gives more accurate and physiological relevant parameters. Fitting data using the new procedure gives not only the equilibrium dissociation constants for high- and low-affinity binding to receptor dimers but also a "cooperativity index" that reflects the molecular communication within the dimer. A comprehensive way to fit binding data from saturation isotherms and from competition assays to a dimer receptor model is reported and compared with the traditional way of fitting data. The new procedure can be applied to any receptor forming dimers; from receptor tyrosine kinases to intracellular receptors (e.g., estrogen receptor) and in general for ligand binding to proteins forming dimers. Cadaso, V., Cortes, A., Ciruela, F., Mallol, J., Ferre, S., Lluis, C., Canela, E.I. and Franco, R. Pharmacological Therapeutics, 116, pp. 343-354, 2007.

Functional Relevance of Neurotransmitter Receptor Heteromers in the Central Nervous System

The existence of neurotransmitter receptor heteromers is becoming broadly accepted and their functional significance is being revealed. Heteromerization of neurotransmitter receptors produces functional entities that possess different biochemical characteristics with respect to the individual components of the heteromer. Neurotransmitter receptor heteromers can function as processors of computations that modulate cell signaling. Thus, the quantitative or qualitative aspects of the signaling generated by stimulation of any of the individual receptor units in the heteromer are different from those obtained during coactivation. Furthermore, recent studies demonstrate that some neurotransmitter receptor heteromers can exert an effect as processors of computations that directly modulate both pre- and postsynaptic neurotransmission. This is illustrated by the analysis of striatal receptor heteromers that control striatal glutamatergic neurotransmission. Ferre, S., Ciruela, F., Woods, A.S., Lluis, C. and Franco, R. Trends Neuroscience, 30, pp. 440-446, 2007.

Molecular Neuropsychiatry Research Branch

Interactions of HIV and Methamphetamine: Cellular and Molecular Mechanisms of Toxicity Potentiation

Methamphetamine (METH) is a highly addictive psychostimulant drug, whose

abuse has reached epidemic proportions worldwide. METH use is disproportionally represented among populations at high risks for developing HIV infection or who are already infected with the virus. Psychostimulant abuse has been reported to exacerbate the cognitive deficits and neurodegenerative abnormalities observed in HIV-positive patients. Thus, the purpose of the present paper is to review the clinical and basic observations that METH potentiates the adverse effects of HIV infection. An additional purpose is to provide a synthesis of the cellular and molecular mechanisms that might be responsible for the increased toxicity observed in co-morbid patients. The reviewed data indicate that METH and HIV proteins, including gp120, gp41, Tat, Vpr and Nef, converge on various caspase-dependent death pathways to cause neuronal apoptosis. The role of reactive microgliosis in METH- and in HIV-induced toxicity is also discussed. Cadet, J.L. and Krasnova, I.N. Neurotoxicology Research 12(3), pp. 181-204, 2007.

A Marked Increase in Cocaine-related Deaths in the State of Florida: Precursor to an Epidemic?

The history of cocaine misuse includes a destructive epidemic during the 1980s. While recent surveys suggest cocaine use is stable or decreasing, IRP scientists have observed increasing trends of cocaine-related death through analysis of medical examiner data collected by the Florida Department of Law Enforcement (FDLE). Florida's per capita cocaine-related death rates nearly doubled from 2001 to 2005. Electronic collection of data such as that collected by the FDLE nationally and in real-time would greatly advance understanding of drug-use patterns and consequences. For example, results from Florida suggest that high school and college students, and members of higher socioeconomic status, appear to be at increased risk of cocaine abuse. Public health interventions are necessary to prevent another full-fledged epidemic. Goldberger, B., Grahan, N., Nelson, S., Cadet, J.L., and Gold, M. J. of Addict..Diseases 26(3), pp. 113-116, 2007.

Transcriptional Responses to Reinforcing Effects of Cocaine in the Rat Hippocampus and Cortex

The psychostimulant effects of cocaine are thought to result from its ability to block dopamine (DA) uptake and increase DA levels in ventral striatum. In addition, cocaine causes biochemical changes in the brain areas involved in learning and memory, including hippocampus and cortex, whose role in drug reinforcement is now being actively investigated. Thus, IRP researchers studied molecular events in the hippocampus and frontal cortex of rats treated with cocaine conditioned place preference (CPP) paradigm. After exposure to cocaine conditioning (cocaine paired), cocaine alone (cocaine non-paired) or saline rats were tested for place conditioning. Cocaine (10 mg/kg) caused increases in time spent in the drug-paired compartment. By using microarray analyses, the authors examined gene expression in the hippocampi and frontal cortices of cocaine-paired rats, cocaine non-paired and saline-treated controls. Their study revealed that 214 transcripts were differentially regulated in the hippocampi of cocaine-paired rats. These include genes that play roles in protein phosphorylation, RNA processing and protein synthesis, ubiquitin-dependent protein degradation and cytoskeleton organization. In contrast, 39 genes were differently expressed in the frontal cortex. These data support the possibility that molecular changes in the hippocampus might participate in the formation and maintenance of memory patterns induced by cocaine in the brain. Differences in the transcriptional responses in the hippocampus and cortex suggest the primary importance of the hippocampus for recent memory processing associated with cocaine-induced CPP. Krasnova, I.N., Li, S.M., Wood, W.H., McCoy, M.T., Prabhu, V.V., Becker, K.G., Katz, J.L. and Cadet, J.L. Genes Brain Behavior July 19, 2007.

Sex-dependent Metabolic, Neuroendocrine, and Cognitive Responses to Dietary Energy Restriction and Excess

Females and males typically play different roles in survival of the species and

would be expected to respond differently to food scarcity or excess. To elucidate the physiological basis of sex differences in responses to energy intake, IRP scientists maintained groups of male and female rats for 6 months on diets with usual, reduced [20% and 40% caloric restriction (CR), and intermittent fasting (IF)], or elevated (high-fat/high-glucose) energy levels and measured multiple physiological variables related to reproduction, energy metabolism, and behavior. In response to 40% CR, females became emaciated, ceased cycling, underwent endocrine masculinization, exhibited a heightened stress response, increased their spontaneous activity, improved their learning and memory, and 44 maintained elevated levels of circulating brain-derived neurotrophic factor. In contrast, males on 40% CR maintained a higher body weight than the 40% CR females and did not change their activity levels as significantly as the 40% CR females. Additionally, there was no significant change in the cognitive ability of the males on the 40% CR diet. Males and females exhibited similar responses of circulating lipids (cholesterols/triglycerides) and energy-regulating hormones (insulin, leptin, adiponectin, ghrelin) to energy restriction, with the changes being quantitatively greater in males. The high-fat/high-glucose diet had no significant effects on most variables measured but adversely affected the reproductive cycle in females. Heightened cognition and motor activity, combined with reproductive shutdown, in females may maximize the probability of their survival during periods of energy scarcity and may be an evolutionary basis for the vulnerability of women to anorexia nervosa. Martin, B., Pearson, M., Kebejian Golden, E., Keselman, A., Bender, M., Carlson, O., Egan, J., Ladenheim, B., Cadet, J.L., Becker, K.G., Wood, W., Duffy, K., Vinayakumar, P., Muudsley, S. and Mattson, M.P. Endocrinology 148(9), pp. 4318-4333, 2007.

Director's Report to the National Advisory Council on Drug Abuse - February, 2008

Program Activities

New NIDA PAs and RFAs

On December 10, 2007, NIDA issued **PAS-08-041** entitled **Design, Synthesis, and Preclinical Testing of Potential Treatment Agents for Drug Addiction (R01)**. Through this FOA NIDA invites research applications aimed at design, synthesis, and preclinical testing of potential treatment agents for drug addiction and/or relapse prevention. Recent advances in molecular neurobiological mechanisms underlying drug addiction provide a basis for development of new therapeutic targets and chemical entities to treat and prevent relapses of drug addiction. This FOA will utilize the NIH Research Project Grant (R01) award mechanism.

On December 21, 2007, NIDA issued **PAS-08-061** entitled **Long Acting, Sustainable Therapies for Opiate Addiction (R01)**. This FOA encourages Research Project Grant (R01) applications from institutions/organizations that propose the development of sustained pharmacotherapies and behavioral treatments to reduce the risk of contraction and transmission of HIV. Specifically, this FOA supports applications directed at the development of (1) heroin/morphine-protein conjugates (heretofore referred to as heroin/morphine conjugate vaccines or HCVs) for the treatment of opiate addiction, (2) clinical systems for the application of currently available long-acting (30-day or longer sustained-release) dosage forms for opiate pharmacotherapies to optimize these sustained pharmacotherapies to effect the reduction of the risk for acquisition and transmission of HIV, and (3) effective clinical treatment modalities, including behavioral treatment in conjunction with pharmacotherapies, to improve the effectiveness of opiate treatment and reduce the risk behaviors associated with transmission of HIV. Clinical studies should include the assessment of HIV risk behaviors as an outcome measure.

On January 14, 2008, NIDA issued **PAR-08-073** entitled **NIDA Core "Center of Excellence" Grant Program (P30)**. This FOA uses the Core Center of Excellence Grant (P30) mechanism. It is expected that a Center will transform knowledge in the sciences it is studying. Incremental work should not be the focus of Center activities; rather, new and creative directions are required. The P30 Center may support pilot research in any area of NIDA's mission. Research may occur in any area of NIDA's mission. Each separate core should bear an essential relationship to the integrating theme. The P30 Center of Excellence is expected to support the education, training, and mentoring of new investigators, who should be given meaningful roles to play in the Center projects. NIDA Centers are expected to share their findings, their data and their resources.

On November 9, 2007 NIDA issued **RFA-DA-08-003** entitled **2008 NIDA Avant-Garde Award Program for HIV/AIDS Research (DP1)**. The NIDA

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Director's Avant-Garde Award Program for AIDS research is meant to complement NIDA's traditional investigator-initiated grant programs by supporting individual scientists of exceptional creativity who propose approaches in the forefront of drug abuse and HIV/AIDS research. This program is intended to fund scientists engaged in basic, clinical, or translational research on drug abuse and HIV/AIDS. The term "avant-garde" is used to describe highly innovative approaches that have the potential to produce an unusually high impact. The proposed research should reflect ideas substantially different from those already being pursued by the investigator or others. The research proposed must be in an area described in the Trans - NIH Plan for HIV-Related Research and be drug abuse relevant but need not be in a conventional biomedical or behavioral discipline. This FOA will utilize the NIH DP1 grant mechanism.

On December 11, 2007, NIDA released **RFA DA-08-024 (R01)** and **DA-08-025 (R03), entitled Extinction and Pharmacotherapies for Drug Addiction**. The purpose of these Funding Opportunity Announcements (FOAs), is to stimulate animal or human research on mechanisms underlying extinction in order to guide the development of interventions for enhancing extinction of drug-seeking behavior. It is expected that research supported under this FOA will ultimately be used to guide and implement combined behavioral/cognitive and pharmacological and/or molecular interventions for the treatment of drug abuse relapse.

In January 2008, NIDA issued three RFAs entitled: **RFA-DA-08-013, Substance Abuse and Glial Regulation of Nervous System Function (R03); RFA-DA-08-014, Substance Abuse and Glial Regulation of Nervous System Function (R01);** and **RFA-DA-08-015, Substance Abuse and Glial Regulation of Nervous System Function (R21)**. Through these FOAs, NIDA requests research grant proposals to study the effects of drugs of abuse on glial cells, and the consequences of these effects on glial-neural cell signaling and communication, neuronal activity, and behavior within the nervous system. It is expected that this initiative will enhance and increase current understanding of the structural and functional interactions between glial and neuronal cells within the central and peripheral nervous systems, and the effects of drugs of abuse on these interactions.

NIDA issued an RFA entitled **The Interaction of HIV, Drug Use, and the Criminal Justice System (R01) (RFA-DA-08-007)**. This initiative solicits R01 applications linking drug abuse, HIV/AIDS prevention or treatment, and the criminal justice system. Applications should include research projects for developing interventions, descriptive research that clearly can lead to effective new interventions, or research on transporting effective interventions into practice.

On November 27, 2007, NIDA issued **RFA-DA-08-011** entitled **Drug Interactions in Substance Abusers with HIV Infection and Other Comorbid Conditions (R01)**. This funding opportunity announcement (FOA) solicits grant applications through the NIH Investigator initiated Research Grant (R01) award mechanism from applicant organizations to gain new knowledge on the subject of drug-drug interactions observed during the treatment of infections in drug addicts. This program fosters the use of investigator initiated research grants mechanism (R01s) to determine the characteristics, extent, and underlying mechanisms of pharmacokinetic/pharmacodynamic interactions between pharmacotherapeutic agents used in the treatment of drug addiction, viral infections including HIV and opportunistic infections (OIs) such as hepatitis C, or other bacterial or fungal infections in drug addicts. This FOA will utilize the R01 research grant program, which can be carried out in a short period of time with limited resources.

On December 17, 2007, NIDA issued **RFA-DA-08-010** entitled **The National Institute on Drug Abuse HIV/AIDS Pilot Proteomics Centers (P20)**. This

FOA solicits applications to establish Pilot Proteomics Centers that will address the complex biological mechanisms of interactions among drugs of abuse and HIV pathogenesis, their treatments, and host responses. The centers will use proteomics technologies and other related technologies (i.e., gene expression profiling) to look for protein changes and molecular signatures of disease progression of HIV/AIDS in combination with substance abuse/addiction, HIV treatment, and/or treatments for substance abuse. These proteomics centers are expected to help identify mechanisms related to susceptibility to and progression of HIV infection, viral replication, and viral evolution, particularly related to neuroAIDS.

On December 27, 2007, NIDA issued **RFA-DA-08-009** entitled **HIV-1 and Host Genetics in Drug Using Populations and Model Organisms (R01)**. This FOA solicits Research Project Grant applications that propose to elucidate the molecular mechanisms by which genetic variations provide protection from or vulnerability to infection, and how drugs of abuse, medications for drug addiction, and HIV-1 treatment interact with both host and viral genes. This FOA will utilize the NIH Research Project Grant (R01) award mechanism.

On January 10, 2008, NIDA issued **RFA-DA-08-020** entitled **Facilitating Self-Control of Substance Abuse Related Brain Activity through Real-Time Monitoring of fMRI Signals (R21/R33)**. Through the issuance of this RFA, NIDA seeks to encourage exploratory (i.e., descriptive, hypothesis-generating, and developmental) research focusing on the use of real time functional magnetic resonance imaging (rt-fMRI) in humans so that subjects can learn to modulate their own brain activity and monitor and control (modulate) activity of brain regions relevant to substance abuse. Proposals may incorporate development, implementation, and dissemination of requisite technology and methods as well as feasibility testing in healthy human subjects or substance abusers. This Funding Opportunity Announcement (FOA) will utilize the NIH R21/R33 Phased Innovation Award ((R21 [Phase I]/R33 [Phase II]) grant mechanism.

On January 14, 2008, NIDA issued **RFA-DA-08-012** entitled **Resource Core Transdisciplinary Prevention Research Centers (P30)**. The overall purpose of the NIDA Transdisciplinary Prevention Research Center (TPRC) program is to support environments in which scientists from the basic and applied/clinical disciplines can come together to develop a coherent program of transdisciplinary research. The ultimate goals of these centers are to encourage: (a) translational research between the basic sciences into the development and testing of novel preventive intervention approaches, and (b) translation of preventive intervention findings back into basic science laboratory studies that can better explicate underlying intervention mechanisms and effects on basic systems such as neurobiology. This type of translation research is bidirectional in nature, with the basic sciences informing intervention development and modification and intervention findings informing basic research inquiry. It is expected that a transdisciplinary approach will explore and catalyze new ways of conceptualizing prevention intervention research. This RFA uses the NIH Resource Core Center Grant (P30) mechanism to support centralized resources and facilities shared by transdisciplinary teams of drug abuse prevention research investigators.

PAs and RFAs with Other NIH Components/Agencies

On October 18, 2007, NIDA, in collaboration with other NIH components issued **PAR-08-010** entitled **Continued Development and Maintenance of Software (R01)**. Biomedical research laboratories increasingly undertake a software development project to solve a problem of interest specifically related 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. This FOA will utilize the NIH Research Project Grant (R01) award mechanism.

On October 22, 2007, NIDA in collaboration with numerous other NIH components issued **PA-08-012 entitled ELSI Regular Research Program (R01)**. This Funding Opportunity Announcement (FOA) issued by the National Human Genome Research Institute, National Institutes of Health, encourages Research Program Grant (R01) applications from institutions/organizations that propose to study the ethical, legal and social implications (ELSI) of human genome research.

On October 22, 2007, NIDA in collaboration with numerous other NIH components issued **PA-08-013** entitled **ELSI Small Research Grant Program (R03)**. This Funding Opportunity Announcement (FOA) issued by the National Human Genome Research Institute, National Institutes of Health, encourages Small Research Grant (R03) applications from institutions/organizations that propose to study the ethical, legal and social implications (ELSI) of human genome research. This announcement is specifically designed to: 1) encourage the development of small, focused research projects by legal, historical, ethics, humanities, social sciences and behavioral scholars; 2) support exploratory studies that may provide preliminary findings or pilot data for larger research proposals; 3) support the secondary analysis of existing data; 4) support the development of new methodologies; and 5) stimulate and facilitate the entry of promising new investigators into ELSI Research. This FOA will utilize the NIH Small Research Grant (R03) award mechanism.

On November 5, 2007, NIDA, in conjunction with numerous other NIH components, issued **PAR-08-023** entitled **Predictive Multiscale Models of the Physiome in Health and Disease (R01)**. This FOA solicits Research Project Grant (R01) applications from institutions/organizations that propose to develop predictive multiscale models of the physiome in health and disease. The goal of this solicitation is to move the field of biomedical computational modeling forward through the development of more realistic and predictive models of health and disease. NIH recognizes the need for sophisticated, predictive, computational models of development and disease that encompass multiple biological scales. These models may be designed to uncover biological mechanisms or to make predictions about clinical outcome and may draw on a variety of data sources including relevant clinical data. Ultimately the models and the information derived from their use will enable researchers and clinicians to better understand, prevent, diagnose and treat the diseases or aberrations in normal development. Specifically this FOA solicits the development of predictive multiscale models of health and disease states that must include higher scales of the physiome. The specific objectives are to develop multiscale models that are physiologically mechanistic and biomedically relevant, to bring together modeling and biomedical expertise to collaborate on building models, to validate and test models with standard datasets, and to develop models that can be explicitly shared with other modelers. This FOA will utilize the NIH Research Project Grant (R01) award mechanism.

On December 13, 2007, NIDA and NCI jointly issued **PAR-08-046** entitled **NIDA Research "Center of Excellence" Grant Program (P50)**. This FOA is to provide support for research centers that conduct drug abuse and addiction research that have outstanding innovative science and that are multidisciplinary, thematically integrated, synergistic, and are/will be serving as national resource(s) for the NIDA research fields. This FOA uses the

Research Center of Excellence Grant (P50) mechanism. There should be evidence that the presence of a center structure is essential for the accomplishment of the research activities. It is expected that a Center will transform knowledge in the sciences it is studying. Incremental work should not be the focus of Center activities; rather, new and creative directions are required.

On December 18, 2007, NIDA, in collaboration with numerous other NIH components issued **PA-08-052** entitled **Nanoscience and Nanotechnology in Biology and Medicine (R01)**. This funding opportunity (FOA) is aimed at enhancing nanoscience and nanotechnology research focused on problems in biology and medicine. Nanoscience and nanotechnology refer to research and development on the understanding and control of matter at a length scale of approximately 1 - 100 nanometers, where novel properties and functions occur because of the size. A major challenge facing medicine is to develop novel and more sophisticated approaches for the diagnosis, treatment and management of an array of diseases and traumatic injuries. Nanotechnology and nanoscience have the capacity to drive a new wave of medical innovation through the engineering of bioactive nanoscale structures, processes and systems based on the advancement of our understanding of biology at the nanoscale. This Funding Opportunity Announcement (FOA) will utilize the R01 grant mechanism.

On December 18, 2007, NIDA, in collaboration with numerous other NIH components issued **PA-08-053** entitled **Nanoscience and Nanotechnology in Biology and Medicine (R21)**. This funding opportunity (FOA) is aimed at enhancing nanoscience and nanotechnology research focused on problems in biology and medicine. Nanoscience and nanotechnology refer to research and development on the understanding and control of matter at a length scale of approximately 1 - 100 nanometers, where novel properties and functions occur because of the size. A major challenge facing medicine is to develop novel and more sophisticated approaches for the diagnosis, treatment and management of an array of diseases and traumatic injuries. Nanotechnology and nanoscience have the capacity to drive a new wave of medical innovation through the engineering of bioactive nanoscale structures, processes and systems based on the advancement of our understanding of biology at the nanoscale. This Funding Opportunity Announcement (FOA) will use the NIH Exploratory/Developmental Research Grant Award (R21) mechanism.

On January 11, 2008, NIDA, in collaboration with NICHD and NIAAA issued **PA-08-068** entitled **The Science and Ecology of Early Development (SEED) (R03).** This Funding Opportunity Announcement (FOA) encourages submission of investigator-initiated research grant applications that seek to develop a comprehensive program of research focused on the mechanisms through which social, economic, cultural, and community-level factors, and their interactions, impact the early cognitive, neurobiological, socio-emotional, and physical development of children. This FOA will utilize the NIH Small Research Grant (R03) award mechanism.

On January 11, 2008, NIDA, in collaboration with NICHD and NIAAA issued **PA-08-069** entitled **The Science and Ecology of Early Development (SEED) (R01)**. This Funding Opportunity Announcement (FOA) encourages submission of investigator-initiated research grant applications that seek to develop a comprehensive program of research focused on the mechanisms through which social, economic, cultural, and community-level factors, and their interactions, impact the early cognitive, neurobiological, socio-emotional, and physical development of children. This FOA will utilize the NIH Research Project Grant (R01) award mechanism.

On January 11, 2008, NIDA, in collaboration with other NIH components involved in the NIH Blueprint for Neuroscience Research issued **PA-08-071** entitled **Lab to Marketplace: Tools for Brain and Behavioral Research**

(SBIR [R43/R44]). This FOA encourages the translation of technologies for brain or behavioral research from academic and other non-small business research sectors to the marketplace. Solicited from Small Business Concerns (SBCs) are Small Business Innovation Research (SBIR) grant applications that propose to further develop, make more robust, and make more user-friendly such technologies in preparation for commercial dissemination. It is expected that this activity will require partnerships and close collaboration between the original developers of these technologies and SBCs, which may be accomplished in any of a number of ways, including the use of multiple principle investigators. This FOA will utilize the SBIR (R43/R44) grant mechanisms for Phase I, Phase II, and Fast-Track applications.

On January 8, 2008, NIDA, in collaboration with other NIH components issued **PAR-08-065** entitled **NIH Revision Awards for Studying Interactions Among Social, Behavioral, and Genetic Factors in Health (R01)**. This FOA invites applications from current NIH-funded investigators to study how interactions among of genetic and behavioral/social factors influence health and disease. This funding opportunity will use the NIH Revision (formerly named Competitive Supplement) award mechanism to supplement existing NIH funded R01 awards.

On January 8, 2008, NIDA, in collaboration with other NIH components issued **PAR-08-066** entitled **NIH Revision Awards for Studying Interactions Among Social, Behavioral, and Genetic Factors in Health (R21)**. This FOA invites applications from current NIH-funded investigators to study how interactions among of genetic and behavioral/social factors influence health and disease. This funding opportunity will use the NIH Revision (formerly named Competitive Supplement) award mechanism to supplement existing NIH funded R21 awards.

On January 8, 2008, NIDA, in collaboration with other NIH components issued **PAR-08-067** entitled **NIH Revision Awards for Studying Interactions Among Social, Behavioral, and Genetic Factors in Health (P01, P20, P50, P60, U01, U10, U54)**. This FOA invites applications from current NIH-funded investigators to study how interactions among of genetic and behavioral/social factors influence health and disease. This funding opportunity will use the NIH Revision (formerly named Competitive Supplement) award mechanism to supplement existing NIH funded P01, P20, P50, P60, U01, U10, U54 awards.

On January 16, 2008, NIDA, in collaboration with other NIH components and the CDC issued **PA-08-074** entitled **Community Participation in Research (R01)**. This FOA solicits R01 grant applications that propose intervention research on health promotion, disease prevention, and health disparities that communities and researchers jointly conduct. For the purposes of this FOA, intervention research is quasi-experimental research projects that seek to influence preventive behaviors, treatment adherences, complementary behaviors, and related attitudes and beliefs. Natural experiments also may fall under the interventions rubric. This FOA will utilize the NIH Research Project Grant (R01) award mechanism.

On January 16, 2008, NIDA, in collaboration with other NIH components issued **PAR-08-075** entitled **Community Participation Research Targeting the Medically Underserved (R01)**. The ultimate goal of this FOA is to solicit Research Project Grant (R01) applications that propose research on health promotion, disease prevention, and health disparities that is jointly conducted by communities and researchers and targets medically underserved areas (MUAs) and medically underserved populations (MUPs) as defined by the Department of Health and Human Services (DHHS) Health Resources and Services Administration (HRSA). This FOA will use the R01 grant mechanism to encourage studies that specifically target medically underserved areas as well as underserved and underrepresented populations.

On January 16, 2008, NIDA, in collaboration with other NIH components issued **PAR-08-076** entitled **Community Participation Research Targeting the Medically Underserved (R21)**. The ultimate goal of this FOA is to solicit applications that propose research on health promotion, disease prevention, and health disparities that is jointly conducted by communities and researchers and targets medically underserved areas (MUAs) and medically underserved populations (MUPs) as defined by the Department of Health and Human Services (DHHS) Health Resources and Services Administration (HRSA). This FOA will use the R21 grant mechanism to encourage studies that specifically target medically underserved areas as well as underserved and underrepresented populations.

On January 25, 2008, NIDA, in collaboration with other NIH Components, the CDC, and the FDA issued **PA-08-050** entitled **PHS 2008-02 Omnibus Solicitation of the NIH, CDC, and FDA for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44])**. This FOA invites eligible United States small business concerns (SBCs) to submit Small Business Innovation Research (SBIR) grant applications. United States SBCs that have the research capabilities and technological expertise to contribute to the R&D mission(s) of the NIH, CDC and FDA awarding components identified in this FOA are encouraged to submit SBIR grant applications in response to identified topics. This FOA will utilize the SBIR (R43/R44) grant mechanisms for Phase I, Phase II, Fast-Track, and Phase II Competing Renewal applications.

On January 25, 2008, NIDA, in collaboration with other NIH Components, the CDC, and the FDA issued **PA-08-051** entitled **PHS 2008-02 Omnibus Solicitation of the NIH, CDC, and FDA for Small Business Innovation Research Grant Applications (Parent STTR [R41/R42])**. This FOA invites eligible United States small business concerns (SBCs) to submit Small Business Innovation Research (SBIR) grant applications. United States SBCs that have the research capabilities and technological expertise to contribute to the R&D mission(s) of the NIH, CDC and FDA awarding components identified in this FOA are encouraged to submit SBIR grant applications in response to identified topics. This FOA will utilize the STTR (R41/R42) grant mechanisms for Phase I, Phase II, Fast-Track, and Phase II Competing Renewal applications.

On January 28, NIDA, in collaboration with NIA issued **PAR-08-081** entitled **Research Education Grants for Statistical Training in the Genetics of Addiction (R25)**. This FOA invites applications focused on research education for the development and testing of new statistical models to address genetics-based research problems in addiction. Applicants are expected to propose a well-integrated research education and training program in statistical models or computational methods in genetics for undergraduate, graduate, and/or postdoctoral level students. This FOA will use the NIH Research Education (R25) grant mechanism.

NIDA, along with NIA, NINDS and NIMH, issued an RFA entitled **Collaborative Research to Explore New Uses for Existing Radioligands (R21/R33) (RFA-DA-08-001)**. This RFA seeks to encourage broader uses of established PET/SPECT radioligands by reducing barriers to their wider distribution, and expanding their utility to the study of diseases or organs for which the radioligand has not previously been studied. Applications for this RFA should demonstrate a high degree of innovation and novelty with regard to the new uses for existing radioligands. Although there is no requirement for preliminary data, a clear scientific rationale is essential. Applications for this RFA are expected to propose multi-institutional collaborations between investigators who have the capacity for routine production of a given radioligand for human use, and investigators who lack access to the radioligand but wish to demonstrate the feasibility of an innovative use for the radioligand in a novel patient population.

On October 19, 2007, NIDA, in collaboration with NIMH, issued **RFA-MH-08-080** entitled **Programs of Excellence in Scientifically Validated Behavioral Treatment (R25)**. The purpose of this FOA is to support curriculum development to train clinician-scientists who can develop, test, and rapidly translate into practice innovative learning-based treatments in the addictive and mental disorders. The goals in establishing the Programs of Excellence Award are to recognize and enhance current clinical training programs that teach and develop research-based clinical practices and to provide a model for clinician education nationwide. This FOA will use the NIH Research Education (R25) grant mechanism.

On November 16, 2007, NIDA in collaboration with NIMH, issued **RFA-DA-08-008** entitled **Research on HIV/AIDS and Drug Use in the Multicenter AIDS Cohort Study (MACS) (R03)**. This FOA solicits grant applications thorough the NIH Small Research Grant (R03) award mechanism from applicant organizations to give added value and gain new knowledge from the Multicenter AIDS Cohort Study or MACS. This program fosters the use of small research grants (R03s) to build on an existing resource, the Multicenter AIDS Cohort Study or MACS. NIDA will support drug use and HIV/AIDS-related clinical epidemiology, socio-behavioral, neuro-AIDS, and medical consequences research utilizing pilot and feasibility studies; secondary analysis of existing data; self-contained research projects; collaborative studies linked to larger research projects; studies of statistical methodologies and modeling; and studies of new assessments and research techniques. NIMH will support similar types of studies that focus on HIV, the central nervous system, pharmacotherapeutics, and biomarker development strategies among non-drug using MSM. This Funding Opportunity Announcement (FOA) will utilize the R03 small research grant program, which can be carried out in a short period of time with limited resources.

On December 13, 2007, NIDA, in collaboration with numerous other NIH components, issued **RFA-NS-08-005** entitled **Centers for Evaluation of Neurodevelopmental Antibodies (CENA, U24)**. The goal of this initiative is to create a center (or centers) to 1) evaluate new monoclonal antibodies (mABs) to neurodevelopmental antigens using multiple model systems and 2) provide detailed information for use of these reagents to the research community. This FOA uses the Resource-Related Research Projects-Cooperative Agreement (U24) award mechanism .

On December 21, 2007, NIDA, in collaboration with the Canadian Institutes of Health Research (CIHR), issued **RFA-DA-08-016** entitled **Non-coding RNAs and Other Post-transcriptional Regulatory Mechanisms in Neuroplasticity and Addiction (R01)**. The purpose of this FOA is to stimulate research on non-coding RNAs and other post-transcriptional regulatory mechanisms as they pertain to addictive processes. This Funding Opportunity Announcement (FOA) will utilize the R01 grant mechanism.

On December 21, 2007, NIDA, in collaboration with the Canadian Institutes of Health Research (CIHR), issued **RFA-DA-08-017** entitled **Non-coding RNAs and Other Post-transcriptional Regulatory Mechanisms in Neuroplasticity and Addiction (R03)**. The purpose of this FOA is to stimulate research on non-coding RNAs and other post-transcriptional regulatory mechanisms as they pertain to addictive processes. This Funding Opportunity Announcement (FOA) will utilize the R03 grant mechanism.

On January 3, 2008, NIDA, in collaboration with SAMHSA, issued **RFA-DA-08-021** entitled **Screening, Brief Intervention and Referral to Treatment (SBIRT) for Drug Abuse in General Medical Settings (R01)**. This FOA invites research applications to develop and test the effectiveness of models that integrate screening, brief intervention, and referral to specialized treatment for individuals with drug abuse entering into primary care and other general medical settings. This is a joint effort between the National Institute on

Drug Abuse (NIDA) and the Substance Abuse and Mental Health Services Administration (SAMHSA). This funding opportunity will use the NIH Research Project Grant (R01) award mechanism.

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. Two proposals have been awarded.

A total of 31 protocols have been initiated since 2001. Over 8,500 participants have enrolled in studies. Of these studies, 20 have completed data lock; two are in the follow-up phase; and three are currently enrolling. Six 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

Primary outcome papers are published or in press for:

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 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 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.

In addition, the following protocols have locked the data:

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

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

Protocol CTN 0015, Women's Treatment for Trauma and Substance Use Disorder: A Randomized Clinical Trial

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.

The following protocols have also locked the data. Final reports have been presented and national presentations took place at the APA, CPDD and AATOD:

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

The following protocols have ended new enrollment and are in follow-up 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 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. The study reached its enrollment target in September 2007. A total of 255 participants were enrolled and randomized.

Three 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 November 30, 2007, there were 547 randomized participants.
CCTN 0027A, START Pharmacogenetics: Exploratory Genetic Studies In Starting Treatment With Agonist Replacement Therapies. This proposal outlines a supplementary pharmacogenetics component to the NIDA START trial. Patients participating in START will be offered the opportunity to volunteer for a genetics study that has the primary objective of genotyping patients for exploratory analyses. Genomic DNA from blood samples sent to an NIH repository will be extracted and saved for study. Investigators at the University of Pennsylvania will study the

frequency of gene variants that have primarily been associated with addiction, while the Medical University of South Carolina researchers will examine the relationship between treatment drug plasma concentrations and gene variants associated with drug disposition and transport. It is expected that the results of this study will contribute to the rational design of future clinical trials for hypothesis-driven pharmacogenetic studies that can be incorporated into the NIDA Clinical Trials Network (CTN).

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. As of November 30, 2007, 209 participants have been randomized.
CTN 0028A, Does Methylphenidate treatment for ADHD increase the rate of smoking in adolescents with comorbid ADHD, SUD, and nicotine dependence? The purpose of this ancillary study is to measure any change in the rate of cigarette smoking among participants in the CTN study 0028 (at the LRADAC site only). The study will use the same urine sample to obtain semi-quantitative cotinine levels using a dipstick urine cotinine measure (NicAlert, Nymox Pharmaceuticals). The hypothesis is that Oros methylphenidate treatment for ADHD among adolescents with comorbid ADHD, SUD, and nicotine dependence will not increase the rate of cigarette smoking. The study will compare self-reported smoking rate and urine cotinine semi-quantitative levels in adolescents receiving Oros methylphenidate vs. those receiving placebo to test the hypothesis above.

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 10 sites. As of November 30, 2007, there were 345 randomized participants.
CTN 0030A, Collection of Economic Data for the Prescription Opioid Addiction Treatment Study. This ancillary study is conducted in collaboration and support with NIDA DESPR. The aims of the proposed data collection supplement are: (1) to supplement POATS data by collecting and validating additional facility data necessary to conduct economic analyses associated with comparisons of bup/nx treatment with SMM and EMM; and (2) to supplement POATS data by collecting additional patient level data necessary to conduct economic analyses associated with comparisons of bup/nx treatment with SMM and EMM. The data collection in the two aims will provide information necessary to conduct cost effectiveness, cost-benefit and cost-utility analyses of treatment models being evaluated in the POATS clinical trial.

Six 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 initial Investigators' meeting to train staff from the three Wave 1 sites (Maryhaven - Ohio Valley Node, ChangePoint - Oregon/Hawaii Node, and Recovery Centers of King County - Washington Node) was convened in Bethesda, MD on December 3-5, 2007. Participant recruitment will commence in January 2008. Three ancillary studies are being conducted in collaboration with the main study:
CTN 0031A, An evaluation of neurocognitive function, oxidative

damage, and their association with treatment outcomes in methamphetamine and cocaine abusers, is being led by Dr. Theresa Winhusen and co-led by Dr. Eugene Somoza, (Ohio Valley Node). It will evaluate the relationships among neurocognitive functioning (as assessed by various measures of executive function), oxidative damage (including DNA, lipid, and protein damage) and substance abuse treatment outcomes (including treatment completion and stimulant use reduction). This study will be funded by the NIDA CTN.

CTN 0031B, The Role of Alcohol Consumption in Classifications of Alcohol Use Disorders: A Clinical Study, is being led by Dr. Deborah Hasin (Long Island Node) and co-led by Dr. Dennis Donovan. It will investigate the utility of adding a frequency measure of alcohol consumption (i.e., the first three items of the Alcohol Use Disorders Identification Test [AUDIT-C]), to the DSM-IV diagnostic criteria for alcohol use disorders. This study is funded by an MOU between NIDA and NIAAA.

CTN 0031C, Organizational Characteristics That Influence the Adoption of Evidence-Based Practices, is being co-led by Dennis McCarty (Oregon/Hawaii Node) and Joseph Guydish (California/Arizona Node). This project will assess core implementation components (staff selection, staff training, coaching and supervision, feedback to participating staff, and administrative supports and interventions) and document their impact on the eventual implementation and adoption of the STAGE-12 intervention. This project is supported by supplemental funds from DESPR. The baseline data obtained in this research will form the foundation for an R01 grant application to be submitted in 2008.

Protocol CTN 0032, HIV Rapid Testing and Counseling in Drug Abuse Treatment Programs in the U.S. 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 (CDCP) have made a priority to bring HIV rapid testing and counseling into outpatient health care settings for high-risk populations, and the investigators have consulted closely with them. A final version of the protocol has been approved. Site selection will likely begin in spring of 2008.

Protocol CTN 0033, Methamphetamine Use Among American Indians. The first area of research emphasis in the National Institute on Drug Abuse's Strategic Plan on Reducing Health Disparities (2004 Revision) is the epidemiology of drug abuse, health consequences and infectious diseases among minority populations. Because there are limited data available on methamphetamine use in American Indian communities, exploratory and pilot studies will be conducted to develop collaborations with tribes and Native American treatment programs and to explore the epidemiology of methamphetamine use and co-occurring problems and disorders in diverse Native American communities. This preliminary research will be coordinated among the Nodes to provide a more comprehensive exploration of methamphetamine problems in Indian country. These studies will provide a solid foundation for more rigorous epidemiologic studies and/or clinical research on methamphetamine dependence in Indian Country. Due to the local considerations, the study will be broken into 3 separate ones. This study and its subcomponents are in development stage.

CTN 0033A, Oregon/Hawaii Node: Methamphetamine Use Among

American Indians (in collaboration with the NIH National Center for Minority Health and Health Disparities). Exploratory and pilot studies will be conducted to develop collaborations with tribes and Native American treatment programs in the Northwest and to explore the epidemiology of methamphetamine use and co-occurring problems and disorders in their diverse Native American communities (reservation-based and urban treatment centers).
CTN 0033B, Southwest Node: Methamphetamine Use and Treatment in Native American Communities in the Southwest. Exploratory and pilot studies will be conducted to develop collaborations with tribes and Native American treatment programs in the Southwest and to explore the epidemiology of methamphetamine use and co-occurring problems and disorders in diverse Native American communities in the Southwest.
CTN 0033C, Pacific Northwest Node: Methamphetamine: Where Does It Fit In the Bigger Picture of Drug Use of American Indian and Alaska Native Communities and Treatment-Seekers? Exploratory and pilot studies will be conducted to develop collaborative working relationships with tribes and tribal treatment programs in the Western Washington and Southeast Alaska to assess the epidemiology of co-occurring health disorders among AIANs seeking treatment for methamphetamine and other substance use in reservation-based and urban treatment centers.

Protocol CTN 0034, Developing Research Capacity and Culturally Appropriate Research Methods: Community-based Participatory Research Manual for Collaborative Research in Drug Abuse for American Indians and Alaska Natives. This study is in collaboration with the NIH National Center for Minority Health and Health Disparities and will be conducted in the Pacific Northwest Node. The specific aim of this proposed supplement is to develop a "user friendly" manual or "field guide" on the use of community-based participatory research (CBPR) and Tribal participatory research (TPR) methods for academic researchers and Tribal communities to develop and implement culturally relevant, truly collaborative research in the areas of substance abuse, HIV/AIDS, mental health, and other areas of health disparities in American Indian/Alaska Native populations. The manual or field guide will be developed by collecting and incorporating information from several sources: (1) review of available literature; (2) focus groups or interviews with participants from Tribal communities; (3) focus groups or interviews with academic representatives; and (4) asking both community and academic partners to provide information about their experiences with research in AIAN communities (via listserv).

Protocol CTN 0035, Access to HIV and Hepatitis Screening and Care Among Ethnic Minority Drug Users In and Out of Drug Treatment. This study is in collaboration with the NIH National Center for Minority Health and Health Disparities and will be conducted in the CA-AZ Node. The primary goal of this study is to identify barriers and facilitators to HIV and hepatitis C screening and treatment among ethnic minority drug users. Using a combination of structured survey and qualitative focus group methods, researchers will interview drug users in and out-of-drug abuse treatment about their previous experiences in accessing HIV and HCV screening and treatment services. They will interview 348 HIV and/or HCV infected drug users recruited from three settings: methadone maintenance, HIV primary care, and syringe exchange programs. Recruiting from these three sites will allow an examination of barriers or facilitating factors that may be relevant

to DUs who are not engaged in drug abuse treatment, HIV care or HCV care (the SEP cohort); DUs who are engaged in drug abuse treatment, but may not be engaged in HIV and or HCV care (methadone maintenance treatment cohort), or are already engaged in HIV care and may or may not be engaged in HCV care (HIV clinic cohort). Thus, recruitment from these three sites will allow us to assess factors related to screening and treatment services across the continuum of engagement in prevention and treatment services. Survey and focus group topics will be in five areas: 1) past and current experiences in accessing HIV and HCV screening and treatment, or other medical care; 2) perceptions of treatment settings and providers; 3) history of psychiatric illness and treatment; 4) HIV and HCV risk behaviors; 5) lifetime substance use and past 30-day use; 6) knowledge of HIV and HCV risk factors; 6) knowledge of HIV and HCV screening and treatment; 7) past and current motivation for screening and treatment; and 8) resource and structural barriers.

Protocol CTN 0036, Epidemiology and Ethnographic Survey of "Cheese" Heroin Use among Hispanics in Dallas County. This study is in collaboration with the NIH National Center for Minority Health and Health Disparities and will be conducted in the Texas Node. The study will focus on the development and implementation of a survey to further characterize the use of cheese-heroin among Hispanic youth in Dallas County. The survey will be administered to active cheese-heroin users in three CTPs within the Texas Node (Nexus Recovery Center, Phoenix House, and Dallas County Juvenile Justice Dept.). The survey will characterize factors related to route(s) of administration, progression to physical dependence (opioid withdrawal syndrome), progression to IV drug use (HIV risk behavior), parental drug use, healthcare utilization, school performance, level of assimilation (both primary user and familial). Additionally, the Addiction Severity Index will be applied to characterize the level of legal, social, psychiatric, occupational, medical, family.

In addition to the primary CTN trials, there are currently 33 funded studies supported by independent grants that use CTN studies as a platform and 21 completed, ongoing, and planned studies funded as supplements to the clinical trials.

NIDA has awarded Brandeis University's NIDA Research Center on Managed Care and Drug Abuse Treatment with an ancillary study to conduct an economic analysis of the interventions examined in the Prescription Opioid Addiction Treatment Study (POATS - CTN 0030). In September 2007, Brandeis University started collecting data to assess the costs and benefits of the two treatment approaches EMM (Enhanced Medical Management) and SMM (Standard Medical Management).

The NIDA Networking Project (NNP)

The National Institute on Drug Abuse (NIDA) launched a new website in October 2007 to reach drug abuse researchers, practitioners, and policy makers. The NIDA Networking Project (NNP) website provides opportunities for information sharing among those interested in addiction research and the potential for research collaboration among scientists across the country. The NNP Website gives users access to the locations, people, expertise, and resources of NIDA's research networks to help create synergies, improve efficiency, and accelerate scientific discovery.

This one-stop portal to drug abuse resources includes the following information:

- Map locations and contacts for about 200 NIDA-supported network sites across the U.S.
- Network missions and descriptions
- Links to more than 15 network-related Websites
- Links to scientific protocols and papers, as well as procedural policies and manuals
- NIDA news and events of interest to scientists, clinicians, and addiction specialists
- The NNP Colleagues Directory--a searchable data base of network members' expertise and research interests.

For more information, please contact: Susan David at 301-435-0640 or davids2@nida.nih.gov.

Health Disparities Supplement Program

Through the Health Disparities Supplement Program for Native Americans/Alaska Natives and Asian American/Pacific Islanders, NIDA awarded seven supplements (two from the support of NCMHD) to current grants to: (1) better understand patterns of drug abuse and addiction in NA/AN and AA/PI populations, (2) identify health, behavioral or social consequences associated with drug abuse, addiction and related disease, and (3) determine if there is a need for more appropriate and better targeted services, treatment and prevention interventions.

The Minority Recruitment & Training Program

The Minority Recruitment & Training Program is now accepting applications for its summer 2008 Program. The NIDA, IRP Minority Recruitment & Training Program (MRTP) is an intramural program that provides training opportunities for students from under-represented groups who are interested in the scientific basis of drug abuse. In this program, students gain basic science and/or clinical laboratory experience, attend student seminars and participate in a summer poster presentation. The goal of this program is to expose students to the realities of research, from experimental design to data analysis, interpretation and presentation. To request an application or to receive additional information, contact Christie Brannock at cbrann@intra.nida.nih.gov.

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

Abi-Dargham, Anissa -- Columbia University Health Sciences
Imaging Dopamine Transmission in Cannabis Dependence

Abood, Mary E. -- California Pacific Medical Center Research Institute
Molecular Characterization of GPR35 and GPR55, Putative Cannabinoid Receptors

Adinoff, Bryon H. -- University of Texas South West Medical Center/Dallas
Impulsivity, Neural Deficits, and Cocaine Relapse

Adler, Martin W. -- Temple University
Opioids, Cannabinoids, Chemokines: Functional Implications of Cross-Talk

Agrawal, Arpana -- Washington University
Cannabis and Tobacco Involvement: A Twin Study

Aharonovich, Efrat -- New York State Psychiatric Institute
Modified Behavioral Treatment for Cocaine Patients with Cognitive Deficits

Aidala, Angela A. -- Columbia University Health Sciences
Drug Abuse, Mental Illness, Homelessness, and HIV: Evaluating Models of Care

Ait-Daoud, Nassima -- University of Virginia Charlottesville
New Medication Treatments for Stimulant Dependence

Akil, Huda -- University of Michigan at Ann Arbor
Antecedents and Consequences of Drug Abuse: Heritability, Stress and Neurplasticity

Akins, Chana K. -- University of Kentucky
Prenatal Cocaine Effects on Sexual Motivation

Aldrich, Jane V. -- University of Kansas Lawrence
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Contingency Management of Psychostimulant Abuse in the Severely Mentally Ill

Riley, Elise D. -- University of California San Francisco
Effects of Housing and HIV on Risk Behavior and Victimization of Indigent Women

Rohde, Paul D. -- Oregon Research Institute
Sequenced vs. Integrated Delivery of Treatment for Adolescent Depression and SUD

Roman, Paul M. -- University of Georgia
CTN Membership and Adoption of Innovative Tx Practices

Rosen, Gerald M. -- University of Maryland Baltimore
EPR Imaging of Brain O2 in Drug Abuse

Salo, Ruth E. -- University of California Davis
Neural Correlates of Methamphetamine Use in Schizophrenia: An MRS Study

Salzman, C. Daniel -- New York State Psychiatric Institute
Neural Mechanisms Underlying Reinforcement Learning

Scarinci, Isabel C. -- University of Alabama at Birmingham
Network for Tobacco Control Among Women in Parana, Brazil

Schensul, Jean J. -- Institute for Community Research
MDMA and STD/HIV Risk Among Hidden Networks of Ecstasy-Using Young Adults

Schmitz, Joy M. -- University of Texas Health Science Center Houston
Contingency Management plus Levodopa/Carbidopa for Treatment of Cocaine Dependence

Schottenfeld, Richard S. -- Yale University
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Malaysia

Schwartz, Robert P. -- Friends Research Institute, Inc.
Entry into Comprehensive Methadone Treatment via Interim Maintenance

Scott, Christy K. -- Chestnut Health Systems, Inc.
Recovery Management Checkups for Women Offenders (RMC-WO) Experiment

See, Ronald E. -- Medical University of South Carolina
Interdisciplinary Medication Development for Multiple Risk Factors in Relapse

Sereno, Margaret -- University of Oregon
New Methods to Improve Measurement and Understanding of Successful Navigation

Sesack, Susan R. -- University of Pittsburgh at Pittsburgh
Persistent Impact of Developmental Nicotine on Cholinergic Input to DA Cells

Shaw, Daniel S. -- University of Pittsburgh at Pittsburgh
Parental Involvement, Extra-Familial Contexts and Prevention of Drug Use Risk

Shetty, Vivek -- University of California Los Angeles
Refinement and Validation of a Portable, Salivary Biosensor of Psychosocial Stress

Shoichet, Brian K. -- University of California San Francisco
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Shrier, Lydia A. -- Children's Hospital Boston
Affect and Marijuana Use in Adolescents and Young Adults

Sigmon, Stacey C. -- University of Vermont and State Agricultural College
Incentive-Based Smoking Cessation for Methadone Patients

Silk, Jennifer S. -- University of Pittsburgh at Pittsburgh
Emotion Regulation in Adolescence: A Social Affective Neuroscience Approach

Silverman, Kenneth -- Johns Hopkins University
A Bridge to Treatment for Out-of-Treatment Injection Heroin Users

Simmons, Janie E. -- National Development and Res Institutes
Barriers to Treatment-Based HIV Prevention for IDU Couples

Sipe, Jack C. -- Scripps Research Institute
Endocannabinoid Biomarkers of Obesity Using Integrated Genomics and Metabolomics

Skosnik, Patrick D. -- Indiana University Bloomington
The Effect of Cannabis Use on Human Cerebellar Function

Sneider, Jennifer Tropp -- McLean Hospital, Belmont, MA
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Soderstrom, Kenneth M. -- East Carolina University
Cannabinoid-Altered Vocal Development

Sofuoglu, Mehmet -- Yale University
Cocaine Withdrawal and Pharmacotherapy Response

Sood, Amit -- Mayo Clinic College of Medicine, Rochester
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Spealman, Roger D. -- Harvard University Medical School
Nonhuman Primate Models of Reinstated Cocaine Seeking

Spoth, Richard L. -- Iowa State University

Partnership Model for Diffusion of Proven Prevention

Sprague, Jon E. -- Ohio Northern University
Hyperthermia: Uncoupling the Agony from Ecstasy

Stall, Ronald -- University of Pittsburgh at Pittsburgh
Long Term Health Effects of Methamphetamine Use in the MACS

Stark, Michael J. -- Multnomah County Health Department
Reducing HIV Risk Among Methamphetamine IDUs through Peer Education

Stein, Lynda A. -- University of Rhode Island
Motivation and Skills for Detained Teen Smokers

Stella, Nephi -- University of Washington
Novel CB Receptors

Stenger, Victor Andrew -- University of Hawaii at Manoa
Parallel MRI for High Field Neuroimaging

Stewart, Katharine E. -- University of Arkansas Medical Sciences Little Rock
Reducing Sexual Risk Behaviors Among Rural African-American Cocaine Users

Stitzel, Jerry A. -- University of Colorado at Boulder
Circadian Variations in Nicotine Sensitivity in Mice

Stolerman, Ian P. -- King's College London
Comprehensive Database of Drug Discrimination and Self-Administration Research

Straiker, Alex -- Indiana University Bloomington
Identification and Characterization of Two Novel Cannabinoid Receptors

Strathdee, Steffanie A. -- University of California San Diego
Drug Market Characteristics: Antecedents and Sequelae on the U.S. Mexico Border

Strecher, Victor J. -- University of Michigan at Ann Arbor
Neural Bases of Effectiveness of Individually-Tailored Smoking Cessation Messages

Sulzer, David L. -- Columbia University Health Sciences
Presynaptic Mechanisms in Dopamine Neurotransmission

Sun, Wenlin -- University of Tennessee Health Science Center
Neural Mechanisms of Cocaine Addiction

Surratt, Christopher K. -- Duquesne University
Monoamine Transporter Structure-Function Studies

Sussman, Steven Y. -- University of Southern California
Drug Abuse Prevention for High Risk Emerging Adults

Tarantino, Lisa M. -- Novartis Institute for Functional Genomics
Fine Mapping Genes for Cocaine Locomotor Response in ENU Mutagenized Mice

Teplin, Linda A. -- Northwestern University
Trajectories of Drugs Abuse in High Risk Youth

Thayer, Stanley A. -- University of Minnesota Twin Cities
Cannabinoid Modulation of Recovery from HIV-Associated Synaptic Toxicity

Thomas, David L. -- Johns Hopkins University
The Progression of Hepatitis C Among IDUs

Tiffany, Stephen T. -- State University of New York at Buffalo

Evaluations of Reactions to Drug Cues in Natural Settings

Tolan, Patrick H. -- University of Illinois at Chicago
Developmental Evaluation of Prevention Effects of the SAFE Children Interven

Toll, Lawrence R. -- SRI International
Mixed NOP/mu Compounds and the Involvement of their Receptors in Analgesia

Torres, Gonzalo E. -- University of Pittsburgh at Pittsburgh
Physical and Functional Link of the Dopamine Transporter with Synaptic Proteins

Torres, Gonzalo E. -- University of Pittsburgh at Pittsburgh
Disrupting DAT Protein-Protein Interactions in Vivo: Implications for Drug Abuse

Traynor, John R. -- University of Michigan at Ann Arbor
Role of Lipid Rafts in Adenylyl Cyclase Sensitization

Trudell, Mark L. -- Louisiana State University-University of New Orleans
Development of Cannabinoid Receptor Based Medications for Drug Addiction

Tyler, Kimberly A. -- University of Nebraska Lincoln
Social Networks, HIV Risk Behaviors, and Homeless Youth

Ursu, Stefan -- University of California Davis
The Human PFC Response to Drug Cues: Outcome Representation vs. Cognitive Control

Venner, Kamilla -- University of New Mexico Albuquerque
Zuni MI/CRA Project

Vernon-Feagans, Lynne -- University of North Carolina Chapel Hill
Children Living In Rural Poverty: The Continuation of the Family Life Project

Vespignani, Alessandro -- Indiana University Bloomington
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Vlahov, David -- New York Academy of Medicine
Heroin Cessation and HIV Risk: A Case-Control Study

Waldron, Holly B. -- Oregon Research Institute
Development of a Family-Based Treatment for Adolescent Methamphetamine Abuse

Waldron, Holly B. -- Oregon Research Institute
Adolescent Substance Abuse: Progressive Treatment

Wallace, Scyatta A. -- Suny Downstate Medical Center
Neighborhood Characteristics, Drug Use, and HIV Risk Among African American Youth

Wang, Jinghua -- University of Minnesota Twin Cities
Opioid Abuse and Host Defense against Streptococcus Pneumoniae Lung Infection

Wang, Qiming Jane -- University of Pittsburgh at Pittsburgh
IMAP-Based Fluorescent Polarization Assay For HTS Protein Kinase D Inhibitors

Wang, Ze -- University of Pennsylvania
SVM Based Group Data Analysis for Drug Abuse Disorder ASL Perfusion Study

Waterhouse, Barry D. -- Drexel University

Neurochemistry and Neurophysiology of MDMA (Ecstasy)

Wei, Li-Na L. -- University of Minnesota Twin Cities
Studies of Mouse Kappa Opioid Receptor Gene Regulation

Weinstein, Harel -- Weill Medical College of Cornell University
Hallucinogens and 5-HT Receptors: Mechanisms and Effects

Wentland, Mark P. -- Rensselaer Polytechnic Institute
Aminobenzomorphan: Potential Cocaine Abuse Medications

White, Tara L. -- Brown University
Imaging Individual Differences in Amphetamine Effects

White, Wesley O. -- Morehead State University
Mechanisms of Amphetamine Withdrawal and Recovery

Whiteaker, Paul -- University of Colorado at Boulder
Alpha-Conotoxin MII: A Selective Nicotinic Receptor Probe

Wightman, Robert M. -- University of North Carolina Chapel Hill
Dynamics of In Vivo Dopamine Release

Williams, Geoffrey C. -- University of Rochester
Creating a Virtual Clinician Research Tool

Wills, Thomas A. -- Yeshiva University
The Project Success Model: Evaluation of a Tiered Intervention

Wines, James D. -- McLean Hospital, Belmont, MA
Risk Factors for Severe Opioid-Related Overdose (ORO)

Winger, Gail D. -- University of Michigan at Ann Arbor
Behavioral Economic Analysis of Polydrug Abuse

Winickoff, Jonathan P. -- Massachusetts General Hospital
Addressing Parental Smoking by Changing Pediatric Office Systems

Winters, Ken C. -- University of Minnesota Twin Cities
Youth Drug Abuse, ADHD and Related Disruptive Behaviors

Wood, Evan -- University of British Columbia
Impacts of Universal Access to HIV/AIDS Care Among HIV+ Injection Drug Users

Wu, Li-Tzy T. -- Duke University
Epdemiology of Non-Medical Prescription Analgesic Use

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

Yi, Richard -- University of Arkansas Medical Sciences Little Rock
The Discounting of Losses by Smokers in Nicotine Withdrawal

Yu, Aiming -- State University of New York at Buffalo
Pharmacogenetics in Indolealkylamine Metabolism and Drug Interactions

Yurgelun-Todd, Deborah A. -- McLean Hospital, Belmont, MA
MRS/FMRI Investigations of Adolescent Cannabis Use

Yurgelun-Todd, Deborah A. -- McLean Hospital, Belmont, MA
Brain Changes with Cannabis and Methamphetamine

Zacny, James P. -- University of Chicago
Abuse-Related Effects of Opioids and Adjuvant Drug Used By Chronic Pain Patients

Zangen, Abraham -- Weizmann Institute of Science
A Conflict Model of Cue-Induced Relapse to Cocaine

Zarkin, Gary A. -- Research Triangle Institute
Modeling Benefits and Costs of Prison-Based Substance Abuse Treatment

Zaveri, Nurulain T. -- SRI International
Discovery of Small-Molecular Orphanin FQ Receptor Ligands

Zhou, Fu-Ming -- University of Tennessee Health Science Center
Non-Transporter Cocaine Mechanisms in Dopamine System

Zimmerman, Marc A. -- University of Michigan at Ann Arbor
A Longitudinal Study of School Dropout and Substance Use

Director's Report to the National Advisory Council on Drug Abuse - February, 2008

Extramural Policy and Review Activities

Receipt, Referral, and Review

NIDA received 956 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 736 applications.

OEA arranged and managed 19 grant review meetings in which 240 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 4 contract proposal and contract proposal concept reviews.

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

Conflicts with the chartered committees
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)
Minority Institutions' Drug Abuse Research Development Program (MIDARP)

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

Concept Review

- N01DA-8-7766: Synthetic Peptides & Other Drugs of Abuse - Purity Determination, Stability Testing & Quantitative Analysis

Phase I SBIR Contract Reviews

- N43DA-8-5539: Topic 096 - Tools to Measure Intervention Costs, Cost Effectiveness, and Net Economic Benefits
- N43DA-8-8874: Topic 091 - Design and Synthesis of Treatment Agents for Drug Abuse

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Phase II SBIR Contract Reviews

- N44DA-8-4404: Rehabilitation for Methamphetamine Induced Impulsivity

CTN-Related Review Activities

The Data and Safety Monitoring Board(s) met:

September 17, 2007 via web conference 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).

October 19, 2007 via web conference to review a proposed ancillary study titled, "An Evaluation of Neurocognitive Function, Oxidative Damage, and their Association with Treatment Outcomes in Methamphetamine and Cocaine Abusers."

November 16, 2007 to review and discuss the progress of study 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).

November 19, 2007 to re-review the proposed study protocol CTN 0032, HIV Rapid Testing and Counseling in Drug Abuse Treatment Programs in the U.S.

November 29, 2007 to review and discuss the progress of study protocol CTN 0030, Prescription Opioid Addiction Treatment Study (POATS).

December 18, 2007 to review and discuss the progress of study protocol CTN 0027, Starting Treatment with Agonist Replacement Therapies (START).

Certificates of Confidentiality

Between August 1 and December 13, 2007, OEA processed 112 Certificate applications, including 25 for extension of expiration dates and 4 for amended protocols.

Staff Training and Development

The OEA Symposium Series, a forum for staff training and sharing of ideas and information, continued through the Fall. Activities included open forums for discussions and presentations that included NIDA's use of the cooperative agreement mechanism with presentations by Drs. Redonna Chandler, Bennett Fletcher, Kevin Conway, Christine Colvis and Dick Hawks.

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Congressional Affairs (Prepared January 25, 2008)

Appropriations

On December 26, 2007, the President signed the Consolidated Appropriations Act, 2008, which included funding for the NIH. The Act provides $29.456 billion (including $150 million for Type I Diabetes) for NIH. This figure reflects the 1.747 percent across-the-board cut to most accounts included in Division G of the law, including NIH. The Act includes a transfer of $295 million within NIH for the Global AIDS Fund; $111 million for the National Children's Study; $504,420,000 for the Common Fund; $96,030,090 for research on chemical, radiological and nuclear countermeasures; $10,000,000 for the Director's Discretionary Fund; and $25,000,000 for the flexible research authority.

NIDA's appropriation within this legislation, after the 1.747 percent across-the-board cut, is $1,000,700,000. This is $335,000 above the President's requested budget, and $79,000 above the final FY 2007 appropriated level.

Hearings, Briefings, and Events of Interest

Friends of NIDA Capitol Hill Briefing: On November 8, 2007, the Friends of NIDA, in conjunction with the Congressional Addiction, Treatment and Recovery Caucus, held its ninth in a series of briefings designed to educate members of Congress and their staff about substance abuse issues. The briefing focused on nicotine and tobacco addiction. While tobacco use is still a very large public health problem, control efforts over the last half century have been very successful, considering that not long ago there were no scientifically validated treatments for tobacco addiction and treatment had little place in health care delivery. Today, however, numerous effective treatments exist, and tobacco use assessment and intervention are considered to be requisite duties of clinicians and health care delivery entities. Nora D. Volkow, M.D., Director of NIDA, opened the briefing with an overview of the Institute's tobacco research portfolio. Timothy Baker, Ph.D., Professor of Medicine at the University of Wisconsin School of Medicine and Public Health and Director of Research at the University of Wisconsin Center for Tobacco Research and Intervention, followed with a discussion of current findings on the treatment of tobacco use that will serve as the basis of the 2008 Public Health Service (PHS) Clinical Practice Guidelines on the Treatment of Tobacco Use and Dependence. Michael Fiore, M.D. Professor of Medicine at the University of Wisconsin School of Medicine and Public Health an Director of the University of Wisconsin Center for Tobacco Research and Intervention, then provided his perspective as both a physician treating smokers and Chair of the panel revising the PHS tobacco treatment guidelines. The event concluded with the success stories of Shirley Reimer and Preston Young, two patients who quit smoking using a combination of national telephone help lines and nicotine replacement therapies. The briefing garnered

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an unprecedented 29 Friends of NIDA scientific and professional organization cosponsors, which reflects the serious concern surrounding the issue.

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. 1011 - 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, 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 marked up and passed by the Health, Education, Labor and Pensions Committee on June 27, 2007. The bill has been placed on the Senate calendar under General Orders. The bill is currently being "held" by Senator Jim DeMint (R-SC). He must release his hold if the bill is to receive full consideration in the Senate. Related issue: On December 13, 2007, the Senate passed under unanimous consent S. 2484, an Act to rename the National Institute on Child Health and Human Development as the Eunice Kennedy Shriver National Institute on Child Health and Human Development. The bill passed the House under suspension of the rules on December 17, 2007. S. 2484 was introduced on December 13 by Senator Orrin Hatch (R-UT), and signed by the President on December 21, 2007.

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. Both the House and Senate passed their bills. 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 House passed the amended Senate bill, thus sending the bill to the President. The President vetoed the bill. Concurrent with his veto, the President issued an Executive Order requiring the Secretary of HHS to enhance funding for research on alternative methods to derive pluripotent stem cells that do not involve human embryos.

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. As mentioned above re: S.5, the President issued an Executive Order requiring the Secretary of HHS to enhance funding for research on alternative methods to derive pluripotent stem cells

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that do not involve human embryos.

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 Wellstone 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 passed its bill in September of 2007; the House bill has been reported favorably by the committees of jurisdiction, and awaits floor 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 passed its bill in November, and the Senate bill awaits further 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. The Senate bill has been amended and reported out by Committee; full Senate action is pending. Further action is also pending in the House.

Crack vs. Powder Cocaine - Several bills have been introduced to address the sentencing differences for those convicted of selling or possessing different forms of cocaine. Most attempt to equalize penalties. Representative Roscoe Bartlett (R-MD) introduced H.R. 79, the Powder-Crack Cocaine Penalty Equalization Act of 2007. Representative Charles Rangel (D-NY) introduced H.R. 460, the Crack-Cocaine Equitable Sentencing Act of 2007. Representative Bobby Scott (D-VA) introduced H.R. 5035, the Fairness in Cocaine Sentencing Act of 2008. Senator Jeff Sessions (R-AL) introduced S. 1383, the Drug Sentencing Reform Act of 2007. Senator Orrin Hatch (R-UT) introduced S. 1685, the Fairness in Drug Sentencing Act of 2007. Senator Joseph Biden

introduced S. 1711, the Drug Sentencing Reform and Cocaine Kingpin Trafficking Act of 2007. All of these bills have been referred to their appropriate committees and further action is pending.

Freedom of Information - Several bills designed to broaden accessibility to government information were introduced last year (H.R. 1309, H.R. 1326, S. 849, S. 2427). Senator Patrick Leahy introduced S. 2488, the Open Government Act of 2007, to combine various proposals, which passed the House and Senate and became law in December. The law aims to promote accessibility, accountability and openness in government by strengthening Section 522 of Title 5, U.S. Code (the Freedom of Information Act).

H.R. 405 - On January 11, 2007, Representative Barbara Cubin (R-WY) 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 Energy and Commerce. See. S. 884.

H.R. 970 - On February 8, 2007, Representative Fred Upton (R-MI) introduced H.R. 970, the Dextromethorphan Distribution Act of 2007, to amend the Federal Food, Drug and Cosmetic Act with respect to the distribution of the drug dextromethorphan, and for other purposes. The bill was passed in October. See also S. 1378, S. 2274.

H.R. 1155 - On February 16, 2007, Representative Eddie Bernice Johnson (D-TX) introduced H.R. 1155, a bill to amend Title XIX of the Social Security Act to remove the exclusion from medical assistance under the Medicaid Program of items and services for patients in an institution for mental diseases (the "IMD Exclusion"). The bill was referred to the Committee on Energy and Commerce.

H.R. 1170 - On February 16, 2007, former 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. The bill was referred to the Committee on Energy and Commerce.

H.R. 1199 - On February 27, 2007, Representative Dennis Cardoza (D-CA) introduced the Drug Endangered Children Act of 2007, to extend the grant program for drug-endangered children. The bill passed in September. See S. 1210

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. 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.

H.R. 1943 - On April 19, 2007, Representative Maxine Waters (D-CA) introduced the Stop AIDS in Prison Act of 2007, to provide for an effective HIV/AIDS program in Federal prisons. The bill passed the House in September, and was sent to the Senate, where it is pending before the Judiciary Committee.

H.R. 2073 - On April 30, 2007, Representative Patrick Kennedy (D-R.I.) introduced the Child Health Care Crisis Act of 2007, to help bring new professionals into the mental health services field. The bill creates educational incentives such as grants, scholarships and loan forgiveness programs to encourage more professionals to enter and remain in child and adolescent mental health. It would also support institutions of higher learning in their efforts to enhance and prioritize children's mental health issues in their curriculum and training opportunities. The bill was referred to the Committees on Energy and Commerce and Ways and Means. See S.1572.

H.R. 2223 - On May 8, 2007, Representative Jon Porter (R-NV) introduced this bill to direct the Director of the Office of National Drug Control Policy, in consultation with the Attorney General and the Secretary of Health and Human Services, to conduct a study on prescription drug take-back programs, and for other purposes. The bill was referred to the Committee on Energy and Commerce.

H.R. 2425 - On May 22, 2007, Representative John Boozman (R-AR) introduced the Stop Marketing Illegal Drugs to Minors Act, to amend the Controlled Substances Act to provide enhanced penalties for marketing controlled substances to minors. The bill was referred to the Committees on the Judiciary and Energy and Commerce. See S. 1211.

H.R. 2552 - On May 24, 2007, Representative Edolphus Towns (D-NY) introduced the Hepatitis C Control and Prevention Act of 2007, to amend the Public Health Service Act to direct the Secretary of Health and Human Services to establish, promote and support a comprehensive prevention, research and medical management referral program for hepatitis C virus infection. The bill was referred to the Committee on Energy and Commerce. See S. 1445.

H.R. 2645 - On June 11, 2007, Representative William Jefferson (D-LA) introduced the Judicial Initiative Mental Health and Substance Abuse Treatment Improvement Act of 2007, to amend the Juvenile Justice and Delinquency Prevention Act of 1974 to improve mental health and substance abuse treatment by providing grants for justice system personnel training, treatment programs and diversion programs, and for other purposes. The bill was referred to the Committees on Education and Labor and Judiciary.

H.R. 2647 - On June 11, 2007, Representative William Jefferson (D-LA) introduced the Mental Health and Substance Abuse Juvenile Services Improvement Act of 2007, to amend the Public Health Service Act to improve mental health and substance abuse services for juveniles. The bill was referred to the Committee on Energy and Commerce.

H.R. 2900 - On June 29, 2007, Congressman John Dingell (D-MI) introduced the FDA Amendments Act of 2007. The bill passed the House and was referred to the Senate in July. See S.1082.

H.R. 2994 - On July 11, 2007, Representative Lois Capps (D-CA) introduced the National Pain Care Policy Act of 2007, to amend the Public Health Service

Act with respect to pain care. The bill was referred to the Committee on Energy and Commerce.

H.R. 3000 - On July 11, 2007, Representative Barbara Lee (D-CA) introduced the Josephine Butler United States Health Service Act. Of interest to NIH are provisions that would establish the United States Health Service and a National Health Board. Upon enactment, NIH, AHRQ, ATSDR, CDC, and SAMHSA would be transferred to the National Health Board. It would also establish the following new institutes: National Institute of Epidemiology; National Institute of Evaluative Clinical Research; the National Institute of Health Care Services; the National Institute of Pharmacy and Medical Supply; and the National Institute of Sociology of Health and Health Care. This bill has been reintroduced continually since the 105th Congress. The bill was referred to the House Committees on Energy and Commerce, Education and Workforce, and Ways and Means.

H.R. 3014 - On July 12, 2007, Representative Hilda Solis (D-CA) introduced the Health Equity and Accountability Act of 2007, to improve the health of minority individuals. Provisions of interest to NIH include a requirement that each Federal health agency develop and implement a national strategic action plan to eliminate disparities on the basis of race, ethnicity, and primary language and improve the health and health care of minority populations through programs relevant to the mission of the agency. NIH-related provisions would amend authorities of the National Center for Minority Health and Health Disparities (NCMHD) to require (1) the Director of the Center, in consultation with the respective Institute and Center (IC) directors or their designees, plan, coordinate, and evaluate research and other activities conducted or supported by the agencies of the NIH and carry out periodic re-evaluations of these activities; (2) annual review and revision of a comprehensive plan and budget for the conduct and support of relevant research; (3) systematic review of research activities, including establishment of mechanisms for tracking minority health and health disparities research conducted within the ICs, with assessments of the appropriateness of such research within the overall goals and objectives of the Plan; and (4) early identification of applications and proposals for grants, contracts, and cooperative agreements supporting relevant extramural training, research, and development that are submitted to the ICs. In addition, provisions would require that the Director, NCMHD, expend all amounts appropriated under section 485E for minority health and health disparities research, in accordance with the section and applicable law and in collaboration with the Director, NIH, and the IC directors. The bill was referred to the House Committees on Energy and Commerce, Ways and Means, Education and Labor, Natural Resources, and Judiciary.

H.R. 3130 - On July 23, 2007, Representative Darlene Hooley (D-OR) introduced the Enhanced Methamphetamine Treatment Grants Assistance Act of 2007, to amend title V of the Public Health Service Act to provide for enhanced comprehensive methamphetamine treatment services. The bill was referred to the Committee on Energy and Commerce.

H.R. 3186 - On July 26, 2007, Representative Rick Larsen (D-WA) introduced the Meth Mouth Prevention and Community Recovery Act, to understand and comprehensively address the oral health problems associated with methamphetamine use. The bill was referred to the Committee on Energy and Commerce. See S. 1906.

H.R. 3187 - On July 26, 2007, Representative Brian Baird (D-WA) introduced the Meth Mouth Correctional Costs and Reentry Support Act, to amend title I of the Omnibus Crime Control and Safe Streets Act of 1968 to understand and comprehensively address the inmate oral health problems associated with methamphetamine use, and for other purposes. The bill was referred to the Committee on the Judiciary. See S. 1907.

H.R. 3409 - On August 3, 2007, Representative Ruben Hinojosa (D-TX) introduced H.R. 3409, the Place to Call Home Act, to create the conditions, structures, and supports needed to ensure permanency for the nation's unaccompanied youth, and for other purposes. The bill contains a number of provisions related to improving funding and coordination of drug and alcohol prevention and treatment services. The bill was referred to the Committees on Education and Labor, Ways and Means, Energy and Commerce, Financial Services, and Judiciary.

H.R. 3411 - On August 3, 2007, Representative Patrick Kennedy (D-RI) introduced H.R. 3411, the Juvenile Crime Reduction Act, to improve the treatment of young people in the juvenile justice system with mental health or substance use disorders. The legislation would establish a number of grant programs to increase training, technical assistance, and coordination of service providers, including those who provide addiction treatment services, to young people who are involved with the juvenile justice system. H.R. 3411 would establish a number of grant programs aimed at improving services for youth in the juvenile justice system with mental health or substance use disorders. The bill was referred to the House Committees on Education and Labor and Energy and Commerce.

H.R. 3433 - On August 3, 2007, Representative Steven Pearce (R-NM) introduced the Methamphetamine Treatment and Rehabilitation Best Practices Act of 2007, to direct the Secretary of Health and Human Services, acting through the Director of the National Institutes of Health, to conduct a survey of research available on methamphetamine addiction and treatment. The bill was referred to the Committee on Energy and Commerce.

H.R. 3434 - On August 3, 2007, Representative Steven Pearce (R-NM) introduced the Americans Saving through Health Research Bonds Act of 2007. The bill would amend 31 USC 3105 to authorize the Secretary to designate one or more series of health research bonds or certificates (or any portion thereof) to benefit each of the NIH institutes. The Secretary would be required to deduct and withhold ten percent of the amount of any interest payable under any such bond, which would be paid to the designated NIH institute to carry out research activities. It would also be required that the amount of any such payment would not be taken into account in making decisions regarding funds appropriated or otherwise provided to the NIH. The bill was referred to the Committee on Ways and Means.

H.R. 3561 - On September 18th, 2007, Representative Gene Green (D-TX) introduced H.R. 3561, the Community Coalitions for Access and Quality Improvement Act of 2007, legislation that would authorize a grant program aimed at better integrating health care delivery. Primarily concerned with expanding and coordinating the delivery of health services, H.R. 3561 seeks to increase access to health care for low-income and uninsured populations. In determining grant eligibility, priority would be given to applicants who seek to expand drug and alcohol addiction and mental health treatment services. The bill was referred to the House Energy and Commerce Committee.

H.R. 3656 - On September 26th, 2007, Representative Phil English (R-PA) introduced H.R. 3656, to require states to withhold assistance to applicants for, and recipients of, temporary assistance for needy families (TANF) with respect to whom there is substantial evidence of recent unlawful drug use. The legislation would require states to drug test TANF applicants and recipients suspected of using illicit drugs. The bill was referred to the Committee on Ways and Means.

H.R. 3749 - On October 4, 2007, Representative Darlene Hooley (D-OR) introduced H.R. 3749, the Methamphetamine Prevention Enhancement Act, to amend the Public Health Service Act to provide for the establishment of a Drug-Free Workplace Information Clearinghouse, to authorize programs to

prevent and improve treatment of methamphetamine addiction, and for other purposes. The bill was referred to the Committee on Energy and Commerce.

H.R. 3992 - On October 30, 2007, Representative Bobby Scott (D-VA) introduced the Mentally Ill Offender Treatment and Crime Reduction Reauthorization and Improvement Act of 2007, to amend Title I of the Omnibus Crime Control and Safe Streets Act of 1968 to provide grants for the improved mental health treatment and services provided to offenders with mental illnesses, and for other purposes. The bill passed the House in January, 2008. See S. 2304.

H.R. 4129 - On November 8, 2007, Representative Hilda Solis (D-CA) introduced the Homeless Access to Recovery through Treatment Act, to amend the Public Health Service Act to strengthen and expand substance abuse and mental health services to persons experiencing homelessness in the United States. The bill was referred to the Committee on Energy and Commerce.

H.R. 4232 - On November 15, 2007, Representative Patrick Kennedy (D-RI) introduced H.R. 4232, the Improving the Quality of Mental and Substance Use Health Care Act of 2007, to improve mental and substance use health care in the U.S. The bill was referred to 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. See H.R. 405.

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 legislation seeks to impose registration and reporting requirements on pharmacies that deliver controlled substances via the Internet. In her comments on the bill's introduction, Senator Feinstein expressed particular concern with the growing problem of prescription drug abuse and addiction. The bill was referred to the Judiciary Committee, which held a hearing in May, and reported the bill favorably in September. Further Senate action is pending.

S. 1082 - On April 10, 2007, Senator Edward Kennedy (D-MA) introduced S. 1082, The Food and Drug Administration Revitalization Act. The bill is focused primarily on FDA and contains sections regarding user fees and drug safety monitoring procedures. As amended, the bill also contains several provisions of interest to NIH. First, 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. Second, S. 1082 includes provisions to reauthorize the Best Pharmaceuticals for Children Act. Third, the bill contains provisions to expand research on pediatric devices. Finally, an amendment offered by Senator Barack Obama (D-IL) was added during floor debate, requiring the Secretary to contract with the Institute of Medicine to make recommendations regarding oversight and regulation of genetic tests. The Senate passed its bill in May.

S. 1210 - On April 25, 2007, Senator Diane Feinstein (D-CA) introduced S. 1210, the Drug Endangered Children Act of 2007, to extend the grant program for drug-endangered children. The bill was referred to the Committee on the Judiciary, where it is pending. See H.R. 1199.

S. 1211 - On April 25, 2007, Senator Diane Feinstein (D-CA) introduced the Saving Kids from Dangerous Drugs Act, to amend the Controlled Substances

Act to provide enhanced penalties for marketing controlled substances to minors. The bill was referred to the Committee on the Judiciary. See H.R. 2425.

S. 1337 - On May 8, 2007, Senator John Kerry (D-MA) introduced the Children's Mental Health Parity Act, to amend title XXI of the Social Security Act to provide for equal coverage of mental health services under the State Children's Health Insurance Program. The bill was referred to the Committee on Finance.

S. 1367 - On May 10, 2007, Senator Tom Harkin (D-IA) introduced the Treatment and Prevention of Methamphetamine Abuse Act of 2007, to amend the Public Health Services Act to provide methamphetamine prevention and treatment services. The bill was referred to the Committee on Health, Education, Labor and Pensions.

S. 1378 - On May 14, 2007, Senator Patty Murray (D-WA) introduced S. 1378, the Dextromethorphan Distribution Act of 2007, to amend the Federal Food, Drug and Cosmetic Act with respect to the distribution of the drug dextromethorphan, and for other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions, where it awaits action. See H.R. 970.

S. 1445 - On May 22, 2007, Senator Edward Kennedy (D-MA) introduced the Hepatitis C Epidemic Control Prevention Act of 2007. The bill directs the Secretary of Health and Human Services to establish, promote, and support a comprehensive prevention, research, and medical management referral program for hepatitis C virus infection. The bill also would require the Director of NIH to establish a Liver Disease Research Advisory Board, which would be charged with developing a Liver Disease Research Plan. The bill was referred to the Committee on Health, Education, Labor, and Pensions. See H.R. 2552.

S. 1470 - On May 23, 2007, Senator Bill Nelson (D-FL) introduced the Drug Free Varsity Sports Act of 2007, to provide States with the resources needed to rid our schools of performance-enhancing drug use. The bill was referred to the Committee on Health, Education, Labor and Pensions.

S. 1572 - On June 7, 2007, Senator Jeff Bingaman (D-NM) introduced the Child Health Care Crisis Relief Act of 2007, to increase the number of well-trained mental health service professionals (including those based in schools) providing clinical mental health care to children and adolescents, and for other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions. See. H.R. 2073.

S. 1882 - On July 26th, 2007, Senator Chuck Hagel (R-NE) introduced S. 1882, the Public Health Preparedness Workforce Development Act of 2007. The bill would create scholarship, loan repayment, and grant programs to recruit and retain public health workers. Intended to increase the ratio of public health workers to the population, S. 1882 would bring doctors, nurses, researchers, technicians, and other medical workers, including those working in the behavioral sciences, into the public health field. The bill was referred to the Committee on Health, Education, Labor and Pensions.

S. 1906 - On July 31, 2007, Senator Max Baucus (D-MT) introduced the Meth Mouth Prevention and Community Recovery Act, to increase understanding and comprehensively address the oral health problems associated with methamphetamine use. The bill would require the Secretary of HHS to expand and intensify clinical research, health services research, and public health research on associations between substance use disorders, oral health, and the provision of dental care in collaboration with Federal and non-Federal entities. In addition, the bill would authorize funds to carry out this section as well as one that would require SAMHSA to support training of dental personnel to be

aware of such findings. The bill was referred to the Committee on Health, Education, Labor, and Pensions. See H.R. 3186.

S. 1907 - On July 31, 2007, Senator Max Baucus (D-MT) introduced the Meth Mouth Correctional Costs and Reentry Support Act., to amend title I of the Omnibus Crime Control and Safe Streets Act of 1968 to understand and comprehensively address the inmate oral health problems associated with methamphetamine use, and for other purposes. The bill was referred to the Committee on the Judiciary. See H.R. 3187.

S. 2237 - On October 25, 2007, Senator Joseph Biden (D-DE) introduced S.2237, a bill to fight crime. The legislation includes several drug-related programs. The bill was referred to the Committee on the Judiciary.

S. 2274 - On October 31, 2007, Senator Joseph Biden introduced S. 2274, the Dextromethorphan Abuse Reduction Act of 2007, to amend the Controlled Substances Act to prevent the abuse of dextromethorphan, and other purposes. The bill was referred to the Committee on the Judiciary.

S. 2304 - On November 5, 2007, Senator Pete Domenici (R-NM) introduced the Mentally Ill Offender Treatment and Crime Reduction Reauthorization and Improvement Act of 2007, to amend Title I of the Omnibus Crime Control and Safe Streets Act of 1968 to provide grants for the improved mental health treatment and services provided to offenders with mental illnesses, and for other purposes. The bill was referred to the Committee on the Judiciary. See H.R. 3992.

Director's Report to the National Advisory Council on Drug Abuse - February, 2008

International Activities

Funding Initiatives

NIDA Commits $1.5 million for International Research Collaborations to Study HIV/AIDS and Drug Abuse
NIDA will award up to $1.5 million during FY 2008 in Exploratory/Developmental (R21) research grants to stimulate research, particularly collaborative efforts between U.S. and foreign scientists, to investigate aspects of the HIV/AIDS - drug abuse nexus. The 1-year, maximum $100,000 awards are designed to address important research questions that cannot be easily or readily addressed within the United States but would have implications for the United States; build research capacity in resource limited countries where HIV/AIDS associated with drug abuse is prevalent; bring basic and clinical science to bear on public health needs; and stimulate new R01 and other applications.

NIDA, Dutch Addiction Program Fund Four New Binational Research Teams
Continuing the uniquely successful binational funding agreement between NIDA and the Dutch Addiction Program (DAP), four new research teams have received funding to use brain imaging, animal models, and Ecological Momentary Assessment to explore ways to address the use of and dependence on marijuana, cocaine, and nicotine. NIDA funds the U.S. researchers; DAP supports the Dutch scientists. The four teams presented their research plans at the Fifth U.S.-Netherlands Binational Research Symposia, held November 28-29, 2007, in Amsterdam. In addition to learning about the newly funded projects, meeting participants heard updates on previously funded projects, met with national experts, and explored topics of mutual interest. The nine research teams who have already received funding have been highly productive, resulting in a NIDA research grant, three new collaborative links inspired by the U.S.-Netherlands projects, 14 books/chapters/reports, 19 scientific journal articles, and 42 presentations at scientific meetings. Dr. Wim van den Brink, University of Amsterdam, and NIDA Deputy Director Dr. Timothy Condon discussed recent advances on addiction research in their respective countries. Nick Ramsey, University Medical Center Utrecht, chaired a discussion of topics for future collaboration between NIDA and DAP that featured NIDA staff, including Dr. David Shurtleff (DBNBR), Dr. Joseph Frascella (DCNBR), Dr. Ivan Montoya (DPMCDA), and Dr. Eve Reider (DESPR). The meeting was co-chaired by Dr. Sineke ten Horn, Dutch Addiction Program, and IP Director Dr. Steven W. Gust. The newly funded research teams include the following:

> Linda Porrino, Wake Forest University, and A.E. Goudriaan, University of Amsterdam, will use fMRI and cognitive testing to study the neurobiological correlates of poor decision making in chronic marijuana users.

Planned Meetings

Publications

Staff Highlights

Grantee Honors

Anna Rose Childress, University of Pennsylvania, and Wim van den Brink, University of Amsterdam, will conduct brain imaging studies to evaluate the effects of Varenicline in the brains of patients who use cocaine to test that compound as a potential cocaine pharmacotherapy.

Andrew Waters, Uniformed Services University, and I.H.A. Franken, Erasmus University, will study how cognitions in drug abusers may influence the success or failure of treatment (i.e., abstinence or relapse) using remote monitoring of craving or urges, with data entered by the subject into a hand-held computer.

Paul Phillips, University of Washington, and Matthijs Feenstra, Netherlands Institute of Neuroscience, will compare compulsive drug use with learning to obtain a natural reward (sugar) in animals that have been characterized as risk prone or risk averse in an effort to discover if there are changes in the neural activity that underlie the formation of habits.

NIDA/CICAD Research Awards and Call for New Applications Announced
Through its Latin America Initiative, NIDA and the Inter-American Drug Abuse Control Commission (CICAD) cosponsor the Competitive Research Award Fund to support drug use research in the region. Awards support pre- or postdoctoral students conducting research in any area of the drug use field. Priority is given to projects involving secondary analysis of existing research databases, such as national drug use surveys. The national drug commissions in Organization of American States member countries review initial applications and forward appropriate projects to the CICAD Inter-American Observatory on Drugs for review by representatives from NIDA, CICAD, and the U.S. National Hispanic Science Network. The call for applications for the second round of awards was issued in October 2007. The first-round awards include:

Bolivia
Christian Arce Vargas Magne and Maria del Pilar Navia Bueno, Universidad Mayor de San Andres - Risk Factors Associated with Drug Consumption Among Adults in the City of La Paz during 2006.

Chile
David Huepe and Jorge Manzi, Pontificia Universidad Catolica de Chile - How Family Relationship and School Factors Relate to the Different Drug Consumption Profiles in the Secondary School Population in Chile: In Search of a Predictive Model.

Erika Eliana Queipul Vera and Gaston Pulido, Universidad de playa Ancha - Self-esteem and its Relationship with Drug Consumption Among Eighth-year Students of "Basic Education" in the Municipal Schools of Manuel Rodriguez and Rudicindo in the Copiapo Community.

Claudia Hernandez Madrid and Bianca Dapelo, Universidad de Vina del Mar - Drug Consumption Among University Students: Protective and Risk Factors.

Jorge Gaete and Ricardo Araya, Universidad de Bristol - Effects of the Student-School Relationship on Cigarette Consumption Among Adolescents in Chile.

Juan Luis Barria and Roberto Moreales Urra, Universidad Austral de Chile - School Attendance and Prevention: The Adolescent View.

Colombia
Mildred Alexandra Viancha Pinzon and Andres Barreto Agudelo,

Universidad de Colombia - Evaluation of the Association between Psychoactive Substance Use and Physical Abuse Among Youth within the Social Protection System.

Carlos Andres Mejia Mosquera and Alberto Palacio Acosta, Universidad de Antioquia - Determining the Association between Antisocial Personality Disorder and the Factors Attributable to Exposure and Population According to Psychoactive Substance Use in the Bellavista Prison in Medellin.

Costa Rica
Ernesto Cortes Amador and Julio Bejarano, Instituto sobre Alcoholismo y Farmacodependencia - Patterns of Alcohol Use Among First-year Students at the University of Costa Rica, Rodrigo Facio Campus.

Ecuador
Myriam Guerra and Rene Unda, Universidad Politecnica Salesiana - The Social Conditions that Predispose Adolescents to Psychoactive Substance Addiction Among Adolescents Attending the Therapeutic Communities Virgilio Gerrero and Buen Pastor.

Uruguay
Higinio Perez and Eleuterio Umpierrez, Facultad de Quimica Polo Tecnologico de la Republica - Application of a Study on Drug Consumption Among New Inmates, 2004-2005.

Soledad Brescia Tudesco, Pablo Fielitz, Gabriela Lopez Rega, and Veronica Santos Spagnuolo, Universidad de la Republica Oriental de Uruguay - Effects of Coca Paste Consumption on Intellectual Performance.

Rodrigo Zaragoza Tejera and Rafael Bayce, Universidad de la Republica - Consumption of Psychoactive Substances Among Secondary School Youth.

Maria Soledad Olave Silva and Ana Valentina Sosa Ontaneda, Centro Latinoamericano para la Economia Humana - Prevention of Drug Consumption Among Secondary School Students in Uruguay.

Gabby Recto and Adriana Insua, Instituto Universitario Centro Latinoamericano para la Economia Humana - Epidemiological Study on the Population Involved in the Plan de Asistencia Nacional a la Emergencia Social (PANES) convoked through the Construyendo Rutas de Salida Prevention Program in Uruguay between October 2006 and March 2007.

Research Results

INVEST Fellows End Productive Fellowships with Publications and Presentations
A pair of South Korean researchers, Dr. Doug Hyun Han and Dr. Young Hoon Sung, have completed productive INVEST Fellowships with their mentor, Dr. Perry F. Renshaw, Harvard Medical School McLean Hospital. Dr. Han was the lead author of a study suggesting that there is a genetic component of reward dependence, and of another study demonstrating that acamprosate produces nonselective effects on craving for drinking and eating in alcoholic patients. In an oral presentation at the 2007 College on Problems of Drug Dependence (CPDD) meeting and an article in the Journal of Addiction Medicine (1(3), pp. 133-138, 2007), Dr. Han and his colleagues suggested that the DRD2 Taq1A1 allele seems to be associated with reward dependence in adolescents who engage in excessive Internet video game play (EIGP). The study on acamprosate was electronically published in Drug and Alcohol Dependence on

November 3, 2007. Dr. Sung was lead author of a study that appeared in Drug and Alcohol Dependence (88(1), pp. 28-35, 2007) suggesting that the methamphetamine-related abnormalities in the brains of drug users may, in part, recover with abstinence in gray matter, but not in the white matter regions. In a poster presentation at the 2007 CPDD meeting, he reported preliminary results on a study of cocaine abusers that found cortical thinning in the prefrontal and temporal cortex areas, suggesting that these deficits may be associated with craving behavior and impaired cognitive function in cocaine abusers. Dr. Sung also conducted research on MDMA-induced changes in -adenosine triphosphate levels, which may provide insight into neurotoxicity mediated by mitochondrial protein uncoupling.

U.S. - Spain Joint Research Supports Community Reinforcement Approach Plus Vouchers in Treating Spanish Cocaine Abusers

A binational team of researchers from the University of Oviedo, Spain, and the University of Vermont has concluded that community reinforcement approach (CRA) plus vouchers treatment is effective and generalizable to a community treatment setting outside the United States. Writing in the Journal of Substance Abuse Treatment (doi:10.1016/j.jsat.2007.03.006), Dr. Roberto Secades-Villa and his colleagues report on a study of Spanish cocaine abusers who sought treatment that found patients who received CRA plus vouchers treatment were more likely than those who received standard care to complete 24 weeks of treatment and remain abstinent from cocaine.

Study Finds International Program Fellowships Contribute to Scientific Productivity

A study of NIDA International Program Fellowship alumni has concluded that participation in the research training and exchange programs appears to contribute to the Fellows' scientific productivity. Between 1990 and 2006, the NIDA International Program has funded 107 fellows from 47 countries, 72 percent of them from low- or middle-income countries. The International Program also recruited 49 DISCA partners and INVEST mentors representing 34 institutions in 20 U.S. states. A web-based survey was distributed in December 2006 to former NIDA INVEST, Humphrey, and Distinguished Scientist (DISCA) program participants, asking them to report on their scientific productivity after completing the research and exchange program. Scientific productivity was defined as scientific publications, presentation at scientific conferences, and acquisition of research funding. The response rate varied from 38% to 70% among participants in the three Fellowships. The outcomes for the INVEST and Humphrey program were combined because these program target early career scientists; the DISCA outcomes are presented separately because the program is restricted to senior level scientists. DISCA scientists represented 11 countries; 55 percent reported a scientific publication, 55 percent reported a scientific presentation, and 100 percent reported receiving a research grant. Four DISCA scientists received funding from the U.S. National Institutes of Health; three, from government agencies in their home country; and one, from a non-governmental organization. The former INVEST and Humphrey Fellows represented 37 countries; 32 percent reported a scientific publication; 32 percent reported a scientific presentation; and 30 percent reported receiving a research grant. Seven former INVEST and Humphrey Fellows received funding from the U.S. National Institutes of Health; 20, from government agencies in their home country; 7, from government agencies outside their home country; and 11, from non-governmental organizations. The study was coauthored by Shyla John, M.B.A., IQ Solutions; International Program Director Steven W. Gust, Ph.D.; and Erin L. Winstanley, Ph.D., Johns Hopkins School of Medicine. Ms. John presented the study results orally at the International Conference on Urban Health, held October 31-November 2, 2007, in Baltimore, Maryland, and as a poster at American Public Health Association Meeting held November 3-7, 2007, in Washington, D.C.

NIDA-Supported Meetings

NIDA Sponsors International Workshop on "Reducing HIV in Drug User Populations" at the American Association for the Treatment of Opioid Dependence Conference
The international session at the American Association for the Treatment of Opioid Dependence (AATOD) conference in San Diego (October 20-24, 2007) was developed by the IP (Dr. Steven Gust) and the CTN (Dr. Petra Jacobs) at NIDA. One of the workshop objectives was to discuss the role of evidence-based drug treatment in preventing HIV transmission in drug users. Dr. Zunyou Wu (Director, National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China) presented how HIV national preventive and treatment programs are addressing HIV in the population of drug users in China. This included the information about availability, accessibility, and structure of methadone programs. In addition, data from two NIDA-funded studies were presented: the impact of naltrexone on reducing HIV in Russia (Dr. George Woody, University of Pennsylvania) and buprenorphine maintenance treatment with behavioral counseling in Malaysia (Dr. Marek Chawarski, Yale University School of Medicine).

NIDA Poster Session at SfN Highlights Young International Neuroscience Researchers
NIDA organized an Early Career Investigators Poster Session on Friday, November 2, 2007 as part of NIDA's mini-convention on Frontiers in Addiction Research at the Society for Neuroscience Research meeting in San Diego, California. The invited poster session showcased drug abuse and drug-related neuroscience research by: Francis Bambico, Canada; Alicia Brusco, Argentina; Resat Cinar, Hungary; Alline Cristina de Campos, Brazil; Daniele De Filippis, Italy; Francois Georges, France; Christ Henstridge and Amy Milton, United Kingdom; Kimo Jensen, Demark; Naoko Kuzumaki, Japan; Manuel Mameli, Switzerland; Petra van Nieuwenhuijzen, Australia; Einav Sudai, Israel; Daifei Wu, Germany; Magdalena Zaniewska, Poland; and Teresa Summavielle, Portugal. The international poster presenters were supported, in part, by NIDA and the International Union of Pharmacology, International Brain Research Organization, International Narcotics Research Conference, College on Problems of Drug Dependence, International Cannabinoid Research Society, and International Drug Abuse Research Society.

NIDA Participates in Peruvian Congress on Addiction
Dr. Jag H. Khalsa, Chief, Medical Consequences Branch, NIDA Division of Pharmacotherapies and Medical Consequences of Drug Abuse (DPMCDA), delivered four talks at the Peruvian 5th National Congress on Addiction, held November 26-28, 2007, in Lima. Representing NIDA Director Dr. Nora Volkow, Dr. Khalsa discussed the Neurobiology of Addiction and Drug Abuse Research Priorities at NIDA. Dr. Khalsa also presented about DPMCDA work on nicotine vaccines and on medical consequences of drug abuse and infections. NIDA also supported participation by Dr. James Anthony, University of Michigan, who spoke on genomic epidemiology of drug addiction. Following the conference sessions, Dr. Khalsa visited a 60-bed drug abuse treatment center in NaNa, Peru, which treats alcohol and drug abuse patients with excellent recovery rates. The in-patient treatment center is directed by Rafael Navarro, M.D., who was also the President of the National Congress.

NIDA Assesses Its Impact on Southern Africa
The NIDA Special Populations Office meeting, Southern Africa Initiative: Research Progress and Perspectives, assembled NIDA officials and representatives from the binational research teams supported by NIDA's Southern Africa Administrative Supplements and other grant funds to discuss ongoing research in Southern Africa, the impact of NIDA funding on research and capacity development, and barriers encountered while conducting research in the region. Presenters discussed findings from projects investigating the

etiology, epidemiology, prevention, and treatment of drug abuse, tobacco use, and HIV and hepatitis - particularly among vulnerable populations such as women, children, adolescents, and prisoners. Significant accomplishments included the installation of the first fMRI unit in Africa and the adaptation and validation of several U.S. interventions for use in South Africa. The research teams also reported that the administrative supplement research has already resulted in three R01 research grant awards and one R21 exploratory/developmental research grant, more than 30 publications in international scientific journals, 137 presentations at scientific meetings, and significant capacity building efforts within South Africa. Capacity building included mentoring for individuals pursuing advanced academic degrees and training programs in research methods, treatment protocols, and prevention interventions. Based on research conducted, two researchers were awarded Ph.D. degrees and one researcher was awarded a Master's degree.

Fellowships

NIDA Selects New INVEST Fellow
NIDA named Dr. Sheng Liu, Ningbo Addiction Research and Treatment Center, China, as an INVEST Drug Abuse Research Fellow. Dr. Liu will work with Dr. Gary Aston-Jones, Medical University of South Carolina, to investigate the role of brain neuromodulatory systems in drug abuse. At the Ningbo Center, Dr. Liu uses immunohistochemistry, intracranial implants, behavioral testing, and imaging studies to conduct neurobiological and psychological studies of heroin addiction and treatment. He will work with Dr. Aston-Jones on studies to examine the roles of lateral hypothalamic orexin neurons and VTA orexin receptors in persistently increased drug preference during abstinence using rat models of behavioral neuropharmacology, neuroanatomy, and neurophysiology. Dr. Liu will concentrate on learning electrophysiology techniques, which along with Dr. Aston-Jones's orexin research, has implications for Dr. Liu's research on electroacupuncture.

First INVEST/CTN Fellows Are Named
NIDA has selected the first three researchers to be named INVEST/CTN Drug Abuse Research Fellows. The Fellows will spend 1 year working with a mentor who is affiliated with one of the 17 NIDA Clinical Trials Network Regional Research and Training Centers. Former NIDA Hubert H. Humphrey Fellow Dr. Amit Chakrabarti, India, will work with Dr. Roger Weiss, McLean Hospital. A professor of pharmacology and epidemiology at the Sikkim Manipal Institute of Medical Sciences, Dr. Chakrabarti will focus on clinical research experience in the treatment of prescription opioid dependence, participating in the CTN Northern New England Node Prescription Opioid Analgesic Treatment Study (POATS), a randomized, controlled, open-labeled clinical trial of buprenorphine/naloxone and the effect of ethnicity on treatment outcome. Drs. Chakrabarti and Weiss intend to develop a collaborative research project based on the POATS project for implementation in the ethnically diverse Sikkim state in India. Dr. Gvantsa Piralishvili, Georgia, will work with Dr. George E. Woody, University of Pennsylvania. As a physician and treatment researcher at the addiction/HIV prevention centers Union Alternative Georgia and New Way Center for Psychosocial Information and Counseling, Dr. Piralishvili will focus on assessing outcomes of methadone maintenance treatment programs. He and Dr. Woody intend to prepare a grant application to investigate methadone maintenance and HIV risks in Georgia, and Dr. Piralishvili will observe CTN Delaware Valley Node studies to learn about integrating research with practice, human subjects protection, good clinical practice, identifying adverse events, quality assurance, Web-based systems, and various research instruments. This fellowship builds on the relationship established between Dr. Woody and former NIDA Hubert H. Humphrey Fellow Dr. David Otiashvili, Union Alternative Georgia. Dr. Chen Hanhui, China, will work with Dr. Walter Ling, University of California, Los Angeles (UCLA). A psychiatrist at the Shanghai Mental Health

Center (SMHC), Dr. Hanhui will study how ethnicity and cultural differences affect the outcomes of contingency management programs designed to address drug use and HIV risk behaviors. Dr. Hanhui intends to learn more about the UCLA model of comprehensive, integrated drug abuse treatment services as China moves to expand both pharmacological and behavioral treatments for opioid dependence. His INVEST/CTN Fellowship award builds on numerous ties between the two institutions: SMHC is affiliated with the CTN Pacific Node and the UNODC TreatNet project, both of which are centered at UCLA. In addition, former NIDA INVEST Fellow and Distinguished International Scientist Dr. Min Zhao has been collaborating with Dr. Ling.

NIDA, State Department Select 2007-2008 Hubert H. Humphrey Drug Abuse Research Fellows
NIDA and the U.S. Department of State have selected nine international drug abuse professionals as 2007-2008 Hubert H. Humphrey Drug Abuse Research Fellows. The two agencies co-sponsor competitive, 10-month awards that provide academic training at the Virginia Commonwealth University and six-week professional affiliations with NIDA-supported researchers. The new VCU Humphrey Fellows include:

Raina Abou El-enein, Egypt
Rawnak Aqrawi, Iraq
Arian Boci, Albania
Fatima El Omari, Morocco
Marisa Felicissimo, Brazil
Rushit Ismajli, Serbia
Boonsiri Junsirimongkol, Thailand
Ruhullah Nassery, Afghanistan
Zar Soe, Myanmar

Travel Support

NIDA supported the participation of Dr. Beatriz Champagne, InterAmerican Heart Foundation, at the Society for Research on Nicotine and Tobacco (SRNT) Latin American Congress and the Iberoamerican Conference on Tobacco Control, which were held in Rio de Janeiro, Brazil, September 5 - 7, 2007. Dr. Champagne was president of the SRNT conference.

NIDA supported the participation of Dr. James Hall, University of Iowa, at the Inter-American Drug Abuse Control Commission (CICAD) meeting of national drug observatories November 27-30, 2007, in Santa Marta, Columbia.

International Visitors

On October 15, 2007 a large group from the Norlien Foundation visited NIDA. Created in 1997 the Norlien Foundation is a private foundation that initiates strategic projects to enhance the quality of life for all Canadians, particularly of those living in Alberta, Canada, with an emphasis on addiction in children and teenagers. The purpose of the meeting was to hear about recent updates to NIDA's research. The group met with NIDA Director Nora Volkow and representatives from each of NIDA's divisions, offices and centers. That evening the Norlien Foundation sponsored a reception at the Canadian Embassy. Several NIDA staff attended the reception.

Representatives of the Chinese Education through Labor Academic Society visited NIDA on October 26, 2007. The Chinese visitors met with Dr. Liz Ginexi and Dr. Akiva Liberman, DESPR, Dr. Cece McNamara Spitznas, DCNBR, Dr. Linda Erinoff, AIDS Research Program, Mary Ellen Michel, Center for Clinical Trials Network and Dr. Steve Gust and Dale Weiss, International Program. The discussion centered on drug abuse research and addiction treatment.

The United States Department of State's International Visitor Leadership Program sponsored a visit to NIDA by six central and regional officers from the Juvenile Rehabilitation Centers in Mexico. The main interests of the group were to hear about research dealing with alternatives for at risk youth, school based prevention programs and media campaigns for drug abuse prevention. While at NIDA the visitors met with Dr. Liz Ginexi, Dr. Liz Robertson, Dr. Augie Diana, and Dr. Eve Reider, DESPR, Dr. Cindy Miner, OSPC and Dale Weiss, International Program.

Dr. Timothy P. Condon, NIDA Deputy Director, presented "National Institute on Drug Abuse Progress, Priorities & Plans for the Future" on November 29, 2007, in Amsterdam, Netherlands.

Dr. David Shurtleff, Director, DBNBR, gave a presentation entitled "An Overview of and Future Directions for NIDA's Basic Science Research Program" at United States-Netherlands Bi-National Addiction Workshop. "Amsterdam, Netherlands on November 29, 2007.

Dr. Wilson M. Compton, M.D., M.P.E., Director, DESPR, participated in the World Health Organization/American Psychiatric Association Joint ICD-DSM workgroup to harmonize revisions to the classification of mental disorders meeting as well as the WHO/APIRE Conference on Public Health Aspects of Diagnosis and Classification of Mental Disorders, 26-28 September 2007, Geneva, Switzerland.

Dr. Wilson M. Compton, M.D., M.P.E. participated in the WHO international meeting on addiction, AIDS and hepatitis, Biarritz, France (October 23-25, 2007), where he Chaired a panel on Drug Abuse Prevention and presented a paper called: "Drug Abuse and Prevention: Preventable Brain Diseases".

On December 6th and 7th, 2007, Dr. Elizabeth Robertson, DESPR, provided consultation to members of the European Monitoring Centre on Drugs and Drug Addiction on the development of the next iteration of the EU-DAP (European Union - Drug Abuse Prevention). EU-DAP was implemented in six European Union countries, the second iteration of the program will be targeted to high risk groups and individuals and will be implemented in eight countries. Representatives of the UNODC (United Nations Office of Drug Control) were also present at the meeting and hope to implement the program in under-developed countries. The meeting was held in Vienna, Austria.

Dr. Eve Reider, Ph.D., represented DESPR at the 2007 U.S.-Netherlands Workshop on Bi-National Research Collaboration on Drug Abuse and Addiction, held November 29, 2007, at the Royal Tropical Institute, Amsterdam, Netherlands.

Dr. Elizabeth Robertson participated in the European Monitoring Centre for Drugs and Drug Addiction planning meeting for the 8 country replication of the European Drug Addiction Prevention Trial. The meeting was held on December 6 - 7, 2007 in Vienna, Austria.

On October 10, 2007, Dr. Peter Hartsock met with representatives from Norway concerning Norwegian advances in reaching high-risk groups in order to research the epidemiology of drug abuse, HIV/AIDS and related problems and interventions using this epidemiology to improve and evaluate their impact. Plans were discussed for joint U.S.-Norwegian research efforts.

Drs. Frank Vocci and Jag Khalsa, DPMCDA, attended and spoke at the SAA clinic's 30th anniversary celebration in Reyjkavik, Iceland on October 1-2, 2007. Dr. Vocci spoke on Addiction as a Brain Disease and Cognitive Deficits in Stimulant Users. Dr. Jag Khalsa gave a talk on Medical Consequences of Drug Abuse and Infections.

Dr. Frank Vocci attended the European College of NeuroPsychopharmacology

meeting in Vienna, Austria from October 13-17, 2007. Dr. Vocci presented in the Efficacy of Disulfiram and Modafinil for the Treatment of Cocaine Dependence.

Drs. Frank Vocci and Jag Khalsa attended and spoke at the FederSerD meeting in Sorrento Italy from October 28-31, 2007. Dr. Vocci spoke on Cognitive Deficits in Stimulant Abusers: Types and Possible Modulation. Dr. Vocci also attended the presentation by Dr. Giorgio Barbarino of the book: Management of Medical Disorders Associated with Drug Abuse and Addiction. Drs. Khalsa and Vocci have a chapter in the book and Dr. Vocci wrote a preface for the book. Dr. Jag Khalsa participated as the invited guest and delivered a talk on 'Management of Dually (HIV/HCV) Infected Drug Addicts'.

Drs. Frank Vocci and Ahmed Elkashef attended the World Psychiatric Association meeting in Melbourne Australia from November 28- December 1, 2007.

Dr. Vocci presented on the US Experience with Buprenorphine for the Treatment of Opiate Dependence and on the Emerging Targets for Stimulant Dependence in a symposium that he and Dr. Ahmed Elkashef co-chaired on Pharmacotherapies for Methamphetamine Dependence.

On September 12-14, 2007, Ivan Montoya gave a seminar in San Jose, Costa Rica about treatment of cocaine and opioid addiction, and drug abuse treatment evaluation.

Drs. Frank Vocci, Ivan Montoya, Ahmed Elkashef and Jag Khalsa participated in the International Society of Addiction Medicine meeting in Cairo, Egypt on October 22-25, 2007. Dr. Vocci spoke on Emerging Targets for the Treatment of Stimulant Dependence and Cigarette Smoking-A Worldwide Pandemic. Dr. Jag Khalsa presented a symposium on: Why Should Addictionologists Care about Infections in Drug Addicts? Dr. Elkashef chaired a symposium on pharmacotherapies for addictions and participated in the nicotine symposium and presented on medications for smoking cessation. Dr. Monotya presented two presentations: 1) Immunotherapies of Drug Addiction and 2) Nicotine Vaccines to Help Smokers Quit. They also participated in a post-conference workshop about drug abuse research opportunities in NIDA that took place in Sharm-el-Sheikh, Egypt on October 26th, 2007.

Dr. Ivan Montoya was a guest speaker at the International Conference on Cocaine Addiction organized by the Ministry of Health of Spain, in Madrid, Spain, on November 15-16, 2007.

Dr. Ivan Montoya participated in Drug Abuse Treatment Workshop organized by the World Health Organization and the Government of Valencia, Spain, in Valencia, Spain, on November 19-23, 2007.

Dr. Ivan Montoya participated in the U.S.-Netherlands Bi-national Collaboration meeting that took place in Amsterdam, on November 28-29, 2007.

Dr. Jag Khalsa participated and co-chaired a session on drug-drug interactions at the OAR/NIH IC-and India-sponsored meeting in New Delhi, India, September 24-27, 2007.

Director's Report to the National Advisory Council on Drug Abuse - February, 2008

Meetings/Conferences

The National Institute on Drug Abuse (NIDA) convened an ad hoc meeting of the **Blending Initiative Task Force** on October 22-23, 2007, in Reno, Nevada. The Task Force was chaired by NIDA's Deputy Director, Dr. Timothy Condon and was coordinated by Dr. Denise Pintello, Special Assistant to the Deputy Director. Task Force members composed of NIDA researchers, SAMHSA's Addiction Technology Transfer Center (ATTC) Directors and Community Treatment Providers (CTP) reviewed content and criteria to include in the future development of a guide to *Selecting, Evaluating, and Utilizing Evidence-Based Practices*.

On November 7, 2007, NIDA's Director, Dr. Nora Volkow and Deputy Director, Dr. Timothy Condon convened the **Medications Development Scientific Workgroup** in Bethesda, Maryland. This meeting was organized and coordinated by Dr. Denise Pintello, Special Assistant to the Deputy Director. The focus of this meeting was to elicit the Workgroup's scientific expertise on NIDA's research portfolio for clinical trials within the Division of Pharmacotherapies and Medical Consequences of Drug Abuse (DPMCDA). Dr. Frank Vocci, DPMCDA Director, presented data to Drs. Volkow and Condon, the Chair, Dr. Peter Kalivas, and to the Work Group members.

Drs. Lisa Onken, Steve Grant, Nicolette Borek, Cecelia Spitznas and Melissa Riddle, from NIDA's Division of Clinical Neuroscience and Behavioral Research, with Dr. Elizabeth Ginexi from NIDA's Division of Epidemiology, Services, and Prevention Research organized a meeting, **"Social Neuroscience: Developing More Powerful Behavioral Interventions."** The meeting was held October 1 & 2, 2007 in Bethesda, Maryland. The goal of this meeting was to discuss current research and emerging issues in social neuroscience, and to identify the potential for translating social neuroscience knowledge into research on developing and/or improving behavioral treatment interventions and/or prevention interventions.

An NIH conference on **Building the Science of Dissemination and Implementation in the Service of Public Health** was held on September 10, 2007. Dennis McCarty (Oregon/Hawaii Node PI) was an invited speaker for the plenary session titled "From Research to Policy." His presentation focused on the CTN and the Blending Initiatives as strategies for promoting linkages between policy, practice and research. Conference attendees included Jeff Selzer (Long Island Node and Research Utilization Committee), Harold Perl (CCTN), and ATTC Directors (Paula Horvatich and Nancy Roget). Sue Storti represented the Blending Initiative. The NIH Office of Behavioral and Social Sciences Research sponsored the meeting with support from NCI, NIAAA, NICHD, NIDA and NIMH.

A workshop co-sponsored by NIDA and NIAAA on **Answering Questions That Change Practice: The Role of Practical Clinical Trials (PCTs)** was held

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October 1-2, 2007. The workshop was chaired by Dr. Betty Tai from NIDA and Dr. Howard Moss from NIAAA. Goals of this meeting were to outline the design parameters of clinical trials that will directly inform decision making in the practice of substance abuse treatment. Large scale trials sponsored by NIAAA, NIDA and NIMH were reviewed. Case studies were also presented by practitioners to illustrate their challenge of decision making in the course of treatment of drug and alcohol addicted patients. Issues of how to identify research questions that once answered would change practice and special considerations and challenges in study design and practical implementation, were also addressed. A white paper is planned to provide "points to consider" to future investigators to pursue research aimed at translating research to practice.

Dr. Harold Gordon of DCNBR organized and chaired a MiniSymposium entitled **Understanding the Neurobiology of Drug Addiction by Studying Sleep Disturbances and Circadian Rhythms** at the Annual Meeting of the Society for Neuroscience, San Diego, November 5, 2007. The meeting was sponsored, in part, by the Office of Science Policy and Communications (OSPC) and by the Society for Neuroscience. The purpose was to demonstrate the interrelatedness of sleep, sleep disturbances, and circadian rhythms with neurological diseases including drug addiction.

On November 1, 2007, a Consultant Meeting for NIDA contract N01DA-4-8849, **Animal Models of Methamphetamine-Induced Cognitive Impairment** was held in San Diego. CA. Mr. Hirsch Davis (DPMC) chaired the meeting, with Drs. Dave McCann and Jane Acri in attendance for NIDA. Drs. John Marshall and Steve O'Dell with their laboratory staff were in attendance for the University of California at Irvine. The consultants were: Drs. Verity Brown, Rex Denton, Paul Fletcher, Mary Jeanne Kallman, and Barry Setlow. The purpose of the meeting was to evaluate the progress made in the development of an animal model to screen compounds for potential efficacy in the treatment of cognitive deficits produced by methamphetamine. John Marshall presented a summary of his work under the contract, emphasizing his work on an object recognition model to test effects of methamphetamine on memory, and his recent work on an attentional set-shift model. Hirsch Davis presented compounds of interest for initial study once a model is ready for use. Consultant reports will be completed in January, after receipt of data from experiments still in progress at the time of the meeting.

The Special Populations Office, OD, NIDA convened a two-day **Special Populations Research Development Seminar** on October 25-27, 2007, in Bethesda, MD. The seminar brought back new investigators, who attended an initial two-day workshop, to present draft research applications for review and discussion in a "mock review" session chaired by NIDA staff. In addition, participants met with NIDA-funded investigators and senior NIDA program staff to discuss research opportunities at NIH.

The Special Populations Office, OD, NIDA and the Substance Abuse Mental Health Services Administration (SAMHSA) hosted the **Substance Abuse, Criminal Justice, and HIV in African Americans: Technical Assistance Workshop** on October 15-16, 2007 in Silver Spring, MD. The workshop convened NIDA/SAMHSA staff and NIDA grantees to serve as speakers and mentors to early/new investigators who plan to prepare grant applications for NIDA program announcements related to substance abuse, criminal justice and HIV/AIDS.

The Special Populations Office, OD, NIDA, convened a meeting of **NIDA's Minority/Ethnic Researchers and Scholars Workgroups** on October 31 - November 1, 2007 at the Bethesda Marriott Conference Center in Bethesda, MD. The meeting was centered on discussion and plans for future activities geared towards increasing the number of underrepresented minorities and women in substance abuse research and training these respective populations.

During the meeting, Dr. Nora Volkow provided an overview of NIDA's mission and research priorities and NIDA's Division Directors discussed their particular division's priorities.

The first NIDA sponsored **Drug Facts Chat Day** was held on October 12, 2007. Some 40 program experts and science writers representing offices and divisions across NIDA responded to 600 questions from students in high schools nationwide. More than 35,000 questions came from 49 states, the District of Columbia, Puerto Rico, the Virgin Islands and Guam, extending NIDA's reach to a key audience with science-based messages about drug abuse and addiction.

The **National CTN Steering Committee Meetings** were held September 23-28, 2007 in Bethesda, MD. The following meetings/committees convened:

- CTP and PI Caucuses
- Members of the Study Teams: Seeking Safety (CTN 0015), START (CTN 0027) and STAGE-12 (CTN 0031)
- Special Interest Groups: Health Services Research and Pharmacotherapy
- Executive Committee
- Research Utilization Committee
- Research Development Committee
- Node Coordinator Workgroup
- Steering Committee, including Preliminary Study Reports
- SBIRT Panel (Screening, Brief Intervention and Referral to Treatment)
- Two workshops: "Approaches to Quantifying Addiction" (Sept. 24), and "Safety Monitoring Workgroup" (Sept. 26).
- DCRI Data & Statistics Center (DSC) Demos: The DSC and CTN Working Together

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Dr. Timothy P. Condon, Deputy Director, NIDA, presented "It's a Brain Disease: The Neuroscience of Addiction" at the Florida Alcohol and Drug Abuse Association Conference, Putting a Face on Addiction & Recovery New Knowledge, New Hope, on August 22, 2007, in Orlando, Florida.

Dr. Timothy P. Condon presented "National Institute on Drug Abuse: Progress, Priorities & Plans for the Future" at the American Psychiatric Association 2007 Academic Consortium on September 6, 2007, in Washington, D.C.

Dr. Timothy P. Condon addressed the American Psychiatric Association Council on Addiction Psychiatry on September 7, 2007, in Washington, D.C.

Dr. Timothy P. Condon addressed the NIDA Methamphetamine Abuse in American Indian and Alaska Native Populations meeting on September 20, 2007, in Washington, D.C.

Dr. Timothy P. Condon presented "It's a Brain Disease: Beyond a Reasonable Doubt - The Neuroscience of Addiction" at the New England Association of Drug Court Professionals on September 21, 2007, in Boston, Massachusetts.

Dr. Timothy P. Condon presented "NIDA Progress, Priorities & Plans for the Future" at the NIDA Clinical Trials Network National Steering Committee Meeting on September 25, 2007, in Bethesda, Maryland.

Dr. Timothy P. Condon presented "Research on Drug Abuse and Addiction: What Have We Learned?" at the National Hispanic Science Network 7th Annual Conference on September 27, 2007, in Miami Beach, Florida.

Dr. Timothy P. Condon briefed and gave a presentation on Methamphetamine

to U.S. Representative Steve Pearce (R - N.M.) on September 28, 2007, in Bethesda, Maryland.

Dr. Timothy P. Condon presented "Advances in Drug Abuse and Addiction from NIDA" and "Using the Science of Addiction to Improve Treatment with the Criminal Justice System" at the Illinois Alcoholism and Drug Dependence Association on October 2, 2007, in Oak Brook, Illinois.

Dr. Timothy P. Condon presented "Using the Science of Addiction to Improve Treatment Outcomes" at the 14th National TASC Conference on Drugs and Crime on October 16, 2007, in Westminster, Colorado.

Dr. Timothy P. Condon presented a "Research Update: What Have We Learned?" at the California Society of Addiction Medicine, Addiction Medicine State of the Art 2007 Conference on October 18, 2007, in Los Angeles, California.

Dr. Timothy P. Condon presented "Our Evolving Understanding of Addiction" at the American Society of Addiction Medicine State of the Art Course on October 25, 2007, in Washington, D.C.

Dr. Timothy P. Condon addressed the ATTC Network Directors Meeting on December 5, 2007, in Silver Spring, Maryland.

Dr. Cindy Miner, Deputy Director, OSPC chaired a Grantwriting Workshop at the American Academy of Child & Adolescent Psychiatry (AACAP) 54th Annual Meeting on October 26, 2007, in Boston, Massachusetts.

Dr. Gayathri J. Dowling, Deputy Chief, Science Policy Branch, OSPC, NIDA, gave a presentation entitled "The Science of Addiction" at the National Alliance for Drug Endangered Children Annual Conference on October 10, 2007, in Kansas City, Missouri.

Dr. Lula Beatty, Chief, Special Populations Office, developed a symposium entitled "African Americans, Drugs and Criminalization: Informing Research to Improve Interventions" that was presented at the convention of the American Psychological Association in San Francisco, CA in August 2007.

Dr. Lula Beatty served as a reviewer for the 2008 Head Start conference.

Dr. Lula Beatty participated in the meeting of the Committee on Women in Psychology of the American Psychological Association in Washington, DC in September 2007.

Dr. Lula Beatty has been serving as NIDA's representative on the NIH Health Disparities Roadmap Committee.

Dr. Lula Beatty presented an overview of NIDA's involvement in HIV/AIDS research at the National African American Advisory Committee meeting of the National Association of State Alcohol and Drug Abuse Directors (NASADAD) in Washington, DC in October 2007.

Dr. Lula Beatty has been serving as NIDA's representative to the NCMHD Forum Planning Committee, a group to plan a 2008 conference on NIH health disparities research and programs.

Dr. Lula Beatty attended the National Leadership Workshop on Mentoring Women in Biomedical Careers sponsored by NIH's Office of Research on Women's Health in November 2007.

Ana Anders, Public Health Analyst, SPO, participated in the National Hispanic Science Network annual conference held in Miami Beach, FL on September 26-28, 2007.

Ana Anders, as a representative of NIDA, participated in the Latino Behavioral Health Institute annual conference in Los Angeles, CA on October 2-4, 2007.

Ana Anders, as 2007 president of the NIH Hispanic Employee Organization, along with the HEODC, chaired the committee that planned the observance of the Hispanic Heritage Month on October 11, where Dr. Nora Volkow was the keynote speaker.

Ana Anders is a member of the Virtual Program for Career Development and Capacity Building for Latin American and Caribbean Women Scientists workgroup, comprised of other NIH Institutes (NIDA has the lead through the NHSN), the WHO, PAHO, UNESCO, and FLACSO from Argentina.

Ana Anders gave a presentation on drug abuse prevention to an association of journalists, young scientists and the "drug czar" at the University of Cardenal Herrera on November 7- 8, 2007 in Valencia, Spain.

Ana Anders was a member of the NIH Diversity Council planning committee, which presented the NIH Art and Science Diversity Expo. on December 5, 2007.

The Addiction Health Services Research Conference (AHSR) was held October 15-17, 2007 in Athens, GA. Dr. Joseph Guydish, CCTN, organized a symposium, entitled Health Services Research in the NIDA Clinical Trials Network: Past, Present and Future, featuring presentations by 3 CTN members, Dr. Lawrence Brown, Dr. Jody Sindelar, and Dr. Jeff Selzer. Dr Harold Perl presented a talk entitled, Integrating Services Research into CTN Clinical Trials: The Synergy is in the Details.

Dr. Harold Perl, CCTN, taught three plenary sessions at the NIH Seminar on Program Funding and Grants Administration hosted by the City University of New York in New York, NY October 19, 2007.

The annual meeting of the American Association for the Treatment of Opioid Dependence (AATOD) was held October 20-24, 2007 in San Diego, CA. Dr. Betty Tai, Director, CCTN, on behalf of Dr. Nora Volkow, presented NIDA's keynote address on "Drug Abuse and Addiction Research." Dr. Tai chaired the National Panel and Dr. Steven Gust chaired the International Panel of the CTN workshop "Reducing HIV in Drug User Population." Dr. Petra Jacobs chaired the CTN pre-conference, and all day workshop titled "Buprenorphine Treatment - Emerging Research Findings, Clinical Practice and Reimbursement."

Dr. Harold Perl represented NIH at the workshop entitled "Working with Federal Agencies" hosted by the Association of American Universities on November 6, 2007 in Washington, DC.

On November 29, 2007, Dr. Betty Tai served as guest lecturer at VCU medical school, and presented the course titled, "Contemporary Issues in Addiction Research." The lecture was on Connecting Research with Practice in the addiction field.

Carmen Rosa, CCTN, organized a symposium titled, "Behavioral Trials: Understanding the Safety Risks" at the Public Responsibility in Medicine and Research (PRIM&R) 2007 Annual HRPP Conference, held December 1-4 2007 in Boston, MA. Faculty included: Kathleen Carroll, Ph.D. (Yale University); Robert Lindblad, M.D. (EMMES Corporation); Felix Gyi, Ph.D. (Chesapeake Research Review, Inc.); and Peter G. Kaufmann, Ph.D. (NHLBI).

Dr. Joe Frascella, Director, DCNBR, participated in a national conference on obesity entitled: "Beyond Individual Behavior: Multidimensional Research in Obesity Linking Biology to Society". This meeting was sponsored by the NIH, the Canadian Institutes of Health, the CDCP, and the McGill Health Challenge Think Tank. Dr. Frascella gave a presentation on factors relating addiction to

obesity within a panel on biological drivers, epigenetics, and neuroscience. This meeting was held in Arlington, VA on October 10-12, 2007.

On September 26-29, 2007 Dr. Ivan Montoya, DPMCDA, participated in the National Hispanic Science Network Meeting in Miami, FL.

Dr. Jag Khalsa, DPMCDA, participated in the Annual Meeting of the Prevention of Tobacco-Related Diseases, led by NIDA Council member, Dr. Warren Bickel, Little Rock, Arkansas, November 2-5, 2007. The meeting was co-funded by NIDA and NCI via an R13 Conference grant mechanism.

Dr. Frank Vocci, Director, DPMCDA, attended the ACNP meeting in Boca Raton, FL from December 10-13, 2007. Dr. Vocci chaired a study panel on efficacy endpoints for clinical trials in addiction. Dr. Vocci also presented on Reduction of Drug or Alcohol Use as an Efficacy Endpoint.

Dr. Wilson M. Compton, M.D., M.P.E., Director, DESPR, participated in a one day meeting convened by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) to develop plans for policy-related research using the NIAAA alcohol policy database, October 18, 2007.

In December 2007, Dr. Wilson M. Compton, M.D., M.P.E. participated in the meeting of the Substance Disorders Workgroup of the DSM-V Taskforce.

In December 2007, Dr. Wilson Compton presented and co-chaired a panel on methamphetamine abuse at the American Academy of Addiction Psychiatry (AAAP), San Diego, California.

In December 2007, Dr. Wilson Compton participated in a study group at the American College of Neuropsychopharmacology (ACNP), Boca Raton, Florida. Dr. Redonna Chandler, DESPR served as discussant on the panel "Unlocking the Mysteries of Implementation Science" presented at the Addiction Health Services Research Conference, Athens, GA, October15-17, 2007.

Dr. Redonna Chandler, DESPR, participated in a panel titled, "Health Services Research in the NIDA Clinical Trials Network: Past, Present and Future" presented at the Addiction Health Services Research Conference, Athens, GA, October 15-17, 2007.

Dr. Elizabeth Robertson, DESPR, served in an advisory capacity at the Collaborative for Academic and Social Emotional Learning at the Garrison Institute, in Garrison, NY, on October 15 through 18, 2007.

Dr. Elizabeth Robertson was a workgroup leader and moderator at The 23rd Annual Rosalynn Carter Symposium on Mental Health Policy on November 7 and 8, 2007. The title of the meeting was 'The Time is Now: Creating a Public Policy Action Agenda on Preventing Mental Illness'.

Drs. Eve Reider and Belinda Sims, DESPR, co-chaired a symposium "Is Early Prevention Intervention Later AIDS Prevention?" at the 115th Annual Convention of the American Psychological Association meeting in San Francisco, CA on August 20, 2007. The panel of presenters included, Drs. David Olds, Prevention Research Center for Family and Child Health, Denver, Colorado, Kenneth Griffin, Weill Medical College of Cornell University, and Karl Hill, University of Washington. Dr. Deborah Capaldi, Oregon Social Learning Center, was the discussant.

Dr. Aria Crump, DESPR, served as a mentor for the NIDA Special Populations Office's Substance Abuse, Criminal Justice, and HIV in African Americans Technical Assistance Workshop held in Silver Spring MD on October 15-16, 2007.

Dr. Aria Crump participated as a mentor in the NIDA Special Populations Office's Research Development Seminar Series meeting that took place on

October 25-26 in Bethesda, Maryland.

Drs. Belinda Sims, Elizabeth Robertson, Eve Reider, and Aria Crump collaborated with staff from NICHD, NIMH, the NIH Office of Behavioral and Social Sciences Research, the Administration for Children and Families, and the Substance Abuse and Mental Health Services Administration to hold a meeting entitled "Intervening Early: Progress and Opportunities in Child Service Settings" on September 18-19, 2007 in Gaithersburg, MD.

Dr. Jessica Chambers, DESPR, chaired a scientific symposium on family violence and drug use trajectories at the recent American Psychological Association meeting held August 20, 2007, in San Francisco, CA.

Drs. Wilson Compton, DESPR, Timothy Condon, Deputy Director, NIDA and Lula Beatty, Director, SPO, participated in a meeting titled Methamphetamine Abuse in American Indian and Alaska Native Populations which was held on September 20-21 in Washington DC. Meeting participants presented the state of the research and discussed future research needs. The meeting was chaired by Dr. Kathy Etz.

Dr. Peter Hartsock, DESPR, participated in a meeting with UNAIDS Secretary General Peter Piot and USAID Office of Global Health Director Kent Hill dealing with PEPFAR, HIV vaccine development, and other forms of AIDS prevention, and related epidemiologic research at the Woodrow Wilson International Center for Scholars held September 20, 2007 in Washington, D.C. Dr. Hartsock presented on NIDA's AIDS modeling program, special work it has done in Russia, its application to vaccine development--both with identifying and accessing high-risk populations such as drug users and speeding up assessment of impact of vaccines, and assessment of other interventions.

Elizabeth Lambert, M.Sc., of DESPR's Epidemiology Research Branch, participated as mentor to workshop participants at NIDA's Substance Abuse, Criminal Justice, and HIV in African Americans Technical Assistance Workshop on October 15-16, 2007 in Silver Spring, MD.

Elizabeth Lambert, M.Sc. with Richard Jenkins, Ph.D., of DESPR's Prevention Research Branch, organized a meeting for NIDA on November 8, 2007 to review the findings and implications of NIDA's Sexual Acquisition and Transmission of HIV Cooperative Agreement Program.

Elizabeth Lambert, M.Sc. served as a faculty mentor and reviewer at NIDA's Research Development Seminar Series Workshop, October 25, 2007 in Bethesda, MD.

Dr. Lula Beatty, SPO/OD and Dr. Tom Brady, DESPR participated in a workshop "Filling the Gap: Meeting Client's Needs" at a SAMHSA conference Women's Alliance to Strengthen Treatment Access and Recovery September 17-18 2007 in Lake Tahoe, NV. Dr. Beatty presented "Health Disparities: What it Means for Women of Color in Drug Abuse Treatment" and Dr. Brady presented "Special Services for Women in Substance Abuse Treatment."

At the annual meeting of the American Public Health Association, Dr. Tom Brady was a co-author on a paper "Impact of Screening and Brief Intervention Grants in Seven States: Substance Use, Criminal Justice, and Education/Employment Outcomes at 6-month Follow-up." Dr. Brady also presented two other papers: "Providing Training in Screening & Brief Intervention for Trauma Care Providers: Lessons Learned" for the APHA Health Promotion and Injury Control section and "A Website Promoting Early Detection and Screening Practice for the Alcohol, Tobacco and Other Drugs section.

Dr. Tom Hilton, DESPR, presented a symposium at the annual Addiction Health Services Research Conference on October 17th, 2007 in Athens Georgia entitled: Unlocking the Mysteries of Implementation Science.

Dr. Dionne Jones, DESPR, reviewed grant applications submitted by junior investigators and participated in a Mock Review session organized by the Special Populations Office on October 25-26, 2007.

Dr. Dionne Jones provided technical assistance and mentoring to junior investigators at a NIDA Research Seminar sponsored by the Special Populations Office on October 15-16, 2007.

Dr. Joe Frascella attended the Society for Neuroscience Annual meeting as well as the NIDA MiniConvention satellite meeting in San Diego, CA, November 1-6, 2007.

Dr. Joe Frascella, along with Drs. Larry Stanford, Vince Smeriglio, Steve Grant, and Bryan Fantie attended the workshop on "Adolescent Susceptibility to Substance Abuse" at The National Academies Keck Center, Washington, DC, November 12, 2007.

Dr. Joe Frascella visited Vanderbilt University and gave two invited talks entitled: "A Roadmap to NIH's Research Teams of the Future" and "A Blueprint for the NIH Grant Process" in Nashville, TN, November 13-14, 2007.

Dr. Steven Grant and Dr. Woody Lin represented NIDA at the Annual Meeting of the Society of Neuroeconomics in Hull, Mass, September 27 - 30, 2007.

Dr. Steven Grant represented NIDA at the Annual Meeting of the American College of Neuropsychopharmacology in Boca Raton, FL, December 8-13, 2007.

Drs. James Bjork, Hal Gordon, Steven Grant, Mary Kautz and Woody Lin represented NIDA at the Annual Meeting of the Society for Neuroscience in San Diego, California, November 2-7, 2007.

Dr. Paul Schnur and Dr. David Shurtleff, Director, DBNBR, organized a symposium on Adaptation to Rapidly Changing Environments presented at the National Hispanic Science Network annual meeting in Miami, September 26, 2007.

Dr. Roger Sorensen, DBNBR, was the keynote speaker at the University of Pennsylvania Health System faculty development workshop on "The Art and Science of Obtaining Research Funding" held on November 28, 2008. His presentation was titled "Grant Writing for Success".

Dr. Lisa Onken, DCNBR, gave a presentation on NIH & NIDA Initiatives on Technology to Facilitate Research on Behavior Change as part of a Federal Policy Panel at the International Conference on Urban Health on November 2, 2007 in Baltimore, MD.

Dr. Lisa Onken co-led a grant-writing workshop at the annual Association for Behavioral & Cognitive Therapies meeting on November 16, 2007 in Philadelphia, PA.

Dr. Nicolette Borek, DCNBR, presented talks on NIDA research funding opportunities at the Research Seminar for Early Investigators and the Grant Writing Workshop and Mock IRG panel sessions at the 54th annual meeting of the American Academy of Child & Adolescent Psychiatry, October 24-28, 2007 in Boston. Dr. Borek also chaired a session on Adolescent Cognition, Behavior, and Brain Development: Relationships to Prenatal Substance Exposure.

On October 27, 2007, Dr. Karen Sirocco, DCNBR, chaired the symposium entitled: The Neurobiology of Risky Decision-Making in Adolescents at the annual conference of the American Academy of Child and Adolescent Psychiatry in Boston, MA.

Debbie Grossman, DCNBR, and Dr. Cora Lee Wetherington, DBNBR,

participated in a meeting with representatives from other government agencies, which focused on the problem of smoking among young adult, low income women: "Tobacco and Young, Low SES Women: Federal Collaboration to Make a Difference".

Dr. Cora Lee Wetherington, DBNBR, chaired and co-organized (with Dr. Allison Chausmer) the symposium, "A Translational Approach to Nicotine, Smoking and Weight," at the National Conference on Tobacco or Health, October 23-26, 2007, in Minneapolis, MN. Speakers included Drs. Andrea King (University of Chicago), Michele Levine (University of Pittsburgh), Amy Copeland (Louisiana State University), and Bonnie Spring (Northwestern University).

Dr. Cora Lee Wetherington chaired the symposium, "New Advances in the Science of Tobacco Addiction," at the National Conference on Tobacco or Health, October 23-26, 2007, in Minneapolis, MN. Speakers included Drs. Tom Kosten (Baylor College of Medicine), Doug Jorenby (University of Wisconsin), Laura Beirut (Washington University School of Medicine), and Jon-Kar Zubieta (University of Michigan). The symposium was organized by Dr. Allison Chausmer.

Dr. Cora Lee Wetherington chaired the session, "Studies Addressing Sex Differences," at the ORWH (Office of Research on Women's Health) Fourth Annual Interdisciplinary Women's Health Research Symposium, in the NIH Mazur Auditorium, November 15, 2007. Two of the speakers were drug abuse researchers and NIDA investigators: Drs. Kathleen Brady (Medical University of South Carolina) and Marc Potenza (Yale University School of Medicine).

Dr. Cora Lee Wetherington gave a grand round, "The Pervasiveness of Sex/Gender Differences in Drug Abuse," at the Yale University School of Medicine, January 15, 2008.

Dr. Allison Chausmer, DBNBR, organized and co-chaired the workshop "Current Issues in Cigarette Smoking in HIV/AIDS" at the NIH Natcher Conference Center, October 9, 2007 in Bethesda, MD. This invitation-only workshop highlighted understudied issues related to cigarette smoking in HIV-infected persons, including 1) Smoking, progression to AIDS-related neurological complications and host defense against opportunistic infections, 2) Interactions between smoking and pharmacotherapy for people with HIV/AIDS, 3) Smoking cessation strategies: special needs for treatment of HIV-infected populations; Co-morbid populations and special etiologies, and 4) Global Implications of Tobacco Use and HIV/AIDS. This workshop was co-organized and co-chaired by Diane Lawrence (NIDA), Cathy Backinger (NCI), Michele Bloch (NCI), Gerald Sharp (NIAID), Xingzhu Liu (FIC), and Francisco Sy (NCMHD).

Dr. Susan Volman, DBNBR, organized and chaired a symposium on "Neuroadaptations and Counteradaptations" at the NIDA "Frontiers in Addiction Research" mini-convention in San Diego, CA on November 2, 2007.

Drs. David Shurtleff, DBNBR, and Sergi Ferre, IRP, organized and co-chaired a symposium on "Heterodimerization of G-Protein-Coupled Receptors: Implications for CNS Function and Dysfunction" at the NIDA "Frontiers in Addiction Research" mini-convention in San Diego, CA on November 2, 2007.

Dr. David Shurtleff gave a presentation on "Behavioral and Social Science at the National Institute on Drug Abuse" to the Federation of Behavioral, Psychological, and Cognitive Sciences, Washington DC on December 3, 2007.

Dr. Susan Volman, DBNBR, organized the Early Career Investigators Poster Session for the NIDA "Frontiers in Addiction Research" mini-convention in San Diego, CA on November 2, 2007.

Dr. Susan Volman, DBNBR, co-chaired a symposium on "Reconciling Molecular and Electrophysiological Evidence of Cocaine-Induced Neural Plasticity" at the

Society for Neuroscience annual meeting in San Diego, CA on November 5, 2007.

Dr. Christine Colvis, DBNBR, attended the NHLBI Proteomics Investigators Meeting Sept 19, 2007, Washington DC.

Dr. John Satterlee, DBNBR, attended the Diet, Epigenetics, and Cancer Prevention Symposium, Gaithersburg, MD, September 26 -27, 2007.

Dr. Christine Colvis organized the workshop, "In Search of Signatures of Chronic Drug Use," Bethesda, MD, September 5, 2007.

On October 5, 2007, Dr. Da-Yu Wu hosted the Workshop on Live Gene Detection in Non-Human Primate Brains for Development and Addiction, sponsored by DBNBR/NIDA and co-sponsored by NIAAA and NIBIB. The goal of the workshop is to identify the possibility, evaluate innovative approaches, and provide recommendation to NIH on how to most effectively promote breakthroughs in research for non-invasive, three-dimensional live detection of gene expression in primate brains.

Dr. Jonathan D. Pollock, DBNBR, gave a talk, entitled, "The Genetics of Substance Abuse" at teaching day on October 7, 2007 at the XV annual meeting of the World Congress on Psychiatric Genetics in New York City.

Dr. Joni Rutter, DBNBR, co-chaired a session with Dr. Jonathan D. Pollock, entitled, "Functional Characterization of Genes/Variants Involved in Nicotine Dependence" at the XV annual meeting of the World Congress on Psychiatric Genetics in New York City on October 9, 2007.

Dr. Jonathan D. Pollock attended the Steering Committee Meeting for the Knockout Mouse Project in Tarrytown, NY on October 10, 2007.

Dr. Christine Colvis presented a report on the Pilot Scale Libraries program to the Molecular Libraries Steering Committee, October 21-23, 2007, Atlanta, GA.

Dr. Jonathan D. Pollock with Dr. John Satterlee organized the symposium, "Complex Human Disease Genes: Help from Animal Models" held at the American Society for Human Genetics Annual meeting in San Diego, CA on October 25, 2007.

Drs. Da-Yu Wu, Diane Lawrence and Dave Thomas, DBNBR, co-chaired the NIDA Mini-Convention Symposium: "Glial Cells and Addiction," held on November 2, 2007.

Drs. John Satterlee and Christine Colvis attended the Short Course: Inhibitory RNAs in Neuroscience, San Diego, CA, November 2, 2007.

Drs. John Satterlee and Da-Yu Wu co-chaired the Society for Neuroscience Mini-symposium: "Non-Coding RNAs in the Brain", which was chaired by DBNBR staff on November 5, 2007.

Dr. Christine Colvis served as a reviewer of supplement requests to US Japan Brain Research Collaborative Program and attended a review meeting on November 7, 2007, San Diego, CA.

Dr. Christine Colvis and Dr. John Satterlee attended the ENCODE Consortium meeting November 28-29, 2007, Rockville, MD.

Drs. John Satterlee and Christine Colvis (members of the GMNRB), and Dr. Joni Rutter are active participants in the NIH Roadmap initiative on epigenetics. Dr. Satterlee is the co-lead of the Roadmap Epigenomics Program with Brenda Weis from NIEHS. Dr. Satterlee is the lead for the Technology Development in Epigenetics RFA. He also coordinates efforts to generate new monoclonal antibody resources for epigenetics and to plan future Epigenomics Program

Workshops. Dr. Satterlee was the main organizer for the "Epigenetics of Human Health and Disease" Roadmap workshop in March. Dr. Rutter is the lead for the Epigenomics Data Analysis and Coordination Center RFA. Dr. Rutter was also involved in organizing the Roadmap Epigenetics Workshop in March. Dr. Colvis is the co-lead for the Reference Epigenome Mapping Centers RFA and was involved in organizing the Roadmap Epigenetics Workshop. On December 7, 2007 Drs. Satterlee, Colvis, and Rutter participated in a Technical Assistance Workshop at NIEHS, in Research Triangle, North Carolina, to answer questions about the six Roadmap Epigenomics RFAs that were just released Drs. Satterlee, Colvis, and Rutter meet as a group twice weekly with other members of the Roadmap Epigenomics Program team.

Dr. Jane Acri, DPMCDA, organized a meeting on the Computational Modeling and Systems Biology of Drug Abuse that was held on January 15, 2008. Twelve speakers discussed topics such as modeling of the addictive process, control theories, simulation models of drug use, decision making from a systems perspective, and neuro-computational and structural models of addiction.

Mr. Lyle Furr, OEA, participated in the 58th AALAS National Meeting on October 14-18, 2007 in Charlotte, NC.

Dr. Gerald McLaughlin, OEA, presented talks about eSubmission, the review process, and coordinated a mock review at the NIDA Special Populations Research Development Seminar Series and an associated Workshop that took place October 25-26, 2007.

Dr. Gerald McLaughlin, OEA, coordinated high school DC Area College Fairs in 2007 for the University of Iowa.

Dr. Gerald McLaughlin, OEA, co-arranged the January 9-11, 2008 NIH Symposium on Mitochondria as co-director of the NIH Mitochondria Interest Group.

Dr. Yavin Shaham, IRP, presented a talk entitled "Relapse to Food Seeking: Roles of CRF, Orexin and Peptide YY3-36" at the Concordia University's Fall Workshop on Food and Addiction on October 4-5, 2007 in Montreal, Canada.

Dr. Bruce Hope, IRP, was invited to present a talk entitled "Neurobiology of Context-specific Sensitization to Cocaine" at the Psychology Department of University of California at Santa Barbara, CA on November 1, 2007.

Dr. Bruce Hope was invited to present a talk entitled "Neurobiology of Context-specific Sensitization to Cocaine" in the NIDA Training Program seminar series at The University of Chicago in Chicago, IL on November 28, 2007.

Dr. Amy Newman, IRP, was an invited participant in the 2007 NIH Research Festival Chemistry Symposium entitled "From Beaker to Bedside." The title of her talk was "Dopamine D3 Receptor Antagonists as Potential Therapeutic Agents for Addiction." This symposium was highlighted in the November-December 2007 issue of the NIH Catalyst.

Dr. Noel Paul, IRP, was a 2007 FARE Travel award winner and presented a poster entitled "Tuning Selectivity on a Novel Bridged Framework for Dopamine D2/D3 Receptor Subtype Ligands" at the 2007 NIH Research Festival.

Dr. Jean Lud Cadet, IRP, gave a talk entitled "Cognitive Effects of Marijuana" at the NIH Academy located in Bethesda, Maryland on October 31, 2007.

Dr. Irina Krasnova, IRP, gave a talk entitled "Neurotoxic Doses of Methamphetamine Cause Cognitive Abnormalities in Mice" at the 37th annual meeting of the Society for Neuroscience held in San Diego, CA on November 3-7, 2007.

Dr. Michael McCoy, IRP, presented a poster entitled, "Serum Withdrawal-

induced Transcriptional Responses in Immortalized Rat Mesencephalic Cells", at the Society for Neuroscience conference held in San Diego, CA on November 3-7, 2007.

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Media and Education Activities

NIDA and NIAAA have been honored with the prestigious **Governors Award by the Academy of Television Arts and Sciences** for their contribution to HBO's *Addiction Project*. This is the first time that NIH institutes have received a primetime Emmy award. *"Addiction"* is a 14-part documentary television series and multimedia initiative revealing the science of addiction, its treatment, recovery, and its costs to families and society. A diverse group of people who were battling alcohol or drug addiction were featured, as well as addiction experts from around the country. The celebrated Governors Award is the Television Academy's highest honor and is given to individuals or organizations committed to important social causes. HBO developed the series, which includes the documentary, independent films, and a Website, in partnership with the National Institute on Drug Abuse, the National Institute on Alcohol Abuse and Alcoholism, and the Robert Wood Johnson Foundation.

NIDA has once again revised and reprinted our popular publication **The Brain: Understanding Neurobiology through the Study of Addiction**. This in depth standards-based curriculum focuses on the fundamentals of neurobiology, including how drugs of abuse change the brain and that drug addiction is a treatable, chronic brain disease. It is designed for teachers to use with high school students and includes 5 lessons that can be used for a weeks worth of lessons or spread out over several weeks. First developed in 2000, this is the third printing.

The first **Drug Facts Chat Day**, organized by a core group from the Public Information & Liaison Branch with the help of the Science Policy Branch (both in OSPC), took place on October 12, 2007. Some 40 program experts and science writers representing offices and divisions across NIDA responded to 600 questions from students in high schools nationwide. More than 35,000 questions came from 49 states, the District of Columbia, Puerto Rico, the Virgin Islands and Guam, extending NIDA's reach to a key audience with science-based messages about drug abuse and addiction. The transcript of answered questions is available at http://www.drugabuse.gov/chat/.

NIDA Director, Dr. Nora D. Volkow spoke to a group of high school students at **The High School for Math, Science and Engineering at City College** about the science of addiction. The dynamic informal discussion was held at the school with over 100 students and counselors. Dr. Volkow was able to hear their candid remarks and concerns and answer questions that ranged from substance abuse during pregnancy, to public policy. Dr. Carl Hart, Associate Professor and Neuroscientist from Columbia University moderated. For two hours, Dr. Volkow sustained a thoughtful, lively, and provocative exchange about drug abuse and brain imaging research.

Dr. Nora D. Volkow spoke at the *92nd Street Y's* **Science and Discovery Series** in New York City on November 19, 2007. This lecture series features

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engaging, candid and provocative discussions with the world's most dynamic and compelling leaders, newsmakers, and visionaries. Dr. Volkow discussed the science of addiction, as well as her innovative, new approaches to prevent and treat substance abuse.

Brian Marquis, OSPC, presented *"NIDA Goes Back to School"* a workshop at the National Middle School Association Annual Conference in Houston, TX on November 9, 2007. Session attendees learned about the campaign and its variety of K-12 science based educational materials about the consequences of drugs abuse on the brain and body. He promoted the new *Brain Power* series for Middle School children and other appropriate materials.

Dr. Vivian Faden, Deputy Director, Division of Epidemiology and Prevention Research (DEPR) at the National Institute on Alcohol Abuse and Alcoholism (NIAAA) presented the CCTN Classroom Series on November 8, 2007. Dr. Faden presented NIAAA's Underage Drinking Research Initiative and discussed the science underlying their thinking and approach to the initiative. She also talked about specific accomplishments of the initiative including their work on the *Surgeon General's Call to Action to Prevent and Reduce Underage Drinking*.

Dr. Bryce Reeve, Psychometrician and Program Director of the Outcomes Research Branch at NCI discussed the NIH roadmap initiative "PROMIS" - Patient-Reported Outcomes Measurement Information System. He presented: Item Banking & PROMIS: Advancing the Science of Patient-Reported Outcomes Assessment in Clinical Trials.

Press Releases

December 13, 2007 - **Early Fine-tuning of Neural Connections May Turn Destructive Later in Life**. The immune system helps to prune excess connections between neurons in the developing brains of young mice, according to scientists funded by the National Institute on Drug Abuse. The study, published in the December 14, 2007 issue of the journal *Cell*, sheds critical new light upon a fundamental process, while hinting at a likely mechanism behind neurodegenerative diseases like glaucoma and Alzheimer's disease.

December 11, 2007 - **NIDA Survey Shows a Decline in Smoking and Illicit Drug Use Among Eighth Graders**. The nation's eighth graders took center stage in the 2007 Monitoring the Future survey, showing a significant decline in both smoking and illicit drug use in the past year, part of a downward trend for all measured age groups in the last decade. In addition, eighth graders showed a substantial long-term decline in past-year alcohol use, down to 31.8 percent from its recent peak of 46.8 percent in 1994. The Monitoring the Future project--now in its 33rd year--is a series of independent surveys of 8th, 10th, and 12th graders conducted by researchers at the University of Michigan under a grant from the National Institute on Drug Abuse. Results from the 2007 survey were announced at a news conference at the White House.

November 27, 2007 - **NIDA Announces New Avant-Garde Award for Innovative AIDS Research**. The National Institute on Drug Abuse announced it is looking for scientists of exceptional creativity to apply for its new NIDA Avant-Garde Award for HIV/AIDS research. In a move to stimulate high-impact research into the link between drug abuse prevention and treatment and HIV/AIDS, NIDA will provide up to $500,000 per year for five years to two or three scientists of exceptional creativity who propose cutting edge - and possibly transformative - approaches to major challenges in biomedical and behavioral research on drug abuse and HIV/AIDS.

November 26, 2007 - **National Institute on Drug Abuse Launches Public Service Campaign for Hispanic Youth on the Link between Non-Injection Drugs and HIV**. The National Institute on Drug Abuse launched its

new, national public service campaign to educate Hispanic teens on the link between non-injection drug use and HIV transmission. The campaign features an innovative television spot blending English and Spanish; a Webisode series that will launch soon on www.hiv.drugabuse.gov; outdoor, transit and print placements; community events and partnerships.

November 15, 2007 - **The National Institute on Drug Abuse Offers Summer Internship Opportunities**. The National Institute on Drug Abuse announced the kick off for the application period for summer research training opportunities at its Intramural Program facility in Baltimore, Maryland. The internship program - now in its 21st year - is part of NIDA's commitment to introducing the science of addiction to some of the best and brightest young scientists in America.

October 29, 2007 - **Drug-Impaired Driving by Youth Remains Serious Problem**. Large numbers of American adolescents are putting themselves and others at great risk by driving while under the influence of illicit drugs or alcohol, according to a study funded by the National Institute on Drug Abuse. In 2006, 30 percent of high school seniors reported driving after drinking heavily or using drugs, or riding in a car whose driver had been drinking heavily or using drugs, at least once in the prior two weeks. These findings are based on data obtained from the Monitoring the Future study, in which nationally representative samples of high school seniors have been surveyed annually since 1975. The data analysis was published in the November 2007 issue of the *Journal of Studies on Alcohol and Drugs*.

September 16, 2007 - **Two NIH Institutes Share Emmy Award for HBO's The Addiction Project**. Two Institutes at the National Institutes of Health have been honored with the prestigious Governors Award by the Academy of Television Arts and Sciences for their contribution to HBO's *Addiction Project. "Addiction"* is a 14-part documentary television series and multimedia initiative revealing the science of addiction, its treatment, recovery, and its costs to families and society. A diverse group of people who were battling alcohol or drug addiction were featured, as well as addiction experts from around the country.

September 10, 2007 - **NIH Scientists Demonstrate Genetic Variant is Linked to Greater Effectiveness of Smoking Cessation Medication**. A genetic variant present in nearly half of Americans of European ancestry is linked to greater effectiveness of the smoking cessation medication bupropion (Zyban), according to research by scientists supported by the National Institute on Drug Abuse and the National Cancer Institute. People with this variant were less likely than those without it to have resumed smoking six months after treatment with bupropion.

Articles of Interest

December 11, 2007, *Associated Press*—"Study: Overall Teen Drug Use Declining"--Mention of 2007 Monitoring the Future Survey.

September 26, 2007, *Associated Press*—"Pregnant Smokers and Depression Tied"--Interview with Nora D. Volkow, M.D.

August 26, 2007, *New York Times*—"Mind Over Matter, With a Machine's Help"--Interview with Nora D. Volkow, M.D.

Dr. Frank Vocci and Dr. Jag Khalsa, DPMCDA, attended and spoke at the SAA clinic's 30th anniversary celebration in Reyjkavik, Iceland on October 1-2, 2007. Both were interviewed by the leading news paper of Reykyavik with their pictures in the newspaper. Both were also interviewed by the local television studio and were aired on their prime time news.

Dr. Steven Grant, DCNBR, provided background information to Bill Campbell of PBS Now for a program on Methamphetamine broadcast on August 31, 2007.

Dr. Steven Grant provided background information to Alana Berry at National Geographic for a program on Addiction.

Dr. Steven Grant provided background information on methamphetamine to Scott McMillan at Montana Quarterly for an article on prisons devoted to substance abuse treatment.

Outreach Activities

Heads Up: Real News About Drugs and Your Body. Through a continuing partnership, NIDA and SCHOLASTIC INC, the global children's publishing and media company, distributed information on the health effects of drugs to nearly 2 million students and teachers in grades 5 through 10 nationwide four times per year, with an emphasis on grades 7 and above. The information is distributed via 2- to 4-page article inserts. Magazines that include Heads Up are Junior Scholastic, Science World, CHOICES, SCOPE, ACTION, and Up Front. Three Student and Teacher compilations were completed for the 2007/08 school year, Out of It - How Drug Abuse Impairs the Way We Think and Function; The Lowdown on Hydrocodone; and Talking with Your Doctor; two were published and distributed. NIDA is unique in that Heads Up is the only regular "run-of-book" insert included in any Scholastic magazine.

Upcoming Confernences/Exhibits

National Association of School Psychologists 40th Annual Convention New Orleans, LA	February 6-9, 2008
Community Anti-Drug Coalitions of America National Leadership Forum XVIII Washington, DC	February 11-14, 2008
10th Annual Lonnie E. Mitchell National Historically Black Colleges and Universities Substance Abuse and Mental Health Conference Atlanta, GA	April 2-5, 2008
American Psychiatric Association 161st Annual Meeting Washington, DC	May 3-8, 2008

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The National Institute on Drug Abuse (NIDA) will participate in a number of sessions at the **Community Anti-Drug Coalitions of America (CADCA) annual National Leadership Forum in Washington, D.C., February 11-14, 2008**. Dr. Timothy Condon, Deputy Director, NIDA, will conduct a workshop with Moira O'Brien, DESPR, NIDA on Emerging Trends in Drug Abuse: Monitoring to Stay Ahead of the Curve and Dr. Frank Vocci, Director, DPMCDA, NIDA will conduct a workshop on Adolescent Smoking: Time to Act. In addition, NIDA Director, Dr. Nora Volkow, will participate in a plenary session.

The National Institute on Drug Abuse (NIDA) is organizing a program at the **American Psychiatric Association (APA) Annual Meeting in Washington, D.C., May 3-8, 2008**. A number of NIDA staff and NIDA researchers will participate in several symposia and workshops at the upcoming meeting on a wide range of topics such as, Drug Abuse, HIV, and the Brain; Gene-Environment-Development Interactions: Implications for Psychiatric and Substance Abuse Disorders; and Diagnosis and Treatment of Adolescents/Young Adults with Substance Use Disorders. This program will build on previous tracks NIDA has been conducting at the APA Annual meeting since 1998.

NIDA will host the seventh **Blending Conference** at the Duke Energy Center in Cincinnati, Ohio on June 2-3, 2008. This 2-day conference is designed to bring clinicians and researchers together to examine the most up-to-date scientific drug abuse and addiction findings and their application to clinical practice.

The National Institute on Drug Abuse (NIDA) is organizing a program at this year's **American Psychological Association (APA) Annual Meeting in Boston, Massachusetts, August 14-17, 2008**. 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.

Drs. Harold Gordon and Steven Grant of DCNBR together with Dr. Kevin Quinn of NIMH are organizing a workshop entitled, **Imaging Imagining--The Mirror System and Beyond: Neural Representation of the Self and Others**. The meeting will be sponsored, in part by the Office of Science Policy and Communications (OSPC) and by the National Institute of Mental Health. The purpose is to explore the latest work of imaging those aspects of cognition that induce activation of brain circuitry including the mirror neuron system. These concepts are important in drug abuse, for example to understand motivations (e.g., craving) underlying decisions to seek and take drugs.

The next **National CTN Steering Committee Meetings** are planned for

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February 25-28, 2008 in Rockville, Maryland and June 3-6, 2008 in Cincinnati, OH.

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Community Monitoring Systems: Tracking and Improving the Well-Being of America's Children and Adolescents
NIH Pub. No.: 07-5852
Monitoring the well-being of children and adolescents is a critical component of efforts for preventing behavioral, psychological and health problems and promoting successful development. This document provides valuable information for community leaders, policy makers and practitioners in developing and using monitoring systems for prevention planning.

Epidemiologic Trends in Drug Abuse - Community Epidemiology Work Group - Volume I - June 2007 ***[pdf]***
NIH Pub No.: 08-6200A-5881A
This report provides an ongoing assessment of drug abuse in major metropolitan areas of the United States with the purpose of keeping both public and private sector policymakers and researchers informed with current and accurate data.

Epidemiologic Trends in Drug Abuse - Community Epidemiology Work Group - Volume II - June 2007
NIH Pub. No. 08-6204A
This report provides an in-depth analysis of the epidemiologic trends and special reports for a limited audience made up primarily of drug abuse researchers who utilize this volume to identify potential areas for further research.

NIDA NOTES

***NIDA NOTES,* Vol. 21, No. 4**
NIH 07-3478
The lead story looks at the neuropeptide orexin and links to the reward system. The Director's Perspective reports on NIDA's role in the NIH obesity task force, and a NIDA at Work feature reports on the Division of Clinical Neuroscience and Behavioral Research. Research reports look at endorphin's role in inhibiting reward from morphine and nicotine in rats, gene experiments that confirm cocaine exposure regulates certain genes, and a study linking anabolic steroids to brain changes in mice. The NIDA Notes Reference Article provides a primer on the impacts of drugs on neurotransmission.

CTN-Related Publications

Eight editions of the CTN Bulletin Board were distributed. The Bulletin Board is

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an electronic report on the progress of the protocols, committees, and node activity in the CTN.

International Publications

NIDA Notes Features International Supplement on Drug Abuse and HIV/AIDS
NIDA Notes 2007; 21(4):19 focused on the NIDA International Program peer-reviewed supplement to Drug and Alcohol Dependence [2006; 82(S1)], Drug Abuse and HIV/AIDS: International Research Lessons and Imperatives.

NIDA International Program E-News Letter
November 2007 - This issue announced four research projects funded by the U.S. - Netherlands Binational Agreement, the results of DISCA-supported research on methamphetamine and the blood brain barrier, IP activities at the American Association for the Treatment of Opioid Dependence Conference and the Society for Neuroscience Meeting, and the call for papers for the second round and announcement of recipients of the first NIDA/CICAD Competitive Research Program awards. The issue also provides links to the online registration and abstract submission sites for the 2008 NIDA International Forum.

September 2007 - The September IP E-News Letter announced FY 2008 funding for the Program Announcement on International Research Collaborations to Study HIV/AIDS and Drug Abuse, the results of U.S. - Spain joint research that supported community reinforcement approach plus vouchers in treating Spanish cocaine abusers, and the IP publication of an international consensus report setting guidelines for future international research into driving under the influence of drugs.

Other Publications

Pickering, R.P., Grant, B.F., Chou, S.P. and Compton, W.M. Are Overweight, Obesity, and Extreme Obesity Associated with Psychopathology? Results from the National Epidemiologic Survey on Alcohol and Related Conditions. The Journal of Clinical Psychiatry 68, pp. 998-1009, 2007.

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Robertson, E.B. and Compton, W.M . Prevention of Drug Use and Drug Use Disorders. In: Wallace, R.B. and Kohatsu, N., (eds.) Public Health and Preventive Medicine, fifteenth edition, pp. 1013 - 1023, 2007.

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Jenkins, R.A. Toward a Broader View of Research Ethics. [Review of the book, "Research Ethics for Social Scientists"]. PsycCRITIQUES--Contemporary Psychology: APA Review of Books 52 (No. 33) Article 50, August 15, 2007.

Lopez, M.F., Compton, W.M., Grant, B.F., and Breiling, J.P. Dimensional Approaches in Diagnostic Classification: A Critical Appraisal. Int. J. Methods Psychiatr. Res. 16 Suppl 1, S6-S7, 2007.

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Gordon, H.W. Sleep, Circadian Rhythm, and Drug Abuse (Editorial) 2007, The

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Bardo, M.T., and Schnur, P. The Motivational Impact of Nicotine and its Role in Tobacco Use: Final Comments and Priorities. In R. Bevins (Ed.), The Nebraska Symposium on Motivation, 2007.

Wetherington, C.L. Sex-gender Differences in Drug Abuse: A Shift in the Burden of Proof. Experimental and Clinical Psychopharmacology, 15, pp. 411-417, 2007. (This article appeared as the lead article in the issue.)

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Wu, D.Y., and Saterlee, J.S. Decoding Drug Abuse in Noncoding RNA? Scientific World Journal 7, pp. 142-145, 2007.

Lawrence, D.M., Thomas, D.A., and Wu, D.Y. Glial Cells and the Neurobiology of Addiction. ScientificWorld Journal 7(S2), pp. 86-88, 2007.

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Staff Highlights

Staff Honors and Awards

2007 NIDA Director's Award of Merit (Groups)

The Health Services Research/Clinical Trials Network Team
Redonna Chandler, Ph.D.
Sarah Duffy, Ph.D.
Petra Jacobs, M.D.
Harold Perl, Ph.D.

The Epigenetics Workgroup
John Satterlee, Ph.D.
Christine Colvis, Ph.D.
Joni Rutter, Ph.D.
Jonathan Pollock, Ph.D.
Da-Yu Wu, Ph.D.
Genevieve deAlmeida-Morris, Ph.D.
Donna Jones

The NIDA/NIH Roadmap Behavioral and Social Sciences Initiative Workgroup
Lisa Onken, Ph.D.
Teresa Levitin, Ph.D.
Gerald McLaughlin, Ph.D.
Kay Nimit., M.D.
Pamela Fleming
Deborah Wertz
Susan Volman, Ph.D.
Denise Pintello, Ph.D.
Elizabeth Ginexi, Ph.D.

The Pain and Opioids Meeting Group
Usha Charya
Wilson Compton, M.D.
Richard Denisco, M.D.
Gaya Dowling, Ph.D.
Dorie Hightower
Carol Krause
Jan Lipkin
Cindy Miner, Ph.D.
Anna Staton
David Thomas, Ph.D.
Susan Weiss, Ph.D.

The NIDA Performance Team

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Sharon Chang
Susan Cook
David Daubert
Donna Jones
Donna Tolson

The HBO Addiction Project Team
Ruben Baler, Ph.D.
Elisabeth Davis
Gaya Dowling, Ph.D.
Jennifer Elcano
Sharan Jayne
Carol Krause
Geoff Laredo
Jan Lipkin
Cindy Miner, Ph.D.
Sara Rosario-Wilson
Jane Smither
Anna Staton
Susan Weiss, Ph.D.

2007 NIDA Director's Award of Merit Individual Recipients
Nora Chiang, Ph.D.
Kathleen Etz, Ph.D.
Pamela Fleming
Steven Grant, Ph.D.
Thomas Haines
Meenaxi Hiremath, Ph.D.
Carol Krause
Cindy Miner, Ph.D.
Ivan Montoya, Ph.D.
Joni Rutter, Ph.D.
Karen Skinner, Ph.D.

NIDA Director's Award for EEO, Diversity and Quality of Worklife
Stacy Gardner

Commissioned Corp Awards

PHS Commendation Medal
Michele Leff
Paul Na

PHS Outstanding Unit Citation
Janice Carico

30 Years of Government Service Awards

Division of Basic Neuroscience and Behavioral Research
Rao S. Rapaka
Joyce Williams

Division of Epidemiology, Services and Prevention Research
Meyer Glantz

Office of Planning and Resource Management
Helene Braun
Maryellen Connell
Kirkland Davis
Suezette Epps
Diane Loeb
Donna Tolson

Office of Science Policy and Communications
Geraldine M. McCarthy

Intramural Research Program
Janice Carico
William Freed
Carla Highkin
Tsung Ping Su

Other Staff Honors and Awards

Dr. Lula Beatty, Chief, SPO, received the Susan Rosenberg Zalk award for mentoring from the Society for the Psychology of Women, American Psychological Association, in September 2007.

Dr. Lula Beatty received the Public Service Award from the Science Directorate, American Psychological Association, in October 2007.

Dr. Yonette Thomas, DESPR, received the National Award of Excellence in Public Service at the annual National Hispanic Science Network on Drug Abuse Meeting, September 27, 2007 held in Miami, FL.

Drs. Belinda Sims, Elizabeth Robertson and **Eve Reider**, PRB/DESPR, received the Administration for Children and Families (ACF) Assistant Secretary's 2007 Partnering for HHS Excellence Award. This award was received for their planning team participation in the ACF Meeting "The Application of Effect Sizes in Research on Children and Families: Understanding Impacts on Academic, Emotional and Behavioral Outcomes." The meeting was held March 5, 2007 at the NIH Natcher Conference Center, Bethesda, MD.

Staff Changes

In November 2007, **Dr. Jessica Campbell Chambers** joined the Behavioral & Integrative Treatment Branch in the Division of Clinical Neuroscience & Behavioral Research. Dr. Chambers was a Health Scientist Administrator in the Epidemiology Branch of the Division of Services and Prevention Research. In DCNBR, she will be handling a grant portfolio on the treatment of children and adolescents.

Dr. James M. Bjork joined the Clinical Neuroscience Branch of the Division of Clinical Neuroscience and Behavioral Research. Dr. Bjork earned his Ph.D. in Biomedical Sciences with a concentration in neuroscience from the University of Texas-Houston Health Science Center in 1999, where he conducted psychopharmacological research on human impulsivity and aggression. Subsequently, he conducted impulsivity research with conduct-disordered adolescents at the Harris County Psychiatric Center (Houston, TX). He then joined the NIAAA Intramural Laboratory of Clinical and Translational Research (Bethesda, MD) as a postdoctoral fellow in 2000. While at NIAAA, Dr. Bjork continued research on different dimensions of impulsivity in substance abuse, and conducted structural and functional magnetic imaging research in persons with or at risk for alcohol use disorders.

Dr. Vincent Smeriglio retired from NIDA on January 4, 2008 from his position as Branch Chief of the Behavioral and Brain Development Branch within the Division of Clinical Neuroscience and Behavioral Research. He has worked for over 18 years advancing NIDA's programs in Human Development, and has held a senior staff position as the NIDA Child and Adolescent Research Coordinator. He also has been involved in several large, multi-institute research projects and programs over the years.

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Grantee Honors

Addiction Treatment Services (ATS) at Johns Hopkins Bayshore Medical Center which is run by **Dr. Robert Brooner** was awarded the 2007 Earnest Codman Award for Excellence in Behavioral Health by the Joint Commission. This award recognized programs which utilize outcome measurement as part of improving healthcare. The ATS was honored for Motivational Stepped Care developed by Dr. Brooner which uses an adaptive approach to continually monitor patient improvement and deterioration and then programs additional treatment accordingly. Initial research on this intervention indicates promise for dramatically reducing cocaine and opioid use.

Dr. Linda Caldwell of the Pennsylvania State University received the Theodore and Franklin Roosevelt Award for Excellence in Recreation and Park Research from the National Recreation and Park Association. This award is presented annually to an individual whose contributions to recreation and park research have significantly advanced the cause of the recreation movement, and whose dedication to the field parallels the same dedication and zeal that was exhibited by both Theodore and Franklin Roosevelt.

Dr. Richard Catalano has been awarded the 2007 August Vollmer Award by the American Society of Criminology. Established in 1959, the Vollmer Award recognizes a criminologist whose research scholarship has contributed to justice or to the treatment or prevention of criminal or delinquent behavior, either through a single outstanding work, a series of theoretical or research contributions, or the senior scholar's accumulated contributions.

Dr. Erik Gunderson received the 2007 Ambulatory Medicine Teacher of the Year Award from the Department of Medicine at Columbia University. The award was based in part on his development of a curriculum on recognition of prescription opioid use disorders and for involvement of medical residents in his clinical research on buprenorphine treatment of opioid dependence in primary care.

Dr. Thomas Kosten of Baylor College of Medicine was presented with the American Academy of Addiction Psychiatry's Founders Award, at the organization's 2007 meeting in Coronado, California. This award recognizes Dr. Kosten's lifetime of commitment and contributions to the field of addiction.

Dr. David MacKinnon, Professor of Psychology in the Social and Quantitative psychology programs at Arizona State University was recently awarded the 2006-2007 Outstanding Graduate Mentor award from the Arizona State University Division of Graduate Studies.

On July 25th, 2007, **Dr. Lisa Marsch** (NDRI) appeared on the Fox News health forum, hosted by Dr. Manny Alvarez, to discuss youthful opiate addiction and her current intervention research which eeks to maximize successful treatment

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outcomes.

Dr. Barbara Mason was given The Pearson Family Chair, a newly endowed position in alcohol and addiction research at The Scripps Research Institute Dr. Mary M. McKay was recently promoted to Head of the Division of Mental Health Services Research at the Mount Sinai School of Medicine.

Constance Weisner, Dr.PH., M.S.W., Northern California Division of Research - Kaiser Permanente, has received the prestigious Betty Ford award from the Association for Medical Education in Research in Substance Abuse (AMERSA) honoring her valuable contributions to the substance abuse field. AMERSA presents the Betty Ford Award annually to an individual who has played a significant role in the treatment and recovery of drug-dependent individuals, particularly women.

Dr. Rebecca Wells of the University of North Carolina received the Health Care Management Division, Academy of Management, 2007 annual national meeting Outstanding Reviewer award. She also received the 2006, John D. Thompson Young Investigator Award. This prize recognizes young investigators based on their contributions to the research literature in the field of health services. Dr. Wells has also been recognized recently by the Mental Health Section of the American Sociological Association for the Best Publication Award.

The Substance Abuse and Mental Health Services Administration (SAMHSA) recently awarded **The Life Link Community Treatment Program** (CTP) in Santa Fe, NM the inaugural Science to Service Award. This award recognizes exemplary implementation of evidence-based interventions to prevent and treat mental illnesses and substance abuse. The Life Link is a CTP in the Southwest Node. **Drs. Carol Luna-Anderson, Raymond Anderson,** and **Michael DeBernardi** of The Life Link made a formal presentation before the SAMHSA National Advisory Board on October 17, 2007 in Washington, D.C. and received the award. The Life Link was recognized for its pioneering and effective use of the Community Reinforcement and Family Training (CRAFT) approach, developed at the University of New Mexico by Robert J. Meyers, Ph.D. CRAFT is a substance abuse treatment modality in which family members are engaged in treatment and taught how to better support the individual who is using alcohol or other drugs. The Life Link has employed CRAFT since 2000, and has assisted in its expansion at the national and international level.

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