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

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

Research Findings - Basic Neuroscience Research

CB2 Receptor Analysis

Understanding the structure and function of the peripheral CB2 cannabinoid receptor requires that it be available in adequate and purified quantities and its various helical and loop amino acid sequences be accurately analyzable by modern techniques. Of particular importance is the precise identification of an amino acid at which a ligand may bind covalently, possibly affecting the function and conformation of the receptor. In a collaborative effort, Dr. Alexandros Makriyannis and Dr. Barry Karger have recently completed a proteomic characterization of the human CB2 receptor (hCB2R), in which refinements in expression, purification, and tryptic digestion gave rise to full "coverage" of the known sequence of this receptor, based on mass spectral analysis of its fragments. In the present example, a membrane-bound hCB2 protein was obtained by expression in Sf-21 insect cells, which showed suitable equilibrium binding of the tritiated cannabinoid agonist CP 55,940. The results described have demonstrated the production of purified human CB2 receptor, the use of complementary proteolytic digestion techniques, the separation of resulting long hydrophobic and short sequence peptides, their analysis by electro spray mass spectrometry, and confirmation of fragments with tandem MS/MS. Zvonok, N., Yaddanapudi, S., Williams, J., Dai, S., Dong, K., Retjar, T., Karger, B. L., and Makriyannis, A., Journal of Proteome Research 6(6), pp. 2068-2079, 2007.

Prenatal Cocaine Exposure and the Developing Brain

Children exposed to cocaine during gestation have a higher incidence of neurobehavioral deficits. The neurochemical bases of these deficits have not been determined but the pharmacology of cocaine and the nature of abnormalities suggest that disruptions in catecolaminergic systems may be involved. In a recent study, NIDA-supported researchers report that prenatal cocaine exposure resulted in lasting changes to the regulation and responsivity of rat locus coeruleus norepinephrine (NE) neurons. From these findings, the researchers speculate that a similar dysregulation of locus coeruleus NE neurons may occur in children exposed to cocaine during gestation, and this may explain, at least partly, the increased incidence of cognitive deficits that have been observed in these subjects. This study was conducted in pregnant rats that received intravenous injection of cocaine twice daily between gestational days 10 and 20 and the progeny was tested as juveniles. The researchers also observed that the locus coeruleus NE system was more responsive to stimuli, such as exposure to a mild stressor, in rats exposed to prenatal cocaine compared to rats exposed to saline solution. Elsworth, J.D., Morrow, B.A., Nguyen, V.T., Mitra, J., Picciotto, M.R., and Roth, R.H. Prenatal Cocaine Exposure Enhances Responsivity of Locus Coeruleus Norepinephrine

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Neurons: Role of Autoreceptors. Neuroscience 147, pp. 419-427, 2007.

A Functional Proteomic Strategy to Discover Inhibitors for Uncharacterized Hydrolases

Hydrolytic enzymes constitute one of the largest and most diverse protein classes in nature and play key roles in nearly all physiological and pathological processes. The mammalian serine hydrolase superfamily contains a remarkable number of uncharacterized members, with at least 40-50% of these enzymes lacking experimentally verified endogenous substrates and products. Assignment of metabolic and cellular functions to these enzymes requires the development of pharmacological tools to selectively perturb their activity. Cravatt et al. provided a functional proteomic strategy to systematically develop potent and selective inhibitors for uncharacterized serine hydrolases and its application to the brain-enriched enzyme alpha/beta-hydrolase-6. The methods described herein will facilitate the development of selective chemical probes to annotate the metabolic and (patho) physiological functions of many of the uncharacterized serine hydrolases that currently populate eukaryotic and prokaryotic proteomes. Li, W., Blankman, J.L., and Cravatt, B.F. A Functional Proteomic Strategy to Discover Inhibitors for Uncharacterized Hydrolases. July 13, 2007 [Epub ahead of print].

Glial-Cell Inhibitor, AV411, Reduces Pain and Attenuates Morphine Analgesia in a Rat Model of Neuropathic Pain

AV411 (ibudilast) is a relatively nonselective phosphodiesterase inhibitor that also suppresses glial-cell activation. Recent data strongly implicates activated glial cells in the spinal cord in the development and maintenance of neuropathic pain. NIDA grantee Dr. Linda Watkins of the University of Colorado, Boulder and colleagues recently tested the efficacy of AV411 as an analgesic in several neuropathic pain models in rats. AV411 was found to be very effective in reducing pain in these models. She also found that AV411 reduced tolerance to morphine in nerve-injured rats. Safety pharmacology, pharmacokinetic and initial mechanistic analyses indicated that that AV411 is safe and effective in diverse models of neuropathic pain, suggesting usefulness of this agent as a treatment for pain, either alone, or in combination with opioids. Ledeboer, A.M., Liu, T., Shumilla, J.A., Mahoney, J.H., Vijay, S., Gross, M.I., Vargas, J.A., Sultzbaugh, L., Claypool, M.D., Sanftner, L.M., Watkins, L.R., and Johnson, K.W. The Glial Modulatory Drug AV411 Attenuates Mechanical Allodynia in Rat Models of Neuropathic Pain. Neuron Glia Biology, (2), pp. 279-291, 2006.

Improved Procedure for the Synthesis of DAMGO

DAMGO (Tyr-D-Ala-Gly-Na-Me-Phe-Gly-ol), a selective u-opioid receptor ligand is a widely used peptide in investigations of u-receptor-mediated pharmacology. Dr. Ivy Carroll and his coworkers previously developed a solution methodology suitable for the preparation of gram amounts of highly pure DAMGO. The synthetic scheme consisted of a (3+1+1) approach in which synthetic Boc-Tyr-D-Ala-Gly-Na-Me-Phe-OH was prepared starting from Boc-Na-Me-Phe-OH in three steps to give TFA*DAMGO in 6% overall yield. They have just reported a new synthetic methodology for introduction of the Gly-ol residue. Specifically, they determined that heating the tetrapeptide, Boc-Tyr-D-Ala-Gly-Na-Me-Phe-OR, in excess ethanolamine led to amidation of the Na-methylpenylalanine methyl ester residue cleanly and quantitatively. Thus, the protected tetrapeptide, Boc-Tyr-D-Ala-Gly-Na-Me-Phe-OR was prepared in three steps (68% overall yield), following the previously described methodology. Condensation with ethanolamine quantitatively afforded the protected penta-peptide, Boc-Tyr-D-Ala-Gly-Na-Me-Phe-Gly-ol. Deprotection of

the Boc group using 50% TFA in CH2Cl2 afforded DAMGO trifluoroacetate in 58% overall yield after purification by preparative high performance liquid chromatography (HPLC). The significantly higher yield resulted primarily from the improved yield obtained in the preparation of precursor tetrapeptide, Boc-Tyr-D-Ala-Gly-Na-Me-Phe-OR (68%) vs. the precursor Boc-Tyr-D-Ala-Gly-Na-Me-Phe-OR (25%) and in the introduction of the fifth Gly-ol residue (85% vs. 24%). In summary, the PI and his associates have developed a racemization-free synthetic protocol that is relatively shorter and affords the product with high overall yield. Reddy, A.P., Lewin, A. and Carroll, I.F. Improved Procedure for the Synthesis of DAMGO Synthetic Communications, 37 (14), pp. 2345-2348, 2007.

Endocannabinoid-Mediated Long-Term Depression Requires cAMP/PKA Signaling

Endocannabinoids (eCBs) have emerged as key activity-dependent signals and their neuropharmacology is of interest to NIDA. The binding of eCBs to presynaptic cannabinoid receptors (i.e., CB1) causes a reduction in neurotransmitter release and neuronal excitability that can be transient (short-term depression) or that can persist long after CB1 receptor activation (long-term synaptic depression, LTD) has occurred. The conundrum is how activation of the same neurotransmitter receptor can produce both transient and long-lasting depression. Previous studies have found that eCB-dependent short-term depression is mediated through CB1-dependent inhibition of voltage -gated calcium channels. However, the molecular events linking CB1 receptors to LTD have been unknown. This paper now reports that in the hippocampus, long-term eCB-dependent depression requires presynaptic cAMP/PKA signaling. Providing additional support for the involvement of cAMP signal transduction in eCB-dependent LTD, it was further shown that the active zone protein RIM1alpha, which is a PKA substrate protein that regulates neurotransmitter release, is a key mediator of both CB1 receptor effects on neurotransmitter release and eCB-dependent LTD. Taken together, these findings show that eCB-dependent short-term and long-term depression occur through distinct mechanisms. Whether CB1 receptor activation by eCBs results in transient or long-term depression should distinctly impact neural circuit processing and behavior. Chevaleyre, V., Heifets, B.D., Kaeser, P.S., Suedhof, T.C., Purpura, D.P., and Castillo, P.E. Endocannabinoid-mediated Long-term Plasticity Requires cAMP/PKA Signaling and RIM1alpha. Neuron, 54(5), pp. 801-812, 2007.

An Opioid Agonist That Does Not Induce Micro-Opioid Receptor-Arrestin Interactions or Receptor Internalization

G protein-coupled receptor desensitization and trafficking are important regulators of opioid receptor signaling that can dictate overall drug responsiveness Furthermore, different mu-opioid receptor (MOR) ligands can lead to varying degrees of receptor regulation, presumably because of distinct structural conformations conferred by agonist binding. For example, morphine binding produces a MOR with low affinity for beta-arrestin proteins and limited "trafficking" and receptor internalization, whereas enkephalin analogs promote robust trafficking of both beta-arrestins and the receptors. Here, Dr. Laura Bohn and her research team at the Ohio State University evaluate MOR trafficking in response to activation by a novel mu-selective agonist derived from the naturally occurring plant product, salvinorin A. It is interesting that this compound, termed "herkinorin," does not promote the recruitment of beta-arrestin-2 to the MOR and does not lead to receptor internalization. Moreover, whereas G protein-coupled receptor kinase over-expression can promote morphine-induced beta-arrestin interactions and MOR internalization, such manipulations do not promote herkinorin-induced trafficking. Studies in mice have shown that beta-arrestin-2 plays an important role in the development of

morphine-induced tolerance, constipation, and respiratory depression. Therefore, drugs that can activate the receptor without recruiting the arrestins may be a promising step in the development of opiate analgesics that distinguish between agonist activity and receptor regulation and may ultimately lead to therapeutics designed to provide pain relief without the adverse side effects normally associated with the opiate narcotics. Groer, C.E., Tidgewell, K., Moyer, R.A., Harding, W.W., Rothman, R.B., Prisinzano, T.E., and Bohn, L.M. An Opioid Agonist that Does Not Induce Micro-opioid Receptor-arrestin Interactions or Receptor internalization. Mol. Pharmacol, Feb 71(2), pp. 549-557, 2007. Epub 2006 Nov 7.

Role of Akt-GSK-3_ Signaling and Synaptic Strength in PCP-Induced Neurodegeneration

N-Methyl-D-aspartate (NMDA) receptor antagonists such as phencyclidine (PCP) and ketamine are abused drugs with powerful effects on behavior. They can replicate positive and negative symptoms of schizophrenia in humans and induce related effects in rodents. In addition, PCP treatment of developing rats induces apoptotic neurodegeneration. Later in life, without further exposure to PCP, these rats exhibit behavioral deficits that mimic some symptoms of schizophrenia. The mechanism of PCP-induced neural degeneration is unknown. Dr. Lei and colleagues investigated the role of the Akt-glycogen synthase kinase 3_ (GSK-3_) pathway in PCP-induced neuronal apoptosis in both neuronal culture and postnatal day 7 rats. Akt-GSK-3_ signaling is thought to be impaired in schizophrenia. Further, the Akt1 gene is thought to be a potential susceptibility gene for schizophrenia, and antipsychotic medications have been reported to enhance Akt-GSK-3_ signaling. Akt is a serine/threonine protein kinase involved in diverse cellular processes. GSK-3_ is one of the downstream substrates for Akt. Normally, Akt decreases GSK-3_ activity by enhancing GSK-3_ phosphorylation, promoting cell survival. PCP administration in vivo and in vitro reduced the phosphorylation of AktSer427 and GSK-3_Ser9, decreasing Akt activity and increasing GSK-3_ activity. Altered Akt-GSK-3_ signaling paralleled the temporal profile of caspase-3 activation by PCP, which has a key role in the final stages of the apoptotic cascade. Reducing GSK-3_ activity by application of selective inhibitors, or depleting GSK-3_ by siRNA, attenuated caspase-3 activity and blocked PCP-induced neurotoxicity. Moreover, increasing synaptic strength by either activation of L-type calcium channels or potentiation of synaptic NMDA receptors completely blocked PCP-induced cell death by increasing Akt phosphorylation. Overall, these data suggest that PCP-induced hypo-function of synaptic NMDA receptors impairs the Akt-GSK-3_ cascade, which is necessary for neuronal survival during development, and that interference with this cascade by PCP or natural factors may contribute to neural pathologies, perhaps including schizophrenia. Lei, G., Xia, Y., and Johnson, K.M. The Role of Akt-GSK-3_ Signaling and Synaptic Strength in Phencyclidine-Induced Neurodegeneration. Neuropsychopharmacology, 2007. [Epub ahead of print]

A Serotonin-Depleting Regimen of MDMA Prevents Mating-Induced Conditioned Place Preference in Rats

Although MDMA ("ecstasy") appears to increase sexual desire and satisfaction shortly after its consumption, human self-reports suggest that repeated use of MDMA results in long-lasting loss of sex interest or pleasure. In the present study, a regimen of MDMA that produced long-lasting depletion of brain serotonin in sexually naive male rats prevented the formation of a mating-induced conditioned place preference (CPP) two weeks following drug treatment. This regimen of MDMA produced no change in parameters of sexual performance 12-40 days following MDMA administration. The failure of MDMA-treated rats to form a CPP response to sex may be due to MDMA-induced long-lasting impairment in brain circuits mediating sexual reward. Straiko, M.M.W.,

Gudelsky, G.A., and Coolen, L.M. Treatment with a Serotonin-Depleting Regimen of MDMA Prevents Conditioned Place Preference to Sex in Male Rats. Behavioral Neuroscience, 121, pp. 586-593, 2007.

Over-expression of Serotonin-6 Receptors in the Nucleus Accumbens Blocks the Rewarding But Not Psychomotor Activating Properties of Cocaine

Repeated exposure to cocaine produces enduring forms of drug experience-dependent behavioral plasticity, including conditioned place preference (CPP) and psychomotor sensitization, a progressive and persistent increase in cocaine's locomotor activating effects. Although serotonin-6 receptors (5-HT6Rs) are abundantly expressed in the brain regions thought to underlie these phenomena, such as the nucleus accumbens (NAc) shell, little is known about the role of 5-HT6Rs in the rewarding and psychomotor activating effects of cocaine. Viral-mediated gene transfer was used to selectively increase 5-HT6R expression in the NAc shell of rats. Increased expression of 5-HT6Rs in the NAc shell blocked CPP to cocaine but had no effect on either the acute locomotor response to cocaine or on the development of cocaine-induced locomotor sensitization. Further, antagonism of 5-HT6Rs (by systemic administration of Ro4368554) facilitated acquisition of CPP to cocaine but had no effect on cocaine-induced stereotypy. These results demonstrate that 5-HT6Rs in the NAc shell can selectively modulate drug reward, possibly through facilitation of reward learning. Ferguson, S.M., Mitchell, E.S., and Neumaier, J.F. Increased Expression of 5-HT6 Receptors in the Nucleus Accumbens Blocks the Rewarding But Not Psychomotor Activating Properties of Cocaine. Biological Psychiatry, 2007. [Epub ahead of print].

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

A study from Dr. Nestler's lab reports that tolerance to morphine reward in rats is due to down-regulation of IRS2-Akt signaling in the ventral tegmental area (VTA), the cell body region of the mesolimbic dopamine reward system. Chronic morphine administration (via subcutaneous pellet) is known to decrease the size of dopamine neurons in the VTA, a key reward region in the brain, yet the molecular basis and functional consequences of this effect were unclear. In this study, the investigators used viral-mediated gene transfer in rat to show that chronic morphine-induced down-regulation of the insulin receptor substrate 2 (IRS2)-thymoma viral proto-oncogene (Akt) signaling pathway in the VTA mediated the decrease in dopamine cell size seen after morphine exposure and that this down-regulation diminished morphine reward, as measured by reduced conditioned place preference. The reduction in size of VTA dopamine neurons persisted for up to 2 weeks after morphine withdrawal, which parallels the tolerance to morphine's rewarding effects caused by previous chronic morphine exposure. These findings directly implicate the IRS2-Akt signaling pathway as a critical regulator of dopamine cell morphology and opiate reward, and may be part of the molecular basis for the observation that addicts report that opiate drugs lose their rewarding effects over time. Russo, S.J., Bolanos, C.A., Theobald, D.E., DeCarolis, N.A., Renthal, W., Kumar, A., Winstanley, C.A., Renthal, N.E., Wiley, M.D., Self, D.W., Russell, D.S., Neve, R.L., Eisch, A.J., and Nestler, E.J. IRS2-Akt Pathway in Midbrain Dopamine Neurons Regulates Behavioral and Cellular Responses to Opiates. Nat Neurosci, 10(1), pp. 93-99. 2007.

Opioid Receptor Expression and Glial Precursor Cell Susceptibility to Toxic Effects of Morphine and HIV-Tat

Previous work by Dr. Hauser and colleagues showed combined effects of

morphine and HIV proteins on astrocyte function. To determine whether opiates and HIV-1 proteins are intrinsically toxic to glial precursors, mouse neural stem cells were isolated and a subset of glial-restricted precursors (GRPs) was tested for opioid receptor expression and effects of morphine and HIV-1 Tat exposure. These investigators found that exposure to either morphine or HIV-1 Tat protein alone significantly increased GRP death in vitro. GRP death was preceded by increases in caspase-3 enzyme activity, and cytotoxicity coincided with the onset of MOR and KOR expression and progressive glial differentiation in vitro. Opioid receptor expression by GRPs was dynamic and highly coordinated with glial maturation, and their findings suggested that opioid receptors are necessary, but not sufficient, in defining critical periods of vulnerability of GRPs and their progeny to opiates. If similar patterns of susceptibility occur in vivo, then the implication for these findings would be that the production and maintenance of glial oligodendroglial populations are preferentially vulnerable to chronic opiate exposure and HIV-1 infection. Buch, S.K., Khurdayan, V.K., Lutz, S.E., Knapp, P.E., El-Hage, N., and Hauser, K.F. Glial-Restricted Precursors: Patterns of Expression of Opioid Receptors and Relationship to Human Immunodeficiency Virus-1 Tat and Morphine Susceptibility In Vitro. Neuroscience, 146, pp. 1546-1554, 2007.

Dynamic BDNF Activity in Nucleus Accumbens with Cocaine use Increases Self-Administration and Relapse

Brain-derived neurotrophic factor (BDNF) is important in regulating synaptic plasticity in the brain areas that process reward information. A new study reports that BDNF in the nucleus accumbens, a brain area critical for the rewarding effects of cocaine, promotes persistent cocaine-seeking behaviors and heightens relapse vulnerability. Dr. David Self and his colleagues tested whether BDNF is necessary and sufficient to mediate cocaine reward. Self and colleagues report that cocaine self-administration produced an increase in the levels of BDNF, whereas natural rewards, such as food, did not. Self and colleagues reported also that injections of BDNF directly into the nucleus accumbens increased cocaine self-administration in rats while an antibody to BDNF decreased cocaine self-administration. Furthermore, rats receiving repeated injections of BDNF worked harder for cocaine than rats working for cocaine without BDNF injections. Thus, BDNF appears to enhance the motivation to cocaine and possibly promote the transition to the addicted state. Self and colleagues report also that cocaine self-administration in response to stress or to cocaine associated cues was enhanced by prior treatment with BDNF, while infusion of the BDNF antibody blocked enhanced responding. Finally, using a genetically engineered mouse Self and his colleagues report that turning off the BDNF gene in the nucleus accumbens decreased BDNF by 40% and decreased the rewarding properties of cocaine. These results suggest that BDNF synthesized in the nucleus accumbens in response to cocaine mediates increases in self-administration and reinstatement of drug seeking behavior. Thus, BDNF may play an important role in the development of addiction. Graham, D.L., Edwards, S., Bachtell, R.K., DiLeone, R.J., and Rios, M. Dynamic BDNF Activity in Nucleus Accumbens with Cocaine Use Increases Self-administration and Relapse. Nature Neuroscience, 10, pp. 1029 - 1037, 2007.

Loss of MicroRNAs in Differentiated Neurons Leads to Neurodegeneration and Death

Our traditional concept of gene regulation has been that a gene made up of DNA is transcribed into mRNA, encoding instructions for making a protein, and sent out into the cytoplasm where the mRNA is then translated into a protein. Recent work now shows that in addition to coding mRNAs our genomes encode thousands of RNAs that do not code for proteins and the functions of some of these non-coding RNAs are just beginning to be elucidated. Do some of these

molecules have special functions in the nervous system? There is evidence for non-coding RNA function in neural development, but little work has been done to investigate the function of non-coding RNAs in adult neurons. Dr. Anne Schaefer and her coworkers in the Greengard laboratory have identified a possible role for some of these non-coding RNAs in neurodegenerative disorders. These researchers eliminated a subset of non-coding RNAs, the ~22 base pair microRNAs, from Purkinje neurons. This was done using a genetic trick, in which Dr. Schaefer and colleagues specifically eliminated the Dicer protein (usually required for proper processing of microRNA precursor molecules into their mature functional forms) from the Purkinje neurons only after these neurons had reached adulthood. This manipulation leads to the reduction and eventual loss of many microRNAs in the Purkinje neurons over time. The normal function of the Purkinje neurons is to control motor output from the cerebellum, and impaired Purkinje neuron function is associated with locomotor function problems such as tremors and ataxia. The researchers found that Purkinje neurons lacking Dicer appeared normal, suggesting that the neurons had developed properly. However over time, these neurons exhibited reduced expression of many microRNA subtypes, altered dendritic spine morphology, neurodegeneration, and eventual cell death. Interestingly the mouse pups that lacked Dicer in the Purkinje cells initially had normal behavior, however these animals began to exhibit both tremor and ataxia, with the ataxia becoming more pronounced over time. This work suggests that microRNAs are required for the survival of Purkinje neurons, and possibly other neuronal subtypes, and that elimination of at least some as yet unidentified microRNAs from these neurons leads to neurodegeneration and eventually death. It is therefore possible that therapeutic agents that modulate microRNAs and their associated molecular pathways may be potentially useful in treating neurodegenerative disorders such as Alzheimer's or Parkinson's disease. The role of microRNAs and other non-coding RNAs in addictive processes is not known, but likely to be a fruitful area for future scientific investigation. Schaefer, A., O'Carroll, D., Tan, C.L., Hillman, D., Sugimori, M., Llinas, R., and Greengard, P. Cerebellar Neurodegeneration in the Absence of MicroRNAs. J. Exp. Med. 204, pp.1553-1558, 2007.

ERK May Play Roles in Addiction through mTOR Pathway Stimulation

Extracellularly regulated kinases (ERK) play important roles in drug addiction. For example, evidence from rodent studies suggest that ERK has roles in cocaine psychomotor sensitization, cocaine reward, consolidation and reconsolidation of memories for cocaine cues, and time-dependent increases in cocaine seeking after withdrawal. However the cellular mechanisms in drug-induced adaptations are not known. A group of NIDA funded researchers at Mount Sinai School of Medicine, New York recently reported that a link of ERK to mammalian target of rapamycin (mTOR) modulated protein translation in dendritic arbor in hippocampus neurons is found. Dendritic protein translations in neurons forming the CA3-CA1 synapses in the hippocampus are required for memory formation. Such protein translations are initiated when these synapses are stimulated, resulting in long term potentiation (LTP) of the stimulated synapses. In the present study, the team observed that ERK regulates mTOR through the stimulation of PI3K/Akt signaling pathway. First, ERK activity is required for the high frequency stimulation induced phosphorylation of p70S6K, an mTOR effector. Second, they discovered that ERK activates the PI3K-mTOR pathway by directly phosphorylating RSK and Akt, thereby activating PI3K upstream and at the same time suppressing the inhibitors of PI3K-mTOR downstream. Since ERK has been identified to mediate drug addiction and drug seeking behavior, elucidating these signaling events is important for the understanding and treatment of drug abuse and addiction. Tsokas, P., Ma, T., Iyengar, R., Landau, E.M., Blitzer, R.D. Mitogen-activated Protein Kinase Upregulates the Dendritic Translation Machinery in Long-term Potentiation by

Controlling the Mammalian Target of Rapamycin Pathway. Journal of Neuroscience, 27, pp. 5885-5894, 2007.

Cyclin-Dependent Kinase 5 Governs Learning and Synaptic Plasticity Via Control of NMDA Receptor Degradation

Since drug addiction seems to involve learning and memory processes, understanding the mechanisms of learning and memory is relevant to understanding drug addiction. Current evidence suggests that learning and the storage of memories occur by strengthening the connections between neurons. The mechanisms by which synapses, the connections between neurons are strengthened, is not entirely understood. A model for memory storage in the hippocampus is long-term potentiation (LTP) in which a brief repetitive electrical stimulation of a neuronal pathway subsequently enhances the strength of the synaptic connection between the pre-synaptic and post-synaptic neuron. In this study, Paul Greengard and colleagues report that conditional knockout of cyclin-dependent kinase 5, Cdk5, in the adult mouse brain improved performance in spatial learning tasks and enhanced hippocampal long-term potentiation and NMDA receptor (NMDAR)-mediated excitatory postsynaptic currents. Enhanced synaptic plasticity in Cdk5 knockout mice was attributed to reduced NMDAR subunit 2B, NR2B, degradation rather than increased expression. The reduced degradation caused elevations in total, surface and synaptic NR2B subunit levels and current through NR2B-containing NMDARs. The next question is how is Cdk5 mediating degradation of NR2B? In this study, Cdk5 and its cofactor p35, were extracted from cells as a complex with NR2B and calpain, a calcium-dependent protease, using co-immunoprecipitation. These data suggest that Cdk5 facilitates the degradation of NR2B by directly interacting with both it and its protease, calpain. The data also imply that Cdk5 is a critical mediator of calpain degradation of NR2B. These findings reveal a previously unknown mechanism by which Cdk5 facilitates calpain-mediated proteolysis of NR2B and may control synaptic plasticity and ultimately learning. Hawasli, A.H., Benavides, D.R., Nguyen, C., Kansy, J.W., Hayashi, K., Chambon, P., Greengard, P., Powell, C.M., Cooper,. D.C, and Bibb, J.A. Cyclin-dependent Kinase 5 Governs Learning and Synaptic Plasticity Via Control of NMDAR Degradation. Nat Neurosci. 10(7), pp. 880-886, 2007. Epub 2007 May 27.

Chromosomal Loci That Influence Oral Nicotine Consumption in C57BL/6J _ C3H/HeJ F2 Intercross Mice

Previous work has suggested that oral consumption of nicotine in mice is under genetic control. Stitzel and his colleagues have begun to map the regions of the mouse genome associated with the oral consumption of nicotine. These regions associated with a quantitative trait such as the amount of nicotine are defined as quantitative trait loci (QTL). To map the QTLs for oral nicotine administration C57BL/6 mice consuming large amounts of nicotine were crossed with C3H mice that consume very little nicotine. The mice were bred for two generations. In the first generation, F1, the offspring has two copies of each gene - one from the C57BL/6 parent and one from the C3H parent, located on two homologous chromosomes. Variants in some of these genes in the two different strains are associated with difference in the amount of oral nicotine consumed. In the course of making gametes, the homologous chromosomes in the F1 offspring pair and recombine resulting in shuffling of the chomosomes. Each offspring of the F1, the second generation (F2), are then born with different amounts of shuffling that has taken place. Because there are genetic markers in the DNA associated with the trait being mapped, it is possible to locate a region of the chromosome for a trait such as nicotine consumption. Stitzel and his colleagues report the identification of 4 major QTLs accounting for 62% of the variance in the amount of nicotine consumed. These chromosomal loci that influence the amount of nicotine consumed per

day are on mouse Chromosome 1, chromosome 4, chromosome 7, and chromosome 15. Loci on chromosomes 1, 4, and 15 were associated with increased consumption while loci on chromosome 7 appeared to be protective. Chromosome 1, which accounts for most of the variance for amount of nicotine consumed, maps to its synthetic regions that have previously been reported to be associated with nicotine consumption in humans Wang et al., 2005; Bergen and Caporaso, 1999; Goode et al., 2003; XC Li, Karadsheh, M.S., Jenkins, P.N., Brooks, J.C., Drapeau, J.A., Shah, M.S., Lautner, M.A., and Stitzel, J.A. Chromosomal Loci that Influence Oral Nicotine Consumption in C57BL/6J _ C3H/HeJ F2 Intercross Mice. Genes, Brain and Behavior 6(5), pp. 401-410, 2007.

Elevated Vulnerability of Male Adult to Drug Abuse after Prenatal Exposure to Cocaine Seen in Animal Model

It is estimated that for children born in the US 20% have been exposed to drugs of abuse in utero. Young adults who had in-utero drug exposure are more likely to abuse substances and show persistent affective and behavioral deficits; however, the biological bases of such deficits are not well understood. A team of NIDA supported researchers at Harvard University and Cornell University show that in animal models cocaine exposure during brain development changed dopaminergic neuron responses to cocaine in mice and increased their drug seeking behavior. Using brain stimulation-reward (BSR) method, Barry Kosofsky and colleagues report that the reinforcing effect of cocaine is greatly increased in adult male mice who were exposed to cocaine in utero. In pharmacological studies, these researchers demonstrate that a dopamine D1-receptor agonist has a similar effect as cocaine on these mice, indicating the involvement of limbic forebrain dopaminergic neural circuit in the BSR shift. Furthermore, they observed that a dopamine D2-receptor agonist had a biphasic effect on the threshold of BSR. Thus, the low doses increased the BSR threshold, but higher doses decrease the threshold. Similarly, they observed enhanced potency of the D2 agonist in the male adult mice that showed enhanced cocaine potency, which suggests adaptations in dopamine receptors may, in part, account for the changes in the rewarding potency of cocaine in adulthood after prenatal cocaine exposure. These results also provide biological evidence of developmental changes in the brain as consequences of early exposure to drugs of abuse. Malanga, C.J., Riday, T.T., Carlezon, W.A., and Kosofsky, B.E. Prenatal Exposure to Cocaine Increases the Rewarding Potency of Cocaine and Selective Dopaminergic Agonists in Adult Mice. Biological Psychiatry, June 21, 2007. Epub (ahead of print).

Opiate Actions on Neural Cell Movement and Functions

Most chemokines are produced and primarily used by glia for movement of these cells in inflammatory reactions to compensate for insults from environmental changes, including invasion by foreign substances. More recently these peptides have been observed in neurons and are utilized by neural cells for different activities or as a cooperative function with glia in compensating for these insults to the nervous system. Two recent articles by different laboratories correlate these systems in neurons with opioid actions. The first study focuses on the chemokine, CXCL12. Its receptor, CXCR4, and morphine's receptor (MOR) are coexpressed in numerous neurons. In this study, the administration of a MOR ligand, DAMGO, was observed to negate the neuroprotective effects of the chemokine and alter neuron survival.The second study focuses on the chemokine CCL2, which plays a pivotal role in the recruitment of inflammatory cells in the nervous system and is one of only a few chemokines produced by neurons. Opiates, have a variety of immuno-modulatory properties that may influence both neuroinflammatory and neurodegenerative disease processes. The effects of opiates on this chemokine in neurons was studied and compared those in glia. Morphine upregulated CCL2

mRNA and protein in neuronal cultures in a concentration- and time-dependent fashion, but had no effect on CCL2 production in astrocyte or microglial cell cultures. The stimulatory effect of morphine was abrogated by an opiate antagonist indicating a morphine-mediated mechanism. The authors conclude that morphine stimulates CCL2 production in neurons via a morphine-related mechanism. This finding provides another mechanism whereby opiates would affect neuroinflammatory responses. Morphine stimulates CCL2 production by human neurons. Rock, RB., Hu, S.X., Sheng, W.S., and Peterson, P.K. Opiate Actions on Neural Cell Movement and Functions. Neuroinflammation 3, p. 32, 2006.

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Research Findings - Basic Behavioral Research

Low Dose Nicotine Pretreatment Increases Cocaine Reward in Adolescent but not Adult Rats

Prior animal behavioral studies have shown that compared to adult rats, adolescent rats exhibit greater sensitivity to nicotine's stimulant and rewarding effects and lesser sensitivity to nicotine's negative effects. In the present study, Dr. Frances Leslie and colleagues at the University of California at Irvine sought to determine if nicotine pretreatment differentially modulates cocaine self-administration in adolescent and adult rats. Male and female rats, aged postnatal day P28 and P86, were treated twice daily with nicotine (0.03 ug/kg/, i.v.) or saline daily for 4 days. At P32 and P90, the rats were tested for 5 consecutive days for acquisition of cocaine (0.2 or 0.5 mg/kg) self-administration. In the first hour of acquisition, there was more cocaine self-administration by the adolescent nicotine-pretreatment group than by adolescent saline-pretreated animals or by adult nicotine and saline groups. Nicotine pretreatment also significantly enhanced cocaine self-administration in the adolescent, but not adult rats, across the first four of five sessions of cocaine self-administration. In a separate similar experiment with adolescent rats, nicotine pretreatment failed to enhance acquisition of sucrose operant responding, suggesting that nicotine's enhancement of cocaine self-administration does not merely reflect a generalized increase in appetitive responding. The authors conclude these findings suggest "that brief treatment with low doses of nicotine in early adolescence, but not adulthood, may cross-sensitize the brain to cocaine reward" (p.70). McQuown, S.C., Belluzzi, J.D., and Leslie, F.M. Low Dose Nicotine Treatment during Early Adolescence Increases Subsequent Cocaine Reward. Neurotoxicology and Teratology, 29, pp. 66-73, 2007.

Sex Differences in Adolescent-onset vs Adult-onset Nicotine Self-administration

Dr. Ed Levin and colleagues at Duke University previously reported higher levels of nicotine self-administration in adolescent female rats than in adult female rats. This enhancement of nicotine self-administration in adolescence was still observed when animals were tested as adults (Levin et al. Psychopharmacology, 169, pp. 141-149, 2003). To complement this previous study, Dr. Levin and his colleagues have now conducted a parallel study in males. They found male adolescent rats, like female adolescent rats, self-administered more nicotine on a per kilogram basis than adults. Additionally, they found two important sex differences. First, males were more vulnerable to this adolescent enhancement effect than females: compared to adult onset nicotine self-administration, the adolescent enhancement was two-fold in females, but three-fold in males. Second, unlike the female rats that persisted

in higher rates of self-administration when they became adults, male rats exhibit adult-like levels of nicotine self-administration after the adolescent period. Thus, male rats appear to be more vulnerable than females to the adolescent enhancement effect, but only females exhibited a persistence of this enhancement into adulthood. Levin, E.D., Lawrence, S.S., Petro, A., Horton, K., Rezvani, A.H., Seidler, F.J., and Slotkin, T.A. Adolescent vs. Adult-onset Nicotine Self-administration in Male rats: Duration of Effect and Differential Nicotinic Receptor Correlates. Neurotoxicology and Teratology, 29, pp. 458-465, 2007.

An Improved Transdermal Drug Delivery Patch using Voltgage-gated Carbon Nanotube Membranes

Dr. Bruce Hinds and his colleagues at the University of Kentucky have developed a novel membrane patch that can be opened or closed by applying a low voltage to provide an improved well-controlled method of transdermal drug delivery. The patch is made of a polymer film through which an array of aligned hollow-core carbon nanotubes passes. These permeable membranes are now being tested with drugs such as nicotine and fentanyl with the goal of providing a patient-controlled, noninvasive flexible dosing regimen. Majumber, M., Zhan, X., Andrews, R., and Hinds B.J. Voltage Gated Carbon Nanotube Membranes. Langmuir 23, pp. 8624-8631, 2007.

Antidepressant-like Properties of Cytisine, a Partial Agonist of Nicotinic Acetylcholine Receptors

Anecdotal and self-reports from smokers suggest that nicotine via cigarette smoking can help regulate mood. Indeed, published reports have indicated that depressed subjects have an increased incidence of smoking and that smoking cessation is often associated with increased signs of depression. Dr. Marina Picciotto and her colleagues at Yale University School of Medicine have studied the role that nicotine may play in modulating neuronal systems that control mood. Specifically, they examined the effects of cytisine, a partial agonist of alpha4-beta2 acetylcholine receptors and a full agonist at alpha3-beta4 receptors, using a number of mouse models of depression and c-fos expression. Cytisine exhibited antidepressant-like activity in the tail suspension, forced swim, and novelty-suppressed feeding tests, all shown by others to be responsive to acute administration of antidepressants in mice. These effects did not appear to involve motivation to acquire food, differences in metabolism, or levels of activity. Effects of cytisine on c-fos activity were examined to determine which particular brain regions might be involved. Interestingly, regions involved with dopaminergic and cholinergic neurotransmission did not appear to be involved, while C-fos activity in the amygdala was markedly reduced. These findings provide new information on the role of cholinergic systems involved in mood regulation, suggesting that cytisine and other such agents acting on the alpha4-beta2 neuronal acetylcholine receptors may be potential target compounds for new antidepressant drugs. Mineur, Y.S., Somenzi, O., and Picciotto, M.R. Cytisine, A Partial Agonist of High-affinity Nicotinic Acetylcholine Receptors, has Antidepressant-like Properties in Male C57BL/6J Mice. Neuropharmacology 52, pp. 1256-1262, 2007.

Effects of Uncontrollable Stress on Responses to Drugs of Abuse

Acute stress has been shown to facilitate the rewarding effects of a number of commonly abused drugs when the stressor is administered either immediately before or during drug administration and often in the same environment. Dr. Steven Maier and his colleagues have previously reported that a single session of uncontrollable (inescapable tailshock, IS), but not controllable (escapable

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tailshock, ES), stress can enhance the conditioned place preference (CPP) response to morphine, even when stressor and drug administration are separated temporally and spatially. However, this persistent, trans-situational enhancement was not seen with amphetamine CPP. In two new studies, they have further explored the ability of IS to enhance drug reward. The first study asked whether the long-term effect of IS is specific to opioids. Rats were exposed to a single session of IS or left in their home cage (HC). Twenty-four hours later, CPP was conducted with oxycodone, cocaine, or ethanol. IS enhanced the subsequent CPP response to oxycodone, but not to cocaine or ethanol. A complementary experiment tested whether enhancement of oxycodone CPP, as in the previous experiments with morphine, was dependent on the "escapability" of the stressor. Rats were exposed to IS, ES, or HC treatment and conditioned with oxycodone 24 h later. The results showed that enhancement was dependent on the stressor, as ES did not affect oxycodone CPP. Collectively, these findings indicate that the long-term, trans-situational enhancing effect of uncontrollable stress on drug reward is specific to opioids. In a second study, they asked whether IS might have a long-lasting effect on responses to drugs other than opioids if drug exposure were immediately preceded by a mild stressor. First, they measured the locomotor response to cocaine 48 h after a single session of IS. Then, this procedure was repeated, except that half of the rats received two footshocks immediately before cocaine administration. Finally, they manipulated the escapability of the initial stressor such that rats received either ES or IS 48 h prior to footshock + cocaine. IS did not affect the subsequent locomotor response to cocaine, but did enhance this response when cocaine administration was immediately preceded by two footshocks, while footshocks alone (in the absence of IC 48 hr earlier) were without effect. This sensitizing effect was dependent on the "escapability" of the initial stressor, as ES did not alter the locomotor response to footshock + cocaine. These results indicate that acute exposure to IS, but not ES, can sensitize the locomotor response to cocaine 48 h later, but only when cocaine administration is immediately preceded by a brief stressor. This research reveals that uncontrollable stress can have long-lasting effects on magnitude of drug reward, but that this effect varies and depends on the drug class. Der-Avakian, A., Rozeske, R.R., Bland, S.T., Watkins, L.R., and Maier, S.F. The Effects of a Single Session of Inescapable Tailshock on the Subsequent Locomotor Response to Brief Footshock and Cocaine Administration in Rats. Psychopharmacology (Berl). 191, pp. 899-907, 2007; Der-Avakian, A., Bland, S.T., Rozeske, R.R., Tamblyn, J.P., Hutchinson, M.R., Watkins, L.R., and Maier, S.F. The Effects of a Single Exposure to Uncontrollable Stress on the Subsequent Conditioned Place Preference Responses to Oxycodone, Cocaine, and Ethanol in Rats. Psychopharmacology (Berl), 191. pp. 909-917, 2007.

Exposure to Marijuana Smoke Impairs Memory Retrieval in Mice

Studies have shown that delta-9-tetrahydrocannabinol (_9-THC) and other cannabinoids disrupt performance in a wide range of animal models of learning and memory. However, few studies have investigated the effects of smoked marijuana in these paradigms, although marijuana smoke contains over 60 cannabinoid components in addition to _9-THC, and several hundred non-cannabinoid chemicals. In addition, cannabinoids are generally administered before acquisition, and retention is evaluated soon afterwards; thus it is difficult to distinguish between processes related to acquisition and retrieval. In the present study, Dr. Aron Lichtman and his colleagues investigated specific effects of marijuana smoke and injected _9-THC on acquisition versus memory retrieval in mice using a repeated acquisition Morris water-maze task. The smoke exposure system was recently developed in Dr. Lichtman's laboratory and has been used in two other recent studies. For the memory tests, in order to distinguish between acquisition and retrieval, subjects were administered _9-THC or exposed to marijuana smoke either 30 min before acquisition or 30 min before the retention test. Inhalation of marijuana smoke or injected _9-

THC impaired the ability of the mice to learn the location of the hidden platform and also to recall the platform location once learning had already taken place. In contrast, when the platform was visible, neither drug impaired performance, indicating that the drugs had not impaired other abilities necessary to perform the task. They also found that the CB1 receptor antagonist rimonabant prevented the memory disrupting effects of both _9-THC and marijuana. This is the first study demonstrating that marijuana smoke impairs memory retrieval through a CB1 receptor mechanism, independent of its effects on sensorimotor performance, motivation, or initial acquisition. Niyuhire, F., Varvel, S.A., Martin, B.R., and Lichtman, A.H. Exposure to Marijuana Smoke Impairs Memory Retrieval in Mice. Journal of Pharmacology and Experimental Therapeutics, June 22, 2007. Epub ahead of print.

Single Gene Affects Nicotine Dependence and Stress-Related Behaviors

NIDA grantee Dr. Noboru Hiroi and colleagues investigated the role of fosB -- a Fos family transcription factor -- as a pleiotrophic factor. That is, their investigation approached the study of fosB as a single genetic factor that affects many phenotypes related to both nicotine-induced behavioral traits and stress-related traits. Genetically modified mice (wild-type and fosB knock-out) were compared using a conditioned place preference procedure. Although animals showed no initial difference in preference for the two sides of the chamber, environments paired with various doses of nicotine were differentially preferred and/or avoided. Specifically, the low dose of nicotine (0.2 mg/kg) was preferred by wild-type (WT) but not knockout (KO) mice. At the moderate dose of nicotine (0.6 mg/kg), WT type mice showed neither a preference nor aversion, however the KO mice showed a conditioned aversion. At the high dose of nicotine (0.8 mg/kg), both WT and KO showed a conditioned place aversion. These data suggest that the KO mice may be less sensitive to the rewarding properties of nicotine, but more sensitive to its negative properties. When WT and KO mice were given access to oral nicotine using a 2-bottle choice paradigm, the WT had greater nicotine intake (a finding that was not due to reduced fluid intake by the KO mice). This finding appears to be nicotine-specific, as there were no significant differences in the levels of saccharin preference or quinine aversion using the same choice paradigm. Paralleling findings from the CPP study, these choice data also suggest that KO mice have reduced sensitivity to the rewarding properties of nicotine. In addition to differences in nicotine reward and aversion, there were also differences in nicotine-suppressed motor activity. Although WT and KO mice displayed similar levels of nicotine-suppressed motor activity following acute, centrally administered nicotine to the nucleus accumbens, the KO mice lost motor suppression more quickly than WT mice. When administered into the nucleus accumbens and caudate putamen, repeated nicotine exposure did not stimulate fosB or delta fosB in the KO mice, but did induce them in WT mice. Testing with behavioral measures of stress (inescapable open field), revealed that KO mice had heightened responses. This was true following either saline or nicotine, indicating that enhanced stress responsivity was not just a selective sensitivity to the drug nicotine. In addition, a series of control experiments revealed that the differences found by Hiroi and colleagues could not be attributed merely to differences in nicotine metabolism, or differences between groups on novelty preference. Collectively, these findings suggest that fosB represents a single genetic factor that affects both nicotine-induced behavior and behavioral sensitivity to environmental stress. Zhu, H., Lee, M., Agatsuma, S., and Hiroi, N. Pleiotropic Impact of Constitutive fosB Inactivation on Nicotine-induced Behavioral Alterations and Stress-related Traits in Mice. Human Mol Genetics, 16(7), pp. 820-836, 2007.

Adolescent Rats Are Less Sensitive to the Aversive Effects of THC

Recent studies show that, compared to their adult counterparts, adolescent animals are more sensitive to the rewarding properties of many drugs of abuse and less sensitive to aversive properties. These differences may account for a propensity to initiate drug use during adolescence and greater risk to escalate and develop dependence. Given the high frequency of marijuana abuse in adolescents, researchers at Duke University Medical Center have been investigating developmental vulnerabilities to THC's behavioral effects. In a 2007 report from Schramm-Sapyta et al., evidence is provided to suggest that adolescent rats (28 days of age) are less sensitive to anxiogenic or aversive effects of 0.5 to 2.5 mg/kg THC than adults tested at 64-66 days of age. The researchers employed two tests of anxiety - the elevated plus maze (EPM) and the light-dark task (LDT). Adolescents were also less sensitive to THC's locomotor reducing effects on these two tasks. Two tests of the aversive properties of THC - conditioned taste aversion (CTA) and conditioned place aversion (CPA)- were employed. While both age groups demonstrated CTA, adults were more sensitive to this effect, showing a greater reduction in THC-paired saccharin than adolescents. On CPA, adults showed an aversion at 5.0 mg kg, and adolescents did not develop an aversion at any dose. The researchers also measured ACTH and corticosterone levels to examine differences in THC-induced HPA activation that might account for these behavioral differences. Adults had a higher ACTH response after THC, suggesting that the drug may induce a greater stress response. In conclusion, the authors report less THC-induced aversive and anxiety related effects in adolescents, that cannot be attributed to differential locomotor effects, since THC doses that produced these effects were associated with the least locomotor changes in these paradigms. Baseline observations corroborate previous studies to suggest that adolescents take more behavioral risks. It is unclear if maturation of central CB1 receptor systems might underlie these observations. Whatever the mechanism, less aversive effects of the drug THC at younger ages may contribute to this drug's popularity during adolescence. Schramm-Sapyta, NL., Cha, Y.M., Chaudhry, S., Wilson, W.A., Swartzwelder, H.S., and Kuhn, C.M. Differential Anxiogenic, Aversive, and Locomotor Effects of THC in Adolescent and Adult Rats. Psychopharmacology, 191, pp. 867-877, 2007.

Self-Control, Symptomatology and Substance Use in 9 yr Old Children

NIDA researcher, Rick Gibbons and colleagues, tested a theoretical model of how self-control constructs are related to psychological symptomatology and variables that predispose to involvement versus noninvolvement in substance use: willingness to use, affiliation with peers who use, and efficacy for resisting use. Data were obtained from a sample of 332 children, mean age = 9.3 years, who were interviewed in their homes. Overall, self-control constructs were significantly related to symptomatology or well-being. Moreover, the results showed significant pathways from symptomatology measures to predisposing factors plus a direct effect from poor self-control to lower resistance efficacy. The study was conducted with a diverse sample of children, and the results were obtained with control for relevant demographic characteristics, including ethnicity and parental education. The results may have implications for preventive interventions. The results suggest that self-control training components can be included in prevention programs focused on adolescent problem behaviors. The results for predisposing factors suggest that prevention programs for younger children can target perceptions of substance users and resistance efficacy, as there is evidence that both processes can be altered through family- or school-based interventions. Furthermore, prevention research may be designed to examine the implications of more distal factors (e.g., neighborhood disadvantage, racial discrimination), as well as more proximal factors such as peer affiliations. Finally, the present results suggest that cognitive and motivational processes are more salient for young boys,

whereas social processes are more salient for young girls. These gender differences need to be replicated, but results of this type need exploration because of their implications for targeted prevention programs. Wills, T.A., Ainette, M.G., Mendoza, D., Gibbons, F.X., and Brody, G.H. Self-Control, Symptomatology, and Substance Use Precursors: Test of a Theoretical Model in a Community Sample of 9-Year-Old Children. Psychology of Addictive Behaviors, 21, pp. 205-215, 2007.

Protection Against Early Onset Of Substance Use And Sexual Behavior Among African Americans

NIDA researcher, Rick Gibbons and his colleagues, tested a theoretical model relevant for averting early onset of substance use and sexual behavior among rural African American youth. The model posits that substance use and early sexual behavior are influenced by a number of variables including the type of parenting a child experiences, self-control, ethnic esteem, academic and social competence, peer behavior, etc. A community sample of 670 African American youth, mean age of 11.2 years, were interviewed in their homes. The main outcome measures were use of cigarettes and alcohol and incidence of sexual behavior. Other variables included measures of parenting (parent-child interaction), racial socialization, self control, ethnic pride and self-esteem, academic and social competence, attitudes towards deviance, substance use willingness, substance use, sexual behavior, etc. Data were collected by self report and from caregivers and teachers where relevant. Prevalence data indicated that rates of substance use and sexual behavior were low but not zero. For alcohol, 14% of the participants indicated that they had ever drunk alcohol. For smoking, 6% of the participants indicated that they had ever smoked cigarettes. For sexual behavior, 3% of the sample indicated they had ever had sex. The data indicated generally low levels of willingness for substance use and high levels of resistance efficacy, consistent with previous data from similar populations. In comparison to data for substance use, the level of actual sexual behavior was lower, but the level of willingness was higher. Structural equation modeling indicated parenting was related to self-control and self-esteem, and racial socialization was related to ethnic pride. Self-control and self-esteem variables were related to levels of deviance-prone attitudes and to perceptions of those who engage in, or abstain from, substance use and sexual behavior. The proximal factors (behavioral willingness, resistance efficacy, and peer behavior) had substantial relations to substance use and sexual behavior. Thus, in this population, self-esteem and self-control are related to parenting approaches and have pathways to attitudes and social perceptions that are significant factors for predisposing to, or protecting against, early involvement in substance use and sexual behavior. Wills, T.A., Murry, V.M., Brody, G.H., Gibbons, F.X., Gerrard, M., Walker, C., and Ainette, M.G. Ethnic Pride and Self-Control Related to Protective and Risk Factors: Test of the Theoretical Model for the Strong African American Families Program. Health Psychology, 26, pp. 50-59, 2007.

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

Research Findings - Behavioral and Brain Development Research

Demographic and Psychosocial Characteristics of Mothers Using Methamphetamine During Pregnancy: Preliminary Results from the Infant Development, Environment, and Lifestyle Study (IDEAL)

The psychological characteristics and caretaking environments of 131 women enrolled in the first longitudinal study of prenatal methamphetamine (MA) exposure and child development were examined. Preliminary results from this study found that prenatal MA use was associated with lower maternal perceptions on quality of life, greater likelihood of substance use among family and friends, increased risk for ongoing legal difficulties, and a markedly increased likelihood of developing a substance abuse disorder. Preliminary findings also suggest that MA using women are more likely to have multiple, intertwined psychosocial risks that may result in maladaptive parenting and caregiving. These factors may impact the developmental outcomes of affected children. Derauf, C., LaGasse, L.L., Smith, L.M., Grant, P., Shah, R., Arria, A., Huestis, M., Haning, W., Strauss, A., Della Grotta, S., Liu, J., and Lester, B.M. Demographic and Psychosocial Characteristics of Mothers Using Methamphetamine During Pregnancy: Preliminary Results of the Infant Development, Environment, and Lifestyle study (IDEAL). The American Journal of Drug and Alcohol Abuse, 33(2), pp. 281-289, 2007.

Impact of Prenatal Cocaine Exposure on Attention and Response Inhibition

This study examined the influence of prenatal cocaine exposure on attention and response inhibition measured by continuous performance tests (CPTs) at ages 5 and 7 years. Participants included 219 cocaine-exposed and 196 non-cocaine-exposed children enrolled prospectively at birth and assessed comprehensively through age 7 years in the longitudinal Miami Prenatal Cocaine Study. Deficits in attention and response inhibition were 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.H., Amado, A.J., Morrow, C.E., Xue, L., Anthony, J.C., Bandstra, E.S. Impact of Prenatal Cocaine Exposure on Attention and Response Inhibition as Assessed by Continuous Performance Tests. Journal of Developmental and

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Behavioral Pediatrics, 28(3), pp. 195-205, 2007.

Children's Language Trajectories Relative to Prenatal Cocaine Exposure

In this ongoing longitudinal study at Case Western Reserve University, language development was assessed at 1, 2, 4, and 6 years of age, and performance was analyzed for two groups of children based on cocaine exposure in utero (209 exposed, 189 not exposed). The groups were compared on receptive, expressive, and total language scores across time. Multiple potentially confounding and moderating factors were included in the analyses. A relationship between prenatal cocaine exposure and language development was seen over time for receptive, expressive, and total language scores, with cocaine exposure related to poorer performance. Analyses also indicated that prenatal tobacco exposure was related to lower receptive language scores, and that environmental factors were associated with language scores. The authors note that their findings are consistent with and extend the findings of other longitudinal studies of prenatal cocaine exposure and language development. In addition, it was noted that both the cocaine-exposed and nonexposed children declined in language performance over time, a result believed to be related to factors common to both groups (such as low SES, education, and poverty), and also consistent with findings from another prenatal cocaine exposure cohort study. Lewis, B.A., Kirchner, H.L., Short, E.J., Minnes, S., Weishampel, P., Satayathum, S., and Singer, L.T. Prenatal Cocaine and Tobacco Effects on Children's Language Trajectories. Pediatrics, 120(1), pp. e78-e85, 2007.

Prenatal Cocaine Exposure and Physical Growth Patterns to Age 8 Years

This report focuses on longitudinal growth patterns in a cohort of children observed from birth until 8 years of age following prenatal exposure to cocaine. Birth weight, length, and head circumference were recorded. Weight, length or height, and head circumference were assessed at 6, 12, 24, 48, 72, and 96 months of age. Analyses were reported for 202 primarily African American/ Caribbean children. Ninety of these children were classified as prenatally unexposed to cocaine, 38 as having heavier cocaine exposure (top quartile of meconium concentration for cocaine metabolites, and/or top quartile days of self-reported use during the entire pregnancy), and 74 as having lighter exposure. Prenatal cocaine and prenatal alcohol exposure were independently associated with lower weight, length, and head circumference at birth. The relationships between prenatal cocaine exposure and longitudinal growth patterns to 8 years of age were analyzed using multiple linear regression models, including covariates of gestational age, gender, ethnicity, age at assessment, current caregiver, birth mother's use of alcohol, marijuana, and tobacco during the pregnancy, and maternal pre-pregnancy weight and height indicators. The association of prenatal cocaine exposure and growth did not persist beyond the neonatal period. The authors report that although the rate of change in growth parameters for cocaine-exposed children (heavier exposure compared to unexposed, and lighter exposure compared to unexposed) exceeded those of unexposed children in the first two years and then lagged up to age 4, the negative association with cocaine ultimately largely dissipated by school age. The authors also note that their findings agree with school-age results from another cohort of children prenatally exposed to cocaine, and differ in some ways from the findings for two other study cohorts, adding that ongoing examination of growth patterns in their cohort as well as in cohorts from other studies will continue to clarify the potential impact of in utero cocaine exposure on growth patterns to school age and beyond. Lumeng, J.C., Cabral, H.J., Gannon, K., Heeren, T., and Frank, D.A. Pre-natal Exposures to Cocaine and Alcohol and Physical Growth Patterns to Age 8 Years.

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Neurotoxicology and Teratology, 29(4), pp. 446-457, 2007.

Visuospatial Working Memory in School-Aged Children Exposed in Utero to Cocaine

Among the neurocognitive impairments reported as associated with prenatal cocaine exposure, slower response time, and less efficient learning in school-aged children are common to findings from several laboratories. This study by Dr. Linda Mayes and her colleagues presents performance data on a spatial working memory task in 75 prenatally cocaine exposed (CE) and 55 nondrug-exposed (NDE) 8- to 10-year-old children. Children were administered a novel neuropsychological measure of immediate- and short-term memory for visuospatial information, the Groton Maze Learning Test (GMLT), a computer-based hidden maze learning test that consists of a "timed chase test" (a simple measure of visuomotor speed), eight learning trials followed by a delayed recall trial after an 8-minute delay and a reverse learning trial. Performance is expressed as correct moves per second and number of errors per trial. Across all trials, the cocaine-exposed group showed significantly slower correct moves per second and made significantly more errors. There were no significant main effects for amounts of alcohol, tobacco, or marijuana exposure. After an 8-minute delay and compared to the eighth trial, cocaine-exposed children showed less consolidation in learning compared to nonexposed children. When asked to complete the maze in reverse, cocaine-exposed children showed a greater decrement in performance (decreased correct moves per second and increased errors) compared to the eighth learning trial. Children exposed in utero to cocaine exhibit a possible impairment in procedural learning and diminished efficiency in creating and accessing an internal spatial map to master the hidden maze. Mayes, L., Snyder, P.J., Langlois, E., and Hunter, N. Visuospatial Working Memory in School-aged Children Exposed in utero to Cocaine. Child Neuropsychology, 13(3), pp. 205-218, 2007.

Multivariate Examination of Brain Abnormality Using Structural and Functional MRI with Adolescents Prenatally-Exposed to Cocaine

This article presents a methodological framework for extracting regional brain features simultaneously from both structural and functional images as a means for detecting brain abnormalities, and reports on the application of this method with a sample of 25 adolescents who had been exposed to cocaine in utero and a socioeconomically-matched comparison group of 24 non-exposed adolescents. High-resolution 3D structural MRI and arterial spin labeling perfusion MRI were the imaging modalities used. The procedure involved a regional statistical feature extraction approach to capture discriminative features from voxel-wise morphometric and functional representations of brain images. This feature extraction method was used in conjunction with a hybrid feature selection method and a nonlinear support vector machine for the classification of brain abnormalities. The investigators conclude that the method is capable of accurately detecting spatially distributed and complex patterns of brain alterations associated with prenatal cocaine exposure in an adolescent sample. Fan, Y., Rao, H., Hurt., H., Giannetta, J., Korczykowski, M., Shera, D., Avants, B.B., Gee, J.C., Wang J., and Shen, D. Multivariate Examination of Brain Abnormality Using Both Structural and Functional MRI. Neuroimage, 36(4), pp. 1189-1199, 2007.

Abnormal Cortical Thickness and Brain-Behavior Correlation Patterns in Individuals with Heavy Prenatal Alcohol Exposure

Quantitative magnetic resonance imaging (MRI) studies in children with fetal alcohol spectrum disorders (FASDs) have shown regional patterns of

dysmorphology, most prominent in parietal and posterior temporal cortices. Various methods of image analysis have been employed in these studies, but abnormalities in cortical thickness have not yet been mapped over the entire cortical surface in individuals with FASD. Further, relationships between cognitive dysfunction and cortical thickness measures have not yet been explored. In this study Dr. Elizabeth Sowell and her colleagues applied cortical pattern matching algorithms and techniques for measuring cortical thickness in millimeters to the structural brain MRI images of 21 subjects with heavy prenatal alcohol exposure (8-22 years, mean age 12.6 years), and 21 normally developing control subjects (8-25 years, mean age 13.5 years). Dissociable cognitive measures, of verbal recall and visuospatial functioning, were correlated with cortical thickness, and group by test score interactions were evaluated for predicting cortical thickness. Significant cortical thickness excesses of up to 1.2 mm were observed in the FASD subjects in large areas of bilateral temporal, bilateral inferior parietal, and right frontal regions. Significant group by test score interactions were found in right dorsal frontal regions for the verbal recall measure and in left occipital regions for the visuospatial measure. These results are consistent with earlier analyses from this and other research groups and, for the first time, show that cortical thickness is also increased in right lateral frontal regions in children with prenatal alcohol exposure. Further, the significant interactions show for the first time that brain-behavior relationships are altered as a function of heavy prenatal alcohol exposure. Sowell, E.R., Mattson, S.N., Kan, E., Thompson, P.M., Riley, E.P., and Toga, A.W. Abnormal Cortical Thickness and Brain-Behavior Correlation Patterns in Individuals with Heavy Prenatal Alcohol Exposure. Cerebral Cortex, April 18, 2007 (e-published ahead of print).

fMRI of Verbal Learning in Children with Heavy Prenatal Alcohol Exposure

Dr. Elizabeth Sowell and her colleagues examined functional MRI activation patterns corresponding to verbal paired associate learning in a group of 11 children (between 8 and 13 years of age) with heavy prenatal alcohol exposure compared with 16 typically-developing children (between 7 and 15 years old). Among the typically developing children, prominent activation was observed in the left medial temporal lobe, left dorsal frontal lobe and bilateral posterior temporal cortices during learning and recall. Analyses revealed significantly less activation in left medial and posterior temporal regions and significantly more activation in right dorsal frontal cortex in the alcohol-exposed children relative to controls, even when group differences in memory test performance were statistically controlled. These results may indicate an increased reliance on frontal memory systems in the children with heavy prenatal alcohol exposure, perhaps compensating for dysfunctional medial temporal memory systems. These findings are consistent with neuropsychological and structural imaging studies, and provide the first evidence for brain activation abnormalities, independent of group performance differences, during verbal learning and recall in children with heavy prenatal alcohol exposure. Sowell, E.R., Lu, L.H., O'Hare, E.D., McCourt, S.T., Mattson, S.N., O'Connor, M.J., and Bookheimer, S.Y. Functional Magnetic Resonance Imaging of Verbal Learning in Children with Heavy Prenatal Alcohol Exposure. NeuroReport, 18(7), pp. 635-639, 2007.

Magnetic Resonance and Spectroscopic Imaging in Prenatal Alcohol-Exposed Children: Preliminary Findings in the Caudate Nucleus

This study was designed to identify and compare the neuroanatomical and neurochemical abnormalities that are associated with prenatal exposure to alcohol in both fetal alcohol syndrome (FAS)-diagnosed children and those diagnosed with fetal alcohol effects (FAE). MR data of three age-, gender- and

race-balanced small groups of children (age range 9.6 to 12.7 years), FAS-diagnosed, FAE-diagnosed, and non-exposed controls, were compared. Effects of prenatal alcohol exposure, regardless of diagnosis, were found in the caudate nucleus. Specifically, a significantly smaller caudate nucleus was found for the FAS and FAE participants compared to the controls. In addition, the metabolite ratio of N-acetyl-aspartate to creatine (NAA/Cr), an indicator of neuronal function, in left caudate nucleus of both the FAS and FAE participants was elevated compared to the control group. Analysis of absolute concentrations revealed that the increase in the ratio of NAA/Cr was due to an increase in NAA alone. Although its exact function in the CNS is unknown, NAA is believed to be a neuronal marker due to its exclusive localization to neurons. Some also speculate a role for NAA in myelination. Elevated NAA in the prenatal alcohol-exposed participants could indicate a lack of normal programmed cell death, dendritic pruning and/or myelination during development. The present study demonstrates that prenatal alcohol-exposed children, with or without facial dysmorphology, have abnormal brain anatomy and chemistry. Corteses, B.M., Moore, G.J., Bailey, B.A., Jacobson, S.W., Delaney-Black, V., and Hannigan, J.H. Magnetic Resonance and Spectroscopic Imaging in Prenatal Alcohol-exposed Children: Preliminary Findings in the Caudate Nucleus. Neurotoxicology and Teratology, 28(5), pp. 597-606, 2006.

Smoking During Teenage Pregnancies and Behavioral Problems in Offspring

In this paper, Cornelius and colleagues at the University of Pittsburgh report on relationships between prenatal tobacco exposure (PTE) and school-age child behavior in a cohort of 357 offspring of teenage mothers. PTE was defined as any exposure across pregnancy for some of the analyses, and exposure within each trimester in other analyses. Interviews were conducted with the mothers at the fourth or fifth prenatal month visit and within 24-36 hours after delivery. Child exposure to environmental tobacco smoke (ETS) was assessed by urinary cotinine. Average age of the offspring in the analyses was 6.4 years. PTE (any exposure across pregnancy) was a significant predictor ($p < .01$) of increased activity (Routh Activity Scale) when controlling for other prenatal substance exposure, demographics, maternal psychological characteristics, home environment, and ETS. When controlling for the same factors, PTE (in each of the three trimesters) significantly ($p < .01$) predicted increased activity, and PTE (in the second trimester) significantly ($p < .05$) predicted attention problems (SNAP). ETS was not a significant predictor of behavioral outcomes when PTE was taken into account. The researchers indicate that their finding of an association of PTE with higher activity levels in exposed offspring agrees with results from animal and other human studies, and adds new evidence of the strength of this association given the extent of control for covariates in this study. Cornelius, M.D., Goldschmidt, L., DeGenna, N., and Day, N.L. Smoking During Teenage Pregnancies: Effects on Behavioral Problems in Offspring. Nicotine and Tobacco Research, 9(7), pp. 739-750, 2007.

Gender-Specific Effects of Prenatal and Adolescent Exposure to Tobacco Smoke on Auditory and Visual Attention

Smoking during pregnancy results in elevated risks of cognitive and auditory processing deficits and of smoking in the offspring. Preclinical studies have revealed that nicotine exposure in the prenatal and/or adolescent period results in a sex-specific pattern of reduction in cortical cholinergic markers. This study was designed to examine gender-specific effects of exposure to smoking in adolescents on auditory and visual attention. The sample consisted of 181 adolescent smokers and nonsmokers who had previously been exposed to maternal smoking or had not. The results demonstrated that both auditory and visual attention performance accuracy was decreased in females who were exposed to tobacco smoke during prenatal or adolescent development;

however, the greatest deficits on these tasks were seen in female smokers who had also been exposed to tobacco smoke in the prenatal period (combined exposure). The pattern was somewhat different in males in that combined exposure resulted in greater deficits during the auditory attention conditions versus the visual processing tasks. Functional neuroimaging was conducted in a subset of 63 subjects while they were engaged in auditory and visual attentional tasks. In those adolescents with prenatal or adolescent exposure, activation of brain regions that support auditory attention was greater relative to controls with no exposure to tobacco smoke. The results of the functional imaging data suggest that reduced cortical cholinergic neurotransmission resulting from prenatal exposure or adolescent exposure to tobacco smoke results in a loss of efficiency in cortical regions that support auditory attention. This study supports the need for effective smoking prevention programs for women of childbearing age and for adolescents. Jacobsen, L., Slotkin, T., Mencl, W., Frost, S., and Pugh, K. Gender-Specific Effects of Prenatal and Adolescent Exposure to Tobacco Smoke on Auditory and Visual Attention. Neuropsychopharmacology, 2007 March 21; (Epub ahead of print).

The Adolescent Trials Network for HIV/AIDS Interventions: A Case Study of Developing Adolescent Health Community-Researcher Partnerships in Fifteen U.S. Communities

This article describes the partner selection process in 15 U.S. communities developing community-researcher partnerships for the Connect to Protect (C2P): Partnerships for Youth Prevention Interventions, an initiative of the Adolescent Trials Network for (HIV/AIDS) Interventions. Each site generated an epidemiological profile of urban youth in their community, selected a focus population and geographic area of youth at risk for HIV, conducted a series of successive structured interviews, and engaged in a process of relationship-building efforts culminating in a collaborative network of community agencies. Sites chose as their primary target population young women who have sex with men (n = 8 sites), young men who have sex with men (n = 6), and intravenous drug users (n = 1). Of 1162 agencies initially interviewed, 281 of 335 approached (84%) agreed to join the partnership (average 19/site). A diverse array of community agencies were represented in the final collaborative network; specific characteristics included: 93% served the sites' target population, 54% were predominantly youth oriented, 59% were located in the geographical area of focus, and 39% reported provision of HIV/STI (sexually transmitted infection) prevention services. Relationship-building activities, development of collaborative relationships, and lessons learned, including barriers and facilitators to partnership, are also described. Study findings address a major gap in the community partner research literature. Health researchers and policymakers need an effective partner selection framework whereby community-researcher partnerships can develop a solid foundation to address public health concerns. Straub, D.M., Deeds, B.G., Willard, N., Castor, J., Peralta, L., Francisco, V.T., Ellen, J., and the Adolescent Trials Network for HIV/AIDS Interventions. Partnership Selection and Formation: A Case Study of Developing Adolescent Health Community-Researcher Partnerships in Fifteen U.S. Communities. Journal of Adolescent Health, 40(6), 489-498, 2007.

Prototypical Images in Condom Scripts among AIDS-Bereaved Adolescents

Twenty-five HIV-negative late adolescents (13 women and 12 men) who had lost a parent to AIDS generated vignettes in which the characters were deciding whether to use a condom (condom scripts). Two clinically trained judges rated the interpersonal tone of the condom scripts on 17 semantic differential scales. Three other clinically trained raters described script characters' attributes by selecting from a list of 36 terms. Multidimensional scaling (MDS) and individual differences hierarchical classes analyses

(INDCLAS) were used to inductively derive a typology of condom scripts. Two dimensions emerged from MDS analysis: incompatibility and inequality. Condom scripts culminating in unprotected sex depicted situations in which partners held unequal influence. INDCLAS results suggested a prototype for equal-influence condom scripts - excited male and assertive, powerful female, and for unequal-influence (unprotected sex) condom scripts - powerful, disengaged male and permissive female. These results inform the development of theoretical models and HIV prevention program materials. Reich, W.A. and Rubin, R.M. Prototypical Images in Condom Scripts among AIDS-bereaved Adolescents, AIDS Education and Prevention, 19(1), pp. 82-94, 2007.

Predictors of Repeat Pregnancy among HIV-1 Infected Women

In the Women and Infants Transmission Study (WITS), a prospective cohort study of HIV-infected pregnant women at six US mainland and Puerto Rican sites, changes in the HIV-1 epidemic have included higher income, better education, and better-controlled HIV disease among more recently enrolled women. Because these changes may alter the reproductive patterns of these women, an awareness of these women's current reproductive behaviors is essential. Predictors of repeat pregnancy among HIV-1-infected women enrolled in the Women and Infants Transmission Study (WITS) were investigated. Women enrolled in WITS without a history of sterilization were included. Using bivariate and multivariate analyses, predictors of a repeat pregnancy were modeled. Changes in risk factors for repeat pregnancy over time were examined and important predictors of repeat pregnancy were determined. Of 2246 eligible women, 22% had more than one WITS-enrolled pregnancy. In bivariate analyses, risk of repeat pregnancy was associated with younger age, lower educational status, higher CD4%, and lower viral loads. There was little change in risk factors for repeat pregnancy over time. HIV-1-infected women who are younger and healthier are more likely to have more than one pregnancy. Factors associated with repeat pregnancy among HIV-1-infected women have remained stable over time. Awareness of these factors will better equip healthcare providers to address the reproductive needs of HIV-1-infected women. Bryant, A.S., Leighty, R.M., Shen, X., Read, J.S., Brouwers, P., Turpin, D.B., LaRussa, P.S., Pacheco-Acosta, E., Paul, M.E., Vajaranant, M., Tuomala, R.E. and the Women and Infants Transmission Study. Predictors of Repeat Pregnancy among HIV-1 Infected Women. Journal of Acquired Immune Deficiency Syndrome, 44(1), pp. 87-92, 2007.

Heritability of Illicit Drug Use and Transition to Dependence in Southwest California Indians

The rates of drug use and dependence are high in Native Americans, but information is lacking regarding the etiology or clinical course in this high risk population. Dr. Cindy Ehlers conducted analyses from data obtained through a larger study conducted to determine risk factors for substance dependence in Southwest California (SWC) Indians. The analyses conducted in this project were designed to answer questions regarding the age of onset, prevalence and heritability of substance use in the following classes of illicit drugs: marijuana, cocaine, stimulants, sedatives, opiates, hallucinogens, phencyclidine (PCP), and solvents. Progression of substance use to dependence was also determined for each drug class in this community sample. Each participant in the sample which included 460 subjects (190 men and 270 women) was administered the Semi-Structured Assessment for the Genetics of Alcoholism. The participants in this sample reported the first used drugs were solvents and marijuana, which typically occurred at age 14-15. Ninety-one percent of the sample reported using at least one of the illicit drug classes with marijuana (88%) and stimulants (60%) being the most commonly tried substances. Using variance component methods from SOLAR, substantial heritability was found for marijuana, opiates, PCP, sedatives and stimulants, but the results were only

modest for initiation to cocaine, hallucinogens, and solvents. The results from this study suggest that heritability of the initiation of substance use, in SWC Indians, may be similar to other population samples; however, once initiation of the substance has occurred, higher rates of dependence are seen in this population for marijuana, opiates and stimulants. Ehlers, C., Wall, T., Corey, L., Lau, P., Glider, D., and Wilhelmsen, K. Heritability of Illicit Drug Use and Transition to Dependence in Southwest California Indians. Psychiatric Genetics, 17(3), pp. 171-176, 2007.

Depressive Symptoms in Adolescents: Associations with White Matter Volume and Marijuana Use

Decreased white matter and reduced hippocampal volumes have been associated with depressed mood. Chronic marijuana use appears moderately associated with an increased risk of depressive symptoms in both adolescents and adults. The purpose of this study was to examine whether marijuana use moderates the relationship between brain structure and depressive symptoms in an adolescent sample aged 16 - 18. Substance use, mood, and anatomical measures were collected after 28 days of monitored abstinence from marijuana users (n = 16) and demographically similar controls (n = 16). Consistent with prior studies, marijuana users demonstrated higher depressive scores compared to controls. A significant negative relationship was found between increased depressive scores on the Beck Depression Inventory and smaller white matter volume in the marijuana users group, but not the control group. The findings suggest that connections between areas involved in mood regulation may be disrupted by subtle neurodevelopmental white matter abnormalities. Longitudinal studies are needed to address the temporal and directional relationship of white matter volume, marijuana use, and depressive symptoms. Medina, K., Nagel, B., Park, A., McQueeny, T., and Tapert, S. Depressive Symptoms in Adolescents: Associations with White Matter Volume and Marijuana Use. Psychology and Psychiatry, 48(6), pp. 592-600, 2007.

Functional MRI of Inhibitory Processing in Abstinent Adolescent Marijuana Users

The results of studies examining marijuana use in adults have revealed abnormal neural inhibitory processing, compensatory hyperactivity, and altered neural processing differences even in the absence of this drug. Marijuana is the most commonly used illicit substance in the adolescent population. Existing data from the relatively few studies examining the effects of marijuana use in adolescent marijuana users on neurocognition indicate that there are deficits in executive functioning and evidence of neural dysfunction. This study utilized blood oxygen level dependent (BOLD) fMRI during a go/no-go task to examine response inhibition in marijuana using adolescents after being abstinent from the drug for at least 28 days. Although the marijuana users did not differ from the non-users on task performance, an increased BOLD response in dorsolateral prefrontal and parietal areas was seen in the marijuana users compared to control adolescents with limited substance use histories. These results may suggest a greater cognitive load associated with attending to the stimuli in marijuana users. However, it is uncertain whether this pattern of increased brain processing predates the onset of regular use or results from it. Additional studies are warranted to determine if altered inhibitory processing is a risk factor for substance use initiation and escalation. Tapert, S., Schweinsburg, A., Drummond, S., Paulus, M., Brown, S., Yang, T., and Frank, L. Functional MRI of Inhibitory Processing in Abstinent Adolescent Marijuana Users. Psychopharmacology (Berl), 2007 June 9; (Epub ahead of print).

Behavioral Impulsivity in Adolescents With Conduct Disorder Who Use Marijuana

Conduct disorder (CD), which is characterized by a variety of disruptive and antisocial behaviors, is frequently comorbid with substance abuse. A common component underlying both CD and substance abuse is impulsivity. Marijuana is the most frequently used illicit substance among adolescents in the United States, but little is known about the effects of marijuana on impulsivity. This study was designed to examine impulsive behavior in adolescents who have a psychiatric diagnosis of CD and who have used marijuana. Three groups of adolescents who were between 13 to 17 years of age were compared on the Immediate Memory Task (a measure of response initiation). The groups consisted of 1) adolescents with a current diagnosis of CD and a positive urine test for marijuana; 2) adolescents with CD, but with a negative urine-drug screen and 3) healthy adolescents without psychiatric diagnosis or previous drug use. The results showed a significant increase in laboratory impulsive responses across the three groups with the highest proportion of impulsive responses being emitted by the individuals who had CD and a positive urine test for marijuana. Although the results are preliminary, in adolescents with CD, marijuana use may further enhance impulsive behavior. Further studies are needed to determine the specific causal mechanisms for these differences. Dougherty, D., Mathias, C., Liguori, A., Marsh, D., Dawes, M., and Moeller, F.G. Behavioral Impulsivity in Adolescents With Conduct Disorder Who Use Marijuana. Addictive Disorders & Their Treatment. 6(1), pp. 43-50, 2007.

Neurocognitive Functioning in Adolescent and Young Adult Smokers

This study examines cognitive performance at 17-21 years of age in relation to current smoking and past regular smoking, while taking into account cognitive functioning prior to initiation of smoking. All participants were part of a longitudinal study in which they were followed from birth, and for whom data were available on multiple aspects of development, including cognitive functioning prior to initiation of smoking (i.e., in the 9-12 year-old age period). When they were 17-21 years old, 112 participants were divided into four groups, determined by urinalysis and self-report: current heavy smokers (> 9 cigarettes per day), current light smokers (< 9 cigarettes per day), former smokers (had smoked regularly in the past, but had not smoked for at least 6 months), and a comparison group who had never smoked regularly. Regular use was defined as smoking at least once daily. After accounting for potential confounders, including educational attainment, family income, marijuana use, and pre-smoking-initiation cognitive performance, current regular smokers performed worse than non-smokers in a variety of cognitive areas, including receptive and expressive vocabulary, oral arithmetic, and auditory memory. Former smokers differed from the non-smokers only in the arithmetic task. The authors note that the impact of current smoking appears to behave in a dose-response and duration-related fashion. They also indicate that the findings suggest that cognitive deficits associated with regular smoking during early adulthood may be reversed upon cessation. Fried., P.A., Watkinson, B., and Gray, R. Neurocognitive Consequences of Cigarette Smoking in Young Adults - A Comparison with Pre-Drug Performance. Neurotoxicology and Teratology, 28(4), pp. 517-525, 2006.

Impact of Smoking Abstinence on Working Memory Neurocircuitry in Adolescent Daily Tobacco Smokers

Recent surveys indicate that 50% of adolescents in the 12th grade report smoking tobacco at some point in their life and 13.5% report daily use of cigarettes. Nicotine exposure has been shown to induce withdrawal-emergent alterations in dopaminergic transmission in rodents during the adolescent period. Dr. Leslie Jacobsen and her colleagues examined whether acute smoking abstinence in adolescent daily tobacco smokers affects the efficiency

of neurocircuitry supporting working memory. Using functional magnetic resonance imaging, fifty-five daily tobacco adolescent smokers were compared with 38 nonsmokers while performing a task with high verbal working memory load. The smokers were tested during smoking and after 24 hours of abstinence from tobacco use. Less accuracy in performance and greater activation of the left ventrolateral prefrontal cortex and left inferior parietal lobe was seen among the smokers relative to nonsmokers. While nonsmoking adolescents exhibited increases in functional connectivity between components of the working memory neurocircuit with increasing memory load, the adolescent smokers during abstinence did not. The reduced efficiency and alterations in the functional coordination between components of the working memory neurocircuit may be due to the effects of nicotine exposure on catecholaminergic systems during adolescent development. These results underscore the need to eliminate smoking in adolescents and of the role that withdrawal-emergent deficits in brain function may play in treatment.
Jacobsen, L., Mencl, W., Constable, R., Westerveld, M., and Pugh, K. Impact of Smoking Abstinence on Working Memory Neurocircuitry in Adolescent Daily Tobacco Smokers. Psychopharmacology, 193(4) pp. 557-566, 2007.

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

Research Findings - Clinical Neuroscience Research

Impulsive Personality Predicts Dopamine-Dependent Changes in Frontostriatal Activity During Working Memory

Dr. Mark D'Esposito and colleagues at University of California, Berkeley used fMRI to demonstrate that individual differences in impulsive personality account for the contrasting effects of dopaminergic drugs on working memory and associated frontostriatal activity. Prior studies have shown that dopaminergic drugs affect a variety of cognitive processes, but the direction and extent of effects vary across individuals and tasks. Paradoxical effects are observed, by which the same drug causes cognitive enhancing as well as adverse effects. In the present study, administration of the dopamine D2 receptor agonist bromocriptine to healthy volunteers improved the flexible updating (switching) of relevant information in working memory in high-impulsive subjects, but not in low-impulsive subjects. These behavioral effects in high-impulsive subjects accompanied dissociable effects on frontostriatal activity. Bromocriptine modulated the striatum during switching but not during distraction from relevant information in working memory. Conversely, the lateral frontal cortex was modulated by bromocriptine during distraction but not during switching. The present results provide a key link between dopamine D2 receptor function, impulsivity, and frontostriatal activity during component processes of working memory. Given the high association of impulsivity with drug abuse, the present findings provide insight into cognitive sequelae of addiction. Cools, R., Sheridan, M., Jacobs, E., and D'Esposito, M. Impulsive Personality Predicts Dopamine-Dependent Changes in Frontostriatal Activity During Component Processes of Working Memory. Journal of Neuroscience, 27(20), pp. 5506-5514, 2007.

Cingulate Cortex Involvement in Error Detection With and Without Awareness

Dr. Hugh Garavan and colleagues at Trinity University used high density electrical recording of brain activity to demonstrate that specific regions of the Cingulate cortex have a differential relationship with awareness of task-related errors. Error-processing research has demonstrated that the brain uses a specialized neural network to detect errors during task performance, but the brain regions necessary for conscious awareness of an error are poorly understood. Two well known error-related event-related potential (ERP) components, the error-related negativity (ERN) and error positivity (Pe) have a differential relationship with awareness of task-related errors. In the present study healthy volunteers performed a manual response inhibition task that was optimized to examine error awareness. While the ERN was unaffected by the participants' conscious experience of errors, the Pe was only seen when participants were aware of committing an error. Source localization of these

components indicated that the ERN was generated by a caudal region of the anterior cingulate cortex (ACC) while the Pe was associated with contributions from a more anterior ACC region and the posterior cingulate-precuneus. Tonic EEG measures of cortical arousal were correlated with individual rates of error awareness and showed a specific relationship with the amplitude of the Pe. The latter finding is consistent with evidence that the Pe represents a P3-like facilitation of information processing modulated by subcortical arousal systems. These data suggest that the ACC might participate in both preconscious and conscious error detection and that cortical arousal provides a necessary setting condition for error awareness. These findings may be particularly important in the context of substance abuse in which a proper understanding of self-monitoring deficits requires an explicit measurement of error awareness. O'Connell R.G., Dockree P.M., Bellgrove M.A., Kelly S.P., Hester R., Garavan H., Robertson I.H., Foxe J.J. The Role of Cingulate Cortex In The Detection Of Errors With And Without Awareness: A High-Density Electrical Mapping Study. European Journal of Neuroscience, 25(8), pp. 2571-2579, 2007.

Activation of Prefrontal Cortex Reduces Risky Decision Making under Ambiguous Conditions

Dr. David Zald of Vanderbilt University collaborated with scientists at the NIH to investigate the role of the dorsolateral prefrontal cortex (DLPFC) on risky decision-making. Weighing of risks and benefits toward decision making involves a complex neural network that includes the DLPFC, but the role of the DLPFC remains unclear. Repetitive transcranial magnetic stimulation studies have shown that disruption of the DLPFC increases risk-taking behavior. Transcranial direct current stimulation (tDCS) allows upregulation of activity in the DLPFC, and it was predicted that this might promote more cautious decision-making. Healthy participants received one of the following treatments while they performed the Balloon Analog Risk Task: (1) right anodal/left cathodal DLPFC tDCS, (2) left anodal/right cathodal DLPFC tDCS, or (3) sham tDCS. This experiment revealed that participants receiving either one of the bilateral DLPFC tDCS strategies adopted a risk-averse response style. In a control experiment, they tested whether unilateral DLPFC stimulation (anodal tDCS over the right or left DLPFC with the cathodal electrode over the contralateral supraorbital area) was sufficient to decrease risk-taking behaviors. This experiment showed no difference in decision-making behaviors between the groups of unilateral DLPFC stimulation and sham stimulation. These findings extend the notion that DLPFC activity is critical for adaptive decision making, possibly by suppressing riskier responses. Anodal tDCS over DLPFC by itself did not significantly change risk-taking behaviors; however, when the contralateral DLPFC was modulated with cathodal tCDS, an important decrease in risk-taking was observed. Also, the induced cautious decision-making behavior was observed only when activity of both left and right DLPFC was modulated. The ability to modify risk-taking behavior may be translated into therapeutic interventions for disorders such as drug abuse, overeating, or pathological gambling. Fecteau, S., Pascual-Leone, A., Zald, D.H., Liguori, P., Theoret, H., Boggio, P.S., and Fregni, F. Activation of Prefrontal Cortex By Transcranial Direct Current Stimulation Reduces Appetite For Risk During Ambiguous Decision Making. Journal of Neuroscience, 27(23), pp. 6212-6218, 2007.

Cortical Inhibition and Excitation in Abstinent Cocaine-Dependent Patients: A Transcranial Magnetic Stimulation Study

Prior transcranial magnetic stimulation studies showed that resting motor threshold is elevated in abstinent cocaine-dependent patients, suggesting a decrease in axonal excitability. In contrast, the increased incidence of seizures and psychosis in this group suggests increased excitability or decreased inhibition. Here, Dr. Nashaat Boutros and colleagues at the Wayne State

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University School of Medicine, studied long-interval intracortical facilitation and long-interval intracortical inhibition, paired-pulse transcranial magnetic stimulation measures that are more directly linked to glutamatergic cortical facilitation and GABAergic inhibition, respectively. Ten cocaine dependent and 10 healthy controls were examined. Resting motor threshold, long-interval intracortical facilitation and long-interval intracortical inhibition were tested from the left motor cortex. The cocaine group showed an elevated resting motor threshold and an increased long-interval intracortical facilitation, whereas long-interval intracortical inhibition was normal. Although the increase in long-interval intracortical facilitation suggests exaggerated cortical glutamatergic excitability, the increase in resting motor threshold may signify a protective mechanism against seizures and psychosis. Sundaresan, K., Ziemann, U., Stanley, J., and Boutros, N. Cortical Inhibition and Excitation in Abstinent Cocaine-Dependent Patients: A Transcranial Magnetic Stimulation Study. Neuroreport, 18(3), pp. 289-292, 2007.

Short-Term Naturalistic Treatment Outcomes in Cigarette Smokers with Substance Abuse and/or Mental Illness

The majority of cigarette smokers have a lifetime diagnosis of substance abuse and/or mental illness, and treatment outcomes for smokers with these comorbidities are generally reported to be worse than for smokers without comorbidities. Dr. Arthur Brody and colleagues at the University of California, Los Angeles sought to examine the effect of specific substance abuse/mental illness diagnoses compared to one another on treatment outcomes. A retrospective chart review of naturalistic treatment for nicotine dependence was performed on male smokers (N = 231) who enrolled in the Greater Los Angeles Veterans Affairs Mental Health Clinic Smoking Cessation Program (Los Angeles, Calif.) over a 1.5-year period (January 2004 to June 2005). Subjects in this program, who were diagnosed with nicotine dependence on the basis of a DSM-IV-based interview and a Fagerstro_m Test for Nicotine Dependence score of >= 3, underwent comprehensive treatment for nicotine dependence (including, but not limited to, group psychotherapy, nicotine replacement therapy, and bupropion hydrochloride). Quitting smoking was defined as a report of at least 1 week of abstinence and an exhaled carbon monoxide less than or equal to 8 parts per million at the final clinic visit. Of the total group, 36.4% (84/231) quit smoking at the end of treatment. Quit rates were affected by the presence of specific diagnoses, with smokers with a history of alcohol abuse/dependence or schizophrenia/schizoaffective disorder having poorer response rates than smokers without such diagnoses. Other substance abuse and mental illness diagnoses did not affect quit rates. Lower quit rates among patients with alcohol abuse/dependence or schizophrenia/schizoaffective disorder may be due to the severity of these conditions and suggest that specialized treatment is needed for these populations of smokers. Smokers with most comorbid diagnoses are successfully treated with standard treatment methods. Gershon Grand, R.B., Hwang, S., Han, J., George, T., and Brody, A.L. Short-Term Naturalistic Treatment Outcomes in Cigarette Smokers with Substance Abuse and/or Mental Illness. The Journal of Clinical Psychiatry, 68(6), pp. 892-898, 2007.

[123I]5-IA-85380 SPECT Imaging of Beta2-Nicotinic Acetylcholine Receptor Availability in the Aging Human Brain

Dr. Kelly Cosgrove and colleagues at Yale University School of Medicine have been investigating in vivo the availability of the beta(2)-containing nicotinic acetylcholine receptor (beta(2)-nAChR) in healthy nonsmokers (18-85 years of age) using [(123)I]5-IA-85380 SPECT imaging. Human postmortem studies have reported decreases with age in high-affinity nicotine binding in brain. Age and regional beta(2)-nAChR availability (VT_) have been observed to be inversely correlated in all brain regions analyzed, with decline ranging from

21% (cerebellum) to 36% (thalamus), or by up to 5% per decade of life. Preliminary results have confirmed postmortem reports of age-related decline in high-affinity nicotine binding with age and may elucidate the role of beta(2)-nAChRs in the cognitive decline associated with aging. Mitsis, E.M., Cosgrove, K.P., Staley, J.K., Frohlich, E.B., Bois, F., Namangan, G.D., Estok, K.M., Seibyl, J.P., and Van Dyck, C.H. [123I]5-IA-85380 SPECT Imaging of Beta2-Nicotinic Acetylcholine Receptor Availability in the Aging Human Brain. Annals of the New York Academy of Science, 1097, pp. 168-170, 2007.

The Effects of Foods, Beverages, and other Factors on Cigarette Palatability

While smokers commonly report that various foods and beverages worsen or enhance the taste of cigarettes, the prevalence and diversity of these phenomena have not been studied. Dr. Francis McClernon and colleagues at Duke University Medical Center administered an open-ended questionnaire to 209 smokers asking for reports of foods or beverages that worsen or enhance the taste of cigarettes. Commonly reported categories that worsen the taste of cigarettes were fruits/vegetables, noncaffeinated beverages, and dairy products. Commonly reported categories that enhance the taste of cigarettes were caffeinated and alcoholic beverages and meat products. Regression analyses indicated that increased sensitivity to both taste-worsening and taste-enhancing were associated with smoking nonmenthol cigarettes. These findings suggest smoking menthol cigarettes reduces both negative and positive effects of food and beverage consumption on smoking satisfaction - thus "evening-out" the smoking experience. McClernon, F.J., Westman, E.C., Rose, J.E., and Lutz, A.M. The effects of foods, beverages, and other factors on cigarette palatability. Nicotine & Tobacco Research, 9(4), pp. 505-510, 2007.

Relationship Between N-Acetyl-Aspartate in Gray and White Matter of Abstinent Methamphetamine Abusers and Their History of Drug Abuse: A Proton Magnetic Resonance Spectroscopy Study

Altered concentrations of the brain metabolites, including N-acetyl-aspartate (NAA) and myo-inositol (MI), may indicate neurotoxicity associated with drug abuse. In this study, Dr. Perry Renshaw of McLean Hospital, along with his colleagues at Seoul National University College of Medicine and Hospital, explored differences in brain metabolites between abstinent methamphetamine (MA) abusers and healthy comparison subjects and the associations between metabolite concentrations and clinical characteristics. Proton magnetic resonance spectroscopy (MRS) was performed on 30 abstinent MA abusers and 20 healthy comparison subjects. Two sets of MA user subgroups were defined depending on abstinence duration (greater or less than 6 months) or the total cumulative MA dose (greater or less than 100 g lifetime). NAA and other metabolites were measured in the frontal gray and white matter and compared between MA abuser groups and healthy comparison subjects. MI concentrations were higher for the MA abusers relative to healthy comparison subjects. NAA concentration was lower in frontal white matter of MA abusers with a 'large' cumulative dose relative to those with a 'small' cumulative dose and to healthy comparison subjects. Additionally, in MA abusers NAA concentrations in frontal white matter correlated inversely with the cumulative MA dose. In contrast, there was no significant difference in frontal gray matter NAA concentration among the three groups. However, frontal gray matter NAA concentrations for MA abusers correlated negatively with the total cumulative MA dose and positively with the duration of abstinence. There were no differences between the different MA user groups for MI. The current findings suggest that MA-induced metabolic alterations of frontal gray and white matter are dose-dependent. Additionally, these findings suggest that the MA-related abnormalities in gray matter may recover, in part, with abstinence but this is not the case in white matter regions. Sung, Y.H., Cho, S.C., Hwang, J., Kim,

S.J., Kim, H., Bae, S., Kim, N., Chang, K.H., Daniels, M., Renshaw, P.F., and Lyoo, I.K. Relationship Between N-Acetyl-Aspartate in Gray and White Matter of Abstinent Methamphetamine Abusers and Their History of Drug Abuse: A Proton Magnetic Resonance Spectroscopy Study. Drug and Alcohol Dependence, (Epub 2006 Nov 7), 88(1), pp. 28-35, 2007.

Reproducibility of GABA Measurements Using 2D J-resolved Magnetic Resonance Spectroscopy

Dr. Napapon Sailasuta of the Huntington Medical Research Institutes and her colleagues from the Royal Edinburgh Hospital determined the reproducibility of GABA (gamma-aminobutyric acid) measurements using 2D J-resolved magnetic resonance spectroscopy (MRS) on a clinical 1.5-T MR imaging scanner. Two-dimensional J-resolved spectra were acquired in vitro across five GABA concentrations using a volume head coil and a 5-in. surface coil. Additional spectra using a sixth GABA phantom with a very low concentration and from a healthy volunteer were recorded in the 5-in. surface coil only. In each case, the 3.01-ppm GABA resonance was quantified; for comparison, the peak integrals of choline (3.2 ppm) and creatine (3.03 ppm) were recorded. At a physiological concentration (1.2 mM), in vitro GABA measurement was significantly more reproducible in the surface coil than in the volume coil (P=.005), with coefficients of variation (CVs) being less than 16% with the surface coil and up to 68% with the volume head coil. At the smallest concentration of in vivo GABA reported using other spectroscopy techniques (0.8 mM) and detected only using the surface coil, the CV for GABA was 23% and was less than 10% for choline and creatine, which compare favorably with results from published studies. In vivo, the CV for GABA measurement was 26%, suggesting that 2D J-resolved MRS would be suitable for detecting physiological changes in GABA similar to those reported using other methods. Lymer, K., Haga, K., Marshall, I., Sailasuta, N., and Wardlaw, J. Reproducibility of GABA Measurements Using 2D J-resolved Magnetic Resonance Spectroscopy. Magnetic Resonance Imaging, (Epub 2006 Nov 30), 25(5), pp. 634-640, 2007.

Cybertherapy—New Applications for Discomfort Reductions. Surgical Care Unit of Heart, Neonatology Care Unit, Transplant Kidney Care Unit, Delivery Room-Cesarean Surgery and Ambulatory Surgery, 27 Case Reports

Dr. Brenda Wiederhold, along with her colleagues at Clinica de Especialidades (Mexico), demonstrated the feasibility of virtual reality scenarios to reduce discomfort in patients during ambulatory and obstetric surgeries and patients hospitalized in postoperative care units from cardiac, nephrology, and neonatology units. Twenty seven patients have participated in these preliminary reports from 3 public hospitals from Mexico City in 2006. The majority of patients demonstrated comfort with virtual scenarios during surgical procedures or hospitalization. In ambulatory surgeries the reduction of medication dosage was real. The authors present the first applications in surgery, obstetrics and care units. The preliminary results must be supported in the future with a greater number of cases and statistical results; however the authors predict the usefulness of this finding because they have found a reduction of medication dosing in ambulatory surgeries. Mosso, J.L., Rizzo, S., Wiederhold, B., Lara, V., Flores, J., Espiritusanto, E., Minor, A., Santander, A., Avila, O., Balice, O., and Benavides, B. Cybertherapy--New Applications for Discomfort Reductions. Surgical Care Unit of Heart, Neonatology Care Unit, Transplant Kidney Care Unit, Delivery Room-Cesarean Surgery and Ambulatory Surgery, 27 Case Reports. Studies in Health Technology and Informatics, 125, pp. 334-336, 2007.

Evidence of Corticostriatal Circuit as a Reservoir of HCV Alerts a

Productive Coinfection Associated with Cognitive Impairment in Individuals Living with HIV

Dr. Igor Grant and associates at the University of California, San Diego reported that Hepatitis C virus (HCV) infection augmented cognitive deficits in HIV+ individuals and methamphetamine-dependent populations. The detection in this study of NS5A and NS3, integral parts of HCV essential for the virus replication, and core antigen of the virus in post-mortem brain samples of HCV/HIV positive subjects, in combination with previous studies detecting negative-strand RNA in the brains of HCV-positive patients, supports the contention that replicating HCV capable of contributing to neurological damage is present in patients co-infected with HIV. HCV immunoreactivity was present in astroglial cells and perivascular macrophages. Abundant astrogliosis was detectable in frontal cortex and basal ganglia with considerable antemortem cognitive impairment. The results support the view that HCV traffics into the HIV-infected brain, where it leads to a productive coinfection associated with cognitive impairment. However, it is not clear whether the neuropsychological dysfunction mirrored HCV penetration into and replication in the brain, or resulted from indirect influence of hepatic HCV products. Letendre, S., Paulino, A.D., Rockenstein, E., Adame, A., Crews, L., Cherner, M., Heaton, R., Ellis, R., Everall, I.P., Grant, I., and Masliah E. HIV Neurobehavioral Research Center Group. Pathogenesis of Hepatitis C Virus Coinfection in the Brains of Patients Infected with HIV, J Infect Dis., 196(3), pp. 361-370, 2007. Letendre, S.L., Cherner, M., Ellis, R.J., Marquie-Beck, J., Gragg, B., Marcotte, T., Heaton, R.K., McCutchan, J.A., and Grant, I. HNRC Group. The Effects of Hepatitis C, HIV, and Methamphetamine Dependence on Neuropsychological Performance: Biological Correlates of Disease, AIDS, 19 Suppl. 3, pp. S72-78, 2005.

Genetic Linkage to Chromosome 22q12 for a Heavy-Smoking Quantitative Trait in Two Independent Samples

Dr. Pamela Madden and her teams at Washington University and in Australia and Finland conducted a genome-wide linkage screen using a "phenotype" described by the quantitative trait of maximum number of cigarettes smoked in a day, which was considered the best self-report measure of nicotine dependence. A panel of 381 autosomal microsatellite markers--spaced at about 10 cM--were assessed in 289 Australian and 155 Finnish families, all of European descent. Suggestive linkage was found for each sample on Chromosome 22 with a LOD score of nearly 6 in the combined sample. The marker giving the strongest signal is located in the intron of the gene DRBK2, encoding the beta-adrenergic receptor kinase 2. This is the first report of consistent evidence of genetic linkage with use of the same trait assessed identically in two independent samples. The next step is to do a fine mapping of the region to determine if there are gene variants that may confer specific vulnerability to nicotine dependence. Saccone, S.F., Pergadia, M.L., Loukola, A., Broms, U., Montgomery, G.W., Wang, J.C. Agrawal, A., Dick, D.M., Heath, A.C., Todorov, A.A., Maunu, H., Heikkliae, Morley, K.I., Rice, J.P., Todd, R.D., Kaprio, J., Peltonen, L., Martin, A.M., and Madden, P.A.F. Genetic Linkage to Chromosome 22q12 for a Heavy-Smoking Quantitative Trait in Two Independent Samples. The American Journal of Human Genetics, 80, pp. 856-866, 2007.

Genetic Linkage to Chromosomes 3 and 9 for Cannabis Dependence Symptoms

Dr. Thomas Crowley and his team at the University of Colorado conducted a genome-wide scan using a "phenotype" of symptom counts for cannabis dependence. A panel of 374 microsatellite markers--spaced about 9.2 cM--were assessed in 324 sibling pairs from 192 families recruited from consecutive

admissions to substance abuse treatment facilities. Suggestive linkage was found on chromosome 3q21 (LOD 2.61) and on chromosome 9q34 (LOD 2.57). This is the first study to report linkage for cannabis dependence symptoms. The LOD scores are somewhat low so that replication is required. However, other reports for illicit substances have located peaks near the one on chromosome 3. Hopfer, C.J., Lessem, J.M., Hartman, C.A., Stallings, M.C., Cherny, S.S., Corley, R.P., Hewitt, J.K., Krauter, K.S., Mikulich-Gilbertson, S.K., Rhee, S.H., Smolen, A., Young, S.E., and Crowley, T.J. A Genome-Wide Scan for Loci Influencing Adolescent Cannabis Dependence Symptoms: Evidence for Linkage on Chromosomes 3 and 9. Drug and Alcohol Dependence, 89, pp. 34-42, 2007.

Transient Catecholamine Depletion Enhances Cognitive Deficits and Differentially Affects Sleep in Abstinent MDMA Users

Dr. Una McCann and colleagues at Johns Hopkins University investigated whether alterations in sleep associated with MDMA use may involve changes in catecholamine neurotransmission in addition to the known effects of MDMA on serotonin. Abstinent MDMA users and non-MDMA using controls were studied to determine whether transient depletion of brain catecholamines (dopamine and norepinephrine) by alpha-methyl-para-tyrosine (AMPT, which inhibits catecholamine synthesis) would differentially affect MDMA users on measures of cognition and sleep, two processes dually modulated by brain serotonergic and catecholaminergic neurons. During a 5-day in-patient study, all subjects underwent formal neuropsychiatric testing, repeated computerized cognitive testing, and all-night sleep studies. At baseline, MDMA users had performance deficits on tasks of verbal and visuospatial working memory and displayed increased impulsivity on several tasks (i.e., performing quickly at the expense of accuracy). Baseline sleep architecture was also altered in abstinent MDMA users compared to controls. AMPT produced larger deficits in MDMA users compared to controls on several cognitive measures, and differential effects on sleep measures. Differences in cognitive performance, impulsivity, and sleep were significantly correlated with MDMA use. These data suggest that lasting effects of MDMA lead to alterations in behaviors reciprocally influenced by 5-HT and catecholamines. McCann, U.D., Peterson, S.C., and Ricaurte, G.A. The Effect of Catecholamine Depletion by Alpha-Methyl-Para-Tyrosine on Measures of Cognitive Performance and Sleep in Abstinent MDMA Users. Neuropsychopharmacology, 32(8), 1695-706, 2007.

Placebo Effects On Human Mu-Opioid Activity During Pain

Dr. Jon-Kar Zubieta and colleagues used PET ligand imaging to investigate central brain mechanisms of opioid release during placebo treatment. This study examined placebo effects in pain by using positron-emission tomography with [(11)C]carfentanil, which measures regional mu-opioid receptor availability in vivo. Noxious thermal stimulation was applied at the same temperature for placebo and control conditions. 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. These regions appeared to be subdivided into two sets, one showing placebo-induced opioid activation specific to noxious heat and the other showing placebo-induced opioid reduction during warm stimulation in anticipation of pain. These findings suggest that a mechanism of placebo analgesia is the potentiation of endogenous opioid responses to noxious stimuli. 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.D., Scott, D.J., and Zubieta, J.K. Placebo Effects On Human Mu-Opioid Activity During Pain. Proc. Natl. Acad. Sci. U S A., 104(26), pp. 11056-11061, 2007.

Amphetamine-Induced Dopamine Release: Markedly Blunted In Cocaine Dependence and Predictive Of the Choice To Self-Administer Cocaine

Dr. Diana Martinez and colleagues at Columbia University used PET ligand imaging to characterize pre- and postsynaptic dopamine function in recently detoxified cocaine-dependent subjects. Dopamine response to an acute amphetamine challenge was assessed in striatal subregions in cocaine-dependent and healthy comparison participants using positron emission tomography (PET). The relationship between this dopamine response and the choice to self-administer cocaine in a laboratory model of relapse was investigated. Twenty-four cocaine-dependent participants and 24 matched healthy subjects underwent [C-11] raclopride scans under a baseline condition and following intravenous amphetamine administration (0.3 mg/ kg). Cocaine-dependent participants also completed cocaine self-administration sessions in which a priming dose of cocaine was followed by the choice to either self-administer subsequent cocaine doses or receive a monetary reward. Cocaine dependence was associated with a marked reduction in amphetamine-induced dopamine release in each of the functional subregions of the striatum (limbic striatum: -1.2% in cocaine-dependent participants versus -12.4% in healthy subjects; associative striatum: -2.6% versus -6.7%, respectively; sensorimotor striatum: -4.3% versus -14.1%). Blunted dopamine transmission in the ventral striatum and anterior caudate was predictive of the choice for cocaine over money. Cocaine dependence is associated with impairment of dopamine function, and this impairment appears to bias choices in a way that would promote relapse. Martinez, D., Narendran, R., Foltin, R.W., Slifstein, M., Hwang, D.R., Broft, A., Huang, Y.Y., Cooper, T.B., Fischman, M.W., Kleber, H.D., and Laruelle, M. Amphetamine-Induced Dopamine Release: Markedly Blunted In Cocaine Dependence and Predictive of the Choice To Self-Administer Cocaine. American Journal of Psychiatry, 164(4), pp. 622-629, 2007.

Beta-Adrenergic Modulation of Cognitive Flexibility During Stress

Dr. Beversdorf and colleagues at Ohio State University investigated the role of the brain norepinephrine system on stress-induced impairments in cognitive flexibility performance in healthy individuals. Cognitive performance, plus psychological and physiological parameters for 16 adults without any history of anxiety disorders, was assessed during four test sessions: stress and no-stress, with each condition tested after administration of propranolol and placebo. The Trier Social Stress Test, a public-speaking and mental arithmetic stressor, was presented to participants for the stress sessions, whereas a similar, but nonstressful, control task (reading, counting) was utilized for the no-stress sessions. Tests of cognitive flexibility included lexical-semantic and associative problem-solving tasks (anagrams, Compound Remote Associates Test). Visuospatial memory and motor processing speed tests served as control tasks. Results indicate that (1) stress impaired performance on cognitive flexibility tasks, but not control tasks; (2) compared to placebo, cognitive flexibility improved during stress with propranolol. These results support the hypothesis that stress-related impairments in cognitive flexibility are related to the noradrenergic system. Decreased cognitive flexibility mediated through the noradrenergic system may contribute to the increased likelihood of substance abuse relapse in response to stress, and that beta-adrenergic antagonists may

be a potential treatment for stress-induced relapse. Alexander J.K., Hillier, A., Smith, R.M., Tivarus, M.E., and Beversdorf, D.Q. Beta-Adrenergic Modulation Of Cognitive Flexibility During Stress. Journal of Cognitive Neuroscience, 19(3), pp. 468-478, 2007.

Yoga Increases Brain GABA Levels

Dr. Chris Streeter and colleagues at McLean Hospital used MRS to determine whether an individual yoga session would be associated with an increase in brain GABA levels. GABA-to-creatine ratios were measured in a 2-cm axial slab using magnetic resonance spectroscopic imaging immediately prior to and immediately after interventions. Eight yoga practitioners completed a 60-minute yoga session and 11 comparison subjects completed a 60-minute reading session prior to obtaining MRS scans. There was a 27% increase in GABA levels in the yoga practitioner group after the yoga session (0.20 mmol/kg) but no change in the comparison subject group after the reading session (-0.001 mmol/kg). These findings demonstrate that in experienced yoga practitioners brain GABA levels increase after a session of yoga. This suggests that the practice of yoga might be explored as a treatment for disorders with low GABA levels such substance abuse. Streeter, C.C., Jensen, J.E., Perlmutter, R.M., Cabral, H.J., Tian, H., Terhune, D.B., Ciraulo, D.A., and Renshaw, P.F. Yoga Asana Sessions Increase Brain GABA Levels: A Pilot Study. Journal of Alternative and Complementary Medicine 13(4), pp. 419-426, 2007.

Effects of Smoking Marijuana on Focal Attention and Brain Blood Flow

Dr. Daniel O'Leary and colleagues at University of Iowa used PET blood flow imaging to determine the effects of marijuana on selective attention using a dichotic listening task requiring attention to left and right ears. Twelve occasional marijuana users (mean age 23.5 years) were imaged with PET using [15-O]water after smoking marijuana or placebo cigarettes as they performed a reaction time (RT) baseline task, and a dichotic listening task with attend-right- and attend-left-ear instructions. Smoking marijuana, but not placebo, resulted in increased rCBF in orbital frontal cortex, anterior cingulate, temporal pole, insula, and cerebellum. rCBF was reduced in visual and auditory cortices. These changes occurred in all three tasks and appear to reflect the direct effects of marijuana on the brain. Smoking marijuana lowered rCBF in auditory cortices compared to placebo but did not alter the normal pattern of attention-related rCBF asymmetry (i.e., greater rCBF in the temporal lobe contralateral to the direction of attention) that was also observed after placebo. These data indicate that marijuana has dramatic direct effects on rCBF, but causes relatively little change in the normal pattern of task-related rCBF on this auditory focused attention task. O'Leary, D.S., Block, R.I., Koeppel, J.A., Schultz, SK., Magnotta, V.A., Ponto, L.B., Watkins, GL., and Hichwa, R.D. Effects of Smoking Marijuana on Focal Attention and Brain Blood Flow. Human Psychopharmacology-Clinical and Experimental, 22(3), pp. 135-148, 2007.

Differential Contribution of the Posterior Insular Cortex and the Striatum to Delay Discounting

Dr. Martin Paulus and colleagues at the University of California, San Diego used fMRI to examine the neural substrates of delayed discounting. Delay discounting refers to the fact that an immediate reward is valued more than the same reward if it occurs some time in the future. Healthy volunteers were instructed to decide between an immediate and parametrically-varied delayed hypothetical reward during event-related functional magnetic resonance imaging. Subject's preference judgments resulted in different discounting slopes for shorter (< 1 year) and for longer (>= 1 year) delays. Neural

activation associated with the shorter delays relative to the longer delays was associated with increased activation in the head of the left caudate nucleus and putamen. When individuals selected the delayed relative to the immediate reward, a strong activation was found in bilateral posterior insular cortex. Several brain areas including the left caudate nucleus showed a correlation between the behaviorally determined discounting and brain activation for the contrast of intervals with delays < 1 and >= 1 year. These results suggest that (1) the posterior insula, which is a critical component of the decision-making neural network, is involved in delaying gratification and (2) the degree of neural activation in the striatum, which plays a fundamental role in reward prediction and in time estimation, may code for the time delay. Wittmann, M., Leland, D.S., and Paulus, M.P. Time and Decision Making: Differential Contribution of the Posterior Insular Cortex and the Striatum During a Delay Discounting Task. Experimental Brain Research, 179 (4), pp. 643-653, 2007.

Attentional Control and Brain Metabolite Levels in Methamphetamine Abusers

Dr. Ruth Salo and colleagues at University of California, Davis combined a computerized measure of selective attention and single-voxel proton magnetic resonance spectroscopy to examine effects of methamphetamine on the relationship between attentional control and brain metabolite levels in the anterior cingulate cortex (ACC) and primary visual cortex (PVC). Subjects were 36 currently abstinent methamphetamine abusers and 16 non-substance-using controls. The methamphetamine abusers exhibited reduced attentional control (i.e., increased Stroop interference) compared with the controls. ACC levels of N-acetyl aspartate (NAA)-creatine and phosphocreatine (Cr) were lower and levels of choline (Cho)-NAA were higher in the methamphetamine abusers compared with the controls. Levels of NAA-Cr, but not of Cho-NAA, within the ACC correlated with measures of attentional control in the methamphetamine abusers (r = -.41), but not in controls (r =.22). No significant correlations were observed in the PVC (methamphetamine abusers, r =.19; controls, r =.38). These results suggest that neurochemical alterations within frontostriatal brain regions, including ACC, may contribute to deficits in attentional control among chronic methamphetamine abusers. Salo, R., Nordahl, T.E., Natsuaki, Y., Leamon, M.H., Galloway, G.P., Waters, C., Moore, C.D., and Buonocore, M.H. Attentional Control and Brain Metabolite Levels in Methamphetamine Abusers. Biological Psychiatry, 61(11), pp. 1272-1280, 2007.

An MR-Compatible Device for Delivering Smoked Marijuana during Functional Imaging

For two of the most commonly abused drugs, nicotine and marijuana, the preferred route of administration is by smoking. Moreover, functional magnetic resonance imaging (fMRI) is becoming a widely-adopted methodology for studying the neurobiological effects acute drug administration. In this publication, Dr. Lisa Nickerson and her colleagues describe the design and testing of an apparatus that allows a subject to smoke a cigarette (whether marijuana or tobacco) while in the bore of a scanner that is acquiring images designed to measure the effects of the drug. The system that is described is shown to contain all smoke and odors from the cigarette and also not to interfere with the imaging protocol (by introducing motion artifacts, for example). This device, therefore, will allow research on the effects of smoked drugs while tests that are compatible with the scanner environment are simultaneously performed. Frederick, B., Lindsey, K., Nickerson, L.., Ryan, E., and Lukas, S. An MR-Compatible Device for Delivering Smoked Marijuana during Functional Imaging. Pharmacology, Biochemistry and Behavior, 87, pp. 81-89, 2007.

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

Research Findings - Epidemiology and Etiology Research

Who is Becoming Hallucinogen Dependent Soon after Hallucinogen Use Starts?

This study, based upon epidemiological survey data from the United States (U.S.) National Household Surveys on Drug Abuse (NHSDA) from 2000 to 2001, presents new estimates for the risk of developing a hallucinogen dependence syndrome within 24 months after first use of any hallucinogen (median elapsed time approximately 12 months). Subgroup variations in risk of becoming hallucinogen dependent also are explored. Estimates are derived from the NHSDA representative samples of non-institutionalized U.S. residents ages 12 and older (n=114,241). A total of 2035 respondents had used hallucinogens for the first time within 24 months prior to assessment. An estimated 2-3% of these recent-onset hallucinogen users had become dependent on hallucinogens, according to the NHSDA DSM-IV computerized diagnostic algorithm. Controlling for sociodemographic and other drug use covariates, very early first use of hallucinogens (age 10-11 years) is associated with increased risk of hallucinogen dependence ($p<0.01$). Excess risk of developing hallucinogen dependence was found in association with recent-onset use of mescaline; excess risk also was found for recent-onset users of ecstasy and of PCP. This study's evidence is consistent with prior evidence on a tangible but quite infrequent dependence syndrome soon after the start of hallucinogen use; it offers leads that can be confirmed or disconfirmed in future investigations. Stone, A., O'Brien, M., De La Torre, A., and Anthony, J. Who is Becoming Hallucinogen Dependent Soon after Hallucinogen Use Starts? Drug Alcohol Depend, 87(2-3), pp. 153-163, 2007.

Twin Study of Stimulant Use/Abuse and Associations with Cannabis

This paper explores the magnitude of, and extent of overlap between, genetic, shared environmental and non-shared environmental influences on lifetime stimulant use and on stimulant abuse/dependence symptoms. It further explores the associations between stimulant use and cannabis use and the extent to which these associations can be attributed to common or correlated genetic and environmental influences. Data came from self report on lifetime stimulant use, DSM-IV abuse/dependence symptoms and corresponding measures of cannabis involvement collected from a sample of 6265 male and female Australian twins born between 1964 and 1971. Results showed that approximately one in five study participants reported lifetime stimulant use while 5% reported experiencing at least one symptom of abuse/dependence. Multivariate genetic model fitting indicated moderate genetic influences on stimulant use (40%) and symptoms (65%) while there was no evidence of sex differences in the magnitude of these influences. Despite moderate overlap,

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65% of the genetic influence on stimulant abuse/dependence was specific to these symptomatologic outcomes. There were also strong genetic and shared environmental correlations between the factors associated with stimulant use and those associated with cannabis use. The authors conclude that there is evidence for both overlapping and distinct genetic factors contributing to stimulant use vs. abuse/dependence, which may have implications for opportunities for intervention, for example if those leading to initiation are in the personality realm and those leading to abuse/dependence are more metabolic. Moreover, the overlap in familial (genetic and environmental) risk factors for both stimulant and cannabis use suggests some degree of non-specificity in the risk for using these substances, although more study is needed. Lynskey, M., Grant, J., Li, L., Nelson, E., Bucholz, K., Madden, P., Statham, D., Martin, N., and Heath, A. Stimulant Use and Symptoms of Abuse/Dependence: Epidemiology and Associations with Cannabis Use--A Twin Study. Drug Alcohol Depend, 86(2-3), pp. 147-153, 2007.

Childhood Antecedents of Exposure to Traumatic Events and Posttraumatic Stress Disorder

The authors prospectively examined childhood antecedents of exposure to traumatic events to estimate the risk of posttraumatic stress disorder (PTSD) among those exposed to trauma. Two consecutive cohorts of children entering first grade of a public school system in a large mid-Atlantic city in the mid-1980s were followed into young adulthood (mean age=21). Exposure to traumatic events and PTSD were assessed in 75% of the original cohort (N=1,698). Childhood assessments, conducted upon entry into the first grade, included standardized measures of reading readiness, teacher ratings of behavioral problems, and child self-reports about depression and anxiety. Family characteristics were assessed by parental report. Young adults who had been rated by their first grade teacher as having aggressive/ disruptive behavior problems were more likely to experience traumatic assaultive violence events (e.g., being mugged/threatened with a weapon, badly beaten-up) (relative risk=2.6) but not PTSD following trauma exposure. Youths with high levels of self-rated depressive and anxious feelings in first grade were more likely to experience PTSD once exposed to trauma (relative risk=1.5). Youths who scored in the highest quartile on a reading test in the first grade were at lower risk for exposure to assaultive violence traumas. Childhood behavioral and depressive/anxious problems may influence the risk for PTSD directly by increasing the vulnerability to the PTSD effects of trauma exposure, and indirectly by increasing the likelihood of exposure to assaultive violence. Storr, C., Ialongo, N., Anthony, J., and Breslau, N. Childhood Antecedents of Exposure to Traumatic Events and Posttraumatic Stress Disorder. Am J Psychiatry, 164(1), pp. 119-125, 2007.

Effect of Televised, Tobacco Company-Funded Smoking Prevention Advertising on Youth Smoking-Related Beliefs, Intentions, and Behavior

The authors examined the association between exposure to televised youth smoking prevention advertising and youths' smoking beliefs, intentions, and behaviors. They obtained commercial television ratings data from 75 US media markets to determine the average youth exposure to tobacco company youth-targeted and parent-targeted smoking prevention advertising, then merged these data with nationally representative school-based survey data (n = 103,172) gathered from 1999 to 2002. Multivariate regression models controlled for individual, geographic, and tobacco policy factors, and other televised anti-tobacco advertising. There was little relation found between exposure to tobacco company-sponsored, youth-targeted advertising and youth smoking outcomes. Among youths in grades 10 and 12, during the 4 months leading up to survey administration, each additional viewing of a tobacco

company parent-targeted advertisement was, on average, associated with lower perceived harm of smoking (odds ratio [OR]=0.93; confidence interval [CI]=0.88, 0.98), stronger approval of smoking (OR=1.11; CI=1.03,1.20), stronger intentions to smoke in the future (OR=1.12; CI=1.04,1.21), and greater likelihood of having smoked in the past 30 days (OR=1.12; CI=1.04,1.19). Exposure to tobacco company youth-targeted smoking prevention advertising generally had no beneficial outcomes for youths. Exposure to tobacco company parent-targeted advertising may have harmful effects on youth, especially among youths in grades 10 and 12. Wakefield, M., Terry-McElrath, Y., Emery, S., Saffer, H., Chaloupka, F., Szczypka, G., Flay, B., O'Malley, P., and Johnston, L. Effect of Televised, Tobacco Company-Funded Smoking Prevention Advertising on Youth Smoking-Related Beliefs, Intentions, and Behavior. Am J Public Health, 96(12), pp. 2154-2160, 2006.

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

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

Male-Female Differences in the Risk of Progression from First Use to Dependence upon Cannabis, Cocaine, and Alcohol

The authors extend prior reports about the risk of dependence on specific drugs by providing developmental-specific risk estimates for progression from first use to meeting criteria for DSM-III-R dependence upon cannabis, cocaine, or alcohol, as well as male-female differences. The data are from the National Comorbidity Survey, with a national probability sample of persons 15-44 years old in the United States, which included many respondents who used cannabis, cocaine and alcohol on at least one occasion (n=3558, 1337, and 6149, for cannabis, cocaine, and alcohol, respectively). Survival analysis procedures provided cumulative risk estimates of progression from first use to dependence upon each drug. The estimated risk of cannabis dependence among male

cannabis users was 1% in the first year after first use, and reached a peak at 4% per year 2 years later, before declining. In contrast, the estimated risk of cannabis dependence among female cannabis users remained at 1% per year for 3 years, without the peak. For both male and female cocaine users, the estimated risk for developing cocaine dependence was 5 to 6% within the first year after first use. Thereafter, the estimated risk declined from the peak value, with a somewhat faster decline for females in the next 3 years after first use. For alcohol, the estimated risk period extended for many years after the first drink, with female drinkers becoming alcohol dependent at a rate of about 1% per year; with somewhat higher risk for male drinkers. For both male and female drinkers, the period of risk for developing alcohol dependence extended for a span of more than 20 years since first use; for cannabis and cocaine, the estimated period of risk was much shorter. There are male-female differences in the risk of becoming cannabis dependent during the first several years after initiation of cannabis use, less pronounced male-female differences for alcohol, and relatively smaller male-female differences for cocaine. These results should interest scientists whose focus is upon the origins of male-female differences in the occurrence of drug dependence. Wagner, F., and Anthony, J. Male-Female Differences in the Risk of Progression from First Use to Dependence Upon Cannabis, Cocaine, and Alcohol. Drug Alcohol Depend, 86(2-3), pp. 191-198, 2007.

Pathways Between Ecstasy Initiation and Other Drug Use

This study aims to shed light on drug use pathways associated with ecstasy use initiation. Data from 54,573 respondents aged 12-21 years old from the 2002-2003 National Survey on Drug Use and Health (NSDUH) public use data files were analyzed via Cox proportional hazards models with time-dependent covariates. Findings showed that marijuana, cocaine, and heroin were significant independent predictors of subsequent ecstasy use. Earlier ecstasy initiation was significantly associated with subsequent other illegal drug initiation (marijuana, cocaine and heroin). The strength of the association was greater for the pathway from earlier marijuana initiation to subsequent ecstasy initiation as compared to the pathway in the opposite direction. The pathway from earlier ecstasy initiation to subsequent cocaine and heroin initiation was also stronger as compared to pathways in the opposite directions. Pathways between ecstasy initiation and marijuana, cocaine and heroin initiation seem to be independent of the association between drug use and psychiatric symptoms/deviant behaviors. Ecstasy initiation seems to play a role in the subsequent initiation of cocaine and heroin. Martins, S., Ghandour, L., and Chilcoat, H. Pathways Between Ecstasy Initiation and Other Drug Use. Addict Behav, 32(7), pp. 1511-1518, 2007.

Gender Differences in Criteria for Cannabis Abuse and Dependence

This study explored whether gender contributes to heterogeneity in the latent construct for abuse and dependence of cannabis, and furthermore, whether after accounting for differences in the mean scores of abuse and dependence across genders, there is any evidence for heterogeneity in the individual abuse and dependence criteria. The authors utilized data on criteria for cannabis abuse and dependence from the NESARC (National Epidemiological Survey on Alcohol and Related Conditions), a large, nationally representative sample including 8172 lifetime cannabis users. Analyses used factor analyses and modeling to examine dimensionality and gender heterogeneity. Results supported a unidimensional construct for cannabis abuse/dependence combined, rather than separate entities, which has also been found in prior research. The authors also identified two abuse (legal and hazard) and two dependence (quit and problems) criteria which showed significant gender heterogeneity; the abuse criteria exhibited higher thresholds in women and the

dependence criteria in men. They concluded that the criteria that serve as indicators of DSM-IV cannabis abuse and dependence do not function identically in men and women and that certain criteria (e.g. hazardous use) require further refinement. These findings have important implications for the revision of the DSM criteria for abuse and dependence, both for questioning a distinction between abuse and dependence and for considering gender-sensitive diagnostic criteria in research and clinical settings. Agrawal, A., and Lynskey, M. Does Gender Contribute to Heterogeneity in Criteria for Cannabis Abuse and Dependence? Results from the National Epidemiological Survey on Alcohol and Related Conditions. Drug Alcohol Depend, 88(2-3), pp. 300-307, 2007.

DSM-IV Abuse and Dependence Criteria: Factor and Item Response Analyses

This paper questions the assumptions underlying DSM that drug abuse and dependence are distinct entities and that the same criteria apply to all drugs. They used a population-based sample of males to test these ideas using factor analysis and item response theory. A total of 4234 males born from 1940 to 1974 from the population-based Virginia Twin Registry were assessed for DSM-IV drug use, abuse and dependence criteria for cannabis, sedatives, stimulants, cocaine and opiates. For each drug class, the pattern of endorsement of individual criteria for abuse and dependence, conditioned on initiation and use, could be best explained by a single factor. There were large differences in individual item performance across substances in terms of item difficulty and discrimination. Cocaine users were more likely to have encountered legal, social, physical and psychological consequences. The authors conclude that the DSM-IV abuse and dependence criteria, within each drug class, are not distinct but best described in terms of a single underlying continuum of risk. Furthermore, because individual criteria performed very differently across substances in IRT analyses, they conclude that the assumption that these items are measuring equivalent levels of severity or liability with the same discrimination across different substances is unsustainable. These findings have implications for nosology, phenotyping, and clinical research. Gillespie, N., Neale, M., Prescott, C., Aggen, S., and Kendler, K. Factor and Item-Response Analysis DSM-IV Criteria for Abuse of and Dependence on Cannabis, Cocaine, Hallucinogens, Sedatives, Stimulants and Opioids. Addiction, 102(6), pp. 920-930, 2007.

Grandmother and Parent Influences on Child Self-Esteem

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

effects on multiple generations. Brook, J., Ning, Y., Balka, E., Brook, D., Lubliner, E., and Rosenberg, G. Grandmother and Parent Influences on Child Self-Esteem. Pediatrics, 119(2), pp. 444-451, 2007.

Injecting and Sexual Risk Correlates of HBV and HCV Seroprevalence among New Drug Injectors

This study examines injecting and sexual risk correlates of hepatitis B (HBV) and hepatitis C (HCV) seroprevalence among new injecting drug users (IDUs) (age 18-30 years, injecting =300 lifetime drug injections. Among men only, HCV seropositivity was associated with >/=40 lifetime number of sex partners (among those never sharing injecting equipment). In this new IDU sample, HBV and HCV seroprevalence differed by gender and were considerably higher than HIV seroprevalence. The findings suggest that early interventions, targeting injecting and sexual risks and including HBV vaccination, are needed among new IDUs to prevent HBV, HCV and, potentially, HIV epidemics. Neaigus, A., Gyamarthy, A., Miller, M., Frajzyngier, V., Zhao, M., Friedman, S., and Des Jarlais, D. Injecting and Sexual Risk Correlates of HBV and HCV Seroprevalence Among New Drug Injectors. Drug Alcohol Depend, 89(2-3), pp. 234-243, 2007.

The Transition from Injection to Non-Injection Drug Use: Long-Term Outcomes among Heroin and Cocaine Users in New York City

Researchers sought to characterize heroin and cocaine users in New York City who have changed from injection to non-injection drug administration and to identify factors associated with long-term non-injection use. They conducted 2 cross-sectional studies of heroin and cocaine users in New York City. New admissions were recruited at drug abuse treatment programs (2000-04) and respondent-driven sampling was used to recruit drug users from the community (2004). Both injecting and non-injecting drug users participated in each study. ''Former injectors'' were defined operationally as people who had used heroin and/or cocaine in the 6 months prior to the interview and who had injected illicit drugs in the past, but whose most recent injection was more than 6 months before the study interview. "Current'' injectors were defined as people who had injected heroin and/or cocaine in the 6 months prior to the interview. A structured interview on drug use history was administered, and a serum sample was collected and tested for HIV. The study found that a total of 104 former injectors were recruited for the drug abuse treatment program study, and 229 current injectors were recruited for the community recruitment study; 160 former injectors and 1731 current injectors were recruited from the drug abuse treatment study. Compared with the current injectors, former injectors were older and more likely to be African American. The former injectors reported long intervals since their most recent injection, a mean of 8 years in the drug abuse treatment program study and a mean of 12 years in the community recruitment study. The most common reasons for stopping injection drug use included concerns about health, social stigmatization and self-image, and preference for intranasal use as a route of drug administration. The results were highly consistent across the two studies. These findings suggest that the transition from injection to non-injection use appears to be a relatively stable behavior change for many former injectors, who report a decade or more without injecting. Developing a greater understanding of the transition from injection to stable non-injection drug use may provide insights into the natural histories of drug use and addiction. Des Jarlais, D., Arasteh, K., Perlis, T., Hagan, H., Heckathorn, D., Mcknight, C., Bramson, H., and Friedman, S. The Transition from Injection to Non-Injection Drug Use: Long-Term Outcomes among Heroin and Cocaine Users in New York City. Addiction, 102(5), pp. 778-785, 2007.

Comorbid Mental Disorders Associated with Nicotine Dependence in Pregnant Women

Dr. Renee Goodwin and colleagues investigated the association between mental disorders and cigarette use and nicotine dependence among pregnant women in the United States. Using a face-to-face general population survey, the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions, 1516 women reporting a pregnancy in the past year were assessed for cigarette smoking and nicotine dependence, as well as DSM-IV-defined mood and anxiety disorders and personality disorders. They found that among pregnant women, 21.7% reported cigarette use and 12.4% met the criteria for nicotine dependence. Among pregnant women with cigarette use, 45.1% met criteria for at least one mental disorder, and among those with nicotine dependence, 57.5% met criteria for at least one other mental disorder. After adjusting for demographics and comorbidity, nicotine dependence during pregnancy significantly predicted any mental disorder (odds ratio [OR] 3.3, 95% confidence interval [CI] 2.1-5.1), any mood disorder (OR 2.5, 95% CI 1.5-4.0), major depression (OR 2.07, 95% CI 1.3-3.4), dysthymia (OR 6.2, 95% CI 2.9-13.1), and panic disorder (OR 3.1, 95% CI 1.6-6.1) in the past year. No significant associations were found between nondependent cigarette use and mental disorders. These results suggest an association between mental disorders and nicotine dependence among pregnant women in the United States, a finding with implications for treatment and service provision. Goodwin, R., Keyes, K., and Simuro, N. Mental Disorders and Nicotine Dependence Among Pregnant Women in the United States. Obstet Gynecol, 109(4), pp. 875-883, 2007.

The Impact of Retail Cigarette Marketing Practices on Youth Smoking Uptake

Authors sought to examine the differential associations of cigarette retail marketing practices on youth smoking uptake. Analyses from 1999 through 2003 Monitoring the Future surveys involved 109,308 students and data on retail cigarette marketing collected from 966 communities in which the students reside, as part of the Bridging the Gap Initiative: Research Informing Practice and Policy for Healthy Youth Behavior. A total of 26,301 students were selected for this study and the exposures of Point-of-sale advertising, promotions, prices, and placement were evaluated. Using a smoking uptake measure to account for stages that identify the process by which adolescents begin smoking, odds ratios and confidence intervals were calculated through generalized ordered logit analyses, with weighted data that controlled for demographic and socioeconomic characteristics and accounted for clustering at the community level. Higher levels of advertising, lower cigarette prices, and greater availability of cigarette promotions were associated with smoking uptake. Advertising increased the likelihood of youth initiating smoking, price increased the likelihood of smoking at most levels of uptake, and availability of promotions increased the likelihood that youth will move from experimentation to regular smoking. Cigarette retail marketing practices increase the likelihood of smoking uptake. These findings suggest that specific restrictions on retail cigarette marketing may reduce youth smoking. Slater, S., Chaloupka, F., Wakefield, M., Johnston, L., and O'Malley, P. The Impact of Retail Cigarette Marketing Practices on Youth Smoking Uptake. Arch Pediatr Adolesc Med, 161(5), pp. 440-445, 2007.

Peer and Parental Influences on Longitudinal Trajectories of Smoking among African Americans and Puerto Ricans

The purpose of this study was to identify distinct trajectories of smoking behavior during a period extending from adolescence (mean age = 14 years) to

young adulthood (mean age = 26 years) among African American and Puerto Rican adolescents/young adults, to examine ethnic and gender differences in group membership, and to assess the ability of peer and parental smoking to distinguish among trajectory groups. A community-based sample of 451 African American and Puerto Rican adolescents was interviewed four times during adolescence and in early adulthood, covering a span of 12 years. For both ethnic/racial groups, four distinct trajectories were identified: Nonsmokers, maturing-out smokers, late-starting smokers, and early-starting continuous smokers. Compared with Puerto Ricans, African Americans were over-represented in the nonsmoking group, whereas Puerto Ricans were over-represented in the early-starting continuous group. Females were more likely than males to be early-starting continuous smokers than late starters. Adolescents who were exposed to peer and parental smoking in early adolescence were more likely to belong to trajectory groups characterized by higher levels of smoking. These findings show that exposure to peer and parental smoking in early adolescence constitutes a risk factor for engaging in elevated levels of smoking behavior at an early age and for continued smoking into adulthood for urban African Americans and Puerto Ricans. To be most effective, smoking prevention programs should address peer group and family influences on adolescent smoking. Brook, J., Pahl, K., and Ning, Y. Peer and Parental Influences on Longitudinal Trajectories of Smoking Among African Americans and Puerto Ricans. Nicotine Tob Res, 8(5), pp. 639-651, 2006.

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

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

A Prospective Study of the Effects of Age of Initiation of Alcohol and Drug Use on Young Adult Substance Dependence

Previous cross-sectional research has disagreed about whether an adolescent's age of onset of alcohol use is a unique predictor of later alcohol dependence or whether it is merely a correlate of those factors that produce alcohol dependence. The current study tests this question in a longitudinal sample, and extends the literature by testing whether age of onset of alcohol and drug use

predicts alcohol and drug dependence. Data from an ongoing study of children of alcoholics and matched controls (n = 395) were collected during three annual interviews during adolescence and two 5-year follow-ups in young adulthood. Taking a first drink of alcohol at or before age 13 was unrelated to the odds of alcohol and drug dependence when the adolescent did not also participate in early drug use or when correlated risk factors were taken into account. On the other hand, early drug use elevated the odds of drug dependence by young adulthood, even while controlling for shared risk factors. The current study provides support for the notion that early-adolescent onset of alcohol use is a marker of risk for later dependence rather than a causal influence. Moreover, it provides evidence for the impact of early drug use on drug-substance dependence. Implications for theory and intervention are discussed. King, K., and Chassin, L. A Prospective Study of the Effects of Age of Initiation of Alcohol and Drug Use on Young Adult Substance Dependence. J Stud Alcohol Drugs, 68(2), pp. 256-265, 2007.

Twentieth Century Rises in Adult Cigarette Use in the U.S. Parallel Rises in Asthma in Children

The prevalence of asthma has increased at least 3-fold during the past several decades. However, the reason for this increase remains unknown. Renee Goodwin of Columbia University examined one possible factor that may be affecting the increase in prevalence of asthma among youth in the United States from 1900 to 2003. She hypothesized that (1) there has been a marked increase in smoking during the past century, (2) this increase in smoking has resulted in a substantial increase in exposure to environmental tobacco smoke among children, and (3) increased exposure to environmental tobacco smoke has contributed to the increase in childhood asthma. Using a sample of 4,500 children from the National Health Interview Survey, data on the incidence of asthma were aggregated and compared on an ecologic level with data on cigarette consumption from the American Lung Association. Her results suggest a parallel increase in the rates of cigarette use among adults and asthma in children. These findings show an increase in cigarette use during the past 4 birth cohorts, with subsequent leveling off at a population level with a progressively more prominent increase in cigarette use among women in the United States. She notes that future studies will be needed to confirm these ecological trends with community-level analyses in a variety of geographic regions. Goodwin, R. Environmental Tobacco Smoke and the Epidemic of Asthma in Children: The Role of Cigarette Use. Ann Allergy Asthma Immunol, 98(5), pp. 447-454, 2007.

Maternal Cigarette Smoking During Pregnancy and Child Aggressive Behavior

This study's objective was to examine the association between maternal smoking during pregnancy and childhood aggressive behavior in African-American and Puerto Rican children, as well as the relationship between maternal unconventional behavior, low maternal affection, and offspring aggression. Participants consisted of African-American and Puerto Rican children (N = 203; mean age = 8.6, SD = 0.87) and their mothers living in an inner city community. An interview consisting of a structured questionnaire was administered to the mothers and their children. Scales with adequate psychometric properties were adapted from previous validated measures. They included maternal smoking during pregnancy, maternal education, unconventionality, and warmth. Controlling for demographic factors, maternal unconventional behavior, and low maternal warmth, maternal smoking during pregnancy was associated with having offspring who were aggressive. Maternal unconventionality and warmth were independently related to childhood aggression. The authors suggest that although causal limitations are noted, it may be that a decrease in smoking during pregnancy is associated with a

reduction in aggression in the offspring. Brook, D., Zhang, C., Rosenberg, G., and Brook, J. Maternal Cigarette Smoking During Pregnancy and Child Aggressive Behavior. Am J Addict, 15(6), pp. 450-456, 2006.

Personality Risk Factors Associated with Trajectories of Tobacco Use

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

Long-Term Effects of Child Abuse and Neglect on Alcohol Use and Excessive Drinking in Middle Adulthood

The purpose of this study was to determine the long-term effects of child abuse and neglect on alcohol use in middle adulthood. Individuals with documented cases of childhood physical and sexual abuse and/or neglect (n = 500) and matched controls (n = 396) from a metropolitan county in the Midwest were followed and interviewed in middle adulthood. Outcomes were Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, diagnoses of alcohol abuse or dependence in young adulthood (age 29) and excessive drinking in middle adulthood (age 40). Women with documented histories of child abuse or neglect reported higher past-year typical quantity ($p < .01$) and past-month number of days drinking eight or more drinks ($p < .05$) than nonabused/nonneglected women. Controlling for parental alcohol/drug problems, the effect of child maltreatment on excessive drinking in middle adulthood was not significant for women. For women, the final structural equation model revealed an indirect path through alcohol diagnosis in young adulthood ($p < .05$) to excessive drinking in middle adulthood ($p < .001$) but no direct path from child abuse and neglect to excessive drinking in middle adulthood. For men, there were no significant paths from child abuse and neglect to alcohol diagnosis in young adulthood or excessive drinking in middle adulthood. For men and women, parental alcohol/drug problems had a significant indirect effect on the offspring's drinking in middle adulthood ($p < .001$) through young adult alcohol diagnosis ($p < .001$). In conclusion, consequences of abuse and neglect persist into middle adulthood for women, through continuation of earlier alcohol problems, suggesting the need for interventions throughout the life course. The influence of parental alcohol and

drug problems warrants further attention. Widom, C., White, H., Czaja, S., and Marmorstein, N. Long-Term Effects of Child Abuse and Neglect on Alcohol Use and Excessive Drinking in Middle Adulthood. J Stud Alcohol Drugs, 68(3), pp. 317-326, 2007.

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

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

How Substance Use Differs among American Secondary Schools

The purpose of this study was to examine (1) the extent to which student drug use and related measures vary among American secondary schools, and (2) how substance use varies among schools by certain school characteristics. Data come from the Monitoring the Future project's annual surveys of nationally representative samples of 8th-, 10th-, and 12th-grade students from 1991 to 2002. The results show that the preponderance of variance in drug use and related variables lies within schools; only a relatively small amount of variance is between schools. Although the variance lies primarily within schools, there remain important school-to-school differences in the extent to which students are exposed to drug use. The analyses of school characteristics show that schools do indeed differ in drug use by their students, particularly by school type, socioeconomic status, and race/ethnicity. Eighth and 10th grade (but not 12th grade) students in public schools are more likely to be cigarette smokers than students in private schools. Students in public middle schools are at higher risk for use of alcohol and marijuana; however, among 12th graders, students in Catholic schools are at higher risk. School size is generally unrelated to substance use, with few exceptions. For the most part, there is a negative association between school socioeconomic status and student substance use among 8th graders; but by 12th grade, the association tends to be positive or not significant. Racial/ethnic composition is significantly associated with student substance use, with majority African American schools typically showing the lowest rates of use at all grades. O'Malley, P., Johnston, L., Bachman, J., Schulenberg, J., and Kumar, R. How Substance Use Differs Among American Secondary Schools. Prev Sci, 7(4), pp. 409-420, 2006.

Predictors of Resilience in Abused and Neglected Children Grown-

Up: The Role of Individual and Neighborhood Characteristics

This paper examines individual, family, and neighborhood level predictors of resilience in adolescence and young adulthood and describes changes in resilience over time from adolescence to young adulthood in abused and neglected children grown up. The sample includes documented cases of childhood physical and sexual abuse and neglect (n=676) from a Midwestern county area during the years 1967-1971 and information from official records, census data, psychiatric assessments, and self-reports were obtained through 1995. Analyses involve logistic regressions, replicated with Mplus to test for possible contextual effects. Almost half (48%) of the abused and neglected children in adolescence and nearly one-third in young adulthood were resilient. Over half of those who were resilient in adolescence remained resilient in young adulthood, whereas 11% of the non-resilient adolescents were resilient in young adulthood. Females were more likely to be resilient during both time periods. Being white, non-Hispanic decreased and growing up in a stable living situation increased the likelihood of resilience in adolescence, but not in young adulthood. Stressful life events and a supportive partner promoted resilience in young adulthood. Neighborhood advantage did not exert a direct effect on resilience, but moderated the relationship between household stability and resilience in adolescence and between cognitive ability and resilience in young adulthood. In conclusion, ecological factors appear to promote or interfere with the emergence and stability of resilience following childhood maltreatment. DuMont, K., Widom, C., and Czaja, S. Predictors of Resilience in Abused and Neglected Children Grown-Up: The Role of Individual and Neighborhood Characteristics. Child Abuse Negl, 31(3), pp. 255-274, 2007.

Growth Trajectories of Sexual Risk Behavior in Adolescence and Young Adulthood

Adolescence and young adulthood (ages 18-25 years) are periods of development and change, which include experimentation with and adoption of new roles and behaviors. Researchers investigated longitudinal trajectories of sexual risk behaviors across these time periods and how these trajectories may be different for varying demographic groups. They developed multilevel growth models of sexual risk behavior for a predominantly African American sample (n=847) that was followed for 8 years, from adolescence to young adulthood and investigated differences in growth parameters by race/ethnicity and gender and their interactions. The final model included linear and quadratic terms for both adolescence and young adulthood, indicating acceleration of sexual risk behaviors during adolescence and a peak and deceleration during young adulthood. African American males exhibited the highest rate of sexual risk behavior in ninth grade, yet had the slowest rate of growth. Compared with their White peers, African American males and females exhibited less sexual risk behavior during young adulthood. These results suggest that youths of different races/ethnicities and genders exhibit varying sexual risk behavior trajectories. Fergus, S., Zimmerman, M., and Caldwell, C. Growth Trajectories of Sexual Risk Behavior in Adolescence and Young Adulthood. Am J Public Health, 97(6), pp. 1096-1101, 2007.

Gender Differences in Injection Risk Behaviors at the First Injection Episode

This study sought to examine gender differences in drug injection equipment sharing at injecting initiation. Young injecting drug users in New York City (February 1999-2003) were surveyed about injection risk behaviors and circumstances at initiation. Analyses were gender-stratified and excluded participants who initiated alone. Multiple logistic regression estimated adjusted odds ratios. Participants (n=249) were 66% male and 82% White. Mean

initiation age was 19.2; mean years since initiating was 3.0. Women were significantly more likely to cite social network influence as a reason for initiating, to have male and sex partner initiators, and to share injecting equipment than men. Among women, sharing any injection equipment was associated with initiation by a sex partner and having >/=2 people present. Among men, being injected by someone else predicted sharing any injection equipment, while using a legally obtained syringe was protective. Social persuasion stemming from sexual and/or social relationships with IDUs may increase women's risk of sharing injection equipment at initiation, and consequently, their early parenteral risk of acquiring blood-borne infections. Effective interventions should focus on likely initiates, especially women in injecting-discordant sex partnerships, and IDUs (potential initiators). Frajzyngier, V., Neaigus, A., Gyarmathy, V., Miller, M., and Friedman, S. Gender Differences in Injection Risk Behaviors at the First Injection Episode. Drug Alcohol Depend, 89(2-3), pp. 145-152, 2007.

An Examination of Pathways from Childhood Victimization to Violence: The Role of Early Aggression and Problematic Alcohol Use

Using prospective data from a cohort design study involving documented cases of child abuse and neglect and a matched control group, the researchers examine two potential pathways between childhood victimization and violent criminal behavior: early aggressive behavior and problematic drinking. Structural equation models, including controls for race/ethnicity, socioeconomic status, parental alcoholism, and parental criminality, revealed different pathways for men and women. For men, child maltreatment has direct and indirect (through aggressive behavior and problematic alcohol use) paths to violence. For women, problematic alcohol use mediates the relationship between childhood victimization and violence, and, independent of child maltreatment, early aggression leads to alcohol problems, which lead to violence. Interventions for victims of childhood maltreatment need to recognize the role of early aggressive behavior and alcohol problems as risk factors for subsequent violence. Widom, C., Schuck, A., and White, H. An Examination of Pathways from Childhood Victimization to Violence: The Role of Early Aggression and Problematic Alcohol Use. Violence Vict, 21(6), pp. 675-690, 2006.

Childhood Victimization and Illicit Drug Use in Middle Adulthood

Using a prospective cohort design, the authors examined in this study whether childhood victimization increases the risk for illicit drug use and related problems in middle adulthood. Court-documented cases of childhood physical and sexual abuse and neglect and matched controls (N = 892) were first assessed as young adults (mean age = 29 years) during 1989-1995 and again in middle adulthood (mean age = 40 years) during 2000-2002. In middle adulthood, abused and neglected individuals were about 1.5 times more likely than controls to report using any illicit drug (in particular, marijuana) during the past year and reported use of a greater number of illicit drugs and more substance-use-related problems compared with controls. The current results reveal the long-term impact of childhood victimization on drug use in middle adulthood. These new results reinforce the need for targeted interventions with abused and neglected children, adolescents, and adults, and particularly for women. Widom, C., Marmorstein, N., and White, H. Childhood Victimization and Illicit Drug Use in Middle Adulthood. Psychol Addict Behav, 20(4), pp. 394-403, 2006.

Consistency Between Adolescent Reports and Adult Retrospective Reports of Adolescent Marijuana Use: Explanations of

Inconsistent Reporting Among an African American Population

This study examines the consistency of marijuana self-reports from adolescence and adulthood and what characterizes inconsistent reporting among a cohort of African American first graders followed longitudinally from age 6 to 32 (N=599, 51% female). Self-reported lifetime adolescent marijuana use (ages 16-17) and retrospective reports at age 32 were combined to categorize respondents as consistent reporters of nonuse (22%), consistent reporters of use (42%), adult recanters (19%), adolescent under reporters (8%), and inconsistent reporters of age of initiation (9%). Overall, about 64% of the population were consistent in their reports of adolescent marijuana use from adolescence to age 32. Multivariate logistic regression analyses found that recanters reported less marijuana use as adolescents, lower parental supervision during adolescence, lower deviant behavior as an adult, and stronger anti-drug values as adults than did consistent reporters. Adolescent under reporters reported less assault behaviors and less alcohol use as adolescents and had lower first grade math achievement than consistent reporters. Family background, depression, criminal arrests, and the field conditions of the interview were not related to inconsistent reporting. Ensminger, M., Juon, H., and Green, K. Consistency Between Adolescent Reports and Adult Retrospective Reports of Adolescent Marijuana Use: Explanations of Inconsistent Reporting Among an African American Population. Drug Alcohol Depend, 89(1), pp. 13-23, 2007.

Early Age of First Sexual Intercourse and Affiliation with Deviant Peers Predict Development of SUD

Researchers sought to assess whether early onset of sexual intercourse and affiliation with deviant peers serve as predictors of the development of SUD, using a prospective longitudinal study of adolescents recruited at the age of 10-12 years, with follow-up evaluations at ages 14, 16, 19, 22, and 25. The sample included 136 male subjects. Cox regression analyses were performed, with age of first intercourse, neurobehavioral disinhibition, exposure to drugs in the neighborhood, and deviant activities of peers as factors in the analyses. Earlier age at first intercourse and deviant activities of peers each predicted a significantly higher risk of subsequently developing a SUD (Wald=8.3, df=1, p=0.004; Wald=7.5, df=1, p=0.006, respectively). The results of this study add evidence to the theory that early onset of sexual intercourse and affiliation with deviant peers predict the early development of substance use disorders, using a prospective longitudinal study design. Cornelius, J., Clark, D., Reynolds, M., Kirisci, L., and Tarter, R. Early Age of First Sexual Intercourse and Affiliation with Deviant Peers Predict Development of SUD: A Prospective Longitudinal Study. Addict Behav, 32(4), pp. 850-854, 2007.

Religiosity and Adolescent Substance Use

The authors tested hypothesized pathways from religiosity to adolescent substance use (tobacco, alcohol, and marijuana) with data from samples of middle school (n = 1,273) and high school students (n = 812). Confirmatory analysis of measures of religiosity supported a 2-factor solution with behavioral aspects (belonging, attendance) and personal aspects (importance, value, spirituality, forgiveness) as distinct factors. Structural modeling analyses indicated inverse indirect effects of personal religiosity on substance use, mediated through more good self-control and less tolerance for deviance. Religiosity was correlated with fewer deviant peer affiliations and nonendorsement of coping motives for substance use but did not have direct effects on these variables. Parental support and parent-child conflict also had significant effects (with opposite direction) on substance use, mediated through self-control and deviance-prone attitudes. Implications for prevention research

are discussed. Walker, C., Ainette, M., Wills, T., and Mendoza, D. Religiosity and Substance Use: Test of an Indirect-Effect Model in Early and Middle Adolescence. Psychol Addict Behav, 21(1), pp. 84-96, 2007.

Childhood Adversity, Poly-Substance Use, and Disordered Eating in Adolescent Latinas

This study examined among Latina adolescents the effects of sexual abuse, physical/ emotional abuse, neglect, disconnection from family, and parental alcohol problems on poly-substance use and disordered eating, and whether five individual characteristics explain or differentiate these outcomes. Data from a community sample of 361 Latina adolescents were analyzed using structural equation modeling. Physical/emotional abuse predicted poly-substance use and weight concerns, and these associations were mediated by impaired current attachment. Disconnection from family predicted bulimic behaviors, and this association was mediated by dysphoria. One indirect path also emerged: Disconnection from family predicted low social conformity, and low social conformity predicted poly-substance use. Childhood sexual abuse did not uniquely predict any adverse outcome or individual characteristic examined. Dysphoria and impaired current attachment appear to play important roles in the development of substance use and disordered eating in Latina adolescents when physical/emotional abuse or disconnection from family predicts these outcomes. Dysphoria and low social conformity may differentiate the development of bulimic behaviors and poly-substance use, respectively, when family disconnection predicts these outcomes. Hodson, C., Newcomb, M., Locke, T., and Goodyear, R. Childhood Adversity, Poly-Substance Use, and Disordered Eating in Adolescent Latinas: Mediated and Indirect Paths in a Community Sample. Child Abuse Negl, 30(9), pp. 1017-1036, 2006.

Conceptual Issues in Studies of Resilience: Past, Present, and Future Research

The researchers begin this article by considering the following critical conceptual issues in research on resilience: (1) distinctions between protective, promotive, and vulnerability factors; (2) the need to unpack underlying processes; (3) the benefits of within-group experimental designs; and (4) the advantages and potential pitfalls of an overwhelming scientific focus on biological and genetic factors (to the relative exclusion of familial and contextual ones). The next section of the article is focused on guidelines for the selection of vulnerability and protective processes in future research. From a basic science standpoint, it is useful and appropriate to investigate all types of processes that might significantly affect adjustment among at-risk individuals. If the research is fundamentally applied in nature, however, it would be most expedient to focus on risk modifiers that have high potential to alter individuals' overall life circumstances. The final section of this article considers conceptual differences between contemporary resilience research on children versus adults. Issues include differences in the types and breadth of outcomes (e.g., the tendencies to focus on others ratings of competence among children and on self-reports of well-being among adults respectively). Luthar, S., Sawyer, J., and Brown, P. Conceptual Issues in Studies of Resilience: Past, Present, and Future Research. Ann N Y Acad Sci, 1094, pp. 105-115, 2006.

Modeling Adolescent Drug-Use Patterns in Cluster-Unit Trials with Multiple Sources of Correlation Using Robust Latent Class Regressions

This paper examines variation in adolescent drug-use patterns by using latent class regression analysis and evaluates the properties of an estimating-equations approach under different cluster-unit trial designs. A set of second-

order estimating equations for latent class models under the cluster-unit trial design are proposed. This approach models the correlation within subclusters (drug-use behaviors), but ignores the correlation within clusters (communities). A robust covariance estimator is proposed that accounts for within-cluster correlation. Performance of this approach is addressed through a Monte Carlo simulation study, and practical implications are illustrated by using data from the National Evaluation of the Enforcing Underage Drinking Laws Randomized Community Trial. The example shows that the proposed method provides useful information about the heterogeneous nature of drug use by identifying two subtypes of adolescent problem drinkers. A Monte Carlo simulation study supports the proposed estimation method by suggesting that the latent class model parameters were unbiased for 30 or more clusters. Consistent with other studies of generalized estimating equation (GEE) estimators, the robust covariance estimator tended to underestimate the true variance of regression parameters, but the degree of inflation in the test size was relatively small for 70 clusters and only slightly inflated for 30 clusters. The proposed model for studying adolescent drug use provides an alternative to standard diagnostic criteria, focusing on the nature of the drug-use profile, rather than relying on univariate symptom counts. The second-order GEE-type estimation procedure provided a computationally feasible approach that performed well for a moderate number of clusters and was consistent with prior studies of GEE under the generalized linear model framework. Reboussin, B., Lohman, K., and Wolfson, M. Modeling Adolescent Drug-Use Patterns in Cluster-Unit Trials with Multiple Sources of Correlation Using Robust Latent Class Regressions. Ann Epidemiol, 16(11), pp. 850-859, 2006.

Predictors of Injection Drug Use Cessation Among Puerto Rican Drug Injectors in New York and Puerto Rico

More than half of all AIDS cases among Puerto Ricans have been attributed to injection drug use. Predictors of injection drug use cessation were examined among Puerto Rican injection drug users (IDUs) in New York and Puerto Rico. Analysis of baseline and 6-month follow-up data from 670 IDUs in NY and 316 in PR showed that 47% NY and 20% in PR reported cessation of injection at follow-up ($p < .001$). In multivariate analyses, having been in drug treatment since baseline was the only significant predictor of cessation for both sites (NY: AOR = 1.80; PR: AOR = 3.10). Increasing availability of methadone maintenance treatment, especially in PR, was indicated. Deren, S., Kang, S., Colon, H., and Robles, R. Predictors of Injection Drug Use Cessation Among Puerto Rican Drug Injectors in New York and Puerto Rico. Am J Drug Alcohol Abuse, 33(2), pp. 291-299, 2007.

Pubertal Maturation and Risk for Alcohol Use and Abuse

This study sought to examine the impact of various aspects of puberty on risk of using alcohol and developing alcohol use disorder (AUD). Data came from the Great Smoky Mountains Study, a longitudinal study of a representative sample of 1420 youth aged 9-13 at recruitment. Participants were interviewed annually to age 16. A parent was also interviewed. Information was obtained about use of a range of drugs including alcohol, drug abuse and dependence, other psychiatric disorders, life events, and a wide range of family characteristics. Pubertal hormones were assayed annually from blood samples, and morphological development was assessed using a pictorial measure of Tanner stage. The authors found that, controlling for age, Tanner stage predicted alcohol use and AUD in both boys and girls. The effect of morphological development was strongest in those who matured early. Early pubertal maturation predicted alcohol use in both sexes, and AUD in girls. The highest level of excess risk for alcohol use was seen in early maturing youth with conduct disorder and deviant peers. Lax supervision predicted alcohol use in early maturing girls, while poverty and family problems were predictive in

early maturing boys. The authors conclude that, among the many biological, morphological, and social markers of increasing maturation, the visible signs of maturity are important triggers of alcohol use and AUD, especially when they occur early and in young people with conduct problems, deviant peers, problem families and inadequate parental supervision. These findings may help target those at greatest risk for early onset and progression of alcohol use and disorders. Costello, E., Sung, M., Worthman, C., and Angold, A. Pubertal Maturation and the Development of Alcohol Use and Abuse. Drug Alcohol Depend, 88 Suppl 1, pp. S50-S59, 2007.

Religiosity and Adolescent Substance Use

The authors use data from the Monitoring the Future study(MTF, N=16,595) and Youth, Education, and Society (related to the MTF study) and multilevel modeling data analytic techniques (HLM) to examine various unresolved issues in the ongoing debate, with a specific focus on the relationships between individual- and contextual-level (i.e., school) religiosity and adolescent's use of tobacco, alcohol, and marijuana. The results indicate first, that the higher adolescents' level of religiosity, the less likely they are to be current tobacco users, to engage in binge drinking, or to have used marijuana in the past year; second, that as the level of religiosity in a school increases, adolescents' frequency of cigarette use, binge drinking, and marijuana use decreases; third, that the religiosity of the school influences students' substance use, over and above their individual religiosity, but that this relationship exists only for marijuana; and fourth, that the strength of the relationship between individual-level religiosity and individual-level substance use varies depending upon the religiosity of the context, such that adolescents who are highly religious and in highly religious contexts are less likely to engage in binge drinking or marijuana use than those who are equally religious but in less religious contexts. Future research should seek to understand the mechanisms through which individual- and contextual-level religiosity influences young people's use of substances and other delinquent behaviors. Wallace, J.M., Yamaguchi, R., Bachman, J.G., O'Malley, P.M., Schulenberg, J.E., and Johnston, L.D. Religiosity and Adolescent Substance Use: The Role of Individual and Contextual Influences. Social Problems, 54(2), pp. 308-327, 2007.

Depression Ratings, Reported Sexual Risk Behaviors, and Methamphetamine Use Among Gay and Bisexual Men in an Outpatient Treatment Program

This study assessed relationships among dynamic changes tracked over time in methamphetamine use, depression symptoms, and sexual risk behaviors (unprotected anal intercourse) in a sample of 145 methamphetamine-dependent gay and bisexual males enrolled in a 16-week outpatient drug treatment research program. Participants were randomly assigned into 1 of 4 conditions: contingency management (CM), cognitive behavioral therapy (CBT; the control condition), combined CM and CBT, and a tailored gay-specific version of the CBT condition. Using latent growth curve models, the authors assessed the relationship of means (intercepts) and the slopes of the 3 measures of interest over time to test whether changes in methamphetamine use predicted declining rates of depression and risky sexual behavior in tandem. Participants with the greatest downward trajectory in methamphetamine use (urine verified) reported the greatest and quickest decreases in reported depressive symptoms and sexual risk behaviors. The control group reported the most methamphetamine use over the 16 weeks; the tailored gay-specific group reported a more rapidly decreasing slope in methamphetamine use than the other participants. Findings indicate that lowering methamphetamine use itself has a concurrent and synergistic effect on depressive symptoms and risky sexual behavior patterns. This suggests that some users who respond well to treatment may show improvement in these

co-occurring problems without a need for more intensive targeted interventions. Jaffe, A., Shoptaw, S., Stein, J., Reback, C., and Rotheram-Fuller, E. Depression Ratings, Reported Sexual Risk Behaviors, and Methamphetamine Use: Latent Growth Curve Models of Positive Change Among Gay and Bisexual Men in an Outpatient Treatment Program. Exp Clin Psychopharmacol, 15(3), pp. 301-307, 2007.

Role of Social Support and Self-Efficacy in Treatment Outcomes Among Clients with Co-Occurring Disorders

The authors investigated the roles of social support and self-efficacy in a sample of 351 clients with co-occurring disorders in residential drug abuse treatment programs (53% male; 35% African American, 13% Hispanic), in an attempt to find intervening variables that may contribute to improvement in treatment outcomes among individuals with co-occurring disorders. They also explored how ethnicity and age influence self-efficacy and access to social support, as well as their relationships to the outcomes. Structural equation modeling was used to examine the impact of the demographics and baseline psychological status, substance use, social support, and self-efficacy on mental health and substance use outcomes 6 months after treatment entry. Time in treatment was included as a control. Greater social support at baseline predicted better mental health status and less heroin and cocaine use; greater self-efficacy predicted less alcohol and cocaine use. Older clients reported less social support. African-American ethnicity was associated with more cocaine use at baseline and follow-up; however, African Americans reported more self-efficacy, which moderated their cocaine use. The current study highlights the potential therapeutic importance of clients' personal resources, even among a sample of severely impaired individuals. Warren, J., Stein, J., and Grella, C. Role of Social Support and Self-Efficacy in Treatment Outcomes Among Clients with Co-Occurring Disorders. Drug Alcohol Depend, 89(2-3), pp. 267-274, 2007.

Alcohol Use and Health-Related Quality of Life among Youth in Taiwan

Researchers examined the extent to which the use of the three most commonly consumed drugs in Taiwan (i.e., alcohol, tobacco, and betel nut) is related with health-related quality of life among adolescents. They probed whether the relationship linking alcohol use with health-related quality varies by health-orientated domains (e.g., physical, social, or emotional) and if it differs with other drug involvement. The data for the study came from a representative sample of 2235 adolescents (aged 12-18 years) collected as part of the 2001 National Health Interview Survey (NHIS), conducted in Taiwan. Recent alcohol, tobacco, and betel nut experiences were assessed by face-to-face interview. The 36-item short form Health Survey (SF-36) was used to assess respondents' generic health status. Youth with recent alcohol use tend to experience a poorer level of health-related quality of life. The estimated associations were not constant over the eight domains of general health examined, and multivariate modeling with generalized linear models and generalized estimating equations found that the strongest inverse relationship appears in the domain of role limitation due to emotional problems (beta = -10.5, 95% confidence interval [CI]: -16.9-4.12, $p < .001$). Greater deleterious effects were not found among youth also using tobacco and/or betel nut. Alcohol use was shown to be associated with impaired levels of health-related quality of life in adolescents. Although the temporality between alcohol involvement and lower levels of mental health is not explicit, the findings suggest that youth who are actively drinking might be a possible target group to intervene and avert mental health-related problems. Chen, C., and Storr, C. Alcohol Use and Health-Related Quality of Life Among Youth in Taiwan. J Adolesc Health, 39(5), pp. 752.e9-752.e16, 2006.

Predictors of Drinking Immediacy Following Daily Sadness: An Application of Survival Analysis to Experience Sampling Data

Previous studies of daily assessments show modest mood-drinking covariation as a function of gender and coping motives; however previous analyses also assume a fixed interval across all individuals in the onset of drinking following negative mood. The current study used survival analysis and experience sampling methods to test whether gender and coping motives predicted shorter sadness-to-drinking intervals among those with greater alcohol-related drinking consequences. A sample of 85 college students (46% male; 78% Caucasian) completed daily assessments over 28 days. Survival analyses showed that women drank more on days following elevated sadness when they reported being motivated to drink to cope and having experienced alcohol-related consequences. For men, the two groups showing greater drinking risk following days of elevated sadness did not report alcohol-related consequences, with those reporting the presence of coping motives showing the greatest risk. Implications of these findings for self-medication mechanisms are discussed. Hussong, A. Predictors of Drinking Immediacy Following Daily Sadness: An Application of Survival Analysis to Experience Sampling Data. Addict Behav, 32(5), pp. 1054-1065, 2007.

Predictors of Unprotected Sex with Non-Cohabitating Primary Partners among Sheltered and Low-Income Housed Women in Los Angeles County

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

Gender-specific Correlates of Sex Trade Among Homeless and Marginally Housed Individuals in San Francisco

Sex exchange is a well-established risk factor for HIV infection. Little is known about how correlates of sex trade differ by biologic sex and whether length of homelessness is associated with sex trade. The researchers conducted a cross-sectional study among a sample of 1,148 homeless and marginally housed individuals in San Francisco to assess correlates of exchanging sex for money or drugs. Key independent variables included length of homelessness; use of crack, heroin or methamphetamine; HIV status; and sexual orientation. Analyses were restricted by biologic sex. In total, 39% of women and 30% of men reported a lifetime history of sex exchange. Methamphetamine use and greater length of homelessness were positively associated with a history of sex trade among women, while heroin use, recent mental health treatment, and homosexual or bisexual orientation were significantly associated with sex trade for men. Crack use was correlated with sex trade for both genders. Correlates of sex trade differ significantly according to biologic sex, and these differences should be considered in the design of effective HIV prevention programs. The

researchers findings highlight the critical need to develop long-term services to improve housing status for homeless women, mental health services for homeless men, and drug treatment services for homeless adults involved in sex work. Weiser, S., Dilworth, S., Neilands, T., Cohen, J., Bangsberg, D., and Riley, E. Gender-Specific Correlates of Sex Trade Among Homeless and Marginally Housed Individuals in San Francisco. J Urban Health, 83(4), pp. 736-740, 2006.

Ethnic Pride and Self-control Related to Protective and Risk Factors

The purpose of this study was to test a theoretical model of how ethnic pride and self-control are related to risk and protective factors. A community sample of 670 African American youth (mean age = 11.2 years) were interviewed on measures of cigarette smoking, alcohol use, and sexual behavior (lifetime to past month). Structural modeling analyses indicated parenting was related to self-control and self-esteem, and racial socialization was related to ethnic pride. Self-control and self-esteem variables were related to levels of deviance-prone attitudes and to perceptions of engagers in, or abstainers from, substance use and sexual behavior. The proximal factors (behavioral willingness, resistance efficacy, and peer behavior) had substantial relations to the criterion variables. Participant gender and parental education also had several paths in the model. Results were generally similar for the 2 outcome behaviors. In this population, self-esteem and self-control are related to parenting approaches and have pathways to attitudes and social perceptions that are significant factors for predisposing to, or protecting against, early involvement in substance use and sexual behavior. Wills, T., Murry, V., Brody, G., Gibbons, F., Gerrard, M., Walker, C., and Ainette, M. Ethnic Pride and Self-Control Related to Protective and Risk Factors: Test of the Theoretical Model for the Strong African American Families Program. Health Psychol, 26(1), pp. 50-59, 2007.

Racial/Ethnic and Socioeconomic Status Differences in Overweight and Health-Related Behaviors among American Students: National Trends 1986-2003

This article reports long-term trends by race/ethnicity and socioeconomic status (SES) in the percent of American students who are overweight and who engage in three health-related behaviors hypothesized to be associated with overweight. Data are from the Monitoring the Future annual surveys, using nationally representative samples of eighth, 10th, and 12th grade students. Participants include 62,156 eighth and 64,899 10th graders who completed the 1993-2003 surveys and 35,107 12th graders who completed the questionnaire form containing the measures pertaining to this study in the 1986-2003 surveys. Trends are presented separately by gender and grade level for different racial/ethnic and SES subgroups, in: (a) percent overweight (body mass index > or = 85th percentile), (b) percent who always or almost always eat breakfast, (c) percent who regularly exercise vigorously, and (d) average hours of weekday television viewing. The prevalence of overweight and of engaging in less healthy behaviors is considerably greater among youth from racial/ethnic minority backgrounds, of lower socioeconomic status, and in higher grades. Trends in overweight and these behaviors are found to vary substantially by gender, racial/ethnic group, socioeconomic status, and grade level. The study findings show well-established and persistent differences in the percent of racial/ethnic minority and low SES youth who are overweight and who's dietary and exercise habits are less healthy. Documentation of these problems may lead to research and policy agendas that will contribute both to understanding and to the reduction of these important health disparities. Delva, J., O'Malley, P., and Johnston, L. Racial/Ethnic and Socioeconomic Status Differences in Overweight and Health-Related Behaviors among

American Students: National Trends 1986-2003. J Adolesc Health, 39(4), pp. 536-545, 2006.

Suicidality, Depression, and Alcohol Use among Adolescents

This review compiles the existing literature on suicidality, depression, and alcohol use among adolescents spanning over the past 15 years. Both Problem Behavior Theory and Stress-coping Theory can explain the relationships among suicidality, depression and alcohol use. The prevention of suicidality is critical, especially during the early school years, when it is associated with depression and alcohol use. Suicidality, depression and alcohol use are three phenomenons that noticeably increase in adolescence marking this time period as an ideal opportunity for prevention efforts to commence. Future empirical work is needed that will further assess the impact of adolescent depression and alcohol use on suicidality. In sum, this review of empirical research highlights critical results and limitations, as well as indicates a need for continued efforts in preventing suicidality, depression, and alcohol use among adolescents. Galaif, E., Sussman, S., Newcomb, M., and Locke, T. Suicidality, Depression, and Alcohol Use among Adolescents: A Review of Empirical Findings. Int J Adolesc Med Health, 19(1), pp. 27-35, 2007.

Adolescent Adjustment over Six Years in HIV-Affected Families

The purpose of this study was to assess predictors of adjustment of adolescents of parents with HIV (PWH) at three and six years after the delivery of either a coping skills intervention or a standard care condition. A randomized controlled intervention trial was conducted with 288 parents with human immunodeficiency virus (HIV) and their adolescent children. Indicators of adolescent adjustment at both three and six years were examined as a function of intervention condition, demographics, prior behaviors, and parental bonds using structural equation modeling (SEM). Adolescent adjustment at six years was also examined as a function of death of the PWH. Authors found that youth in the intervention condition reported significantly less substance use three and six years later. In addition, positive parental bonds reported at baseline reduced emotional distress at three years and increased positive future expectations at six years. On the other hand, substance use at three years predicted heightened sexual risk behaviors, continued substance use, and lower future expectations at six years. Early emotional distress and being Latino predicted increased emotional distress at three years. Parental death by three years predicted more sexual risk behavior and lowered future expectations at six years. A time-limited, family based intervention with adolescents of PWH demonstrated both direct and indirect benefits lasting into early adulthood, especially in decreasing substance use, and identifies key risk factors for problematic adjustment, including the death of a PWH. Rotheram-Borus, M., Stein, J., and Lester, P. Adolescent Adjustment over Six Years in HIV-Affected Families. J Adolesc Health, 39(2), pp. 174-182, 2006.

Impact of Program Services on Treatment Outcomes of Patients with Comorbid Mental and Substance Use Disorders

This study examined the outcomes of individuals with co-occurring disorders who received drug treatment in programs that varied in their integration of mental health services. Patients treated in programs that provided more on-site mental health services and had staff with specialized training were expected to report less substance use and better psychological outcomes at follow-up. Participants with co-occurring disorders were sampled from 11 residential drug abuse treatment programs for adults in Los Angeles County. In-depth assessments of 351 patients were conducted at treatment entry and at follow-up six months later. Surveys conducted with program administrators

provided information on program characteristics. Latent variable structural equation models revealed relationships of patient characteristics and program services with drug use and psychological functioning at follow-up. The authors found that individuals treated in programs that provided specific dual diagnosis services subsequently had higher rates of utilizing mental health services over six months and, in turn, showed significantly greater improvements in psychological functioning (as measured by the Brief Symptom Inventory and the RAND Health Survey 36-item short form) at follow-up. More use of psychological services was also associated with less heroin use at follow-up. African Americans reported poorer levels of psychological functioning than others at both time points and were less likely to be treated in programs that provided mental health services. These study findings support continued efforts to provide specialized services for individuals with co-occurring disorders within substance abuse treatment programs as well as the need to address additional barriers to obtaining these services among African Americans. Grella, C., and Stein, J. Impact of Program Services on Treatment Outcomes of Patients with Comorbid Mental and Substance Use Disorders. Psychiatr Serv, 57(7), pp. 1007-1015, 2006.

Predictors of Suicide Attempts: State and Trait Components

The authors examined the state and trait components of 3 predictors of suicide attempts (depression, hopelessness, and anxiety), and their relationship to suicidal behavior. Self-report questionnaire and interview data from 180 adolescents enrolled in a prospective naturalistic study were analyzed. Between 23% and 30% of the variance in the predictors was attributable to subjects' trait levels of these variables; the trait, as well as the state, components of the predictor variables were interrelated; and trait levels of these variables were consistently related to suicide attempts. To reduce long-term risk of suicide attempts, clinicians should focus not only on reducing short-term distress but also on reducing individuals' more enduring patterns (trait levels) of negative affectivity. Goldston, D., Reboussin, B., and Daniel, S. Predictors of Suicide Attempts: State and Trait Components. J Abnorm Psychol, 115(4), pp. 842-849, 2006.

Learning Disabilities and Intellectual Functioning in School-Aged Children with Prenatal Cocaine Exposure

Risk for developing a learning disability (LD) or impaired intellectual functioning by age 7 was assessed in full-term children with prenatal cocaine exposure drawn from a cohort of 476 children born full term and enrolled prospectively at birth. Intellectual functioning was assessed using the Wechsler Intelligence Scale for Children-Third Edition (Wechsler, 1991) short form, and academic functioning was assessed using the Wechsler Individual Achievement Test (WIAT; Wechsler, 1993) Screener by examiners blind to exposure status. LDs were categorized based on ability-achievement discrepancy scores, using the regression-based predicted achievement method described in the WIAT manual. The sample in this report included 409 children (212 cocaine-exposed, 197 non-cocaine-exposed) from the birth cohort with available data. Cumulative incidence proportions and relative risk values were estimated using STATA software (Statacorp, 2003). No differences were found in the estimate of relative risk for impaired intellectual functioning (IQ below 70) between children with and without prenatal cocaine exposure (estimated relative risk = .95; 95% confidence interval [CI] = 0.65, 1.39; p = .79). The cocaine-exposed children had 2.8 times greater risk of developing a LD by age 7 than non-cocaine-exposed children (95% CI = 1.05, 7.67; p = .038; IQ >/= 70 cutoff). Results remained stable with adjustment for multiple child and caregiver covariates, suggesting that children with prenatal cocaine exposure are at increased risk for developing a learning disability by age 7 when compared to their non-cocaine-exposed peers. Morrow, C., Culbertson, J., Accornero, V.,

Xue, L., Anthony, J., and Bandstra, E. Learning Disabilities and Intellectual Functioning in School-Aged Children with Prenatal Cocaine Exposure. Dev Neuropsychol, 30(3), pp. 905-931, 2006.

Testosterone Levels and Sexual Maturation Predict Substance Use Disorders in Adolescent Boys

Authors sought to determine whether testosterone level and sexual maturation in boys biased development of socially nonnormative behavior culminating in a substance use disorder (SUD). The subjects were 179 boys recruited in late childhood through a high-risk paradigm. Path analysis was used to evaluate the influence of testosterone level and sexual maturation in early adolescence (age 12-14) on attitudes toward antisociality, affiliation with deviant peers, and social potency in middle adolescence (age 16), illicit drug use by late adolescence (age 19), and SUD in young adulthood (age 22). Testosterone level predicted social potency and approval of aggressive/antisocial behavior. Sexual maturation mediated the relation between testosterone level in early adolescence and later affiliation with deviant peers. Social potency, approval of aggressive/antisocial behavior, and deviant peer affiliations predicted illicit drug use by late adolescence that in turn predicted SUD in young adulthood. This study demonstrated that pubertal processes in early adolescence influence the risk for SUD via effects on psychosocial functioning. Reynolds, M., Tarter, R., Kirisci, L., Kirillova, G., Brown, S., Clark, D., and Gavaler, J. Testosterone Levels and Sexual Maturation Predict Substance Use Disorders in Adolescent Boys: A Prospective Study. Biol Psychiatry, 61(11), pp. 1223-1227, 2007.

Examination of the Nicotine Metabolite Ratio in a Multiethnic/Multiracial Sample

The recent development of a noninvasive measure of nicotine metabolism, the nicotine metabolite ratio (trans-3 hydroxycotinine/cotinine), makes it possible to examine the association between rate of nicotine metabolism and smoking behavior in the general population. Dr. Denise Kandel and colleagues examined group differences in the ratio measured in urine and the association between the ratio and multiple measures of smoking behavior and nicotine dependence in a large, nationally representative sample of young adults. The sample included 900 daily smokers aged 18-26 years from wave III (2001-2002) of the National Longitudinal Survey of Adolescent Health. Nicotine dependence was measured by using the Fagerstroem Test for Nicotine Dependence. Females had higher nicotine metabolite ratios than males; Whites and Hispanics had higher nicotine metabolite ratios than African Americans or Asians. This finding is consistent with those from laboratory studies of older smokers based on intravenous infusion of nicotine. No significant association was found between the nicotine metabolite ratio and number of cigarettes smoked per day or nicotine dependence. The availability of a noninvasive measure makes possible systematic testing of causal hypotheses generated by laboratory studies in the general population. Kandel, D., Hu, M., Schaffran, C., Udry, J., and Benowitz, N. Urine Nicotine Metabolites and Smoking Behavior in a Multiracial/Multiethnic National Sample of Young Adults. Am J Epidemiol, 165(8), pp. 901-910, 2007.

Self-Control, Symptomatology, and Substance Use Precursors

The authors tested a theoretical model of how self-control constructs are related to psychological symptomatology and variables that predispose to involvement versus noninvolvement in substance use: willingness to use, affiliation with peers who use, and efficacy for resisting use. Data were obtained from a sample of 332 children (mean age = 9.3 years) who were interviewed in households. Structural equation modeling showed that good

self-control was related to more positive well-being and less externalizing symptomatology, whereas poor self-control was related to more externalizing and to more internalizing symptomatology. Externalizing had paths to willingness and peer use, well-being had inverse paths to these variables, and poor self-control had a direct effect to lower resistance efficacy. Multiple-group analyses indicated gender differences in paths from symptomatology to predisposing factors. Implications for understanding vulnerability to substance use are discussed. Wills, T., Ainette, M., Mendoza, D., Gibbons, F., and Brody, G. Self-Control, Symptomatology, and Substance Use Precursors: Test of a Theoretical Model in a Community Sample of 9-year-old Children. Psychol Addict Behav, 21(2), pp. 205-215, 2007.

Measurement of Negative Consequences of Substance Use in Street Youth

The Rutgers Alcohol Problem Index (RAPI) was used to assess negative consequences due to both alcohol and drug use. Data were collected from 173 substance using homeless adolescents (13-19 years of age, 58% male) who were grouped based on the substances rated: alcohol only, alcohol and drugs, or drugs only. The RAPI retained good internal consistency across substance categories, exhibited strong measurement construct congruence, and good convergent validity based upon correlations with assessed DSM diagnostic criteria (both dependence and abuse). Discussion focuses on the RAPI as a reliable instrument for the measurement of negative consequences for alcohol and drug use. Ginzler, J., Garrett, S., Baer, J., and Peterson, P. Measurement of Negative Consequences of Substance Use in Street Youth: An Expanded Use of the Rutgers Alcohol Problem Index. Addict Behav, 32(7), pp. 1519-1525, 2007.

The Puerto Rico-New York Airbridge for Drug Users: Description and Relationship to HIV Risk Behaviors

This study examined mobility on the airbridge between New York (NY) and Puerto Rico (PR) for Puerto Rican drug users and its relationship to HIV risk. Over 1,200 Puerto Rican injection drug users (IDUs) and crack smokers were recruited by outreach workers in NY and PR; interview data included questions on mobility (lifetime residences and recent trips). Two-thirds of the NY sample had lived in PR; one-quarter of the PR sample had lived in NY; the most commonly sited reasons for moving were family-related. Fewer than 10% had visited the other location in the prior 3 years. Variables related to risk were number of moves, recent travel, and having used drugs in PR (all with $p < 0.05$). Implications included the need to enhance risk reduction efforts for IDUs in PR and address sexual risk among mobile drug users. Deren, S., Kang, S., Colon, H., and Robles, R. The Puerto Rico-New York Airbridge for Drug Users: Description and Relationship to HIV Risk Behaviors. J Urban Health, 84(2), pp. 243-254, 2007.

A Study of Latino Adolescent Health Behaviors and Weight in the United States of America

The authors examined, by gender, differences in being overweight among adolescents of Mexican, Puerto Rican, and other Latin American heritage who live in the United States of America, and investigated the relationships between these differences and socioeconomic status, health-related behaviors, and family characteristics. The study analyzed data from nationally representative samples of Latino 8th and 10th graders in the Monitoring the Future study from 1991 to 2004 (N = 11 265). Investigators found a higher proportion of Mexican-American girls were overweight than other Latin American girls, both before and after adjusting for many confounders. For both genders, being

overweight was inversely associated with socioeconomic status and frequency of vigorous exercise, and positively associated with the amount of television viewing. No family characteristic variable examined was associated with overweight. Time spent exercising and time spent watching television are two potentially modifiable risk factors that, if targeted, may result in important reductions in overweight. The findings indicate the need to identify gender- and culturally-appropriate interventions that can increase physical activity and reduce sedentary activities among Latino adolescents, particularly in families of low socioeconomic status. Delva, J., O'Malley, P., and Johnston, L. Health-Related Behaviors and Overweight: A Study of Latino Adolescents in the United States of America. Rev Panam Salud Publica, 21(1), pp. 11-20, 2007.

A Comparison of Psychosocial and Behavioral Characteristics of Adolescent Male Bullies, Victims, and Bully-Victims

The authors sought to determine among male adolescents whether bully-victims would report the poorest psychosocial health, the worst attitudes toward school, more problem behavior (delinquency, weapons possession, and substance use), and more physical injury compared with bullies, victims, and neutral students. Ethnic differences in bullying category membership were also assessed. Employing multisample latent variable models, authors contrasted 1,312 males in grades 7-12 classified as bullies (n = 299), victims (n = 180), bully-victims (n = 195), and neutral (n = 638) on school attitudes, psychosocial health, problem behaviors, and physical injury. Hypotheses were generally confirmed, especially contrasts between bully-victims and neutrals. However, bullies did not have better school attitudes than bully-victims, and victims only marginally reported better psychological health than bully-victims. The boys of mixed ethnicity were more likely to be victims. Greater awareness of the problems associated with boys who both bully and are victimized is necessary for improved intervention. Stein, J., Dukes, R., and Warren, J. Adolescent Male Bullies, Victims, and Bully-Victims: A Comparison of Psychosocial and Behavioral Characteristics. J Pediatr Psychol, 32(3), pp. 273-282, 2007.

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

Research Findings - Prevention Research

Intervention Effects on Foster Preschoolers' Attachment Behaviors

This study examined change in attachment-related behaviors among foster preschoolers participating in a randomized trial of the Multidimensional Treatment Foster Care Program for Preschoolers (MTFC-P). Measures of secure, resistant, and avoidant behaviors were collected using a caregiver-report diary at 3-month intervals during the 12 months following a new foster placement. Children randomly assigned to the MTFC-P intervention condition (n = 57) showed significant increases in secure behavior and significant decreases in avoidant behavior relative to children assigned to the regular foster care condition (n = 60). Both groups showed significant decreases in resistant behavior over time. Analyses also revealed a significant interaction between treatment condition and age at first foster placement on change in secure behavior, suggesting that foster preschoolers placed earlier tended to show greater increases in secure behavior over time. Results are discussed in terms of the importance of early intervention and prevention services for foster preschoolers. Fisher, P.A., and Kim, H.K. Intervention Effects on Foster Preschoolers' Attachment-Related Behaviors from a Randomized Trial. Prev Sci, 8(2), pp. 161-170, 2007.

Preventing Youth Violence and Delinquency

Violence is an important public health problem among adolescents in the United States. Substance use and violence tend to co-occur among adolescents and appear to have similar etiologies. The present study examined the extent to which a comprehensive prevention approach targeting an array of individual-level risk and protective factors and previously found effective in preventing tobacco, alcohol, and illicit drug use is capable of decreasing violence and delinquency. Schools (N=41) were randomly assigned to intervention and control conditions. Participants in the 20 intervention schools received the Life Skills Training prevention program including material focusing on violence and the media, anger management, and conflict resolution skills. Survey data were collected from 4,858 sixth grade students prior to the intervention and three months later after the intervention. Findings showed significant reductions in violence and delinquency for intervention participants relative to controls. Stronger prevention effects were found for students who received at least half of the preventive intervention. These effects include less verbal and physical aggression, fighting, and delinquency. The results of this study indicate that a school-based prevention approach previously found to prevent tobacco, alcohol, and illicit drug use can also prevent violence and delinquency. The authors suggest future research to determine whether these effects are durable, and whether they extend to more serious forms of violence. Botvin,

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G., Griffin, K., and Nichols, T. Preventing Youth Violence and Delinquency Through a Universal School-Based Prevention Approach. Prev Sci, 7(4), pp. 403-408, 2006.

Long-Term Effects of Brief Substance Use Interventions 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, the study compared the long-term efficacy of 2 brief substance use feedback interventions for mandated college students. The study followed up mandated 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 postintervention. 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. The 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. 1-12, 2007.

Crystal Methamphetamine Use Among Young Adults in the USA

The aim of this study was to examine the prevalence and correlates of crystal methamphetamine use among young adults in the USA. The design consisted of cross-sectional analyses of nationally representative data of young adults from the National Longitudinal Study of Adolescent Health (Add Health); in-home interviews were conducted in 2001-02. Participants included 14,322 respondents aged 18-26 years. Measurements used were past year and 30-day crystal methamphetamine use, crime/violence (ever arrested, past year drug selling, past year violent behavior) and sexual risk behaviors (multiple partners, poor condom use, regretted sex, sex for money). Findings showed prevalence of past year crystal methamphetamine use was 2.8% and past month was 1.3%. White or Native American race, residence in the west or south, having an ever-incarcerated father, marijuana, cocaine, intravenous drug use and high novelty seeking were associated with greater likelihood of past year use in multivariate analyses. Compared to marijuana and cocaine users, crystal methamphetamine users were more likely to be male, unemployed, reside in the west or south, have an ever-incarcerated father and less likely to be black or Hispanic. Frequent users were no different from occasional users, except being more likely to have dropped out of school. Although crystal methamphetamine use was associated with crime and risky sex, controlling for covariates greatly diminished this relationship. It was

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concluded that most users are occasional users, but any past year use is associated with risky and antisocial behaviors, including other illicit drug use. Further research is needed to examine how other drug addiction is associated with methamphetamine use, and to identify longitudinal antecedents for prevention. Iritani, B., Hallfors, D., and Bauer, D. Crystal Methamphetamine Use Among Young Adults in the USA. Addiction, 102(7), pp. 1102-1113, 2007.

Patterns of Heavy Drinking from Ages 18 to 30

The purpose of this study was to illustrate the use of latent class analysis to examine change in behavior over time. Patterns of heavy drinking from ages 18 to 30 were explored in a national sample; the relationship between college enrollment and pathways of heavy drinking, particularly those leading to adult heavy drinking, was explored. Latent class analysis for repeated measures is used to estimate common pathways through a stage-sequential process. Common patterns of development in a categorical variable (presence or absence of heavy drinking) are estimated and college enrollment is a grouping variable. Data were from the National Longitudinal Survey of Youth (N = 1,265). Eight patterns of heavy drinking were identified: no heavy drinking (53.7%); young adulthood only (3.7%); young adulthood and adulthood (3.7%); college age only (2.6%); college age, young adulthood, and adulthood (8.7%); high school and college age (4.4%); high school, college age, and young adulthood (6.3%); and persistent heavy drinking (16.9%). The researchers found no evidence that prevalence of heavy drinking for those enrolled in college exceeds the prevalence for those not enrolled at any of the four developmental periods studied. In fact, there is some evidence that being enrolled in college appears to be a protective factor for young adult and adult heavy drinking. College-enrolled individuals more often show a pattern characterized by heavy drinking during college ages only, with no heavy drinking prior to and after the college years, whereas nonenrolled individuals not drinking heavily during high school or college ages are at increased risk for adult heavy drinking. Lanza, S.T., and Collins, L.M. A Mixture Model of Discontinuous Development in Heavy Drinking From Ages 18 to 30: The Role of College Enrollment. J Stud Alcohol, 67(4), pp. 552-561, 2006.

Marijuana Use and Education Level Predict Late Onset Cigarette Smoking in African American Males

This study examined adolescent risk factors for late-onset cigarette smoking among African American males. Data came from the Pittsburgh Youth Study, a longitudinal study of young men followed from age 13 to age 25. Individuals who began smoking at age 17 or older were compared with those who began smoking by age 16 and with those who never smoked in terms of risk factors measured in middle (at age 16) and late adolescence (from age 17 to 19). The study included 281 African American young men. A total of 18 psychological, behavioral and environmental risk factors were measured at age 16, and 19 risk factors were measured between ages 17 and 19. Several risk factors at age 16 differed between early-onset and late-onset smokers or nonsmokers; however, in multivariate analyses, only peer drug use and truancy were significant. Among the age 16 risk factors, only truancy differentiated late-onset smokers from nonsmokers. Late adolescence behavioral risk factors were significantly related to late-onset smoking. However, only smoking marijuana and highest grade completed differentiated late-onset smokers from nonsmokers in multivariate analyses. Well-established predictors of cigarette smoking assessed in middle adolescence could identify individuals who already smoked but could not distinguish between those who would and would not begin smoking later. Late adolescence life transitions were not related to late-onset smoking. More research is needed to examine contextual factors in late adolescence and early adulthood that protect against and precipitate late-onset of smoking for African Americans. White, H., Violette, N., Metzger, L., and

Stouthamer-Loeber, M. Adolescent Risk Factors for Late-Onset Smoking Among African American Young Men. Nicotine Tob Res, 9(1), pp. 153-161, 2007.

The Role of Gender and Acculturation on Drug-related Outcomes for "Keepin' it REAL" Prevention Program

This study examined whether the efficacy of the Keepin' it REAL school-based prevention program was moderated by gender, ethnicity, and acculturation. Data came from a randomized trial in Phoenix AZ middle schools involving 4622 mostly Latino 7th graders. Youth participated in the prevention program that involved 10 classroom lessons and 5 videos developed based on extensive input from youth. Previous research on the program has demonstrated its efficacy with regard to slowing initiation of drug use. In the current study, using multi-level mixed models, results for the total sample showed no gender differences in program effects on recent substance use. However, the program was more effective in fostering anti-drug norms among boys than among girls. Subgroup analyses indicated that there were more beneficial program effects for less acculturated boys than less acculturated girls. Specifically, there was less alcohol and cigarette use and stronger anti-drug norms post intervention for less acculturated boys in the intervention group than their female counterparts. It is notable that less acculturated Latino boys had higher baseline substance use rates and stronger pro-drug norms than less acculturated Latino girls, and the lower risk of use for less acculturated girls may have attenuated the potential for program effects. The results of this study, while generally verifying the efficacy of gender-inclusive prevention strategies, suggest that efforts may be strengthened by attending to the special risks and resilience of certain subgroups of female and male youth. Kulis, S., Yabiku, S.T., Marsiglia, F.F., Nieri, T., and Crossman, A. Differences By Gender, Ethnicity, and Acculturation in the Efficacy of the Keepin' it REAL Model Prevention Program. J Drug Educ, 37(2), pp. 123-144, 2007.

Experimental Treatment Effects Compared to Care as Usual Depend on the Type of Care As Usual

In psychotherapy, effectiveness of an experimental treatment often is compared to care as usual. However, little if any attention has been paid to the heterogeneity of care as usual. The authors examined the effectiveness of manualized behavior therapy on school-aged disruptive behavior disordered (DBD) children in everyday clinical practice. A total of 77 DBD children (8-13 years) were randomly assigned to the Utrecht Coping Power Program (UCPP) condition or the care as usual condition. Care as usual consisted of family therapy (FT) or behavior therapy (BT). Decrease in parent-reported overt aggression was significantly larger in the UCPP condition than in the FT condition, but UCPP and BT did not differ significantly in this respect. The effect sizes of difference scores on other variables were more in favor of UCPP when compared to FT than to BT. The comparison of an experimental treatment to care as usual depends on the type of usual treatment. Van de Wiel, N., Matthys, W., Cohen-Kettenis, P., Maassen, G., Lochman, J., and van Engeland, H. The Effectiveness of an Experimental Treatment when Compared to Care as Usual Depends on the Type of Care as Usual. Behav Modif, 31(3), pp. 298-312, 2007.

Effects of Iowa Strengthening Families Program on Internalizing Symptoms and Polysubstance Use in Adolescence

This study evaluated effects of the Iowa Strengthening Families Program, a family-focused universal preventive intervention, on growth patterns of adolescent internalizing (anxiety and depressive symptoms) and monthly polysubstance use (alcohol, tobacco, marijuana, inhalants, and other illicit

drugs), as well as the association between internalizing and polysubstance growth factors. The sample consisted of rural Midwestern adolescents (N=383), followed from sixth through twelfth grade. Compared to the control group, the intervention group adolescents showed a slower rate of increase in internalizing symptoms and polysubstance use. Intervention effects on internalizing symptoms were similar for boys and girls; however, girls demonstrated a higher overall level and a greater rate of increase across time. The intervention slowed the rate of increase in polysubstance use significantly more for girls than for boys, although overall levels of use were lower in the intervention group for both genders. Associations between internalizing and polysubstance use growth factors were found for girls, but not for boys, suggesting gender differences in psychosocial development. Trudeau, L., Spoth, R., Randall, G.K., and Azevedo, K. Longitudinal Effects of a Universal Family-Focused Intervention on Growth Patterns of Adolescent Internalizing Symptoms and Polysubstance Use: Gender Comparisons. Journal of Youth and Adolescence, 36(6), pp. 725-740, 2007.

HIV Prevention for Injection Drug Users in China and Vietnam

A pattern of serious injection drug user (IDU) driven HIV epidemics in Asia, with emerging evidence of generalization through heterosexual transmission, indicates the need for interventions focusing on both drug- and sex-related risk reduction. In a cross-border HIV prevention project for IDUs in northern Vietnam and southern China, peer educators disseminated risk reduction information to IDUs in the community and provided 20,000-25,000 sterile needles/syringes and 4,000-6,000 condoms per month. Since implementation of these interventions, the frequency of both injecting and sexual risk behaviors fell significantly, HIV prevalence among IDUs declined or stabilized, and HIV incidence dropped. There is official support for harm reduction interventions in both countries but this appears precarious in view of persistently powerful political and financial support for a law enforcement approach. Hammett, T.M., Des Jarlais, D., Johnston, P., Kling, R., Ngu, D., Liu, W., Chen, Y., Van, L. K., and Donghua, M. HIV Prevention for Injection Drug Users in China and Vietnam: Policy and Research Considerations. Global Public Health, 2 (2), pp. 125-139, 2007.

Community Coalition Structure Influences Adoption of Evidence-Based Drug Abuse Prevention Programs

This study examined the effect of community coalition network structure on the effectiveness of an intervention designed to accelerate the adoption of evidence-based substance abuse prevention programs. At baseline, 24 cities were matched and randomly assigned to 3 conditions (control, satellite TV training, and training plus technical assistance). 415 community leaders were surveyed at baseline and 406 at 18-month follow-up about their attitudes and practices toward substance abuse prevention programs. Network structure was measured by asking leaders whom in their coalition they turned to for advice about prevention programs. The outcome was a scale with 4 subscales: coalition function, planning, achievement of benchmarks, and progress in prevention activities. Multiple linear regression and path analysis were used to test hypotheses, and the two intervention conditions were combined for analyses. The intervention had a significant effect on decreasing the density of coalition networks. The change in density subsequently increased adoption of evidence-based practices. Optimal community network structures for the adoption of public health programs are unknown, but it should not be assumed that increasing network density or centralization are appropriate goals. Lower-density networks may be more efficient for organizing evidence-based prevention programs in communities. Valente, T.W., Chou, C.P., and Pentz, M.A. Community Coalitions as a System: Effects of Network Change on Adoption of Evidence-Based Substance Abuse Prevention. Research and

Practice, 97(5), pp. 880-886, 2007.

Real-World Universal Prevention Reduces Drug Use

This study examined the effects of "real-world," community-based implementation of universal preventive interventions selected from a menu, including effects specific to higher- and lower-risk subsamples delivered via the PROSPER community-university partnership model. School districts were selected based on size and location, and then randomly assigned to a control condition or to an experimental condition in a cohort sequential design. The study included 28 public school districts in Iowa and Pennsylvania that were located in rural towns and small cities, ranging in size from 6,975 to 44,510. Sixth and seventh graders in these school districts participated in the study (n=12,022). Community teams were mobilized, with each team implementing one of three evidence-based, family-focused interventions (5 to 12 sessions) and one of three evidence-based school interventions (11 to 15 sessions), for 6th and 7th graders, respectively. Observations showed that interventions were implemented with fidelity. Outcomes included student reports of past month, past year, and lifetime use of alcohol, cigarettes, marijuana, methamphetamines, ecstasy, and inhalants, as well as indices of gateway and illicit substance initiation, at pretest and at a follow-up assessment 18 months later. Intent-to-treat analyses demonstrated significant effects on substance initiation (marijuana, inhalants, methamphetamines, ecstasy, gateway index, illicit-use index), as well as past-year use of marijuana and inhalants, with positive trends for all substances measured. For three outcomes, intervention effects were stronger for higher-risk students than lower-risk students. Community-based implementation of brief universal interventions designed for general populations has potential for public health impact by reducing substance use among adolescents. Spoth, R., Redmond, C., Shin, C., Greenberg, M., Clair, S., and Feinberg, M. Substance-Use Outcomes at 18 Months Past Baseline: The PROSPER Community-University Partnership Trial. Am J Prev Med, 32(5), pp. 395-402, 2007.

The Cost of ADHD in Childhood and Adolescence

Using a cost of illness (COI) framework, this article examined the economic impact of attention-deficit/hyperactivity disorder (ADHD) in childhood and adolescence. A review of published literature identified 13 studies, most conducted on existing databases by using diagnostic and medical procedure codes and focused on health care costs. Two were longitudinal studies of identified children with ADHD followed into adolescence. Costs were examined for ADHD treatment-related and other health care costs (all but 1 study addressed some aspect of health care), education (special education, 2 studies; disciplinary costs: 1 study), parental work loss (2 studies), and juvenile justice (2 studies). Based on this small and as yet incomplete evidence base, the researchers estimated annual COI of ADHD in children and adolescents at $14,576 per individual (2005 dollars). Given the variability of estimates across studies on which that number is based, a reasonable range is between $12,005 and $17,458 per individual. Using a prevalence rate of 5%, a conservative estimate of the annual societal COI for ADHD in childhood and adolescence is $42.5 billion, with a range between $36 billion and $52.4 billion. Estimates are preliminary because the literature is incomplete; many potential costs have not been assessed in extant studies. Limitations of the review and suggestions for future research on COI of ADHD are provided. Pelham, W.E., Foster, E.M., and Robb, J.A. The Economic Impact of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. J Pediatr Psychol, 32(6), pp. 711-727, 2007.

Strengths-Based Case Management: Implementation with High Risk Youth

Few effective methods of intervention exist for youth at risk for negative life outcomes. One method used successfully with both adults with chronic mental illness and adults with substance abuse problems is strengths-based case management (SBCM). Based on the principles of strengths theory, SBCM aims to assist individuals in identifying and achieving personal goals, with an emphasis on the case manager-client relationship and client self-determination. In the current study, the authors report findings from a feasibility study that implemented SBCM with adolescent runaways. Challenges to implementation, such as financial status, the role of families, abuse and neglect, developmental issues, education, peer relationships, and transportation, were examined. The current findings suggest that it is feasible to successfully implement SBCM with adolescents, but the challenges to application are different with this group compared with adults, given the developmental differences between adolescents and adults. Arnold, E.M., Walsh, A.K., Oldham, M.S., and Rapp, C.A. Strengths-Based Case Management: Implementation with High-Risk Youth. Families in Society-The Journal of Contemporary Social Services, 88(1), pp. 86-94, 2007.

Differences in Perceived Implementation: Standard Versus Peer-Led Prevention Program

The objective of this study was to assess perceived implementation of 2 substance-abuse prevention programs: a standard one and a peer-led interactive one. Data from 16 health educators were collected after 504 classroom sessions, 63 of which were observed by 24 monitors. In the interactive program, health educators (HEs) followed the curriculum less closely, reported less favorable classroom processes and less off-task talking than in the standard one. These data indicate that an interactive substance-abuse prevention program does not necessarily entail more off-task discussion but also does not necessarily guarantee more favorable program implementation. Valente, T., Okamoto, J., Pumpuang, P., Okamoto, P., and Sussman, S. Differences in Perceived Implementation of a Standard Versus Peer-Led Interactive Substance Abuse Prevention Program. Am J Health Behav, 31(3), pp. 297-311, 2007.

School-Level Influences on Discipline Referrals in First Grade

School discipline referrals (SDRs) may be useful in the early detection and monitoring of disruptive behavior problems to inform prevention efforts in the school setting, yet little is known about the nature and validity of SDRs in the early grades. For this descriptive study, SDR data were collected on a sample of first grade students who were at risk for developing disruptive behavior problems (n = 186) and a universal sample (n = 531) from 20 schools. Most SDRs were given for physical aggression and the predominant consequence was time out. As expected, boys and at-risk students were more likely to receive an SDR and to have more SDRs than were girls and the universal sample. A large difference between schools regarding the delivery of SDRs was found. A zero-inflated Poisson model clustered by school tested the prediction of school-level variables. Students in schools that had a systematic way of tracking SDRs were more likely to receive one. Also, schools with more low-income students and larger class sizes gave fewer SDRs. SDRs predicted teacher ratings, and to a lesser extent, parent ratings of disruptive behavior at the end of first grade. Thus, practitioners and researchers should examine school-level influences whenever first grade discipline referrals are used to measure problem behavior for the purpose of planning and evaluating interventions. Rusby, J.C., Taylor, T.K., and Foster, E.M. A Descriptive Study of School Discipline Referrals in First Grade. Psychol Sch, 44(4), pp. 333-350, 2007.

Stigma Affects Drug Users Readiness to Change Behavior

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 (Santibanez et al., Journal of Urban Health, 83[1], 86-100, 2006). Targeted behavior change efforts are often explicitly built upon the risk perception of targeted individuals. In this article, the researchers consider the efficacy of behavior change based on IDUs' perceptions of elevated risk. This 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. The researchers argue that effective HIV prevention should explicitly acknowledge and address the stigmatized IDU identity, rather than assuming readiness for behavior change. Smith, K.C., Tle, L.L., and Latkin, C.A. 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.

HIV Risk Reduction is Affected by Beliefs about HIV Treatment Efficacy

This study describes the sexual behavior of HIV-positive women within new versus more established relationships and determines whether beliefs about HIV antiretroviral therapy (ART) impact these behaviors. The Women's Interagency HIV Study is a longitudinal cohort study of HIV among women in the United States. Sexually active HIV-positive women (N = 1,090) completed interviews on beliefs and behaviors at 6-month intervals. Data were analyzed for the period between April 2002 and March 2003. Of 1,517 sexual partners reported, 32% were newly acquired within the previous 6 months. As compared with more established sexual relationships, newer partnerships were characterized by greater condom use consistency (odds ratio = 1.8, 95% confidence interval = 1.4-2.3). Holding beliefs that ART is protective for HIV transmission impacted the relationship between partner type and condom use. In established relationships, 63% reported consistent condom use if they believed that ART is not protective, whereas 54% reported consistent condom use if they believed that ART is protective. These findings highlight the importance of ongoing support for sexual risk reduction among women with HIV-infection and for strategies that reduce the strength of relationships between ART beliefs and sexual risk behavior. Wilson, T.E., Feldman, J., Vega, M.Y., Ghandi, M., Richardson, J., Cohen, M.H., McKaig, R., Ostrow, D., Robison, E., and Gange, S.J. Acquisition of New Sexual Partners Among Women With HIV Infection: Patterns of Disclosure and Sexual Behavior within New Partnerships. AIDS Educ Prev, 19(2), pp. 151-159, 2007.

Racial and Gender Differences in Adolescent Sexual Attitudes and Associations with Coital Debut

Delay of sexual debut is an important strategy in reducing the risk of negative adolescent health outcomes. Race and gender are known to be related to sexual behavior and outcomes, but little is known about how these characteristics affect sexual attitudes. This article examines differences in coital and pregnancy attitudes by gender and race, the influence of attitudes on transition to first coitus for each subgroup, and implications for prevention. Data are from Waves I and II of the National Longitudinal Study of Adolescent Health, limited to Non-Hispanic White and African American adolescents (n = 6652). The authors' factor analyzed attitude items, and examined effects of race, gender, and their interaction, controlling for sexual debut at Wave I.

Next, sexual debut over time was predicted by attitudes for virgins (n = 3281) separately for each subgroup, controlling for covariates. Results showed that compared with boys, girls perceived less positive benefits from sex and more shame and guilt with sex, but had fewer negative perceptions about pregnancy. Compared with White boys, African American boys perceived less shame and guilt about sex; girls did not differ by race. Higher perceived benefits of sex increased the likelihood of sexual debut among African American girls. Perceived shame and guilt lowered the likelihood for White boys and girls. It was concluded that reinforcing protective attitudes through gender and race-specific programs may delay sexual intercourse, but more research is needed. Specifically, it will be important to examine whether there is an optimal coital age after which negative health outcomes are attenuated, and whether this differs by gender and race. Cuffee, J., Hallfors, D., and Waller, M. Racial and Gender Differences in Adolescent Sexual Attitudes and Longitudinal Associations with Coital Debut. J Adolesc Health, 41(1), pp. 19-26, 2007.

Mothers' Relational Schemas Predict Adolescent Antisocial Behavior

Relational schemas, as described and measured in this study, refer to automatic, unconscious response tendencies that reflect the nature of one's relationship to another person. In this research, these are measured through interpreting speech samples where a mother (biological, step, or adoptive) is describing her relationship with a target adolescent. These samples were assessed using the Family Affective Attitude Rating Scale for coding 5-minute speech samples. The internal consistency and validity of positive relational schema and negative relational schema scales were also evaluated. Data were collected from a multiethnic subsample of early-starting antisocial (n = 20) and successful (n = 20) urban adolescents and their families, using direct observations of parent-adolescent interactions, 5-minute speech samples, and questionnaires. The negative relational schema and positive relational schema scales were internally consistent, correlated reliably with critical and positive dimensions of 5-minute speech samples expressed emotion and with observed parent-adolescent interactions, and discriminated between antisocial and successful adolescents. The negative relational schema scale accounted for unique variance in adolescent antisocial behavior when controlling for previous problem behavior and observed coercion. A significant interaction was also found between negative relational schema rating and observed parent-adolescent dynamics when escalations in adolescent problem behavior were added to the model. Relational schema narratives provided unique information in the prediction of adolescent antisocial behavior and should be considered in the assessment of family dynamics and the design of interventions to prevent and treat adolescent behavior problems. Bullock, B., and Dishion, T. Family Processes and Adolescent Problem Behavior: Integrating Relationship Narratives Into Understanding Development and Change. J Am Acad Child Adolesc Psychiatry, 46(3), pp. 396-407, 2007.

Substance Use and Risk for Suicide

This study examined the association between onset of substance use and risk factors related to suicide. 1252 adolescents in two urban school districts completed surveys as part of a large, randomized controlled prevention effectiveness trial. Risk factors measured included depressive symptoms, suicide ideation, suicide ideation specifically with alcohol and/or drug use, endorsement of suicide as a personal option, and suicide attempt. Results from multivariate models controlling for current substance use and demographic characteristics indicated that earlier onset of hard drug use among boys was associated with all five suicide risk factors. In comparison, among girls, earlier onset of regular cigarette smoking, getting drunk, and hard drug use was associated with some suicide risk factors. The findings confirm the importance

of screening for substance use in early adolescence. The association between early substance use and suicide risk factors differed by gender; both research and intervention efforts need to incorporate gender differences. Cho, H., Hallfors, D., and Iritani, B. Early Initiation of Substance Use and Subsequent Risk Factors Related to Suicide Among Urban High School Students. Addict Behav, 32(8), pp. 1628-1639, 2007.

Effects of Prenatal and Postnatal Parental Substance Use on Child Maltreatment

Parental substance use is a well-documented risk for children. However, little is known about specific effects of prenatal and postnatal substance use on child maltreatment and foster care placement transitions. In this study, the authors' unpacked unique effects of (a) prenatal and postnatal parental alcohol and drug use and (b) maternal and paternal substance use as predictors of child maltreatment and foster care placement transitions in a sample of 117 maltreated foster care children. Models were tested with structural equation path modeling. Results indicated that prenatal maternal alcohol use predicted child maltreatment and that combined prenatal maternal alcohol and drug use predicted foster care placement transitions. Prenatal maternal alcohol and drug use also predicted postnatal paternal alcohol and drug use, which in turn predicted foster care placement transitions. Findings highlight the potential integrative role that maternal and paternal substance use has on the risk for child maltreatment and foster care placement transitions. Smith, D., Johnson, A., Pears, K., Fisher, P., and DeGarmo, D. Child Maltreatment and Foster Care: Unpacking the Effects of Prenatal and Postnatal Parental Substance Use. Child Maltreat, 12(2), pp. 150-160, 2007.

Peer Standing and Substance Use in Early-Adolescence

Two competing hypotheses were tested concerning the associations between current alcohol and cigarette use and measures of individual, group, and network peer standing in an ethnically-diverse sample of 156 male and female adolescents sampled at two time points in the seventh grade. Findings lent greater support to the person hypothesis, with early regular substance users enjoying elevated standing amongst their peers and maintaining this standing regardless of their maintenance of or desistance from current use later in the school year. In the fall semester, users (n=20, 13%) had greater social impact, were described by their peers as more popular, and were more central to the peer network than abstainers (i.e., those who did not report current use). Conversely, in the spring semester, there were no differences between users (n=22, 13%) and abstainers in peer ratings of popularity or social impact. Notably, the spring semester users group retained fewer than half of the users from the fall semester. Further, students who had reported current use in the fall, as a group, retained their positions of elevated peer standing in the spring, compared to all other students, and continued to be rated by their peers as more popular and as having greater social impact. The authors discuss the findings in terms of the benefit of employing simultaneous systemic and individual measures of peer standing or group prominence, which in the case of peer-based prevention programs, can help clarify the truly influential from the "pretenders" in the case of diffusion of risk-related behaviors. Killeya-Jones, L.A., Nakajima, R., and Costanzo, P.R. Peer Standing and Substance Use in Early-Adolescent Grade-Level Networks: A Short-Term Longitudinal Study. Prev Sci, 8(1), pp. 11-23, 2007.

Trajectories of Physical Violence and Theft are Related to Neurocognitive Performance

Neurocognitive mechanisms have long been hypothesized to influence

developmental trajectories of antisocial behavior. However, studies examining this association tend to aggregate a variety of problem behaviors that may be differentially affected by neurocognitive deficits. This study sought to describe the developmental trajectories of physical violence and theft from adolescence to adulthood, their associations, and the neurocognitive characteristics of individuals following different patterns of trajectory association. An accelerated cohort-sequential, longitudinal design was used to examine these issues in the Rutgers Health and Human Development Project. Participants were six hundred ninety-eight men. Self-reports of physical violence (ages 12-24 years) and theft (ages 12-31 years) were collected across 5 waves. Neurocognitive performance was assessed with executive function and verbal IQ tests between late adolescence and early adulthood. The majority (55%) of subjects showed an increased frequency of theft during the study period, while only a minority (13%) evinced an increasing frequency of physical violence. Executive function and verbal IQ performance were negatively related to high frequency of physical violence but positively related to high frequency of theft. Developmental trajectories of physical violence and theft during adolescence and early adulthood are different and differently related to neurocognitive functioning. Global indexes of antisocial behavior mask the development of antisocial behavior subtypes and putative causal mechanisms. Barker, E., Seguin, J., White, H., Bates, M., Lacourse, E., Carbonneau, R., and Tremblay, R. Developmental Trajectories of Male Physical Violence and Theft: Relations to Neurocognitive Performance. Arch Gen Psychiatry, 64 (5), pp. 592-599, 2007.

Relationship of Perceived Prevalence of Drug Use to Subsequent Drug Use

The investigators examined the effects of perceived prevalence of drug use among same-age peers on adolescents' subsequent drug use. This study involved 1,723 youth participating in a prevention trial who were administered a survey in the fall of 7th grade then 18 months later in the spring of 8th grade. On the first survey, students reported on their own use of alcohol and marijuana, receipt of offers to use these drugs, and frequency of contact with peers who use these drugs. Students also estimated the percentage of 7th grade students in their school who used alcohol or marijuana at least once per month. These estimates were compared with the actual percentage of 7th graders who reported using these substances. On the follow up survey, students reported on their alcohol and marijuana use. Overall, students overestimated alcohol use in the sample by 9.5% and students overestimated marijuana use by 8.0%. Although perceived prevalence of drug use predicted subsequent alcohol and marijuana use when controlling for actual prevalence, these effects did not remain when participants' prior drug use and proximal peer contacts were considered. Juvonen, J., Martino, S.C., Ellickson, P. L., and Longshore, D. "But Others Do It!: Do Misperceptions of Schoolmate Alcohol and Marijuana Use Predict Subsequent Drug Use Among Young Adolescents?" Journal of Applied Social Psychology, 37(4), pp. 740-758, 2007.

Physical Environmental Influences on Early Externalizing Behaviors

Research on the development of externalizing behaviors during early childhood has focused on child and parenting factors. Fewer studies have investigated effects of aversive features of the micro-level physical environment, such as overcrowding and chaos in the home, and the macro-level environment, such as neighborhood quality. This study extends research on physical environmental factors by examining their association with children's early externalizing behaviors, and exploring how maternal monitoring may serve as a protective factor in such contexts. One hundred twenty male toddlers at high risk for developing early externalizing behaviors, participating in an ecologically-based family preventive intervention were followed from ages 2 to

5 years. Direct longitudinal associations were found for micro-level environmental factors beginning at age 2 and for neighborhood risk beginning at age 3. Maternal monitoring served as a protective factor for child externalizing behaviors in the context of neighborhood risk. Implications for prevention research and the development of early externalizing behaviors are discussed. Supplee, L.H., Unikel, E., and Shaw, D.S. Physical Environmental Adversity and the Protective Role of Maternal Monitoring in Relation to Early Child Conduct Problems. Journal of Applied Developmental Psychology, 28(2), pp. 166-183, 2007.

Parental Substance Use and Foster Care Placements

Research has established the coincidence of parental alcohol and other drug (AOD) use and child maltreatment, but few studies have examined the placement experiences and outcomes of children removed because of parental AOD use. The present study examined demographic characteristics and placement experiences of children removed from their homes because of parental AOD use (n = 1,333), first in comparison to the remaining sample of children in foster care (n = 4,554), then in comparison to a matched comparison group of children in foster care who were removed for other reasons (n = 1,333). Relative to the comparison sample, children removed for parental AOD use are less likely to experience co-occurring removal because of neglect and physical or sexual abuse and are more likely to be placed in relative foster care. In addition, these children remain in care longer, experience similar rates of reunification, and have significantly higher rates of adoption. Implications for specialized services and prevention are discussed. Vanderploeg, J., Connell, C., Caron, C., Saunders, L., Katz, K., and Tebes, J. The Impact of Parental Alcohol or Drug Removals on Foster Care Placement Experiences: A Matched Comparison Group Study. Child Maltreat, 12(2), pp. 125-136, 2007.

Adolescent Peer Group Identification: A Review of the Literature

This study provides an exhaustive review of 44 peer-reviewed quantitative or qualitative data-based peer-reviewed studies completed on adolescent peer group identification. Adolescent peer group identification is one's self-perceived or other-perceived membership in discrete teenage peer groups. The studies reviewed suggest that adolescent peer groups consist of five general categories differentiable by lifestyle characteristics: Elites, Athletes, Academics, Deviants, and Others. The researchers found that the Deviant adolescent group category reported relatively greater participation in drug use and other problem behaviors across studies, whereas Academics and Athletes exhibited the least participation in these problem behaviors. Additional research is needed in this arena to better understand the operation of adolescent group labels. Sussman, S., Pokhrel, P., Ashmore, R.D., Brown, B.B., and Brown, B.B. Adolescent Peer Group Identification and Characteristics: A Review of the Literature. Addict Behav, 32(8), pp. 1602-1627, 2007.

Ethnic Identity as a Predictor of Substance Use Norms and Behaviors

This paper explores whether ethnicity and three ethnic identity instruments are useful in predicting substance use outcomes among three samples of ethnically diverse middle school youth. Participants were 7th and 8th grade youth attending a multiethnic school in an urban low-income community who were subsampled from participants in a larger prevention research study. More than half of the participants in the research were of Hispanic origin. Results suggest that age, gender, and/or racial/ethnic group membership influenced the strength of ethnic identity. In addition, age, sex, and strength of ethnic identity

influenced substance use norms and behaviors. In each case where effects were significant, a stronger sense of ethnic identity as measured by two of the instruments predicted more negative attitudes toward and less use of alcohol, cigarettes, and marijuana. Holley, L.C., Kulis, S., Marsiglia, F.F., and Keith, V.M. Ethnicity Versus Ethnic Identity: What Predicts Substance Use Norms and Behaviors. Journal of Social Work Practice in the Addictions, 6(3), pp. 53-79, 2006.

Quality of Parent-Child Interaction Predicts Child Problem Behaviors

This article reports on two exploratory studies where the hypothesis is tested that there will be an inverse relationship between the quality of parent-child interactions and adolescent problem behaviors. Study 1 involves survey data from Midwestern parents of boys (n=377) and girls (335) between the ages of 11 and 13 years. Study 2, conducted to replicate the findings of Study 1, was similarly constructed with parents of boys (n=279) and girls (n=269). The quality of parent child interactions latent construct was formed from indicators of effective child management and parent-child affective quality, both self-reported by parents. Child problem behaviors were assessed with indicator measures of aggressive and oppositional behavior, school-related problems, and problematic peer relations. Multisample latent variable structural equation modeling confirms that a higher level of parent-child interaction quality was associated with a lower level of problem behaviors. This relationship was significant for parent-reported behavior, for both boys and girls, in both Study 1 and Study 2. The amount of variance explained indicated a moderate relationship between these variables and is consistent with earlier studies indicating that parent-child interaction quality is associated with problem behaviors among rural dwelling early adolescents. Spoth, R., Neppl, T., Goldberg-Lillehoj, C., Jung, T., and Ramisetty-Mikler, S. Gender-Related Quality of Parent-Child Interactions and Early Adolescent Problem Behaviors: Exploratory Study with Midwestern Samples. Journal of Family Issues, 27(6), pp. 826-849, 2006.

Cross-sectional Study of Female Students Reporting Anabolic Steroid Use

The objective of this article was to determine the characteristics of female US high school students reporting anabolic steroid use. This paper reports findings from cross-sectional assessments collected as part of the 2003 Centers for Disease Control and Prevention national school-based Youth Risk Behavior Survey database. The data come from a nationally representative sample of US high schools, and the focus was on Female students in grades 9 through 12 (n = 7544). Participants' self-reported anabolic steroid use was compared with other health-related behaviors and with sports participation. Prior or ongoing anabolic steroid use was reported by 5.3% of female high school students. Those adolescent girls had a marked increase in other health-compromising behaviors, including past 30-day use of alcohol (odds ratio [OR], 8.83; 95% confidence interval [CI], 5.49-14.20]), cigarettes (OR, 5.14; 95% CI, 3.14-8.42), marijuana (OR, 7.91; 95% CI, 5.20-12.04), cocaine (OR, 10.78; 95% CI, 6.18-18.81), and diet pills (OR, 4.86; 95% CI, 2.98-7.93). They were more likely to carry a weapon (OR, 7.54; 95% CI, 4.83-11.76), have had sexual intercourse before age 13 years (OR, 2.90; 95% CI, 1.58-5.33), and have had feelings of sadness or hopelessness almost every day for at least 2 consecutive weeks (OR, 4.13; 95% CI, 2.57-7.22). They were less likely to play school-sponsored team sports (OR, 0.52; 95% CI 0.34-0.80). Steroid users participating in sports shared the same problem behaviors as steroid users not participating in team athletics. Self-reported anabolic steroid use is not confined to adolescent girls in competitive athletics and is an indicator of adolescent girls with a marked increase in a cluster of other health-harming

behaviors. Elliot, D.L., Cheong, J., Moe, E.L., and Goldberg, L. Cross-Sectional Study of Female Students Reporting Anabolic Steroid Use. Arch Pediatr Adolesc Med, 161(6), pp. 572-577, 2007.

An HIV-Preventive Intervention for Youth Living with HIV

As the number of youth infected with HIV rises, secondary prevention programs are needed to help youth living with HIV meet three goals: (a) increase self-care behaviors, medical adherence, and health-related interactions; (b) reduce transmission acts; and (c) enhance their quality of life. This article describes an intervention program for youth living with HIV. Youth engage in small-group activities with other infected peers to modify their behavioral patterns. The intervention aims to (a) reduce substance use and sexual behaviors that may transmit or enhance transmission of the HIV virus; (b) reduce negative impacts of substance use on seeking and utilizing health care, assertiveness, and adherence to health regimens; and (c) enhance the quality of life to maintain behavior changes over time. Interventions that target youth living with HIV are warranted. A variety of delivery strategies are discussed for secondary interventions. Lightfoot, M., Rotheram-Borus, M., and Tevendale, H. An HIV-Preventive Intervention for Youth Living With HIV. Behav Modif, 31(3), pp. 345-363, 2007.

Narcissism and Self-Esteem Predicts Proactive and Reactive Child Aggression

The present study examined the importance of psychopathy-linked narcissism in predicting proactive and reactive aggression and conduct problems in a group of 160 moderately to highly aggressive children (mean age of 10 years, 9 months). Children's self-report of self-esteem and parent and teacher report of dimensions of psychopathy [narcissism, callous-unemotional (CU) traits, and impulsivity], proactive and reactive aggression, and conduct problems were collected. Composites of parent and teacher ratings of children's behavior were used. Consistent with the study's hypotheses, narcissism predicted unique variance in both proactive and reactive aggression, even when controlling for other dimensions of psychopathy, demographic variables associated with narcissism, and the alternative subtype of aggression. As hypothesized, impulsivity was significantly associated with only reactive aggression. CU traits were not related to proactive or reactive aggression once the control variables were entered. All dimensions of psychopathy predicted unique variance in conduct problems. Consistent with prediction, narcissism was not significantly related to general self-esteem, providing support that narcissism and self-esteem are different constructs. Furthermore, narcissism and self-esteem related differentially to proactive aggression, reactive aggression, and conduct problems. Furthermore, narcissism but not self-esteem accounted for unique variance in aggression and conduct problems. Barry, T., Thompson, A., Barry, C., Lochman, J., Adler, K., and Hill, K. The Importance of Narcissism in Predicting Proactive and Reactive Aggression in Moderately to Highly Aggressive Children. Aggress Behav, 33(3), pp. 185-197, 2007.

Engagement in Daily Activities and Adolescent Mood

This study explored the combined influences of daily activities and autonomy in activity engagement on adolescent daily positive and negative moods. Ecological momentary assessments (EMA) were used to obtain information about 8th- and 10th-grade students' (N = 517) mood, activities, and situation throughout the day. Participants responded to random prompts on the EMA device and, when prompted, rated mood adjectives and reported on their current activity and perceived autonomy in activity engagement. Mixed-effects regression models examined changes in mood across specific activity

categories. Positive mood significantly improved when engaging in numerous activities; negative mood improved during social activities as well as "arty" and "hanging out" events but was fairly consistent across other activities. Stronger mood-activity relations were found after controlling for autonomy in activity engagement. Weinstein, S., and Mermelstein, R. Relations Between Daily Activities and Adolescent Mood: The Role of Autonomy. J Clin Child Adolesc Psychol, 36(2), pp. 182-194, 2007.

A Review of Research on Caretaking of Children of Incarcerated Parents

This paper reviews the literature for research findings on caretaking-related problems associated with the absence of parents from the home following incarceration. It focuses on the impact of incarceration on the welfare and adjustment of urban African American children and on the assumption of caretaking responsibilities by other caretakers, principally maternal grandmothers. Noting the complex situational difficulties involved and the potential burdens associated with surrogate parenting in general, and with this population in particular, the service-provider implications of this parenting arrangement are considered in this review. Findings indicate that problems associated with incarceration of parents tend to be intergenerational and vary considerably in complexity and severity. To the extent that they impact the children involved, these issues should be addressed in coordinated service delivery focusing on prevention. Hanlon, T.E., Carswell, S.B., and Rose, M. Research on the Caretaking of Children of Incarcerated Parents: Findings and Their Service Delivery Implications. Children and Youth Services Review, 29(3), pp. 348-362, 2007.

Young Adults' Reasons for Using Marijuana

Previous research has evaluated marijuana motives among adolescents and emerging adults using a predetermined set of motives, largely adapted from the alcohol literature. This research was designed to identify marijuana motives from the perspective of the user. Recent high school graduates who reported using marijuana (N=634) provided self-generated reasons for using. They also provided information on how many times they used marijuana in the past three months and negative consequences of marijuana use. The study authors independently reviewed all 2258 open ended reasons for using marijuana and developed a list of definitions for 19 distinct marijuana motives that emerged from the list. These definitions were provided to five raters who classified each of the statements. The most frequently reported reasons for using marijuana included enjoyment/fun, conformity, experimentation, social enhancement, boredom, and relaxation. Regression analyses revealed that experimentation was consistently associated with less use and fewer problems whereas enjoyment, habit, activity enhancement, and altered perception or perspectives were associated with heavier use and more problems. Current strategies for intervention may be enhanced by highlighting and understanding the individual reasons a person may choose to use marijuana. Lee, C., Neighbors, C., and Woods, B. Marijuana Motives: Young Adults'Reasons for Using Marijuana. Addict Behav, 32(7), pp. 1384-1394, 2007.

The Role of Delinquency and Depressed Mood in Late Adolescent Substance Use

This study examines the extent to which delinquency and depressed mood, measured at ages 11, 12, 13, 14, and 16, predict problem substance use at age 18. This study also examines mediation of these effects through alcohol use at age 16 across gender. Participants were 429 rural youths (222 girls and 207 boys) and their families who participated in Project Family, a prevention

research study. Problem substance use was defined through both youth and parent responses to survey items reflecting problems with alcohol and drug use. Both delinquency and depressed mood appeared to play a role in the development of problem substance use, but their effects may be moderated by gender and may vary throughout adolescence. Indirect positive effects of delinquency on problem substance use were observed for boys, while direct positive effects of depressed mood were observed for girls. These findings have potential implications for specific targets of early prevention and how these may differ for boys and girls. Mason, W., Hitchings, J., and Spoth, R. Emergence of Delinquency and Depressed Mood Throughout Adolescence as Predictors of Late Adolescent Problem Substance Use. Psychol Addict Behav, 21(1), pp. 13-24, 2007.

Neighborhood Effects on Youth Substance Abuse

This study examines neighborhood influences on alcohol, cigarette, and marijuana use among a predominantly Latino middle school sample. Drawing on theories of immigrant adaptation and segmented assimilation, the authors test whether neighborhood immigrant, ethnic, and socioeconomic composition, violent crime, residential instability, and family structure have differential effects on substance use among youth from different ethnic and acculturation backgrounds. Data are drawn from self-reports from 3,721 seventh-grade students attending thirty-five middle schools in the Southwest. Analysis was restricted to the two largest ethnic groups: Latino students of Mexican heritage and non-Hispanic Whites. After adjusting for individual-level characteristics and school-level random effects, the only neighborhood effect found for the sample overall was that neighborhood instability predicted recent cigarette use. Subgroup analyses by individual ethnicity and acculturation was more revealing. Living in neighborhoods with high proportions of recent immigrants was protective against alcohol, cigarette, and marijuana use for Latino students at different acculturation levels. However, living in predominantly Mexican heritage neighborhoods with mostly non-immigrants was a risk factor for alcohol and marijuana use for less acculturated Latinos. Neighborhood poverty and crime had effects on cigarette and alcohol use respectively, but only for more acculturated Latinos. No neighborhood effects emerged for non-Hispanic White students. Results suggest that disadvantaged neighborhoods increase substance use among some ethnic minority youth, and immigrant enclaves appear to provide some protection against these effects. Kulis, S., Marsiglia, F.F., Sicotte, D., and Nieri, T. Neighborhood Effects on Youth Substance Use in a Southwest City. Sociological Perspectives, 50(2), pp. 273-301, 2007.

Family Process Influences Competence in Rural African American Youth

This paper investigates the effects of a family process on social and cognitive competence and on aggressive and deviant behavior among rural African American adolescents. The data were collected as a part of a study of 465 families who were randomly assigned to either a 6-week family process group or a control group and assessed at pretest, posttest, and follow-up. There were no significant differences between the experimental and control groups who participated in the research. However, families with a more routine environment and more parent-child interaction had adolescents with higher levels of competence and fewer behavioral problems. Pre-existing family characteristics better predicted adolescent success factors than participation in the family process group. Toldson, I. A., Harrison, M. G., Perine, R., Carreiro, P., and Caldwell, L. D. Assessing the Impact of Family Process on Rural African American Adolescents' Competence and Behavior Using Latent Growth Curve Analysis. Journal of Negro Education, 75(3), pp. 430-442, 2007.

Development and Validation of the Communities that Care Survey

The Communities That Care Youth Survey measures risk and protective factors shown in prior studies to predict adolescent problem behaviors such as drug use, delinquency, and violence. This paper describes the development and validation of cut points for the risk and protective factor scales in the Communities That Care Youth Survey that distinguish youths at higher risk for involvement in problem behaviors from those at lower risk. Using these cut points, populations surveyed with this instrument can be described in terms of the proportions of youths experiencing risk and the proportions experiencing protection on each predictor. This facilitates communities' prioritization of specific factors for attention. This paper compares different cut points, and evaluates the discriminant validity of selected cut points. Results indicate that cut points with sufficient sensitivity and selectivity can be established for each of the scales, and that risk and protective factors can be profiled as prevalence rates. Implications of these findings for prevention planning are discussed. Arthur, M.W., Briney, J.S., Hawkins, J.D., Abbott, R.D., Brooke-Weiss, B.L., and Catalano, R.F. Measuring Risk and Protection in Communities Using the Communities that Care Youth Survey. Evaluation and Program Planning, 30(2), pp. 197-211, 2007.

Relation Between Competence Skills and Substance Use

Only a few studies have found competence skills to be a protective factor against adolescent alcohol use; others did not find a direct effect on alcohol. A possible reason for this is that competence skills may moderate the effects of risk factors for alcohol use and that aspect has not been examined often or in a longitudinal design. This study tested whether several competence skills served either as direct protective factors against alcohol use or moderators of the impact of social risk factors on alcohol use. Participants (N = 1318) completed questionnaires that included measures of decision-making skills, refusal skill techniques, resisting media influences, friends' drinking and perceived social benefits of drinking, as well as current drinking amount and future drinking at baseline, one-year follow-up and two-year follow-up. Data analyses were conducted using multi-level mixed effects generalized linear models with random intercept. All the competence skills and the risk factors predicted current and future drinking. Several significant interactions were found between (1) perceived social benefits of drinking and decision-making skills, (2) perceived social benefits of drinking and refusal skill techniques and (3) friends' drinking and refusal skill techniques. Competence skills served as protective factors, as well as moderators. One possible reason that competence enhancement approaches to alcohol prevention are effective may be due to the inclusion of the competence skills component. Epstein, J., Zhou, X., Bang, H., and Botvin, G. Do Competence Skills Moderate the Impact of Social Influences to Drink and Perceived Social Benefits of Drinking on Alcohol use Among Inner-City Adolescents? Prev Sci, 8(1), pp. 65-73, 2007.

New Methods for More Potent Interventions

In this article two new methods for building and evaluating interventions are described. The first is the Multiphase Optimization Strategy (MOST). It consists of a screening phase, in which intervention components are efficiently identified for inclusion in an intervention or for rejection, based on their performance; a refining phase, in which the selected components are fine tuned and issues such as optimal levels of each component are investigated; and a confirming phase, in which the optimized intervention, consisting of the selected components delivered at optimal levels, is evaluated in a standard randomized controlled trial. The second is the Sequential Multiple Assignment Randomized Trial (SMART), which is an innovative research design especially suited for building time-varying adaptive interventions. A SMART trial can be used to

identify the best tailoring variables and decision rules for an adaptive intervention empirically. Both the MOST and SMART approaches use randomized experimentation to enable valid inferences. When properly implemented, these approaches will lead to the development of more potent preventive interventions. Collins, L., Murphy, S., and Strecher, V. The Multiphase Optimization Strategy (MOST) and the Sequential Multiple Assignment Randomized Trial (SMART) New Methods for More Potent eHealth Interventions. Am J Prev Med, 32(5 Suppl), pp. S112-S118, 2007.

Applying Engineering Principles to Inform Adaptive Interventions

The goal of this paper is to describe the role that control engineering principles can play in developing and improving the efficacy of adaptive, time-varying interventions. It is demonstrated that adaptive interventions constitute a form of feedback control system in the context of behavioral health. Consequently, drawing from ideas in control engineering has the potential to significantly inform the analysis, design, and implementation of adaptive interventions, leading to improved adherence, better management of limited resources, a reduction of negative effects, and overall more effective interventions. This article illustrates how to express an adaptive intervention in control engineering terms, and how to use this framework in a computer simulation to investigate the anticipated impact of intervention design choices on efficacy. The potential benefits of operationalizing decision rules based on control engineering principles are particularly significant for adaptive interventions that involve multiple components or address co-morbidities, situations that pose significant challenges to conventional clinical practice. Rivera, D., Pew, M., and Collins, L. Using Engineering Control Principles to Inform the Design of Adaptive Interventions: A Conceptual Introduction. Drug Alcohol Depend, 88 Suppl 2 pp. S31-S40, 2007.

Identifying Typologies of Alcohol Users in Emerging Adulthood

Longitudinal analyses identified unique multidimensional classes of alcohol use and examined individuals' movement among these classes during emerging adulthood. Latent transition analysis was used to identify a developmental model of alcohol use incorporating four aspects of use: use in the past year, frequency of use, quantity of use, and heavy episodic drinking. Participants were drawn from the Reducing Risk in Young Adult Transitions study (N = 1,143). Participants' alcohol use was assessed at mean ages of 18.5, 20.5, and 22.5 years. Through exploratory analysis, a five-class developmental model was identified as the best description of participants ' alcohol use between ages 18.5 and 22.5 years. This model consisted of five multidimensional alcohol-use latent variables: no use, occasional low use, occasional high use, frequent high use, and frequent high use with heavy episodic drinking. Analyses provided information regarding the proportion of participants in each latent class in the model at each measurement occasion and patterns of participants' movement among latent classes during the observed age period. Although alcohol use increased overall for study participants between ages 18.5 and 22.5, participants in lower-level alcohol-use latent classes were more likely to remain in low-level latent classes over time, and participants in moderate- and high-level latent classes were more likely to be in the frequent high use with heavy episodic drinking latent class over time. Implications for the prevention of heavy episodic drinking are discussed. Auerbach, K., and Collins, L. A Multidimensional Developmental Model of Alcohol Use During Emerging Adulthood. J Stud Alcohol, 67(6), pp. 917-925, 2006.

An Innovative, Effective and Cost Effective Survey Methodology

Maximizing the response rate to surveys involves thoughtful choices about

survey design, sampling and collection methods. This paper describes an innovative survey method designed to provide immediate reinforcement for responding and to minimize response cost. This method involves using questionnaires printed as checks on security (anti-fraud) paper with questions and responses separated using a perforated tear off section. Once a participant completes the survey, the response area is detached from the questions, thus protecting the confidentiality of the subject, and the check is returned via the banking system. This report describes the survey-check methodology, the survey flow process, and the results from four research studies which have used this method. These studies include (1) a technology accessibility survey of parents with children enrolled in a low-income preschool program; (2) a parent report of their child's behavior used as screening criteria for inclusion in a computer-mediated parent education project; (3) a follow-up questionnaire as part of a longitudinal study of child behavior, covering home and classroom interventions, and service utilization, and; (4) a survey of dentists in support of efforts to recruit them to participate in a randomized control trial of tobacco cessation in dental offices. The results of using this method show great improvement in response rates over traditionally administered surveys for three of the four reported studies. Results are discussed in terms of future applications of this method, limitations, and potential cost savings. Feil, E., Severson, H., Taylor, T., Boles, S., Albert, D., and Blair, J. An Innovative, Effective and Cost Effective Survey Method Using a Survey-Check Response Format. Prev Sci, 8(2), pp. 133-140, 2007.

Methods for Improving Estimates of Alpha Coefficients

The point estimate of sample coefficient alpha may provide a misleading impression of the reliability of the test score. Because sample coefficient alpha is consistently biased downward, it is more likely to yield a misleading impression of poor reliability. The magnitude of the bias is greatest precisely when the variability of sample alpha is greatest (small population reliability and small sample size). Taking into account the variability of sample alpha with an interval estimator may lead to retaining reliable tests that would be otherwise rejected. In this article, the authors report on simulation studies conducted to investigate the behavior of asymptotically distribution-free (ADF) versus normal-theory interval estimators of coefficient alpha under varied conditions. Normal-theory intervals were found to be less accurate when item skewness >1 or excess kurtosis >1. For sample sizes over 100 observations, ADF intervals are preferable, regardless of item skewness and kurtosis. A formula for computing ADF confidence intervals for coefficient alpha for tests of any size is provided, along with its implementation as an SAS macro. Maydeu-Olivares, A., Coffman, D., and Hartmann, W. Asymptotically Distribution-Free (ADF) Interval Estimation of Coefficient Alpha. Psychol Methods, 12 (2), pp. 157-176, 2007.

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

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

Bupropion and Cognitive Behavioral Treatment for Depression in Smoking Cessation

Dr. Richard Brown and colleagues at Brown Medical School and Butler Hospital conducted this randomized, double-blind, placebo-controlled clinical trial to examine the effects of an intensive cognitive-behavioral mood management treatment (CBTD) and of Bupropion, both singularly and in combination, on smoking cessation in adult smokers. Participants were 524 smokers who were randomized to one of four 12-week treatments: (1) standard, cognitive-behavioral smoking cessation treatment (ST) plus Bupropion (BUP); (2) ST plus placebo (PLAC); (3) standard cessation treatment combined with cognitive-behavioral treatment for depression (CBTD) plus BUP; and (4) CBTD plus PLAC. Follow-up assessments were conducted 2, 6, and 12 months after treatment. Consistent with previous studies, Bupropion, in comparison with placebo, resulted in better smoking outcomes in both intensive group treatments. Adding CBTD to standard intensive group treatment did not result in improved smoking cessation outcomes. Also, neither CBTD nor Bupropion, either alone or in combination, was differentially effective for smokers with single past episode of major depressive disorder (MDD), recurrent MDD or elevated depressive symptoms. However, findings with regard to recurrent MDD and elevated depressive symptoms should be interpreted with caution given the low rate of recurrent MDD and the low level of depressive symptoms in the sample. An a priori test of treatment effects in smokers with these depression vulnerability factors is warranted in future clinical trials. Brown, R.A., Niaura, R., Lloyd-Richardson, E.E., Strong, D.R., Kahler, C.W., Abrantes, A.M., Abrams, D., and Miller, I.W. Bupropion and Cognitive Behavioral Treatment for Depression in Smoking Cessation. Nicotine and Tobacco Research, 9(7), pp. 721-730, 2007.

Citalopram Combined with Behavioral Therapy Reduces Cocaine Use

The purpose of this study was to evaluate whether citalopram would reduce cocaine positive urines in a 12-week, double-blind, placebo-controlled trial. Seventy-six cocaine dependent subjects received either citalopram (20 mg/day) or placebo along with cognitive behavioral therapy (CBT) and contingency management (CM). In this study, citalopram treated subjects showed a significant reduction in cocaine-positive urines during treatment compared to placebo. There were no differences in retention between the two groups. Moeller, F.G., Schmitz, J.M., Steinberg, J.L., Green, C.M., Reist, C., Lingo, Y.L., Swann, A.C., and Grabowski, J. Citalopram Combined with Behavioral Therapy Reduces Cocaine Use: A Double-blind, Placebo-controlled Trial. Am. J. Drug and Alcohol Abuse, 33, pp. 367-378, 2007.

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Cognitive Interviews For Measurement Evaluation of the Fagerstro_m Test For Nicotine Dependence (FTND) in Smokers with Schizophrenia Spectrum Disorders

Dr. Judith Prochaska and colleagues at the University of California, San Francisco, conducted this study to determine if the Fagerstro_m Test for Nicotine Dependence (FTND), the most widely used measure of nicotine dependence, is appropriate to use with smokers diagnosed with schizophrenia. The current study employed cognitive interviews to evaluate the FTND with smokers diagnosed with schizophrenia spectrum disorders, recruited from an acute inpatient psychiatry setting, and a comparison group of smokers recruited from the community. The groups were comparable on tobacco use variables and FTND scores. Detailed qualitative cognitive interviews indicated all subjects understood the FTND items. For both groups, the FTND missed nocturnal smoking, reported as weekly by 80% of patients and 47% of controls. Finishing other people's cigarettes also was under-reported. The cognitive interview methodology proved useful for understanding how individuals interpreted and answered the FTND items. Overall, the qualitative findings identified limitations in the FTND for both groups, with the limitations generally more pronounced among patients with schizophrenia. Prochaska, J.J., Leek, D.N., Hall, S.E., and Hall, S.M. Cognitive Interviews for Measurement Evaluation of the Fagerstrom Test for Nicotine Dependence (FTND) in Smokers with Schizophrenia Spectrum Disorders. Addictive Behaviors, 32, pp. 793-802, 2007.

Voucher Reinforcement Improves Medication Adherence In HIV-Positive Methadone Patients: A Randomized Trial

Dr. Sorensen and colleagues conducted the present study to examine the use of voucher-based contingency management in a novel application, to reinforce taking HAART medication in HIV-positive methadone maintenance patients. After a 4-week baseline observation phase, eligible participants (N=66) were randomly assigned to (a) medication coaching sessions every other week to assist with adherence strategies (comparison group) or (b) medication coaching plus voucher reinforcement for opening electronic medication caps on time (voucher group). The intervention was provided for 12 weeks, with a 4-week follow-up. The primary outcome results of the clinical trial indicated effectiveness during the intervention, with significant mean adherence differences between voucher and comparison groups using electronic measurement (78% vs. 56%), pill count (86% vs. 75%), and self report (87% vs. 69%). Differences between groups faded after vouchers were discontinued. Contingency management shows promise as a strategy to promote antiretroviral medication adherence in this population. Sorensen, J.L., Haug, N.A., Delucchi, K.L., Gruber, V., Kletter, E., Batki, S.L., Tulsky, J.P., Barnett, P., and Hall, S. Voucher Reinforcement Improves Medication Adherence in HIV-positive Methadone Patients: A Randomized Trial. Drug and Alcohol Dependence, 88, pp. 54-63, 2007.

Contingencies for Change in Complacent Smokers

Dr. Richard Lamb and colleagues at the University of Texas Health Science Center conducted this study to determine if contingencies can be used to produce change in complacent smokers, who are less likely to quit than other smokers. The authors compared complacent smokers randomly assigned to receive incentives for breath carbon monoxide (BCO) (n=18) or noncontingent incentives (n=19) for 3 months. Contingent incentives were associated with (a) reduced BCO; (b) more BCO samples indicative of abstinence; (c) fewer cigarettes smoked and more days abstinent at study end; and (d) lower

salivary cotinine. These behaviors can predict future cessation, and 2 of the 18 smokers (11%) receiving BCO-contingent incentives reported quitting as compared with none of those in the control group. Contingency management procedures may effectively promote cessation among complacent smokers and provide a model for understanding the possible effects of some environmental interventions, such as workplace smoking bans, on the behavior of complacent smokers. Lamb, R.J., Morral, A.R., Kirby, K.C., Javors, M.A., Galbicka, G., Iguchi, M. Contingencies for Change in Complacent Smokers. Experimental and Clinical Psychopharmacology, 15(3), pp. 245-255, 2007.

Delay Discounting Predicts Postpartum Relapse to Cigarette Smoking Among Pregnant Women

Investigators conducted this study to examine whether delay discounting (DD), a measure of impulsivity, predicts treatment outcome among cigarette smokers. More specifically, the authors examined whether baseline discounting for hypothetical monetary rewards predicted smoking status at 24 weeks postpartum among women who discontinued smoking during pregnancy. Participants were 48 pregnant women who participated in a clinical trial examining the use of incentives to prevent postpartum relapse. Several sociodemographic characteristics (being younger, being less educated, and reporting a history of depression) assessed at study entry were associated with increased baseline DD, but in multivariate analyses only DD predicted smoking status at 24 weeks postpartum. Greater baseline DD was a significant predictor of smoking status at 24 weeks postpartum. DD was reassessed periodically throughout the study and did not significantly change over time among those who eventually resumed smoking or those who sustained abstinence. The results extend the association of DD with risk for substance abuse to pregnant and recently postpartum cigarette smokers and demonstrate a significant relationship between DD and treatment outcome. Yoon, J.H., Higgins, S.T., Sugerbaker, R.J., Thomas, C.S., and Badger, G.J. Delay Discounting Predicts Postpartum Relapse to Cigarette Smoking Among Pregnant Women. Experimental and Clinical Psychopharmacology, 15 (2), pp. 176-186, 2007.

Improved Adherence with Contingency Management

Dr. Rosen and colleagues conducted this study to determine if contingency management (CM) can improve adherence to prescribed medications. Fifty-six participants with histories of illicit substance use who were prescribed antiretroviral medication but evidenced suboptimal adherence during a baseline assessment were randomly assigned to 16 weeks of weekly CM-based counseling or supportive counseling, followed by 16 additional weeks of data collection and adherence feedback to providers. The CM intervention involved review of data generated by electronic pill-bottle caps that record bottle opening (MEMS) and brief substance abuse counseling. CM participants were reinforced by MEMS-measured adherence with drawings from a bowl for prizes and bonus drawings for consecutive weeks of perfect adherence. Potential total earnings averaged $800. Mean MEMS-measured adherence to the reinforced medication increased from 61% at baseline to 76% during the 16-week treatment phase and was significantly increased relative to the supportive counseling group ($p=.01$). Furthermore, mean log-transformed viral load was significantly lower in the CM group. However, by the end of the 16-week follow-up phase, differences between groups in adherence and viral load were no longer significantly different. Proportions of positive urine toxicology tests did not differ significantly between the two groups at any phase. A brief CM-based intervention was associated with significantly higher adherence and lower viral loads. Further studies should evaluate methods to extend effects for longer term benefits. Rosen, M.I., Dieckhaus, K., McMahon, T.J., Valdes, B., Petry, N.M., Cramer, J., and Rounsaville, B. Improved Adherence with Contingency Management. AIDS Patient Care, 21(1), pp. 30-40, 2007.

A Mindfulness-Based Stress Reduction Intervention Can Be Integrated Into a Therapeutic Community Setting

Dr. Marianne Marcus of the University of Texas at Houston and colleagues report on using a stage model of therapy development to integrate a mindfulness intervention into a therapeutic community (TC) for substance abuse treatment. Consistent with the stage model, Dr. Marcus collected data to describe the target population (drug abusers in a TC setting), drafted a mindfulness intervention manual iteratively with stakeholder input, trained interventionists in the integrated mindfulness/TC approach, and tested the intervention in a small-scale pilot study comparing the experimental condition to a historical control condition at the same site. Also consistent with the stage model of therapy development, careful attention was paid to monitoring treatment integrity (i.e., the degree to which the intervention was delivered faithfully and competently). Results of the pilot test will be published in a future manuscript. Marcus, M.T., Liehr, P.R., Schmitz, J., Moeller, F.G., Swank, P., Fine, M., Cron, S., Granmayeh, L.K., and Carroll, D.D. Behavior Therapy Trials: A Case Example. Nursing Research, 56, pp. 210-216, 2007.

Helping Students Overcome Substance Abuse: Effective Practices for Prevention and Intervention

Dr. Jason Burrow-Sanchez of the University of Utah and colleague Dr. Leanne Hawken published a book aimed at translating scientific advances into practical strategies that can be implemented by school mental health professionals to address the needs of students at risk for or already abusing drugs. This book provides guidance for school counselors about screening for substance use and abuse, designing individual-based or group-based intervention programs in school settings, and interpreting the implications of policy for school-based intervention. Burrow-Sanchez, J.J., and Hawken, L.S. Helping Students Overcome Substance Abuse: Effective Practices for Prevention and Intervention. The Guilford Press, New York, NY, 2007.

If Substance Abuse Is a Chronic, Relapsing Condition, Substance Abuse Treatment May Need to Be Chronic and Addressing Relapse Too

Drs. Suniya Luthar of Columbia University, Nancy Suchman of Yale University, and Michelle Altomare published the results of a randomized clinical trial testing Relational Psychotherapy Mothers' Group (RPMG) for substance-abusing, methadone-maintained mothers with young children. A total of 60 mothers participated in RPMG and 67 participated in recovery training (RT). At 6 months after starting treatment, women in the RPMG group showed greater improvements in child maltreatment and cocaine abuse, and children of women in RPMG reported greater improvements in emotional adjustment than did other children. However, these treatment gains were not sustained once treatment was discontinued. These results lend support to the notion of substance abuse as a chronic, relapsing condition that may best be treated by ongoing monitoring and intervention. Luthar, S.S., Suchman, N.E., and Altomare, M. Relational Psychotherapy Mother's Group: A Randomized Clinical Trial for Substance Abusing Mothers. Development and Psychopathology, 19, pp. 243-261, 2007.

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

Research Findings - Research on Pharmacotherapies for Drug Abuse

Smoked Cocaine Self-administration is Decreased by Modafinil

This study investigated the effects of modafinil maintenance on cocaine self-administration by frequent users (4 days/week) under controlled laboratory conditions. In this 48-day double-blind, crossover design study, the effects of modafinil maintenance (0, 200, and 400 mg/day) on response to smoked cocaine (0, 12, 25, and 50 mg) were examined in 8 nontreatment-seeking cocaine dependent individuals. Cocaine significantly increased self-administration, subjective-effect ratings, and cardiovascular measures. Modafinil at both doses (200 and 400 mg/day) markedly attenuated these effects. This data supports the potential of modafinil as a pharmacotherapy for cocaine dependence. Hart, C.L., Haney, M., Vosburg, S.K., Rubin, E., and Foltin, R. Smoked Cocaine Self-administration is Decreased by Modafinil. Neuropsychopharmacology, pp. 1-8, 2007.

Gabapentin Shows Poor Treatment Retention and Ineffectiveness in Reducing Cocaine Use Versus Tiagabine which Significantly Reduced Cocaine taking Behavior Compared to Placebo or Gabapentin among methadone-stabilized cocaine abusers

In this study, 76 treatment seeking, cocaine dependent, methadone-maintained subjects were randomly assigned to tiagabine 24 mg/day, gabapentin 2400 mg/day, or placebo in a 10-week double-blind placebo-controlled trial. The primary outcome measure was thrice-weekly drug free urine samples. All subjects were required to participate in a 1-h weekly manual driven individual CBT psychotherapy session. Treatment retention was significantly less for the gabapentin group relative to the other groups. The proportion of cocaine-free urine samples during weeks 6 - 10 was significantly larger in the tiagabine treated group. The longitudinal data showed significant change in thrice-weekly cocaine free urines that reached a greater abstinence rate for the tiagabine treated group (22%) compared to gabapentin (5%) or placebo (13%) treated groups. The study results showed that gabapentin resulted in poor treatment retention and ineffectiveness in reducing cocaine use. Tiagabine significantly reduced cocaine taking behavior compared to placebo or gabapentin among methadone-stabilized cocaine abusers. Gonzalez, G., Desai, R., Sofuoglu, M., Poling, J., Oliveto, A., Gonsai, K. and Kosten, T. Clinical Efficacy of Gabapentin Versus Tiagabine for Reducing Cocaine Use Among Cocaine Dependent Methadone-treated Patients. Drug and Alcohol Dep, 87, pp. 1-9, 2007.

N-acetylcysteine May Reduce Desire to Use Cocaine

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Animal models suggest that N-acetylcysteine inhibits cocaine-seeking. The present pilot study evaluated whether N-acetylcysteine would suppress reactivity to cocaine-related cues in cocaine-dependent humans. In this double-blind, placebo-controlled trial, 15 participants received N-acetylcysteine or placebo during a 3-day hospitalization. Participants were crossed over to receive the opposite condition on a second, identical 3-day stay occurring 4 days later. During each hospital stay, participants completed a cue-reactivity procedure that involved collecting psychophysical and subjective data in response to slides depicting cocaine and cocaine use. Results suggest that while taking N-acetylcysteine, participants reported less desire to use and less interest in response to cocaine slides and watched cocaine slides for less time. The inhibition of cocaine cue reactivity is consistent with existing preclinical data and supports the use of N-acetylcysteine as a treatment for cocaine dependence. In sum, the reduced subjective reports of desire to use and interest in cocaine indicate that N-acetylcysteine may be a promising new treatment and that cysteine-glutamate exchange may be a potential pharmacotherapeutic target for treating cocaine dependence. LaRowe, S.D., Myrick, H., Hedden, S., Mardikian, P., Saladin, M., McRae, A., Brady, K., Kalivas, P.W., and Malcolm, R. Is Cocaine Desire Reduced by N-acetylcysteine? Am J Psychiatry. 164(7), pp. 1115-1117, 2007.

Subjective and Cardiovascular Effects of Cocaine During Treatment with Amantadine and Baclofen in Combination

This study assessed the subjective and cardiovascular effects of relevant doses of cocaine administration during steady-state treatment of the combination of amantadine and baclofen compared to placebo in 8 healthy, male, cocaine-dependent, non-treatment-seeking individuals. Data were collected prior to and following double-blind iv administration of cocaine (0, 20, and 40 mg). Data were collected at baseline, following 5 days of treatment with placebo, and again following 5 days of treatment with a combination of amantadine 100 mg. t.i.d. and baclofen 30 mg t.i.d. counterbalanced for order of medication and placebo in a cross-over design. Results showed no significant alterations to cardiovascular variables from treatment using combination medication or placebo in the presence of cocaine. Self-rated 'desire' for cocaine was significantly lower during cocaine administrations while participants were receiving treatment with amantadine-baclofen compared to infusions while taking placebo medication, although there was no difference in the intensity of cocaine-induced euphoria, or reduction in the likelihood to use cocaine if given access. Study findings support the safety of the amantadine-baclofen combination treatment for cocaine dependence. Rotheram-Fuller, E., De La Garza II, R., Mahoney III, J.J., Shoptaw, S., and Newton, T.F. Subjective and Cardiovascular Effects of Cocaine during Treatment with Amantadine and Baclofen in Combination. Psychiatry Res., 2007 (e-publication ahead of print).

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). This study compared baseline characteristics and treatment outcome between cocaine-dependent patients with major depressive disorder (MDD, n=66), 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 in racial makeup, with more Caucasians and Hispanics among patients with MDD and 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 (40% to 50%). Among cocaine-dependent patients who achieved abstinence at baseline, those with MDD alone and those with ADHD had better outcome over time as compared to patients with CD alone. 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.R., Bisaga, A., Raby, W., Aharonovich, E., Rubin, E., Mariani, J., Brooks, D.J., Garawi, F., and Nunes, E.V. Effects of Major Depressive Disorder and Attention-Deficit/Hyperactivity Disorder on the Outcome of Treatment for Cocaine Dependence. J. Substance Abuse Treatment, 2007 (e-publication ahead of print).

Neither Citalopram nor Citalopram Augmented with Bupropion are more Effective than Placebo in the Treatment of Opioid Abuse

This study evaluated the efficacy of citalopram (an SSRI) augmented with bupropion in the treatment of illicit opiate use in 60 methadone-stabilized subjects. In this 12-week randomized, double-blind, outpatient clinical trial, subjects were randomly assigned to placebo, citalopram (40 mg/day) plus placebo, or citalopram (40 mg/day) plus bupropion (50 mg/day). The primary outcome was opioid use, as measured by thrice-weekly urine toxicology results for opiates. A secondary analysis was illicit cocaine urine toxicology. Study results did not find any impact of either citalopram alone or in combination with bupropion, either for opioid abuse or for cocaine abuse (although the level of cocaine use in the study was low). These results suggest that an antidepressant intervention alone may not be sufficient to treat opiate or cocaine abuse. Previous studies using desipramine or bupropion and contingency management (CM) have demonstrated that a combination of medication and CM can reduce illicit drug use. Antidepressants could still continue to be investigated in combination with an effective behavioral intervention, as this combination may produce a synergistic treatment effect greater than either treatment alone. Poling, J., Pruzinsky, R., Kosten, T.R., Gonsai, K., Sofuoglu, M., Gonzalez, G., and Oliveto, A. Clinical Efficacy of Citalopram Alone or Augmented with Bupropion in Methadone-Stabilized Patients. Am. J. on Addictions, 16, pp. 187-194, 2007.

Modest Opioid Withdrawal Suppression Efficacy of Oral Tramadol in Humans

Tramadol is in an unscheduled atypical analgesic with low rates of diversion and abuse and mixed pharmacologic actions, including modest opioid agonist activity. The purpose of the current study was to characterize the opioid withdrawal suppression efficacy of oral tramadol. Residential, opioid-dependent adults (n = 10) were maintained on morphine (15 mg subcutaneously, quad in diem) for approximately 6 weeks. Spontaneous opioid withdrawal was produced by substituting placebo for scheduled morphine doses 17.5 h before experimental sessions that occurred twice weekly. The acute effects of placebo, tramadol (50, 100, 200, and 400 mg orally), naloxone (0.1 and 0.2 mg intramuscularly [IM]), and morphine (15 and 30 mg IM) were tested under double-blind, double-dummy, randomized conditions. Results indicated that Naloxone and morphine produced prototypic opioid antagonist and agonist effects, respectively. Tramadol 50 and 100 mg produced effects most similar to placebo. Tramadol 200 and 400 mg initially produced significant dose-related increases in ratings of "bad effects" and "feel sick," followed by evidence of

opioid withdrawal suppression. Tramadol did not produce significant increases on measures of positive drug effects nor any clinically significant physiologic changes. Tramadol 200 and 400 mg show evidence of opioid withdrawal suppression without significant observer- and subject-rated opioid agonist effects. The profile of action did not suggest a high risk for tramadol abuse in opioid dependent individuals. Tramadol may be a useful medication for treating opioid withdrawal. Lofwall, M.R., Walsh, S.L., Bigelow, G.E., and Strain, E.C., Modest Opioid Withdrawal Suppression Efficacy of Oral Tramadol in Humans. E-publication Psychopharmacology, 2007.

Antagonist Effects of Depot Naltrexone on the Reinforcing, Subjective, and Physiological Effects of Heroin

Although naltrexone is highly effective in completely antagonizing the effects of opioids, noncompliance has been an ongoing obstacle to treatment with this medication. This study evaluated the time course, safety, and effectiveness of a depot formulation of naltrexone (Depotrex(R)). Five heroin-dependent individuals participated in an 8-week inpatient study. Following a 1-week detoxification period, the effects of a range of heroin doses (0, 6.25, 12.5, and 25 mg, iv) were examined. Participants then received 384 mg depot naltrexone, and the effects of heroin were again evaluated for the next 6 weeks. One dose of heroin was tested per day, and the entire dose range was tested per week. During a morning sample session, participants received a dose of heroin and $20 and subjective, performance, and physiological effects were measured both before and after drug administration. During an afternoon choice session, participants were given the opportunity to choose the sampled heroin dose and/or amount of money using a modified progressive ratio procedure. In this study, depot naltrexone antagonized both the reinforcing and subjective effects of heroin for 4-5 weeks. Subjective ratings of withdrawal were reduced after week 2 and throughout the remainder of the study. The effects of heroin on mean trough pupil diameter began to emerge by week 5. The findings extended previous findings by this group that the reinforcing effects of heroin are reduced for 4-5 weeks after administration of 384 mg depot naltrexone. Sullivan, M.A., Vosburg, S.K., and Comer, S.D. Depot Naltrexone: Antagonism of the Reinforcing, Subjective, and Physiological Effects of Heroin. Psychopharmacology 189, pp. 37-46, 2006.

Memantine Produces Modest Reductions in Heroin-Induced Subjective Responses in Human Research Volunteers

The objective of this study was to evaluate the utility of a noncompetitive NMDA antagonist as a treatment medication for opioid dependence. In this 8-week inpatient study, 8 participants were maintained on the low-affinity, NMDA antagonist memantine (0, 30, and 60 mg/day, PO) and under each maintenance dose condition, the effects of IN heroin (0, 12.5, and 50 mg, IN) were examined. Following a 1-week detoxification period, all participants received all of the memantine and heroin dose combinations. Participants first sampled a dose of heroin and $20. During a subsequent choice session, participants could self-administer heroin and/or money. Responses were made under a progressive ratio schedule, and subjective, performance, and physiological effects were measured. In this study, memantine produced modest reductions in subjective ratings of drug quality, liking, willingness to pay for the drug, and craving for heroin. However, memantine produced few changes in the reinforcing effects of heroin. Comer, S.D. and Sullivan, M.A. Memantine Produces Modest Reductions in Heroin-induced Subjective Responses in Human Research Volunteers. Psychopharmacology, 193, pp. 235-245, 2007.

Low, Repeated Doses of Buprenorphine /Naloxone May be an

Effective Mechanism for Safely Dosing this Medication in Persons with Higher Levels of Physical Dependence

Acute doses of bupenorphine can precipitate withdrawal in opioid dependent persons. The likelihood of this withdrawal increases as a function of the level of physical dependence. The objective of this study was to test the acute effects of sublingual buprenorphine/naloxone tablets in subjects with a high level of physical dependence, and identify a dose that would precipitate withdrawal, then determine if withdrawal could be attenuated by splitting this dose. In Phase 1 of this randomized, double blind, triple dummy, residential laboratory study, 16 subjects maintained on 100 mg/day methadone were given sublingual buprenorphine/naloxone (4/1, 8/2, 16/4, 32 mg/8kg), intramuscular naloxone (0.2 mg), oral methadone (100 mg) or placebo. Medication conditions were randomized, but buprenorphine/naloxone were ascending within the randomization. In Phase 2 of the study, conditions were methadone, placebo, naloxone, 100% of the buprenorphine/naloxone dose that precipitated withdrawal in Phase 1 (full dose) and 50% of this dose administered twice in a session (split dose). Six patients did not complete the study. Of the 10 who completed, 3 tolerated up to 32 mg/8 mg buprenorphine/naloxone without evidence of precipitated withdrawal. For the 7 subjects completing both phases, split doses generally produced less precipitated withdrawal compared to full doses. The conclusion of the study was that there is considerable between subject variability in sensitivity to buprenorphine's antagonist effects, and that low, repeated doses of buprenorphine/naloxone (e.g. 2 mg/0.5 mg) may be an effective mechanism for safely dosing this medication in persons with higher levels of physical dependence. Rosado, J., Walsh, S., Bigelow, G.E., and Strain, E. Sublingual Buprenorphine/Naloxone Precipitated Withdrawal in Subjects Maintained on 100 mg of Daily Methadone. Drug and Alcohol Dep 2007 (e-publication ahead of print).

Buprenorphine's Pharmacological Profile may Permit Intermittent Dosing that may be Effective Over Periods of Up to 98 h

Buprenorphine has a long duration of action that allows less than daily dosing for opioid dependence. Pharmacologic characterization of buprenorphine's duration of effects over multiple days has not been fully explored. The purpose of this study was to assess opioid blockade and spontaneous withdrawal effects of buprenorphine/naloxone (B/N) over a 98 h period. 8 residential opioid-dependent volunteers were maintained, in randomized sequence, on each of three different daily sublingual B/N doses (8/2, 16/4, 32/8 mg). After 2 weeks on each maintenance dose, participants underwent challenge sessions on each weekday for 1 week. Challenges consisted of within-session, ascending dose administration of IM Hydromorphone (0, 6, and 12 mg). During that week, active B/N dose was given only on Monday; double-blind placebo was administered on the remaining weekdays. These sessions assessed the extent of both opioid blockade and spontaneous withdrawal at 2, 26, 50, 74, and 98 h after the last active B/N dose. All three maintenance doses provided substantial but incomplete blockade against opioid agonist effects for 98 h. The extent of blockade diminished steadily but modestly over time and did not differ as a function of B/N maintenance dose. Withdrawal did not differ as a function of B/N maintenance dose. Study results suggest that there are no substantial differences between buprenorphine doses, both with respect to spontaneous withdrawal assessments and blockade efficacy, over the 98 h period, and that buprenorphine/naloxone doses greater than 8/2 mg may provide minimal incremental value in terms of opioid blockade and withdrawal suppression. The results also suggest that although the efficacy of B/N diminishes over 98 h at a steady rate, there remains blockade efficacy even after 4 days of placebo dosing without substantial or distressing opioid withdrawal. Correia, C.J., Walsh, S.L., Bigelow, G.E., and Strain, E.C. Effects Associated with Double-blind Omission of Buprenorphine/Naloxone Over a 98-h Period.

Psychopharmacology 189, pp. 297-306, 2006.

Acute d-Amphetamine Pretreatment Does Not Alter Stimulant Self-administration in Humans

d-Amphetamine has been reported as currently being tested as an agonist therapy for cocaine and methamphetamine dependence. There is a concern, however, that d-amphetamine may increase drug-taking behavior because acute administration of d-amphetamine decreases inhibition in cocaine-using individuals. The purpose of this study was to determine whether acute d-amphetamine pretreatment would alter the reinforcing, subject-rated, and cardiovascular effects of d-amphetamine in 7 subjects with prior experiences in stimulant abuse. Subjects sampled doses of oral d-amphetamine (0, 8, and 16 mg), then were allowed to self-administer these sampled doses using a modified progressive-ratio procedure in two sessions in which they received pretreatment with either 0 or 15 mg oral d-amphetamine 2 h prior to completing the modified progressive-ratio procedure. d-Amphetamine produced prototypical stimulant-like effects and maintained responding on the modified progressive-ratio schedule. Pretreatment with 15 mg d-amphetamine also produced prototypical stimulant-like effects, but failed to alter break points for d-amphetamine on the modified progressive-ratio procedure relative to placebo pretreatment. These results indicate that acute d-amphetamine pretreatment does not increase stimulant self-administration. Stoops, W.W., Vansickel, A.R., Lile, J.A., and Rush, C.R. Acute d-Amphetamine Pretreatment Does Not Alter Stimulant Self-administration in Humans. Pharmacology, Biochemistry, and Behavior 87, pp. 20-29, 2007.

Women and Men Do Not Appear to Differ in Response to the Discriminative-Stimulus Effects of d-Amphetamine

The results of animal and human laboratory studies are mixed regarding gender differences in response to stimulant drugs. This study performed a retrospective analysis of six studies conducted by this team that used identical procedures and methods. Thirteen women and 14 men learned to discriminate 15 mg of oral d-amphetamine, then the effects of a range of doses of d-amphetamine (0, 2.5, 5, 10, and 15 mg) alone and in combination with other drugs, were assessed. In these studies, d-amphetamine functioned as a discriminative stimulus and dose-dependently increased drug-appropriate responding. Women and men did not differ in their ability to discriminate d-amphetamine, but differed on participant-ratings of high (women < men), nausea (women > men) and sluggish (women < men); women also experienced greater increases in diastolic pressure than men following the administration of higher d-amphetamine doses (10 and 15 mg). Changes in menstrual cycle and hormone levels were not evaluated in the current study. Because the study results may have been confounded by the training procedures, future research should use other behavioral arrangements (e.g. drug self-administration) to determine if women and men respond differently to the effects of d-amphetamine. Vansickel, A.R., Lile, J.A., Stoops, W.W., and Rush, C.R. Similar Discriminative-Stimulus Effects of d-Amphetamine in Women and Men. Pharmacology, Biochemistry and Behavior, 87, pp. 289-296, 2007.

Varenicline is a Partial Agonist at alpha4beta2 and a Full Agonist at alpha7 Neuronal Nicotinic Receptors

In rat nicotinic receptors expressed in Xenopus laevis oocytes, varenicline was shown as being a potent, partial agonist at alpha4beta2 receptors and having a lower potency and higher efficacy at alpha3beta4, alpha3beta2 and alpha6-containing receptors. In addition, varenicline is a potent, full agonist at alpha7

receptors. Thus, varenicline is a partial agonist at some heteromeric neuronal nicotinic receptors, but a full agonist at the homomeric alpha7 receptor. Combination of these actions may be involved in its mechanism as a smoking cessation aid. Mihalak, K.B., Carroll, F.I., and Luetje, C.W. Mol Pharmacol 70(3), pp. 801-805, 2006.

Trace Amine-associated Receptor 1 is a Modulator of the Dopamine Transporter

This study reported that Rhesus monkey TAAR1 expressed with DAT in human embryonic kidney 293 cells was dose-dependently activated by dopamine or (+)-methamphetamine and resulted in large cAMP increases and a transient reduction in [3H]dopamine accumulation within the cells. TAAR1 effects on dopamine uptake could be blocked by a protein kinase A or protein kinase C (PKC) inhibitor. [3H]Dopamine efflux in Eagle's medium was TAAR1-dependent and dose-dependently augmented by dopamine or (+)-methamphetamine but blocked by either methylphenidate or a PKC inhibitor. This study provides evidence that TAAR1 is involved in functional regulation of DAT and suggests that TAAR1 is a potentially important target for therapeutics for methamphetamine addiction. Xie, Z., and Miller, G.M., J Pharmacol Exp Ther. 321(1), pp. 128-136, 2007.

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

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

The 2004 Australian Prison Entrants' Blood-borne Virus and Risk Behavior Survey

The objective of this study was to assess the prevalence of blood-borne viruses and associated risk factors among prison entrants at seven Australian prisons across four States. For this work a consecutive cross-sectional design was employed. Voluntary confidential testing of all prison entrants for serological markers of human immunodeficiency virus (HIV), hepatitis C (HCV) and hepatitis B (HBV) was carried out over 14 consecutive days in May 2004. Demographic data and data related to risks for blood-borne virus transmission, such as sexual activity, body piercing, tattooing, and injecting drug use, were collected. National prevalence for HIV was 1%, hepatitis B core antibody 20%, and hepatitis C antibody 34%. Fifty-nine per cent of participants had a history of injecting drug use. Among injecting drug users, the prevalence of HIV was 1%, hepatitis C antibody 56%, and hepatitis B core antibody 27%. Forty-one per cent of those screened reported a previous incarceration. In the multivariate model, Queensland and Western Australian (WA) prison entrants were significantly less likely to test positive for HCV than those in New South Wales (NSW). Amphetamine was the most commonly injected drug in Queensland, Tasmania and WA. In NSW, heroin was the most common drug injected. In the multivariate analysis a history of injecting drug use, being aged 30 years or more, and a prior incarceration were positively associated with hepatitis C infection. For hepatitis B core antibody, age over 30 years and a history of injecting drug use were associated with an increased risk. The findings support the view that prisoner populations are vulnerable to blood-borne virus infection, particularly hepatitis B and C. Prisoner populations should be included in routine surveillance programs so as to provide a more representative picture of blood-borne virus epidemiology in Australia. Butler, T., Boonwaa, L., Hailstone, S., Falconer, T., Lems, P., Ginley, T., Read, V., Smith, N., Levy, M., Dore, G., and Kaldor, J. Aust N Z J Public Health. Feb;31(1), pp. 44-50, 2007.

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

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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. 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.H., Thomas, D.L., and Cox, A.L. J Infect Dis. 2007 Mar 15;195(6):857-63. Epub February 7, 2007.

Effect of Exposure to Injection Drugs or Alcohol on Antigen-Specific Immune Responses in HIV and Hepatitis C Virus Coinfection

Ongoing substance use is a potential confounder for immunological studies on hepatitis C virus (HCV), but there is little in the literature regarding the effects of injection drug use (IDU) or alcohol on HCV-specific immune responses. The authors wanted to determine whether IDU or alcohol affected immune responses in HCV-infected and human immunodeficiency virus (HIV)/HCV coinfected subjects. Eighty-four subjects with HIV/HCV and 57 with HCV were classified as either injection drug users, drinkers, or nonusers based on questionnaire results. Immune responses were studied with enzyme-linked immunosorbent spot assay for interferon (IFN)- gamma, interleukin (IL)-10, and tumor necrosis factor (TNF)- alpha against HCV proteins Core, NS3, and NS5 and recall antigens. Subjects with HIV/HCV, in aggregate, had significantly lower HCV-specific IFN- gamma and TNF- alpha responses than subjects with HCV. However, HIV/HCV injection drug users had HCV-specific IFN- gamma and IL-10 responses that were similar to those of HCV injection drug users and were significantly higher than in nonusers with HIV/HCV. Conversely, subjects who drank alcohol had similar immune responses to those who were abstinent, among both subjects with HIV/HCV and subjects with HCV. Studies that examine IFN- gamma or IL-10 immune responses in HIV/HCV-coinfected or HCV-infected persons need to consider current IDU. Alcohol, at levels consumed in this cohort, does not appear to have as much of an effect on antigen-specific immune responses. Graham, C.S., Wells, A., Edwards, E.M., Herren, T., Tumilty, S., Stuver, S.O., Samet, J.H., Nunes, D., Horsburgh, C.R., and Koziel, M.J. J Infect Dis. 2007 Mar 15;195(6), pp. 847-856. Epub February 2, 2007.

Proteomic Analyses of Methamphetamine (METH)-induced Differential Protein Expression by Immature Dendritic Cells (IDC)

In the US, the increase in methamphetamine (METH) use has been associated with increased human immunodeficiency virus (HIV-1) infection. Dendritic cells (DC) are the first line of defense against HIV-1. DC plays a critical role in harboring HIV-1 and facilitates the infection of neighboring T cells. However, the role of METH on HIV-1 infectivity and the expression of the proteome of immature dendritic cells (IDC) have not been elucidated. Authors hypothesize that METH modulates the expression of a number of proteins by IDC that foster the immunopathogenesis of HIV-1 infection and utilized LTR amplification, p24 antigen assay and the proteomic method of difference gel electrophoresis (DIGE) combined with protein identification through high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) to analyze the effects of METH on HIV-1 infectivity (HIV-1 IIIB; CXCR4-tropic, X4 strain) and the proteomic profile of IDC. Results demonstrate that METH potentiates HIV-1 replication in IDC. Furthermore, METH significantly differentially regulates the

expression of several proteins including CXCR3, protein disulfide isomerase, procathepsin B, peroxiredoxin and galectin-1. Identification of unique, METH-induced proteins may help to develop novel markers for diagnostic, preventive and therapeutic targeting in METH using subjects. Reynolds, J.L., Mahajan, S.D., Sykes, D.E., Schwartz, S.A., and Nair, M.P. Biochim Biophys Acta. 2007 Apr;1774(4), pp. 433-442. Epub February 13, 2007.

Heroin-Induces Differential Protein Expression by Normal Human Astrocytes (NHA)

Heroin use is postulated to act as a cofactor in the neuropathogenesis of human immunodeficiency virus (HIV-1) infection. Astrocytes, integral components of the CNS, are reported to be susceptible to HIV-1 infection. Upon activation, astrocytes release a number of immunoregulatory products or modulate the expression of a number of proteins that foster the immunopathogenesis of HIV-1 infection. However, the role of heroin on HIV-1 infectivity and the expression of the proteome of normal human astrocytes (NHA) have not been elucidated. Authors hypothesize that heroin modulates the expression of a number of proteins by NHA that foster the neuoropathogenesis of HIV-1 infection and utilized LTR amplification and the p24 antigen assay to quantitate the effect of heroin on HIV-1 infectivity while difference gel electrophoresis (DIGE) combined with protein identification through high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) to analyze the effects of heroin on the proteomic profile of NHA. Results demonstrate that heroin potentiates HIV-1 replication in NHA. Furthermore, heroin significantly increased protein expression levels for protein kinase C (PKC), reticulocalbin 1 precursor, reticulocalbin 1, tyrosine 3-monooxgenase/tryptophan 5-monooxgenase activation protein, chloride intracellular channel 1, cathepsin D preproprotein, galectin 1 and myosin light chain alkali. Heroin also significantly decreased protein expression for proliferating cell nuclear antigen, proteasome beta 6 subunit, tropomyosin 3, laminin receptor 1, tubulin alpha 6, vimentin, EF hand domain family member D2, Tumor protein D54 (hD54), ATP synthase, H+ transporting, mitochondrial F1 complex and ribosomal protein S14. Identification of unique, heroin-induced proteins may help to develop novel markers for diagnostic, preventative and therapeutic targeting in heroin using subjects. Reynolds, J.L., Mahajan, S.D., Sykes, D., and Nair, M.P. Am J Infect Dis. 2(2), pp. 49-57, 2006.

Suppression of Human Immunodeficiency Virus Type 1 Viral Load with Selenium Supplementation: A Randomized Controlled Trial

Despite findings that selenium supplementation may improve immune functioning, definitive evidence of its impact on human immunodeficiency virus (HIV) disease severity is lacking. High selenium yeast supplementation (200 mug/d) was evaluated in a double-blind, randomized, placebo-controlled trial. Intention-to-treat analyses assessed the effect on HIV-1 viral load and CD4 count after 9 months of treatment. Unless otherwise indicated, values are presented as mean +/- SD. Of the 450 HIV-1-seropositive men and women who underwent screening, 262 initiated treatment and 174 completed the 9-month follow-up assessment. Mean adherence to study treatment was good (73.0% +/- 24.7%) with no related adverse events. The intention-to-treat analyses indicated that the mean change (Delta) in serum selenium concentration increased significantly in the selenium-treated group and not the placebo-treated group (Delta = 32.2 +/- 24.5 vs 0.5 +/- 8.8 microg/L; P<.001), and greater levels predicted decreased HIV-1 viral load (P<.02), which predicted increased CD4 count (P<.04). Findings remained significant after covarying age, sex, ethnicity, income, education, current and past cocaine and other drug use, HIV symptom classification, antiretroviral medication regimen and adherence, time since HIV diagnosis, and hepatitis C virus coinfection. Follow-up analyses evaluating treatment effectiveness indicated

that the nonresponding selenium-treated subjects whose serum selenium change was less than or equal to 26.1 microg/L displayed poor treatment adherence (56.8% +/- 29.8%), HIV-1 viral load elevation (Delta = +0.29 +/- 1.1 log(10) units), and decreased CD4 count (Delta = -25.8 +/- 147.4 cells/microL). In contrast, selenium-treated subjects whose serum selenium increase was greater than 26.1 microg/L evidenced excellent treatment adherence (86.2% +/- 13.0%), no change in HIV-1 viral load (Delta = -0.04 +/- 0.7 log(10) units), and an increase in CD4 count (Delta = +27.9 +/- 150.2 cells/microL). The authors conclude that daily selenium supplementation can suppress the progression of HIV-1 viral burden and provide indirect improvement of CD4 count. The results support the use of selenium as a simple, inexpensive, and safe adjunct therapy in HIV spectrum disease. Trial Registration isrctn.org Identifier: ISRCTN22553118. Hurwitz, B.E., Klaus, J.R., Llabre, M.M., Gonzalez, A., Lawrence, P.J., Maher, K.J., Greeson, J.M., Baum, M.K., Shor-Posner, G., Skyler, J.S., and Schneiderman, N. Arch Intern Med. 167(2), pp. 148-154, 2007.

Rates and Predictors of Hepatitis C Virus Treatment in HCV-HIV-Coinfected Subjects

True treatment rates and the impact of comorbidities on treatment rates for hepatitis C virus in the HCV-HIV-coinfected subjects are unknown. The aim of this research was to quantify the rates of treatment prescription and the effect of comorbidities on hepatitis C virus treatment rates in HCV-HIV-coinfected veterans. The Veterans Affairs National Patient Care Database was used to identify all hepatitis C virus-infected subjects between 1999 and 2003 using ICD-9 codes. Demographics, comorbidities and pharmacy data were retrieved. Authors used logistic regression to compare the predictors of hepatitis C virus treatment in hepatitis C virus-monoinfected and HCV-HIV coinfected subjects and identified 120 507 hepatitis C virus-infected subjects, of which 6502 were HIV coinfected. 12% of the hepatitis C virus-monoinfected and 7% of the -coinfected subjects were prescribed hepatitis C virus treatment (P < 0.0001). Those not prescribed treatment were older (48.6 years vs. 47.7 years, P _ 0.007) and more likely to be black (52% vs. 32%, P < 0.0001). HIV coinfected subjects were less likely to be prescribed hepatitis C virus treatment (OR 0.74, 95% CI: 0.67-0.82). Among the coinfected subjects, the following were associated with non-treatment (OR, 95% CI): black race (0.45, 0.35-0.57); Hispanic race (0.56, 0.38-0.82); drug use (0.68, 0.53-0.88); anemia (0.17, 0.11-0.26); bipolar disorder (0.63, 0.40-0.99); major depression (0.72, 0.53-0.99); mild depression (0.47, 0.35-0.62). The authors conclude that a small number of HCV-HIV-coinfected veterans are prescribed treatment for hepatitis C virus. Non-treatment is associated with increasing age, minority race, drug use and psychiatric illness. Further studies are needed to determine the eligibility for treatment and reasons for non- treatment for hepatitis C virus. Butt, A.A., Justice, A.C., Sakanderson, M., Good, C., and Kwoh, C.K. Aliment Pharmacol Ther 24(4), pp. 585-591, 2006.

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 co-infected persons. The 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 to 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 to 5.15). Significant predictors of having a detectable HCV RNA level were female sex (OR, 3.81; 95% CI, 1.18 to 12.25); HIV co-infection (2.45; 95% CI, 1.14 to 5.26); and ever being treated for HCV (OR, 1.96; 95% CI, 1.10 to 3.48). The authors conclude that 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.A., Tsevat, J., Ahmad, J., Shakil, A.O., and Mrus, J.M. Am J Med Sci. 333(5), pp. 271-275, 2007.

Alimentary Pharmacology & Therapeutics Awareness of Hepatitis C Diagnosis is Associated with Less Alcohol Use Among Persons Co-infected with HIV

It is unknown whether testing HIV-infected individuals for hepatitis C virus (HCV) and informing them of their HCV status impacts subsequent alcohol use. The authors hypothesized that HIV-infected individuals with current or past alcohol problems who reported being told they had HCV were more likely to 1) abstain from alcohol and 2) not drink unhealthy amounts compared to individuals who had not been told. Data from a prospective, observational cohort study (HIV-Longitudinal Interrelationships of Viruses and Ethanol) were used to assess the association between awareness of having HCV at baseline and subsequent abstinence and not drinking unhealthy amounts as reported at 6-month follow-up intervals. General estimating equations logistic regression was used to account for the correlation from using repeated observations from the same subject over time. The authors adjusted for age, sex, race, homelessness, injection drug use, depressive symptoms, and having abnormal liver tests. Participants who reported being told they had HCV were more likely to report abstaining from alcohol (AOR = 1.60; 95% CI: 1.13 to 2.27) and not drinking unhealthy amounts (AOR = 1.46; 95% CI: 1.01 to 2.11). The authors conclude that among patients infected with HIV who had a history of alcohol problems, reporting being told one had HCV was associated with greater abstinence from alcohol and less unhealthy amounts of drinking. Tsui, J.I., Saitz, R., Cheng, D.M., Nunes, D., Libman, H., Alperen, J.K., and Samet, J.H. J Gen Intern Med. 22(6), pp. 822-825, 2007. Epub February 23, 2007.

Impact of Hepatitis C on HIV Progression in Adults with Alcohol Problems

Coinfection of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) is a substantial medical and public health concern due to its increasing prevalence and complex patient management. Alcohol use may worsen HCV-related liver disease and interfere with adherence to antiretroviral therapy (ART) and medical care. The authors therefore studied the association between HCV infection and markers of HIV disease progression in adults with alcohol problems. This is a longitudinal study of 396 HIV-infected persons with alcohol problems, 199 (50%) of whom were coinfected with HCV (positive HCV RNA test). CD4 cell counts and HIV RNA levels were assessed at baseline and then every 6 months for up to 42 months. Hepatitis C virus RNA status was determined at study enrollment. The authors examined the relationship between HCV infection and laboratory markers of HIV progression (CD4 cell count and log10 HIV RNA) by fitting multivariable longitudinal regression models for each outcome. Among subjects who were adherent to ART, the

presence of HCV infection was associated with a lower CD4 cell count (adjusted mean difference -46.0 cells/microL, p=0.03). There was no association observed between HCV infection and CD4 cell count among those not adherent to ART or those not taking ART. No significant association was observed between HCV infection and HIV RNA regardless of ART status. The authors concluded that Hepatitis C virus infection has an adverse effect on CD4 cell count in patients with alcohol problems who are adherent to ART. Addressing HCV coinfection among these patients may confer additional immunologic benefit for this patient population. Cheng, D.M., Nunes, D., Libman, H., Vidaver, J., Alperen, J.K., Saitz, R., and Samet, J.H. Alcohol Clin Exp Res. 31(5), pp. 829-836, 2007. Epub March 31, 2007.

HIV Infection is Associated with an Increased Risk for Lung Cancer, Independent of Smoking

HIV-infected persons have an elevated risk for lung cancer, but whether the increase reflects solely their heavy tobacco use remains an open question. The ALIVE or AIDS Link to the Intravenous Experience Study has prospectively observed a cohort of IDU in Baltimore, MD since 1988, using biannual collection of clinical, laboratory, and behavioral data. Lung cancer deaths were identified through linkage with the National Death Index. Cox proportional hazards regression was used to examine the effect of HIV infection on lung cancer risk, controlling for smoking status, drug use, and clinical variables. Among 2086 ALIVE participants observed for 19,835 person-years, 27 lung cancer deaths were identified; 14 of the deaths were among HIV-infected persons. All but 1 (96%) of the patients with lung cancer were smokers, smoking a mean of 1.2 packs per day. Lung cancer mortality increased during the highly active antiretroviral therapy era, compared with the pre-highly active antiretroviral therapy period (mortality rate ratio, 4.7; 95% confidence interval, 1.7-16). After adjusting for age, sex, smoking status, and calendar period, HIV infection was associated with increased lung cancer risk (hazard ratio, 3.6; 95% confidence interval, 1.6-7.9). Preexisting lung disease, particularly noninfectious diseases and asthma, displayed trends for increased lung cancer risk. Illicit drug use was not associated with increased lung cancer risk. Among HIV-infected persons, smoking remained the major risk factor; CD4 cell count and HIV load were not strongly associated with increased lung cancer risk, and trends for increased risk with use of highly active antiretroviral therapy were not significant. These findings indicate that HIV infection is associated with significantly increased risk for developing lung cancer, independent of smoking status, but specifically how or why this is so remains as yet unknown. Kirk, G., Merlo, C., O'Driscoll, P., Mehta, S., Galai, N., Vlahov, D., Samet, J., and Engels, E. HIV Infection is Associated with an Increased Risk for Lung Cancer, Independent of Smoking. Clin Infect Dis, 45(1), pp. 103-110, 2007.

Injection Drug Use and Patterns of Highly Active Antiretroviral Therapy Use: An Analysis of ALIVE, WIHS, and MACS Cohorts

Sustained use of antiretroviral therapy has been consistently shown to be one of the primary predictors of long-term effectiveness. Switching and discontinuation reflect patient and provider decisions that may limit future treatment options. In this study, researcher's utilized data reported at semi-annual study visits from three prospective cohort studies, the AIDS Link to IntraVenous Exposure (ALIVE), the Women's Interagency HIV Study (WIHS), and the Multicenter AIDS Cohort Study (MACS), to investigate determinants of HAART modification with a particular focus on reported injection drug use (IDU). Longitudinal data collected between 1996 and 2004 contributed from 2,266 participants (37% with a reported history of IDU) who reported initiating their first HAART regimen during follow-up were utilized. Separate proportional-hazards models were used to identify factors measured prior to HAART-initiation associated with the time to first HAART discontinuation and

first switch of components of HAART among continuous HAART users. The use of PI- vs. NNRTI-based regimens among HAART users with and without any history of IDU was similar over follow-up. The median time to a first report of discontinuation of HAART was 1.1 years for individuals with a history of IDU but 2.5 years for those without a history of IDU and multivariate analyses confirmed overall that individuals with a history of IDU were at greater risk for HAART discontinuation (adj RH = 1.24, 95% CI: 1.03-1.48). However, when restricting to data contributed after 1999, there was no longer any significant increased risk (adj RH = 1.05, 95% CI: 0.81-1.36). After adjusting for pre-HAART health status and prior ARV exposure, individuals who were ethnic/racial minorities, reported an annual income < $10,000/year, and were not employed were at significantly greater risk for HAART discontinuation. The median time to a first change in HAART regimen was approximately 1.5 years after first HAART report and was not elevated among those with a history of IDU (adj RH = 1.09, 95% CI: 0.89-1.34). The researchers analyses demonstrate that injection drug use by itself does not appear to be an independent risk factor for HAART switching or discontinuation in more recent years. However, as continued HAART use is of paramount importance for long-term control of HIV infection, efforts to improve maintenance to therapy among disadvantaged and minority populations remain greatly needed. Morris, J., Golub, E., Mehta, S., Jacobson, L., and Gange, S. Injection Drug Use and Patterns of Highly Active Antiretroviral Therapy Use: An Analysis of ALIVE, WIHS, and MACS Cohorts. AIDS Res Ther, 4, pp. 12-20, 2007.

HIV Seropositive Drug Users' Attitudes towards Partner Notification (PCRS): Results from the SHIELD Study in Baltimore, Maryland

Researchers assessed the attitudes of HIV seropositive current or former drug users towards HIV partner counseling and referral services (PCRS) and determined if opinion varies by partner type. They used a cross-sectional survey using structured and semi-structured questions to measure attitudes towards PCRS. The majority of the sample was African-American (97%), male (63%) and had been diagnosed with HIV for a mean of 7.9 years. Most agreed that PCRS would help stop the spread of HIV and AIDS (87%). A range of reactions to scenarios of their drug and sex partners being informed were observed and included positive reactions (e.g. PCRS as a means to facilitate testing of their partners and early treatment) to negative (e.g. feelings about guilt, shame and concern about partner responses). Data from this study indicate that HIV positive drug users view PCRS as a viable practice for preventing the spread of HIV, though barriers exist to engaging clients to identify partners. The range of reactions noted in this study underscore the importance of providing flexible options for PCRS based on partner type. Additional training for counselors, time for case-management and meetings with sex and drug partners and fieldwork for locating contacts are important considerations for providers. Tobin, K., Muessig, K., and Latkin, C. HIV Seropositive Drug Users' Attitudes towards Partner Notification (PCRS): Results from the SHIELD Study in Baltimore, Maryland. Patient Educ Couns, 67(1-2), pp. 137-142, 2007.

Sexual and Other Noninjection Risks for HBV and HCV Seroconversions among Noninjecting Heroin Users

Many heroin users do not inject drugs but may still be at risk of infection with Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), and Hepatitis C Virus (HCV), via sexual or other non-injection related activity. Non-injecting heroin users (NIUs) in New York City who were recruited and prospectively followed during March 1996-February 2003 were tested for anti-HIV, anti-hepatitis B core antigen, and anti-HCV and were interviewed about their sexual and other non-injecting risk. A seroconversion is represented by the first

positive test result after the last negative test result. Hazard ratios (HRs) (P<.05) were estimated by use of Cox proportional hazards regression. Of 253 HIV-negative participants, 2 seroconverted (0.29/100 person-years at risk [pyar]); of 184 HBV-negative participants, 16 (3.3/100 pyar); and, of 219 HCV-negative participants, 16 (2.7/100 pyar). Independent predictors of seroconversion were, for HBV, being a female who engages in unprotected receptive anal sex (HR, 6.8), having short-term sex partners (HR, 6.2), and being a male with male sex partners (HR, 5.7); for HCV, being a male who receives money/drugs for sex (HR, 5.6) and sharing non-injecting crack-use equipment (HR, 4.5). These findings suggest that NIUs are at considerable risk of HBV infection via high-risk sex; and, for HCV, via high-risk sexual activity and the sharing of non-injecting crack-use equipment. Interventions for NIUs should seek to reduce high-risk sexual activity and the sharing of non-injecting drug-use equipment. Neaigus, A., Gyarmathy, V., Zhao, M., Miller, M., Friedman, S., and Des Jarlais, D. Sexual and Other Non-injection Risks for HBV and HCV Seroconversions among Non-injecting Heroin Users. J Infect Dis, 195(7), pp. 1052-1061, 2007.

Trends in Hepatitis B Virus, Hepatitis C Virus, and Human Immunodeficiency Virus Prevalence, Risk Behaviors, and Preventive Measures among Seattle Injection Drug Users Aged 18-30 Years, 1994-2004

Injection drug users (IDUs) are at risk for infection with hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV). Information on time trends in prevalence of these viruses among IDUs and in behaviors influencing their transmission can help define the status of these epidemics and of public health efforts to control them. Researchers conducted a secondary data analysis combining cross-sectional data from IDUs aged 18-30 years enrolled in 4 Seattle-area studies from 1994 to 2004. Participants in all 4 studies were tested for antibody to HIV (anti-HIV), hepatitis B core antigen (anti-HBc), and HCV (anti-HCV), and completed behavioral risk assessments. Logistic regression was used to investigate trends in prevalence over time after controlling for sociodemographic, drug use, and sexual behavior variables. Between 1994 and 2004, anti-HBc prevalence declined from 43 to 15% ($p < 0.001$), anti-HCV prevalence fell from 68 to 32% ($p < 0.001$) and anti-HIV prevalence remained constant at 2-3%. Declines in anti-HBc and anti-HCV prevalence were observed within the individual studies, although not all these declines were statistically significant. The declines in anti-HBc and anti-HCV prevalence remained significant after control for confounding. Although coincident declines in injection equipment sharing practices were not observed, there were increases in self-reported needle-exchange use, condom use, and hepatitis B vaccination. These findings suggest that a substantial and sustained reduction in prevalence rates for HBV and HCV infection among young Seattle IDUs, while HIV rates have remained low and stable. Burt, R., Hagan, H., Garfein, R., Sabin, K., Weinbaum, C., and Thiede, H. Trends in Hepatitis B Virus, Hepatitis C Virus, and Human Immunodeficiency Virus Prevalence, Risk Behaviors, and Preventive Measures among Seattle Injection Drug Users Aged 18-30 Years, 1994-2004. J Urban Health, 84(3), pp. 436-454, 2007.

Non-injection Drug Use and Hepatitis C Virus: A Systematic Review

This systematic review examined the evidence on the prevalence of the Hepatitis C Virus (HCV) in non-injecting drug users (NIDUs) who sniff, smoke or snort drugs such as heroin, cocaine, crack or methamphetamine. The search included studies published from January 1989 to January 2006. Twenty-eight eligible studies were identified and the prevalence of HCV in these NIDU populations ranged from 2.3 to 35.3%. There was substantial variation in study

focus and in the quality of the NIDU data presented in the studies. The results of the researchers systematic review suggested that there are important gaps in the research of HCV in NIDUs. The researchers identified a problem of study focus; much of the research did not aim to study HCV in users of non-injection drugs. Instead, NIDUs were typically included as a secondary research concern, with a principal focus on the problem of transmission of HCV in IDU populations. Despite methodological issues, HCV prevalence in this population is much higher than in a non-drug using population, even though some IDUs might have inadvertently been included in the NIDU samples. These studies point to a real problem of HCV in NIDU populations, but the causal pathway to infection remains unclear. Scheinmann, R., Hagan, H., Lelutiu-Weinberger, C., Stern, R., Des Jarlais, D., Flom, P., and Strauss, S. Non-injection Drug Use and Hepatitis C Virus: A Systematic Review. Drug Alcohol Depend, 89(1), pp. 1-12, 2007.

Individual and Couple-Level Risk Factors for Hepatitis C Infection among Heterosexual Drug Users: A Multilevel Dyadic Analysis

Hepatitis C virus (HCV) is the most common blood borne pathogen in the United States and is a leading cause of liver-related morbidity and mortality. Although it is known that HCV is most commonly transmitted among IDUs, the role of sexual transmission in the spread of HCV remains controversial because of inconsistent findings across studies involving heterosexual couples. A novel multilevel modeling technique designed to overcome the limitations of previous research was performed to assess multiple risk factors for HCV while partitioning the source of risk at the individual and couple level. The analysis was performed on risk exposure and HCV screening data obtained from 265 drug-using couples in East Harlem, New York City. In multivariable analysis, significant individual risk factors for HCV included a history of injection drug use, tattooing, and older age. At the couple level, HCV infection tended to cluster within couples, and this interdependence was accounted for by couples' drug-injection behavior. Individual and couple-level sexual behavior was not associated with HCV infection. These results are consistent with prior research indicating that sexual contact plays little role in HCV transmission. Rather, couples' injection behavior appears to account for the clustering of HCV within heterosexual dyads. McMahon, J., Pouget, E., and Tortu, S. Individual and Couple-Level Risk Factors for Hepatitis C Infection among Heterosexual Drug Users: A Multilevel Dyadic Analysis. J Infect Dis, 195(11), pp. 1572-1581, 2007.

Reasons for Condom Use or Non-use Among Drug Users

In this study, Rosengard, Anderson, and Stein, interviewed two hundred and seventy-seven drug using adults regarding details of their most recent sexual encounter. Demographic, attitudinal, and context variables were associated with condom use and non-use. Greater perceived risk of STDs/HIV and positive attitudes toward condoms effect on sexual pleasure were associated with greater likelihood of reporting condom use. Common reasons for not using condoms included lower perceived risk of contracting HIV/STDs, negative attitudes toward condoms effect on pleasure, and lack of condom availability. Tailoring messages to modifiable perceptions of risk and condom attitudes may be useful in reducing sexual risk among drug-using individuals. Rosengard, C., Anderson, B., and Stein, M. Correlates of Condom Use and Reasons for Condom Non-use Among Drug Users. Am J Drug Alcohol Abuse, 32(4), pp. 637-644, 2006.

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

Previous studies described infective endocarditis (IE) in the era before highly active antiretroviral therapy (HAART); however, IE has not been well studied in the current HAART era. The incidence of, risk factors for, clinical presentation, and 1-year outcomes of IE in HIV-infected patients were evaluated. All cases of IE diagnosed between 1990 and 2002 in patients followed at the Johns Hopkins Hospital outpatient HIV clinic were evaluated. To identify factors associated with IE in the current era of HAART, a nested case-control analysis was employed for all initial episodes of IE occurring between 1996 and 2002. Logistic regression analyses were used to assess risk factors for IE and factors associated with 1-year mortality. IE incidence decreased from 20.5 to 6.6 per 1000 person years (PY) between 1990 and 1995 and 1996 and 2002. The majority of IE cases were male (66%), African American (90%), and injection drug users (IDUs) (85%). In multivariate regression, an increased risk of IE occurred in IDUs (AOR, 8.71), those with CD4 counts, 50 cells/mm3, and those with HIV-1 RNA .100,000 copies/mL (AOR, 3.88). Common presenting symptoms included fever (62%), chills (31%), and shortness of breath (26%). The most common etiologic organism was Staphylococcus aureus (69%; of these 11 [28%] were methicillin resistant).Within 1 year, 16% had IE recurrence, and 52% died. Age over 40 years was associated with increased mortality. IE rates have decreased in the current HAART era. IDUs and those with advanced immunosuppression are more likely to develop IE. In addition, there is significant morbidity and 1-year mortality in HIV-infected patients with IE, indicating the need for more aggressive follow-up, especially in those over 40 years of age. Future studies investigating the utility of IE prophylaxis in HIV patients with a history of IE may be warranted. Gebo, K.A., Burkey, M.D., Lucas, G.M., Moore, R.D., and Wilson, L.E. Incidence of, Risk Factors for, Clinical Presentation, and 1-Year Outcomes of Infective Endocarditis in an Urban HIV Cohort. J Acquir Immune Defic Syndr, 43(4), pp. 426-432, 2006.

HIV Risk Behaviors Among Rural Stimulant Users: Variation By Gender and Race/Ethnicity

Data were examined from a community sample of rural stimulant users (n = 691) in three diverse states to identify gender and racial/ethnic differences in HIV risk behaviors. Bivariate and logistic regression analyses were conducted with six risk behaviors as dependent variables: injecting drugs, trading sex to obtain money or drugs, trading money or drugs to obtain sex, inconsistent condom use, multiple sex partners, and using drugs with sex. Controlling for state, income, age, heavy drinking, and type of stimulant used, men had lower odds than women for trading sex to obtain money or drugs (adjusted odds ratio [AOR] =0.4, confidence interval [CI] = 0.28-0.59; p < .0001), greater odds than women for trading money or drugs to obtain sex (AOR = 44.4, CI = 20.30-97.09; p < .0001), greater odds than women of injecting drugs (adjusted odds ratio (AOR =1.6, CI = 1.11-2.42; p = .01), and lower odds than women of using condoms inconsistently (AOR = 0.6, CI = 0.35-0.92; p = .02); African Americans had lower odds than Whites of injecting drugs (AOR = .08, CI = 0.04-0.16; p < .0001), greater odds than Whites for trading sex to obtain money or drugs (AOR = 1.7, CI = 1.01-2.85; p = .04) and for trading money or drugs to obtain sex (AOR = 2.9,CI = 1.53-5.59; p = .001), and greater odds than Whites of using drugs with sex (AOR = 3.9, CI = 1.47-10.09; p = .006). These findings indicate HIV prevention efforts should be tailored to address gender and racial/ethnic differences in risk behaviors among rural stimulant users. Booth, B.M., Wright, P.B., Stewart, K.E., Fischer, E.P., Carlson, R.G., Falck, R., Wang, J., and Leukefeld, C.G. HIV Risk Behaviors Among Rural Stimulant Users: Variation by Gender and Race/Ethnicity. AIDS Educ Prev, 12(2), pp. 137-150, 2007.

A Within-subject Comparison of Withdrawal Symptoms During Abstinence from Cannabis, Tobacco, and Both Substances

A cannabis withdrawal syndrome has been characterized, but its clinical significance remains uncertain. One method of assessing the significance of cannabis withdrawal is to compare it directly to an established withdrawal syndrome. The present study was a within-subject comparison of cannabis, tobacco, and combined cannabis and tobacco withdrawal among users of both substances. Participants (N=12) completed three 5-day periods of abstinence in a randomized order, separated by 9-day periods of usual substance use. Overall withdrawal severity associated with cannabis alone and tobacco alone was of a similar magnitude. Withdrawal during simultaneous cessation of both substances was more severe than for each substance alone, but these differences were of short duration and substantial individual differences were noted. These results are consistent with other evidence suggesting cannabis withdrawal is clinically important and warrants detailed description in the DSM-V and ICD-11. Additional research is needed to replicate these findings and to further investigate the effects of abstaining from multiple drugs simultaneously. Vandrey, R.G., Budney, A.J., Hughes, J.R., and Liguori, A. Drug Alcohol Depend. July 21, 2007 [Epub ahead of print].

Effects of Pregnancy on Nicotine Self-administration and Nicotine Pharmacokinetics in Rats

Dr. Pentel's group at Minneapolis Medical Research Foundation developed an animal model of smoking during pregnancy by initially characterizing nicotine self-administration (NSA) in pregnant rats. In addition, they also began to explore the effects of pregnancy on nicotine pharmacokinetics in rats. NSA decreased over the course of pregnancy with NSA significantly lower in the third trimester compared to nonpregnant controls. NSA remained suppressed for up to 10 days into lactation. Locomotor behavior was also significantly suppressed during the second and third trimesters and throughout lactation. Nicotine elimination was slower in pregnant females compared to nonpregnant females only in the third trimester. In conclusion, NSA, locomotor behavior, and nicotine elimination in rats are decreased during late pregnancy. The present study is the first to characterize NSA during pregnancy in animals, providing a potential model of maternal smoking in humans. Lesage, M.G., Keyler, D.E., Burroughs, D., and Pentel, P.R. Effects of Pregnancy on Nicotine Self-administration and Nicotine Pharmacokinetics in Rats. Psychopharmacology (Berl), July 7, 2007 [Epub ahead of print].

Maternal Separation Alters Drug Intake Patterns in Adulthood in Rats

Dr. Kuhar's group at Emory University, Atlanta, Georgia, examined the effects of maternal separation and drug intake patterns in adulthood in rats. Maternal separation/handling (MS/H) is an animal model of early life stress that causes profound neurochemical and behavioral alterations in pups that persist into adulthood. Many recent studies have used the MS/H model to study changes in drug effects in adulthood that are linked to behavioral treatments and stressors in the perinatal period. The drug effects focused on in this review are the reinforcing properties of the abused drugs, cocaine and alcohol. A striking finding is that variations in maternal separation and handling cause changes in ethanol and cocaine self-administration. Further, these changes indicate that various manipulations in the perinatal period can have long lasting effects of interest to biochemical pharmacologists. This article reviewed recent studies on ethanol and cocaine self-administration using the MS/H model and the neurochemical alterations that may play a role in the effects of MS/H on ethanol and cocaine self-administration. Studying the MS/H model can provide important clues into the vulnerability to drug abuse and perhaps identify a crucial window of opportunity for therapeutic intervention. Moffett, M.C., Vicentic, A., Kozel, M., Plotsky, P., Francis, D.D. and Kuhar, M.J. Maternal Separation Alters Drug Intake Patterns in Adulthood in Rats. Biochem

Pharmacology, 73(3), pp. 321-330, 2007.

Using Hapten Design to Discover Therapeutic Monoclonal Antibodies for Treating Methamphetamine Abuse

When generating monoclonal antibodies (mAb) against small molecules, the chemical composition and molecular orientation of the drug-like hapten on the antigen is a crucial determinant. This is especially important when attempting to discover therapeutic mAb against the drugs of abuse (+)-methamphetamine [(+)-METH], (+)-amphetamine [(+)-AMP], and the related compound (+)-3,4-methylenedioxymethamphetamine [(+)-MDMA, the plus isomer in the racemic mixture known as MDMA or ecstasy]. The goal of these studies was to design and synthesize (+)-METH-like haptens with structural attributes that could make them effective for generating monoclonal antibodies for treating medical problems associated with these stimulant drugs of abuse. Five prototype (+)-METH-like haptens were synthesized and used to generate mAb. After screening for anti-(+)-METH IgG antibodies in more than 25,000 potential mouse hybridoma cell lines, one prototype mAb from each of the five haptens was selected and studied in detail for molecular properties and preclinical efficacy. One antibody (designated mAb4G9) exhibited high affinity and specificity to (+)-METH, (+)-MDMA, and (+)-AMP, without significant cross-reactivity against other METH-like ligands, over-the-counter medications, or endogenous neurotransmitters. Considered together, discovery of mAb4G9 and the other antibodies in this report represent an important step in understanding the process for custom design of drug class-specific therapeutic antibodies for the treatment of drug addiction. Peterson, E.C., Gunnell, M., Che, Y., Goforth, R.L., Carroll, F.I., Henry, R., Liu, H., and Owens, S.M. Using Hapten Design to Discover Therapeutic Monoclonal Antibodies for Treating Methamphetamine Abuse. J Pharmacol Exp Ther. 322(1), pp. 30-39, 2007.

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

Research Findings - Services Research

Outpatient Treatment Engagement and Abstinence Rates Following Inpatient Opioid Detoxification

Many patients with chronic opioid dependence are referred to drug-free outpatient treatment following inpatient detoxification even though successful outpatient treatment engagement and abstinence from opioids occur only in a minority of cases. To determine if a setting that optimizes patient support can produce better outcomes, the authors performed a retrospective cohort analysis of medical records. These records document the post-discharge outcome in a treatment setting that maximizes the support during transition to abstinence-oriented outpatient care, with comprehensive social, medical and mental health services, including the availability of naltrexone. Participants were male veterans (N = 112) admitted at an urban VA medical center. Most patients (78%) successfully completed acute detoxification, 49% initiated naltrexone, and 76% accepted a VA aftercare plan. At 90-day follow-up, only 22% remained in aftercare, and < 3% had toxicology-verified abstinence from opioids. At one-year follow-up, 1 out of 5 had been readmitted for detoxification and 4.5% had died. This shows that most patients successfully detoxified from opioids, but even with intensive associated support services very few remained engaged and stabilized in abstinence-oriented outpatient treatment. Furthermore, this finding has broad and significant implications for post-detoxification referral practices in patients with opioid addiction throughout the addiction treatment field. Davison, J., Sweeney, M., Bush, K., Davis Correale, T., Calsyn, D., Reoux, J., Sloan, K., and Kivlahan, D. Outpatient Treatment Engagement and Abstinence Rates Following Inpatient Opioid Detoxification. J Addict Dis, 25(4), pp. 27-35, 2006.

Interim Methadone Maintenance Enhances Patient Engagement in Treatment

A total of 319 individuals meeting the criteria for current heroin dependence and methadone maintenance treatment, were randomly assigned to either interim methadone maintenance, consisting of an individually determined methadone dose and emergency counseling only for up to 120 days, or referral to community-based methadone treatment programs. Significantly more participants assigned to the interim methadone maintenance condition entered comprehensive methadone maintenance treatment by the 120th day from baseline (75.9%) than those assigned to the waiting list control condition (20.8%) (P<.001). Overall, in the past 30 days at follow-up, interim participants reported significantly fewer days of heroin use (P<.001), had a significant reduction in heroin-positive drug test results (P<.001), reported spending less money on drugs (P<.001), and received less illegal income (P<.02) than the waiting list participants. Thus interim methadone

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maintenance results in a substantial increase in the likelihood of entry into comprehensive treatment, and is an effective means of reducing heroin use and criminal behavior among opioid-dependent individuals awaiting entry into a comprehensive methadone treatment program. Schwatz, R.P., Brady, J.V., and Callaman, J.M. A Randomized Controlled Trial of Interim Methadone Maintenance. Arch Gen Psychiatry, 63 (Jan), pp. 102-109, 2006.

Requirements for Using Standard Screening Instruments Increased in Health Plans

Data from a nationally representative sample of health plans were used to detect trends in behavioral health care screening requirements for primary care providers between 1999 (N=424) and 2003 (N=368). The percentage of plans with any behavioral health screening requirement remained steady between 1999 and 2003 at 34%. However, among those that require screening, the percentage of plans that required primary care providers to use a standard screening questionnaire specifically designed to detect drug problems increased from 7.6% to 77.9% during that time. Plans most likely to require the use of a standard screening instrument include preferred provider organizations or point of service plans, for profit plans, those that do not contract out behavioral health services, those in the Western region of the country, and those in market areas of more than 4 million people. Horgan, C.M., Garnick, D.W., Merrick, E.L., and Hoyt, A. Health Plan Requirements for Mental Health and Substance Use in Primary Care. J Gen Intern Med, 22 pp. 930-936, 2007.

Behavioral Health Care Carve-Outs Useful in Addressing Utilization, Access, and Cost

This review article assesses the evolution of behavioral health carve-outs, explains their underlying principles, and provides an overview of what is known about their performance in cost, access, and quality of care. As of 2003, some 170 million insured Americans receive their behavioral health care coverage through some type of carve-out arrangement. Research consistently finds that carve-outs reduce behavioral health care spending, on the order of 30%-40% when compared to fee-for-service or preferred provider arrangements, largely by reducing inpatient care and lowering payment rates for providers. Most studies find that carve-outs result in increased access by reducing out-of-pocket costs, although the quantity of services consumed by those who do consume services may have declined. The effects of carve-outs on quality of care is under researched, although there is some reason for concern that those with substance abuse disorders and very severe and complex mental disorders may be fairing worse under carve-outs. Managed behavioral health care organizations are experimenting with mechanisms to improve integration of medical and behavioral health care services, and include coverage of psychotropic medications in the plans, while public payers are attempting to establish purchasing cooperatives to decrease administrative costs and benefit from the resulting economies of scale. Frank, R.G., and Garfield, R.L. Managed Behavioral Health Care Carve-Outs: Past Performance and Future Prospects. Annu Rev Public Health, 28, pp. 303-320, 2007.

Availability of Drug Treatment Services for Adult Offenders

National Criminal Justice Treatment Practices, a nationally representative survey of prisons, jails, and community correctional agencies was conducted to estimate the prevalence of entry into and accessibility of correctional programs and drug treatment services for adult offenders. Substance abuse education and awareness is the most prevalent form of service provided, being offered in 74% of prisons, 61% of jails, and 53% of community correctional agencies; at the same time, remedial education is the most frequently available correctional

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program in prisons (89%) and jails (59.5%), whereas sex offender therapy (57.2%) and intensive supervision (41.9%) dominate in community correctional programs. Most substance abuse services provided to offenders are offered through correctional programs such as intensive supervision, day reporting, vocational education, and work release, among others. Although agencies report a high frequency of providing substance abuse services, the prevalence rates are misleading because less than a quarter of the offenders in prisons and jails and less than 10% of those in community correctional agencies have daily access to these services through correctional agencies; in addition, these are predominantly drug treatment services that offer few clinical services. Given that drug-involved offenders are likely to have dependence rates that are four times greater than those among the general public, the drug treatment services and correctional programs available to offenders do not appear to be appropriate for the needs of this population. The National Criminal Justice Treatment Practices survey provides a better understanding of the distribution of services and programs across prisons, jails, and community correctional agencies and allows researchers and policymakers to understand some of the gaps in services and programs that may negatively affect recidivism reduction efforts. Taxman, F., Perdoni, M., and Harrison, L. Drug Treatment Services for Adult Offenders: The State of the State. J Subst Abuse Treat, 32(3), pp. 239-254, 2007.

Availability of Drug Treatment Services for Juvenile Offenders

Despite consensus about the value of substance abuse treatment for delinquent youth, information about its prevalence and availability is inadequate and inconsistent. This article presents findings about treatment and other correctional service provision from a nationally representative survey of directors of 141 juvenile institutional and community corrections (CC) facilities, as part of the National Criminal Justice Treatment Practices Survey, conducted as part of the Criminal Justice Drug Abuse treatment Studies. Educational/General Educational Development programming and drug and alcohol education were the most prevalent types of correctional and substance abuse services. Other common services included physical health services and mental health assessment, provided to about 60% of youth across facilities, and mental health counseling, life and communication skills, and anger management, provided to about half of the youth. As with most other services, substance abuse treatment was more prevalent in large, state-funded residential facilities (where 66% provided treatment) than in local detention centers (20%) and CC facilities (56%). The number of youth attending substance abuse treatment in all types of facilities on any given day was very low. Young, D., Dembo, R., and Henderson, C. A National Survey of Substance Abuse Treatment for Juvenile Offenders. J Subst Abuse Treat, 32 (3), pp. 255-266, 2007.

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

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

Kidorf, M. S., Neufeld, K. S., and Brooner, R. K. DSM-III-R Versus DSM-IV Substance Use Disorders: Concordance in Drug Users Homogeneous for Chronic and Severe Problems. Addictive Disorders & Their Treatment, 5(4), pp. 165-171, 2006.

Substance Abuse Treatment Prevention, and Policy

It has been proposed that the substance abuse treatment delivery system cut across different components of the criminal justice continuum in order to reduce criminal recidivism and drug use. Arrest, at the front end of this continuum, may represent a critical moment to motivate people with substance use disorders (SUD) to seek treatment but is often over looked as an intervention point. Data from the 2002 National Survey on Drug Use and Health (NSDUH) were used to compare treatment need and recent treatment admission for participants with no criminal justice (CJ) involvement in the past year, past-year arrest, and CJ supervision (i.e., probation or parole status). Of those arrested, 44.8% met criteria for an SUD. However, only 14% of those arrested with an SUD received treatment in the year of their arrest. In multivariate modeling, arrest was an independent predictor of treatment admission (odds ratio (OR) = 8.74) similar in magnitude to meeting criteria for an SUD (OR = 8.22). Those further along the continuum - under supervision - were most likely to receive treatment (OR = 22.62). Arrest involves the largest number of individuals entering the criminal justice system. The NSDUH suggests that nearly 6 million individuals in the US experience an arrest annually and that nearly half meet criteria for an SUD. Although arrest involves the largest number of individuals entering the criminal justice system, it is also the most fleeting point as individuals can move in and out rather quickly. Minimally, arrest imposes contact between the individual and a law enforcement person and can be an opportunity for early intervention strategies such as pre-arraignment diversion into treatment or brief intervention strategies. Using brief intervention at this early point in the continuum may motivate a greater number of individuals to seek treatment or decrease drug and alcohol use. Pimlott Kubiak, S., Arfken, C.L., Swartz, J.A., and Koch, A.L. Substance Abuse Treatment Prevention, and Policy. BioMed Central, 1(20), pp. 1-10, 2006.

Screening for Serious Mental Illness in Populations with Co-occurring Substance Use Disorders: Performance of the K6 Scale

Serious mental illnesses (SMIs) such as schizophrenia, bipolar disorder, and major depression are prevalent among individuals with substance use disorders, particularly those in drug treatment programs. No screening tool has yet become the gold standard for identifying SMI among individuals with substance use disorders. One candidate instrument, the K6 screening scale, is brief, easy to administer and score, and has performed well, detecting SMI in studies using general population samples. The National Survey on Drug Use and Health data was used to examine the K6's psychometric properties in a sub sample of persons with substance use disorders and found that the K6 accurately screened for severe psychological distress associated with SMI among individuals with substance use disorders and across different psychiatric disorders. Swartz, J. A., and Lurigio, A.J. Screening for Serious Mental Illness in Populations with Co-occurring Substance Use Disorders: Performance of the K6 Scale. J Subst Abuse Treat, 31 pp. 287-296, 2006.

Prevalence of Drug Problems, Mental Health Problems, and Criminal Histories Among the Offending Sample of the CJDATS Studies

The national Criminal Justice Drug Abuse Treatment Studies (CJ-DATS) is a

multisite research program to improve outcomes for offenders with drug problems who are reentering the community after incarceration. Baseline data from three ongoing CJ-DATS studies were pooled to examine the characteristics of study participants. These analyses suggest that CJ-DATS study participants have serious drug problems, criminal histories, and mental health problems that can decrease the likelihood of successful community reentry unless addressed. HIV-risk behavior was associated with several categories of criminal acts, suggesting that the relationship between sexual risk behaviors and crime may need further investigation. Fletcher, B.W., Lehman, W.E., Wexler, H.K., and Melnick, G. Who Participates in the Criminal Justice Drug Abuse Treatment Studies (CJ-DATS)? The Prison Journal, 87(1), pp. 1-33, 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 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.

Organizational Characteristics Associated with Treatment Orientation in Services for Offenders

This article examines the association between the organizational characteristics of drug abuse treatment programs for offenders and the provision of wraparound services and three types of treatment orientations. Data are from the National Criminal Justice Treatment Practices Survey, which was conducted with program directors (N = 217). More wraparound services were provided in inpatient treatment, specialized treatment facilities, community setting (vs. correctional), when services were provided for more types of client populations, when staff were college-educated, and when treatment was planned for over 180 days. Therapeutic community orientation provided more often in prison-based treatment and specialized treatment facilities. Services with a cognitive-behavioral therapy orientation were provided more often when community treatment was perceived as more important, when staff had more influence on treatment, and when treatment was for 91-180 days. Services with a 12-step orientation were provided more often by staff specialized in substance abuse. Study findings have implications for developing effective reentry programs for offenders that bridge correctional and community treatment. Grella, C., Greenwell, L., Prendergast, M., Farabee, D., Hall, E., Cartier, J., and Burdon, W. Organizational Characteristics of Drug Abuse Treatment Programs for Offenders. J Subst Abuse Treat, 32(3), pp. 291-300, 2007.

Organization, Financing, Promotion, and Cost of U.S. Quitlines

Quitlines have been established as an effective, evidence-based, population-wide strategy to deliver smoking-cessation treatment, and are now available in most states across America. However, little is known about the organization, financing, promotion, and cost of state quitlines. To determine this, in 2004, the North American Quitline Consortium surveyed the 50 states and Washington DC to obtain information about state quitlines. Data were analyzed in fall 2005 through spring 2006. Analyses of these data are reported in this paper. It was found that 38 states reported having a quitline in 2004. State governments funded most (89.5%) quitlines. Median state quitline operating budgets in 2004 were 500,000 dollars; this translates into a modest annual median operating cost of 0.14 dollar per capita or 0.85 dollar per adult smoker. A lesser amount was spent for quitline promotion. Quitline services varied, with 97.4% of respondents providing mailed self-help resources, 89.5% providing proactive telephone counseling, and 89.2% providing referrals to other services. Many quitlines provide services in languages other than English. Only 21.1% of quitlines reported providing cessation medication at no cost. Promotional strategies varied widely. From this study it was found that a large majority of U.S. smokers live in states with tobacco quitlines, which provide cessation treatment at a remarkably modest per capita cost. There is a great deal of congruence in services and promotional strategies among states. Further research is required to determine how external factors such as the federal National Network of Tobacco Cessation Quitlines funding for state quitlines and the availability of a national portal number (1-800-QUITNOW), both implemented in 2004, affect state quitlines. Keller, P., Bailey, L., Koss, K., Baker, T., and Fiore, M. Organization, Financing, Promotion, and Cost of U.S. Quitlines, 2004. Am J Prev Med, 32(1), pp. 32-37, 2007.

Evaluation of a Combined Online and In Person Training in the Use of Buprenorphine

A specific physician training course is required to prescribe buprenorphine to patients. To evaluate this buprenorphine training methodology, the authors surveyed physicians who had completed a combined online and in person buprenorphine curriculum. Of 53/70 (76%) survey respondents, 57% were psychiatrists and 40% generalists. On a scale of 1 (very poor) to 7 (superlative), the overall training rated a mean of 5.8. The online course (5.0) rated lower than in person training components ($p < .001$) except for material that addressed the logistics of office practice. The in person patient interview received the highest rating (mean 6.3, $p < .001$). The 67% of physicians who intended to prescribe buprenorphine after the training were more likely than hesitant physicians to agree that the course provided enough information ($p < .05$) and that telephone access to experienced providers would improve their confidence ($p < .05$). Among physicians hesitant to prescribe, 41% cited lack of experience as the main barrier, with 24% concerned about induction difficulty and reimbursement. Overall, physicians preferred in person instruction and may benefit from additional experiential training and support after curriculum participation. These findings suggest important ways to overcome barriers to physicians prescribing of buprenorphine. Gunderson, E., Fiellin, D., Levin, F., Sullivan, L., and Kleber, H. Evaluation of a Combined Online and In Person Training in the Use of Buprenorphine. Subst Abuse, 27(3), pp. 39-45, 2006.

Smoking Cessation via the Internet: a Randomized Clinical Trial of an Internet Intervention as Adjuvant Treatment in a Smoking Cessation Intervention

Internet interventions for smoking cessation are ubiquitous. Yet, to date, there

are few randomized clinical trials that gauge their efficacy. To address this question, the authors performed a randomized clinical trial (N= 284, n= 140 in the treatment group, n= 144 in the control group) of an Internet smoking cessation intervention. Smokers were randomly assigned to receive either bupropion plus counseling alone, or bupropion and counseling in addition to 12 weeks of access to the Comprehensive Health Enhancement Support System for Smoking Cessation and Relapse Prevention (CHESS SCRP; a Web site which provided information on smoking cessation as well as support). It was found that access to CHESS SCRP was not significantly related to abstinence at the end of the treatment period (OR= 1.13, 95% CI 0.66-2.62) or at 6 months post quit (OR= 1.48, 95% CI 0.66-2.62). However, the number of times participants used CHESS SCRP per week was related to abstinence at both ends of treatment (OR= 1.79, 95% CI 1.25-2.56) and at the 6-month follow-up (OR= 1.59, 95% CI 1.06-2.38). Participants with access to CHESS SCRP logged in an average of 33.64 times (SD=30.76) over the 90-day period of access. Rates of CHESS SCRP use did not differ by ethnicity, level of education or gender (all p>.05). In sum, results suggest that participants used CHESS SCRP frequently and that CHESS SCRP use was related to success in smoking cessation. Japuntich, S., Zehner, M., Smith, S., Jorenby, D., Valdez, J., Fiore, M., Baker, T., and Gustafson, D. Smoking Cessation via the Internet: a Randomized Clinical Trial of an Internet Intervention as Adjuvant Treatment in a Smoking Cessation Intervention. Nicotine Tob Res, 8 Suppl 1, pp. S59-S67, 2006.

Mechanisms of Prescription Drug Diversion Among Drug-Involved

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

Depression Predicts Smoking Early but Not Late in a Quit Attempt

This study examined the relationship between a history of depression, and smoking after a quit attempt. A total of 677 smokers participating in a randomized smoking cessation trial (Smith et al., 2001), for this study they provided recent data on current depression, depression history, and

depression-related measures and smoking at 1 week and 6 months after a quit date. Depression history predicted smoking at 1 week postquit but not at 6 months postquit. Smoking during the first week was not predictive of smoking at 6 months in those with a history of depression but was predictive among those with no history of depression. Prediction models including depression history and depression-related measures (e.g., negative affect, negative cognitive style) showed that depression history was a powerful predictor of smoking early in the quit attempt. Japuntich, S., Smith, S., Jorenby, D., Piper, M., Fiore, M., and Baker, T. Depression Predicts Smoking Early but Not Late in a Quit Attempt. Nicotine Tob Res, 9(6), pp. 677-686, 2007.

Evidence-Based Treatment for Drug-Involved Adult Offenders

This study was designed to estimate the extent and organizational correlates of evidence-based practices (EBPs) in correctional facilities and community-based substance abuse treatment programs that manage drug-involved adult offenders. The authors' surveyed correctional administrators and treatment program directors affiliated with a national sample of 384 criminal justice and community-based programs providing substance abuse treatment to adult offenders in the United States in 2004. Correctional administrators reported the availability of up to 13 specified EBPs, and treatment directors up to 15. The sum total of EBPs indicates their extent. Linear models were used to estimate the extent of EBPs on variables measuring structure and leadership, culture and climate, administrator attitudes, and network connectedness of the organization. The authors found that most programs offer fewer than 60% of the specified EBPs to drug-involved offenders. In multiple regression models, offender treatment programs that provided more EBPs were community based, accredited, and network connected, with a performance-oriented, nonpunitive culture, more training resources, and leadership with a background in human services, a high regard for the value of substance abuse treatment, and an understanding of EBPs. The authors felt that this study supports the contention that the use of EBPs among facility- and community-based programs that serve drug-involved adult offenders has room for improvement. Initiatives to disseminate EBPs might target these institutional and environmental domains, but further research is needed to determine whether such organization interventions can promote the uptake of EBPs. Friedmann, P., Taxman, F., and Henderson, C. Evidence-Based Treatment Practices for Drug-Involved Adults in the Criminal Justice System. J Subst Abuse Treat, 32(3), pp. 267-277, 2007.

National Criminal Justice Treatment Practices Survey: Methods and Procedures

The National Criminal Justice Treatment Practices (NCJTP) survey provides a comprehensive inquiry into the nature of programs and services provided to adult and juvenile offenders involved in the justice system in the United States. The multilevel survey design covers topics such as the mission and goals of correctional and treatment programs; organizational climate and culture for providing services; organizational capacity and needs; opinions of administrators and staff regarding rehabilitation, punishment, and services provided to offenders; treatment policies and procedures; and working relationships between correctional and other agencies. The methodology generates national estimates of the availability of programs and services for offenders. This article details the methodology and sampling frame for the NCJTP survey, response rates, and survey procedures. Limitations of the survey methods are also discussed. Taxman, F., Young, D., Wiersema, B., Rhodes, A., and Mitchell, S. The National Criminal Justice Treatment Practices Survey: Multilevel Survey Methods and Procedures. J Subst Abuse Treat, 32(3), pp. 225-238, 2007.

Organizational Context of Effective Drug Treatment Practices for Juvenile Offenders

This study examined the extent to which organizational context predicted use of consensus-based elements of effective substance abuse treatment practices with juvenile offenders. Data was obtained as part of the National Criminal Justice Treatment Practices Survey, conducted as part of the Criminal Justice Drug Abuse Treatment Studies. Surveys were conducted with directors of substance abuse treatment programs located in residential facilities (institutional sample) or directors of community-based treatment agencies providing services to adolescents in their home communities (community sample). The two settings differed significantly in the number and types of effective practices they were using. Community programs were more likely to have staff qualified to deliver substance abuse treatment, involve families in treatment, and assess their treatment outcomes. In contrast, institutional programs were more likely to provide comprehensive services. Resources dedicated to training, internal support for new programming, and network connectedness with non-criminal-justice facilities were associated with greater use of effective practices. These findings highlight the importance of establishing corrections-community partnerships designed to promote continuity of care for juvenile offenders. Henderson, C., Young, D., Jainchill, N., Hawke, J., Farkas, S., and Davis, R. Program Use of Effective Drug Abuse Treatment Practices for Juvenile Offenders. J Subst Abuse Treat, 32(3), pp. 279-290, 2007.

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

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

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

Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) in rural America has been described as an epidemic, and the HIV prevalence rate among criminal justice populations is higher than the general population. Thus, criminally involved populations in Southern rural areas are at elevated risk for contracting HIV because of drug and sexual practices; however, little is known about HIV/AIDS in the fastest growing criminal justice population - probationers. This study examined possible explanations for the lack of HIV seropositivity found in a purposive sample of rural probationers. Data were examined from 800 felony probationers from 30 counties in

Kentucky's Appalachian region. Measures included HIV prevalence within the 30 counties, migration patterns, HIV knowledge, substance use, and sexual risk behaviors. These probationers had a high level of HIV knowledge, reported minimal injection drug use, practiced serial monogamy, and reported minimal engagement in transactional sex. However, these probationers also reported negligible condom use, and injection drug users shared needles and works. Findings suggest the importance of developing programs targeting safe sex practices in rural areas. Oser, C.B., Smiley McDonald, H.M., Havens, J.R., Leukefeld, C.G., Webster, J.M., and Cosentino-Boehm, A.L. Lack of HIV Seropositivity Among a Group of Rural Probationers: Explanatory Factors. J Rural Health, 22(3), pp. 273-275, 2006.

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 researchers 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. The authors' 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.

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.

The Role of African-American Clergy in Providing Informal Services to Drug Users in the Rural South: Preliminary

Ethnographic Findings

To date, no ethnographic studies of the role of African-American clergy in providing informal services to drug users in the rural South have been reported. The researchers conducted qualitative interviews with 15 African-American ministers and 26 African-American drug users in Arkansas' Mississippi River Delta region to explore this issue. All drug users reported significant religiosity, and 9 had discussed drug problems with clergy. Every minister had provided assistance to at least one drug user or his/her family during the previous year, including direct counseling, referrals to treatment programs, aiding negotiations with formal institutions, and providing for basic needs. Ministers stated that clergy are not well-prepared to address drug problems, and most acknowledged a need for professional training. They also discussed barriers to education. The findings contribute to understanding rural informal drug treatment resources. It is suggested that professional treatment providers should investigate the potential benefits of improving outreach efforts to assist African-American ministers who are engaged in drug abuse issues. Sexton, R.L., Carlson, R.G., Siegal, H.A., and Leukefeld, C.G. The Role of African-American Clergy in Providing Informal Services to Drug Users in the Rural South: Preliminary Ethnographic Findings. J Ethn Subst Abuse, 5(1), pp. 1-21, 2006.

Organizational Effects on HIV Testing in Corrections

This study compares the provision of HIV testing in a nationally representative sample of correctional agencies and community-based substance abuse treatment programs and identifies the internal organizational-level correlates of HIV testing in both organizations. Data are derived from the administrator/director survey included in the Criminal Justice Drug Abuse Treatment Study's' National Criminal Justice Treatment Practices Survey. Using an organizational diffusion theoretical framework, organizational characteristics were examined for their relationship to HIV testing in correctional agencies and treatment programs. Administrators/directors were asked: "Is HIV/AIDS testing offered to clients at your facility/location?" 49%-50% of both correctional and treatment programs conducted HIV testing. Organizational correlates were more predictive of HIV testing in correctional agencies, in multivariate logistic regression analyses. Specifically, larger correctional agencies, those with more financial resources, and those with more training and development were more likely to test. At the same time, correctional agencies with administrators with more education, and with greater systems integration with the judiciary, were less likely to test. In community treatment programs for offenders, only program size was related to testing, with larger programs more likely to test. One implication is that staff training is likely to be effective in increasing HIV testing in corrections. Oser, C., Tindall, M., and Leukefeld, C. HIV Testing in Correctional Agencies and Community Treatment Programs: The Impact of Internal Organizational Structure. J Subst Abuse Treat, 32(3), pp. 301-310, 2007.

Organizational, but Not Client, Factors Associated with Substance Abuse Treatment Cost

This study uses data from the Alcohol and Drug Services Survey (ADSS) to estimate the statistical associations between organizational and client characteristics on per client and per day costs of outpatient substance abuse treatment. Variables examined include facility ownership, average length of stay, and visits per enrollment day, and client characteristics such as gender, age, and primary drug of abuse. The authors found several organizational characteristics were statistically significant in the model estimating cost per episode, including log of point prevalence client count (-0.53, $p<.01$), log of

average length of stay (0.73, p<.01), log of visits per enrollment day (0.45, p<.01), log of labor cost index (0.50, p<.01), proportion of counselor time spent in direct counseling (-0.52, p<.01), and location outside a metropolitan area (-0.19. p<.05). None of the client variables are statistically significant in this model. These findings suggest there exists increasing returns to scale in outpatient substance abuse treatment indicating that mergers of substance abuse treatment programs may be economically beneficial. Beaston-Blaakman, A., Shepard, D., Horgan, C., and Ritter, G. Organizational and Client Determinants of Cost in Outpatient Substance Abuse Treatment. J Ment Health Policy Econ, 10(1), pp. 3-13, 2007.

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

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

When Interaction Terms are Correlated, the Power Needed to Detect Mediated Moderation can be Problematic

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

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Clinical Trials Network Research

Health Services for HIV/AIDS, HCV, and Sexually Transmitted Infections in Substance Abuse Treatment Programs

The National Drug Abuse Treatment Clinical Trials Network conducted this study to determine the availability of and factors associated with infection-related health services in substance abuse treatment settings. In a cross-sectional descriptive design, state policies, reimbursement for providers, state level of priority, and treatment program characteristics were studied via written surveys of administrators of substance abuse treatment programs and of state health and substance abuse departments. Data from health departments and substance abuse agencies of 48 states and from 269 substance abuse treatment programs revealed that human immunodeficiency virus/acquired immunodeficiency syndrome-related services are more frequent than hepatitis C virus or sexually transmitted infection-related services, and that nonmedical services are more frequent than medical services. While the availability of infection-related health services is associated with medical staffing patterns, addiction pharmacotherapy services, and state priorities, reimbursement was the most significant determining factor. These findings suggest that greater funding of these health services in substance abuse treatment settings, facilitated by supportive state policies, represents an effective response to the excess morbidity and mortality of these substance use-related infections. Brown, Jr, L.S., Kritz, S., Goldsmith, R.J., Bini, E.J., Robinson, J., Alderson, D., and Rotrosen, J. Health Services for HIV/AIDS, HCV, and Sexually Transmitted Infections in Substance Abuse Treatment Programs. Public Health Reports, 122(4), pp. 441-451, July-August 2007.

AIDS Research in the NIDA Clinical Trials Network: Emerging Results

Prevention and treatment of HIV/AIDS among drug users continue to be vexing problems. Scientifically validated interventions have been developed to prevent and treat HIV/AIDS among substance users. The Clinical Trials Network (CTN) of the National Institute on Drug Abuse (NIDA) is conducting multi-site clinical trials, with emerging results that address both prevention and treatment of HIV/AIDS. This is a report of preliminary results from several of those trials, presented at a workshop of the College on Problems of Drug Dependence. Lawrence Brown surveyed over 120 CTN clinics and reports on the state of the clinics in treating HIV/AIDS and other infectious diseases. Robert Booth summarized preliminary data from over 600 participants in a multi-site trial of HIV and hepatitis C virus (HCV) interventions in drug detoxification settings. Donald Calsyn reported preliminary results from an effectiveness trial of a gender-specific, action-oriented, safer-sex group intervention for 575 men in drug treatment programs. Susan Tross reported on a similar study focusing on

515 women in 12 clinics. Yong Song presented the perspective of treatment programs in conducting clinical trials. Jacques Normand added comments from the perspective of the Director of the NIDA AIDS research program. Sorensen, J.L., Brown, L., Calsyn, D., Tross, S., Booth, R.E., Song, Y.,and Normand, J. AIDS Research in the NIDA Clinical Trials Network: Emerging Results. News & Views Section Drug Alcohol Depend. 89(2-3), pp. 310-313, 2007.

Issues in Designing and Implementing a Spanish-Language Multi-Site Clinical Trial

To address at least in part health disparities in Hispanic populations, the NIDA Clinical Trials Network implemented the first multi-site randomized clinical trial of substance abuse treatment conducted entirely in Spanish. This trial was intended to evaluate the effectiveness of Motivational Enhancement Therapy in a diverse population of Hispanics. In the conduct of this trial, several barriers to the successful implementation of a Spanish-language multi-site trial had to be addressed, including the appropriate translation of assessment instruments, shortage of appropriately trained Spanish-speaking clinical staff, and barriers to recruitment and retention of this population. To encourage similar research, strategies are described that were developed by the study team to meet these challenges. Suarez-Morales, L., Matthews, J., Martino, S., Ball, S.A., Rosa, C., Farentinos, C., Szapocznik, J., and Carroll. K.M. (the MET Spanish Team). Issues in Designing and Implementing a Spanish-Language Multi-Site Clinical Trial. Am J Addict. 16(3), pp. 206-215, 2007.

Organizational Readiness for Change and Opinions toward Treatment Innovations

Program administrators and staff in treatment programs participating in the National Drug Abuse Treatment Clinical Trials Network completed surveys to characterize participating programs and practitioners. A two-level random-effects regression model assessed the influence of Organizational Readiness for Change (ORC) and organizational attributes on opinions toward the use of four evidence-based practices (manualized treatments, medication, integrated mental health services, and motivational incentives) and practices with less empirical support (confrontation and noncompliance discharge). The ORC scales suggested greater support for evidence-based practices in programs where staff perceived more program need for improvement, better Internet access, higher levels of peer influence, more opportunities for professional growth, a stronger sense of organizational mission, and more organizational stress. Support for confrontation and noncompliance discharge, in contrast, was strong when staff saw less opportunity for professional growth, weaker peer influence, less Internet access, and perceived less organizational stress. The analysis provides evidence of the ORC's utility in assessing agency strengths and needs during the implementation of evidence-based practices. Fuller, B.E., Rieckmann, T., Nunes, E.V., Miller, M., Arfken, C., Edmundson, E., and McCarty, D. Organizational Readiness for Change and Opinions Toward Treatment Innovations. Journal of Substance Abuse Treatment. 33(2), pp. 183-192, September 2007.

Site Matters: Multisite Randomized Trial of Motivational Enhancement Therapy in Community Drug Abuse Clinics

This study examined the effectiveness of motivational enhancement therapy (MET) in comparison with counseling as usual (CAU) for increasing retention and reducing substance use in a multisite randomized clinical trial. Participants were 461 outpatients treated by 31 therapists within 1 of 5 outpatient substance abuse programs. There were no retention differences between the 2 brief intervention conditions. Although both 3-session interventions resulted in

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reductions in substance use during the 4-week therapy phase, MET resulted in sustained reductions during the subsequent 12 weeks whereas CAU was associated with significant increases in substance use over this follow-up period. This finding was complicated by program site main effects and higher level interactions. MET resulted in more sustained substance use reductions than CAU among primary alcohol users, but no difference was found for primary drug users. An independent evaluation of session audiotapes indicated that MET and CAU were highly and comparably discriminable across sites. Ball, S.A., Martino, S., Nich, C., Frankforter, T. L., Van Horn, D., Crits-Christoph, P., Woody, G.E., Obert, J.L., Farentinos, C., and Carroll, K.M. Site Matters: Multisite Randomized Trial of Motivational Enhancement Therapy in Community Drug Abuse Clinics. J Consult Clin Psychol. 75(4), pp. 556-567, 2007.

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Research Findings - International Research

Research Publications by International Program Alumni

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

Former NIDA INVEST Drug Abuse Research Fellows

Drug Use Opportunities and the Transition to Drug Use among Adolescents from the Mexico City Metropolitan Area

Benjet, C., Borges, G., Medina-Mora, M.E., Blanco, J., Zambrano, J., Orozco, R., Fleiz, C., Rojas, E. Drug Alcohol Depend. 2007 Mar 21; [Epub ahead of print]

INVEST Fellow: Guilherme Borges, Mexico, 1997-1998

The earliest stage of drug involvement is being presented with the opportunity to use drugs. During adolescence these opportunities increase. Because of the scarcity of data for the Mexican population, the aim is to estimate the prevalence of drug use opportunities among Mexican adolescents, the prevalence of drug use among those who were presented with the opportunity, and the socio-demographic correlates of both. A multistage probability survey was carried out among 12-17 year olds from Mexico City. Adolescents were administered the adolescent version of the World Mental Health Composite International Diagnostic Interview. The response rate was 71% (n=3005). Descriptive and logistic regression analyses were performed considering the multistage and weighted sample design. Twenty-nine percent have had the opportunity to try illicit drugs; of those presented with an opportunity, 18% have done so. Males, older adolescents, school drop-outs, and those whose parent has had drug problems are more likely to have been exposed to drug use opportunities while more religious adolescents are less likely. Given the chance to try drugs, older adolescents and school drop-outs are more likely to do so and those with high parental monitoring and religiosity are less likely. These results suggest that less substance use among females in Mexico may be due in part to fewer opportunities to use since females were equally likely to use drugs given the opportunity. Given the increase in opportunity among older adolescents, preventive efforts should start by age 12 and with special attention to adolescents who have dropped out of school. PMID: 17382489 [PubMed - as supplied by publisher]

Mental Disorders among English-speaking Mexican Immigrants to the US Compared to a National Sample of Mexicans

Breslau, J., Aguilar-Gaxiola, S., Borges, G., Castilla-Puentes, R.C., Kendler, K.S., Medina-Mora M.E., Su, M., Kessler, R.C.. Psychiatry Res. 2007 Mar 13; [Epub ahead of print].

INVEST Fellow: Guilherme Borges, Mexico, 1997-1998

Understanding of the relationship between immigration and mental health can be advanced by comparing immigrants pre- and post-immigration with

residents of the immigrants' home countries. DSM-IV anxiety and mood disorders were assessed using identical methods in representative samples of English-speaking Mexican immigrants to the US, a subsample of the US National Comorbidity Survey Replication (NCSR), and Mexicans, the Mexican National Comorbidity Survey (MNCS). Retrospective reports of age of onset of disorders and, in the immigrant sample, age of immigration were analyzed to study the associations of pre-existing mental disorders with immigration and of immigration with the subsequent onset and persistence of mental disorders. Pre-existing anxiety disorders predicted immigration (OR=3.0; 95% CI 1.2-7.4). Immigration predicted subsequent onset of anxiety (OR=1.9; 95% CI 0.9-3.9) and mood (OR=2.3; 95% CI 1.3-4.0) disorders and persistence of anxiety (OR=3.7 95% CI 1.2-11.2) disorders. The results are inconsistent with the "healthy immigrant" hypothesis (that mentally healthy people immigrate) and partly consistent with the "acculturation stress" hypothesis (i.e., that stresses of living in a foreign culture promote mental disorder). Replication and extension of these results in a larger bi-national sample using a single field staff are needed.

Mental Disorders among Adults with Asthma: Results from the World Mental Health Survey

Scott, K.M., Von Korff, M., Ormel, J., Zhang, M.Y., Bruffaerts, R., Alonso, J., Kessler, R.C, Tachimori, H., Karam, E., Levinson, D., Bromet, E.J., Posada-Villa, J., Gasquet, I., Angermeyer, M.C., Borges, G., de Girolamo, G., Herman, A., and Haro, J.M. Gen Hosp Psychiatry. Mar-Apr;29(2), pp.123-133, 2007.
INVEST Fellow: Guilherme Borges, Mexico, 1997-1998
Research objectives were (a) to determine which common mental disorders are associated with asthma in the general population after controlling for age and sex, and (b) to assess whether the associations of mental disorders with asthma are consistent across diverse countries. Eighteen population surveys of household-residing adults were carried out in 17 countries (N=85,088). Mental disorders were assessed with the Composite International Diagnostic Interview 3.0, a fully structured diagnostic interview. The disorders considered here are 12-month anxiety disorders (generalized anxiety disorder, panic disorder/agoraphobia, posttraumatic stress disorder and social phobia), depressive disorders (dysthymia and major depressive disorder) and alcohol use disorders (abuse and dependence). Asthma was ascertained by self-reports of lifetime diagnosis among a subsample (n=42,697). Pooled estimates of age-adjusted and sex-adjusted odds of mental disorders among persons with asthma relative to those without asthma were 1.6 [95% confidence interval (95% CI)=1.4, 1.8] for depressive disorders, 1.5 (95% CI=1.4, 1.7) for anxiety disorders and 1.7 (95% CI=1.4, 2.1) for alcohol use disorders. This first cross-national study of the relationship between asthma and mental disorders confirms that a range of common mental disorders occurs with greater frequency among persons with asthma. These results attest to the importance of clinicians in diverse settings being alert to the co-occurrence of these conditions.

The Price of Seizure Control: Dynorphins in Interictal and Postictal Psychosis

Bortolato, M., and Solbrig, M.V. Psychiatry Res. 2007 Mar 27; [Epub ahead of print]
INVEST Fellow: Marco Bortolato, Italy, 2004-2005
Postictal and interictal psychoses are relatively common complicating factors in the clinical course of epilepsy, yet their neurobiological substrates are poorly understood. Recent evidence shows that kappa opioid receptor (KOR) activation elicits anticonvulsant and psychotomimetic effects. In view of this background, here we introduce the hypothesis that epilepsy-related psychoses may partially result from excessive hippocampal dynorphin release and kappa opioid receptor overstimulation aimed at seizure control.

An 18-norspirostanol Saponin with Inhibitory Action against COX-2

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Production from the Underground Part of Trillium Tschonoskii
Wang, J., Zou, K., Zhang, Y., Liu, C., Wu, J., Zhou, Y., Dan, F., and Zhang, Y.
Chem Pharm Bull (Tokyo). Apr;55(4), pp. 679-681, 2007
INVEST Fellow: Chaung Liu, China, 2000-2001
A novel 18-norspirostanol saponin (1), along with Trillenoside A (2), was obtained from the underground parts of Trillium tschonoskii MAXIM., collected in Shennongjia Forest District, China. Based on the chemical and spectroscopic evidences, their structures were determined as shown in Fig. 1. 1 and 2 displayed marked inhibitory action towards COX-2 production in macrophagocytes of the mouse abdominal cavity stimulated by LPS at 10 microg/ml.

A New Method for Screening and Determination of Diuretics by On-line CE-ESI-MS
Lu, M., Tong, P., Xiao, H., Xia, S., Zheng, X., Liu, W., Zhang, L., and Chen, G.
Electrophoresis. 2007 Mar 19; [Epub ahead of print]
INVEST Fellow: Lan Zhang, China, 2004-2005
A rapid, high-resolution and effective new method for analyzing 12 diuretics by CE-ESI-MS was established in this paper. Ten diuretics (except two neutral compounds) could be fast separated by CE with a DAD at 214 nm with a 20 kV voltage within 6 min, using a 50 mum id and 48.5 cm effective length uncoated fused-silica capillary in a 40 mM ammonium formate buffer (pH 9.40). CE was coupled to the mass spectrometer applying an orthogonal electrospray interface with a triple-tube sheath liquid arrangement. The sheath liquid was composed of isopropanol-water (1:1 v/v) containing 30 mM acetic acid with a flow rate of 4 muL/min. Mass spectrum was employed in the positive mode and both full scan mode and SIM scan mode were utilized. All 12 diuretics could be detected and confirmed by MS in a single analysis. Under optimized conditions, LODs for the 12 diuretics were in the range of 0.13-2.7 micromol/L at an S/N of 3, and the correlation coefficients R(2) were between 0.9921 and 0.9978. The RDSs (n = 5) of the method was 0.24-0.94 % for migration times and 1.6-8.8 % for peak areas. The recoveries of spiked samples of 12 diuretics were between 72.4% and 118%. The real urine samples were injected directly for analysis, with only simple filtration through a 0.22 microm membrane filter in order to remove solid particles, which may cause capillary blockage. Based on the migration times and characteristic ions, the diuretics in urine samples were detected successfully. This CE-ESI-MS method for analyzing diuretics will hopefully be applied to doping control.

Risk for Psychiatric Disorder among Immigrants and their US-born Descendants: Evidence from the National Comorbidity Survey Replication
Breslau, J., Aguilar-Gaxiola, S., Borges, G., Kendler, K.S., Su, M., and Kessler, R.C., J Nerv Ment Dis. Mar;195(3), pp. 189-195, 2007.
INVEST Fellow: Guilherme Borges, Mexico, 1997-1998
Although previous research has consistently documented that immigrants to the United States have better mental health than US natives, little is known about why this difference occurs. DSM-IV anxiety, mood, impulse control, and substance use disorders were assessed in a nationally representative survey of the US household population, the National Comorbidity Survey Replication. Differences in risk for disorder between immigrants (N = 299) and 5124 natives (N = 5124) were examined using discrete time survival models. Differences were estimated by generation, age of immigration, and duration of residence in the United States. Immigrants had lower lifetime risk of disorder than natives (OR = 0.7; 95% CI, 0.5-0.9). Risk was equally large for natives who were children of immigrants as for natives of subsequent generations. For mood and impulse control disorders, risk equal to that of natives was also found among immigrants who arrived in the United States as children (12 years of age or younger). Immigrants had lower risk than natives prior to arrival in the United States, but there was a trend toward equalization of risk with longer duration of residence in the United States. Differences in risk for

disorder emerge within a single generation following immigration, consistent with a strong effect of environmental factors on changes in risk among immigrant populations. This pattern is consistent with either of two causal processes, one involving early socialization in the United States and the other involving postmigration experiences among immigrants who arrive in the United States as adults.

Post-mortem Stability and Redistribution of Carbohydrate-deficient Transferrin (CDT)

Rainio, J., De Paoli, G., Druid, H., Kauppila, R., De Giorgio, F., Bortolotti, F., and Tagliaro, F. Forensic Sci Int. 2007 Apr 30; [Epub ahead of print].

INVEST Fellow: Henrik Druid, Sweden, 2000-2001

Post-mortem diagnosis of chronic alcohol abuse is a challenge for forensic experts due to the lack of pathognomonic morphological findings and often also inadequate background information. Objective methods demonstrating chronic excessive alcohol consumption would therefore be a useful tool for forensic pathologists. In clinical practice, several markers of chronic alcohol abuse have recently been introduced, among which carbohydrate-deficient transferrin (CDT) is the most accepted, but the use of these markers in autopsy has not yet been established. The authors examined post-mortem stability and possible post-mortem redistribution of CDT and compared two analytical methods, capillary zone electrophoresis and high-performance liquid chromatography. According to their results, CDT remains stable for an appreciable time after death. The results further indicate that CDT is not subject to major post-mortem redistribution.

P2X(7)-related Modulation of Pathological Nociception in Rats

McGaraughty, S., Chu, K.L., Namovic, M.T., Donnelly-Roberts, D.L., Harris, R.R., Zhang, XF., Shieh, C.C., Wismer, C.T., Zhu, C.Z., Gauvin, D.M., Fabiyi, A.C., Honore, P., Gregg, R.J., Kort, M.E., Nelson, D.W., Carroll, W.A., Marsh, K., Faltynek, C.R., and Jarvis, M.F.

Neuroscience. 2007 May 1; [Epub ahead of print]

INVEST Fellow: Steven McGaraughty, Canada, 1995-1996

Growing evidence supports a role for the immune system in the induction and maintenance of chronic pain. ATP is a key neurotransmitter in this process. Recent studies demonstrate that the glial ATP receptor, P2X(7), contributes to the modulation of pathological pain. To further delineate the endogenous mechanisms that are involved in P2X(7)-related antinociception, the authors utilized a selective P2X(7) receptor antagonist, A-438079, in a series of in vivo and in vitro experiments. Injection of A-438079 (10-300 mumol/kg, i.p.) was anti-allodynic in three different rat models of neuropathic pain and it attenuated formalin-induced nocifensive behaviors. Using in vivo electrophysiology, A-438079 (80 mumol/kg, i.v.) reduced noxious and innocuous evoked activity of different classes of spinal neurons (low threshold, nociceptive specific, wide dynamic range) in neuropathic rats. The effects of A-438079 on evoked firing were diminished or absent in sham rats. Spontaneous activity of all classes of spinal neurons was also significantly reduced by A-438079 in neuropathic but not sham rats. In vitro, A-438079 (1 muM) blocked agonist-induced (2,3-O-(4-benzoylbenzoyl)-ATP, 30 muM) current in non-neuronal cells taken from the vicinity of the dorsal root ganglia. Furthermore, A-438079 dose-dependently (0.3-3 muM) decreased the quantity of the cytokine, interleukin-1beta, released from peripheral macrophages. Thus, ATP, acting through the P2X(7) receptor, exerts a wide-ranging influence on spinal neuronal activity following a chronic injury. Antagonism of the P2X(7) receptor can in turn modulate central sensitization and produce antinociception in animal models of pathological pain. These effects are likely mediated through immuno-neural interactions that affect the release of endogenous cytokines.

Prophylactic Role for Complementary and Alternative Medicine in Perinatal Programming of Adult Health

Hodgson, D.M., Nakamura, T., and Walker, A.K. Forsch Komplementarmed.

Apr;14(2), pp. :92-101, 2007. Epub 2007 Apr 23
INVEST Fellow: Tamo Nakamura, Australia, 2002-2003
The health status of an individual in adulthood is proposed to be determined by events occurring in the prenatal and early postnatal period. A common early life event proven to have long lasting effects on the developing fetus is stress, including pain. Exposure of fetal and neonatal infants to repetitive psychological (e.g., maternal stress) or physiological (e.g., pain, infection, and noise) stress during this period is proposed to alter mechanisms involved in the regulation of stress, immunological maturation, pain perception, and cognition. Such changes, which persist into adulthood, may occur via alterations in the development of the hypothalamic-pituitary-adrenal (HPA) axis. This process is typically referred to as 'perinatal programming'. Ontogenic alterations in the development of the HPA-axis have been related to a number of adult pathologies such as cardiovascular disease, type 2 diabetes, asthma, as well as psychopathologies such as anxiety and depression. In this review, the effectiveness of complementary and alternative medicine (CAM), such as music, dietary supplements, massage and aromatherapy, in reducing perinatal stress in mothers and infants is examined. An emphasis is placed on these therapies as preventative measures which may be of value to individuals at risk of developing disease profiles associated with the consequences of adverse perinatal programming. The widening interest in perinatal programming and CAM suggests the potential for CAM to become a valuable tool in offsetting negative adult health outcomes resulting from perinatal programming associated with adverse gestational early life environments.

Parenting Interventions for Drug-Dependent Mothers and Their Young Children: The Case for an Attachment-Based Approach
Suchman, N., Pajulo, M., Decoste, C., and Mayes, L. Fam Relat. Apr; 55(2), pp. 211-226, 2006.
INVEST Fellow: Marjaterttu Pajulo, Finland, 2003-2004
Maternal substance abuse is the most common factor involved when children come to the attention of the child welfare system. Although there is a clear need for clinical trials to evaluate parenting interventions for drug-dependent women, few studies to date have systematically examined the efficacy of interventions for this population. The authors first review six published reports of outpatient interventions that aimed to enhance the caregiving skills of substance-abusing mothers caring for children between birth and 5 years of age. After discussing implications of these preliminary studies, they then describe an attachment-based intervention that addresses these implications and has demonstrated preliminary feasibility in a pilot trial.

Chinese Herbal Medicine for Schizophrenia: Cochrane Systematic Review of Randomized Trials
Rathbone, J., Zhang, L., Zhang, M., Xia, J., Liu, X., Yang, Y., and Adams, C.E. Br J Psychiatry. May 190, pp.379-384, 2007.
INVEST Fellow: Lan Zhang, China, 2004-2005
Chinese herbal medicine has been used to treat millions of people with schizophrenia for thousands of years. The aim of this study was to evaluate Chinese herbal medicine as a treatment for schizophrenia. A systematic review of randomized controlled trials (RCTs) in which seven trials were included was examined. Most studies evaluated Chinese herbal medicine in combination with Western antipsychotic drugs; in these trials results tended to favor combination treatment compared with antipsychotic alone (Clinical Global Impression ;not improved/worse' n=123, RR=0.19, 95% CI 0.1-0.6, NNT=6,95% CI 5-11; n=109, Brief Psychiatric Rating Scale ;not improved/worse' RR=0.78,95% CI 0.5-1.2; n=109, Scale for the Assessment of Negative Symptoms ;not improved/worse' RR=0.87,95% CI 0.7-1.2; n=109, Scale for the Assessment of Positive Symptoms ;not improved/worse' RR=0.69,95% CI 0.5-1.0, NNT=6 95% CI 4-162). Medium-term study attrition was significantly less for people allocated the herbal/antipsychotic mix (n=897, four RCTs, RR=0.34,95% CI 0.2-0.7, NNT=23,95% CI18-43). Results suggest that combining Chinese

herbal medicine with antipsychotics is beneficial.

Drug Dependence in Adolescents 1978-2003: A Clinical-based Observation from North India

Saluja, B.S, Grover, S., Irpati, A.S., Mattoo, S.K., and Basu, D. Indian J Pediatr. May; 74(5), pp. 455-458, 2007.
INVEST Fellow: Debasish Basu, India, 2001-2002
The objective of this work was to study the demographic and clinical profile of adolescent subjects (< or =18 yr) presenting to a state-funded drug de-addiction centre in north India. Data on demographic and clinical features were extracted from available case notes of adolescent patients who presented to the centre during 1978-2003 (n=85). Many adolescents came from nuclear family (63.5%), of urban background (83.5%) and were school dropouts (54.1%). Mean age-at-first-use of the primary substance was 14.8 yr and mean age at first presentation was 17 yr. The most commonly used primary class of substance was opioids (76.2%) and the most commonly used opioid was heroin (36.5%). More than half of the subjects (54.2%) were also nicotine dependent at the time of presentation. The most common reason for starting the use of drugs was curiosity (78.8%). About one-fifth (21.2%) of the subjects indulged in high-risk behavior such as having sexual intercourse with multiple sexual partners. Nearly half of the subjects had positive family history of either drug dependence (40.2%) or psychiatric disorder (5.5%). The results suggest that the development of substance dependence in children and adolescents is a combination of familial and social vulnerability factors, including the drug culture of the social milieu.

Psychiatric Disorders in Mexico: Lifetime Prevalence in a Nationally Representative Sample

Medina-Mora, M.E., Borges, G., Benjet, C., Lara, C., and Berglund, P. Br J Psychiatry. Jun; 190, pp. 521-528, 2007. INVEST Fellow: Guilherme Borges, Mexico, 1997-1998 No national data on lifetime prevalence and risk factors for DSM-IV psychiatric disorders are available in Mexico. The aim of this study was to present data on lifetime prevalence and projected lifetime risk, age at onset and demographic correlates of DSM-IV psychiatric disorders assessed in the Mexican National Comorbidity Survey. The survey was based on a multistage area probability sample of non-institutionalized people aged 18-65 years in urban Mexico. The World Mental Health Survey version of the Composite International Diagnostic Interview was administered by lay interviewers. Of those surveyed, 26.1% had experienced at least one psychiatric disorder in their life and 36.4% of Mexicans will eventually experience one of these disorders. Half of the population who present with a psychiatric disorder do so by the age of 21 and younger cohorts are at greater risk for most disorders. These results suggest an urgent need to re-evaluate the resources allocated for the detection and treatment of psychiatric illnesses in Mexico.

Body Mass Index and the Prevalence of Metabolic Syndrome among Children and Adolescents in Two Mexican Populations

Halley Castillo, E., Borges, G., Talavera, J.O., Orozco, R., Vargas-Alemanm C., Huitron-Bravom G., Diaz-Montiel, J.C., Castanon, S., and Salmeron, J. J Adolesc Health. Jun; 40(6), pp. 521-526, 2007. Epub 2007 Mar 21, 2007.
INVEST Fellow: Guilherme Borges, Mexico, 1997-1998 The purpose of this study was to report the prevalence of metabolic syndrome (MS) among children and adolescents living in central Mexico, and its association with body mass index (BMI). In a sample of 1366 subjects from 7 to 24-years-old, a self-administered questionnaire was used to determined demographic characteristics. The definition of pediatric MS was determined using analogous criteria to Adult Treatment Panel III (ATPIII) as > or = 3 of the following: concentration of triglycerides > or = 100 mg/dL, HDL cholesterol < 45 mg/dL for males and < 50 mg/dL for females, waist circumference > or = 75th percentile (sex specific), glucose concentration > or = 110 to < 126 mg/dL, and systolic or diastolic blood pressure > or = 90th percentile (age, height, and

sex specific). Most of the sample was in the 10-14- (32.4%) and the 15-19-year (35.4%) age groups, mostly females (57%), and 31% of this young sample was overweight (mean BMI = 21.6 kg/m2). About 1 in every 5 participants had full criteria for MS (19.2%, 95% confidence interval [CI]: 16.4-22.1 among females, and 20.2%, 95% CI: 17.1-23.7 among males), and only 1 in every 10 was free of any MS component. The most common component was a low HDL level, observed in 85.4% of the sample. Unfavorable fat distribution, as indicated by a large waist circumference, was present in 27.9% of the sample. About 66% of those 10-14-year-olds with a large BMI were positive for MS. MS and overweight are major problems for youth in Mexico. Immediate and comprehensive actions at home and schools are needed if Mexico wants to avoid the heavy burden that this disorder will have for its population in the near future.

Smoking and Suicidal Behaviors in the National Comorbidity Survey: Replication

Kessler, R.C., Berglund, P.A., Borges, G., Castilla-Puentes, R.C., Glantz, M.D., Jaeger, S.A., Merikangas, K.R., Nock, M.K., Russo, L.J., and Stang, P.E. J Nerv Ment Dis. May;195(5), pp. 369-377, 2007.

INVEST Fellow: Guilherme Borges, Mexico, 1997-1998

Controversy exists about the role of mental disorders in the consistently documented association between smoking and suicidal behavior. This controversy is addressed here with data from the nationally representative National Comorbidity Survey-Replication (NCS-R). Assessments were made of 12-month smoking, suicidal behaviors (ideation, plans, attempts), and DSM-IV disorders (anxiety, mood, impulse-control, and substance use disorders). Statistically significant odds ratios (2.9-3.1) were found between 12-month smoking and 12-month suicidal behaviors. However, the associations of smoking with the outcomes became insignificant with controls for DSM-IV mental disorders. Although clear adjudication among contending hypotheses about causal mechanisms cannot be made from the cross-sectional NCS-R data, the results make it clear that future research on smoking and suicidal behaviors should focus more centrally than previous research on mental disorders either as common causes, markers, or mediators.

Antidepressant-like Activity of the Fatty Acid Amide Hydrolase Inhibitor URB597 in a Rat Model of Chronic Mild Stress

Bortolato, M., Mangieri, R.A., Fu, J., Kim, J.H., Arguello, O., Duranti, A., Tontini, A., Mor, M., Tarzia, G., and Piomelli, D. Biol Psychiatry. 2007 May 16; [Epub ahead of print].

INVEST Fellow: Marco Bortolato, Italy, 2004-2005

The endocannabinoid anandamide may be involved in the regulation of emotional reactivity. In particular, it has been shown that pharmacological inhibition of the enzyme fatty acid amide hydrolase (FAAH), which catalyzes the intracellular hydrolysis of anandamide, elicits anxiolytic-like and antidepressant-like effects in rodents. Authors investigated the impact of chronic treatment with the selective FAAH inhibitor, URB597 (also termed KDS-4103), on the outcomes of the chronic mild stress (CMS) in rats, a behavioral model with high isomorphism to human depression. Daily administration of URB597 (.3 mg.kg(-1), intraperitoneal [IP]) for 5 weeks corrected the reduction in body weight gain and sucrose intake induced by CMS. The antidepressant imipramine (20 mg.kg(-1), once daily, IP) produced a similar response, whereas lower doses of URB597 were either marginally effective (.1 mg.kg(-1)) or ineffective (.03 mg.kg(-1)). Treatment with URB597 (.3 mg.kg(-1)) resulted in a profound inhibition of brain FAAH activity in both CMS-exposed and control rats. Furthermore, the drug regimen increased anandamide levels in midbrain, striatum, and thalamus. URB597 exerts antidepressant-like effects in a highly specific and predictive animal model of depression. These effects may depend on the ability of URB597 to enhance anandamide signaling in select regions of the brain.

Functional Differences in Epigenetic Modulators-Superiority of Mercaptoacetamide-Based Histone Deacetylase Inhibitors Relative to Hydroxamates in Cortical Neuron Neuroprotection Studies
Kozikowski, A.P., Chen, Y., Gaysin, A., Chen, B., D'Annibale, M.A., Suto, C.M., and Langley, B.C. J Med Chem. 2007 Jun 1; [Epub ahead of print].
INVEST Fellow: Yufeng Chen, China, 2003-2004
Authors compare the ability of two structurally different classes of epigenetic modulators, namely, histone deacetylase (HDAC) inhibitors containing either a hydroxamate or a mercaptoacetamide as the zinc binding group, to protect cortical neurons in culture from oxidative stress-induced death. This study reveals that some of the mercaptoacetamide-based HDAC inhibitors are fully protective, whereas the hydroxamates show toxicity at higher concentrations. The present results appear to be consistent with the possibility that the mercaptoacetamide-based HDAC inhibitors interact with a different subset of the HDAC isozymes [less activity at HDAC1 and 2 correlates with less inhibitor toxicity], or alternatively, are interacting selectively with only the cytoplasmic HDACs that are crucial for protection from oxidative stress.

From the Cover: A-803467, A Potent and Selective Nav1.8 Sodium Channel Blocker, Attenuates Neuropathic and Inflammatory Pain in the Rat
Jarvis, M.F., Honore, P., Shieh, C.C., Chapman, M., Joshi, S., Zhang, X.F., Kort, M., Carroll, W., Marron, B., Atkinson, R., Thomas, J., Liu, D., Krambis, M., Liu, Y., McGaraughty, S., Chu, K., Roeloffs, R., Zhong, C., Mikusa, J.P., Hernandez, G., Gauvin, D., Wade, C., Zhu, C., Pai, M., Scanio, M., Shi, L., Drizin, I., Gregg, R., Matulenko, M., Hakeem, A., Gross, M., Johnson, M., Marsh, K., Wagoner, P.K., Sullivan, J.P., Faltynek, C.R., and Krafte, D.S. Proc Natl Acad Sci U S A. May 15;104(20), pp. 8520-8525, 2007.. Epub 2007 May 2.
INVEST Fellow: Steven McGaraughty, Canada, 1995-1996
Activation of tetrodotoxin-resistant sodium channels contributes to action potential electrogenesis in neurons. Antisense oligonucleotide studies directed against Na(v)1.8 have shown that this channel contributes to experimental inflammatory and neuropathic pain. The authors report here the discovery of A-803467, a sodium channel blocker that potently blocks tetrodotoxin-resistant currents (IC(50) = 140 nM) and the generation of spontaneous and electrically evoked action potentials in vitro in rat dorsal root ganglion neurons. In recombinant cell lines, A-803467 potently blocked human Na(v)1.8 (IC(50) = 8 nM) and was >100-fold selective vs. human Na(v)1.2, Na(v)1.3, Na(v)1.5, and Na(v)1.7 (IC(50) values >or=1 microM). A-803467 (20 mg/kg, i.v.) blocked mechanically evoked firing of wide dynamic range neurons in the rat spinal dorsal horn. A-803467 also dose-dependently reduced mechanical allodynia in a variety of rat pain models including: spinal nerve ligation (ED(50) = 47 mg/kg, i.p.), sciatic nerve injury (ED(50) = 85 mg/kg, i.p.), capsaicin-induced secondary mechanical allodynia (ED(50) approximately 100 mg/kg, i.p.), and thermal hyperalgesia after intraplantar complete Freund's adjuvant injection (ED(50) = 41 mg/kg, i.p.). A-803467 was inactive against formalin-induced nociception and acute thermal and postoperative pain. These data demonstrate that acute and selective pharmacological blockade of Na(v)1.8 sodium channels in vivo produces significant antinociception in animal models of neuropathic and inflammatory pain.

Relationship Between N-acetyl-aspartate in Gray and White Matter of Abstinent Methamphetamine Abusers and their History of Drug Abuse: A Proton Magnetic Resonance Spectroscopy Study
Sung, Y.H., Cho, S.C., Hwang, J., Kim, S.J., Kim, H., Bae, S., Kim, N., Chang, K.H., Daniels, M., Renshaw, P.F., and Lyoo, I.K. Drug Alcohol Depend. Apr 17;88(1), pp. 28-35, 2007. Epub 2006 Nov 7.
INVEST Fellow: Young Hoon Sung, South Korea, 2005-2006
Altered concentrations of the brain metabolites, including N-acetyl-aspartate (NAA) and myo-inositol (MI), may indicate neurotoxicity associated with drug abuse. In this study, the authors explored differences in brain metabolites

between abstinent methamphetamine (MA) abusers and healthy comparison subjects and the associations between metabolite concentrations and clinical characteristics. Proton magnetic resonance spectroscopy (MRS) was performed on 30 abstinent MA abusers and 20 healthy comparison subjects. Two sets of MA user subgroups were defined depending on abstinence duration (greater or less than 6 months) or the total cumulative MA dose (greater or less than 100 g lifetime). NAA and other metabolites were measured in the frontal gray and white matter and compared between MA abuser groups and healthy comparison subjects. MI concentrations were higher for the MA abusers relative to healthy comparison subjects. NAA concentration was lower in frontal white matter of MA abusers with a 'large' cumulative dose relative to those with a 'small' cumulative dose and to healthy comparison subjects. Additionally, in MA abusers NAA concentrations in frontal white matter correlated inversely with the cumulative MA dose. In contrast, there was no significant difference in frontal gray matter NAA concentration among the three groups. However, frontal gray matter NAA concentrations for MA abusers correlated negatively with the total cumulative MA dose and positively with the duration of abstinence. There were no differences between the different MA user groups for MI. The current findings suggest that MA-induced metabolic alterations of frontal gray and white matter are dose-dependent, for primarily male subjects. Additionally, these findings potentially suggest that the MA-related abnormalities may, in part, recover with abstinence in gray matter, but not in the white matter regions.

Effect of Ketamine on Endotoxin-induced Septic Shock in Rats and its Mechanism

Xiao, H., Xu, H.W., Liu, H., and Zhang, L. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue. May;19(5), pp. 303-305, 2007. Chinese.

INVEST Fellow: Lan Zhang, China, 2004-2005

The objective of this research was to explore the effect of ketamine on septic shock in rat and its mechanism. Sixty SD rats were randomly divided into control group, model group and ketamine group. Septic shock was replicated by intraperitoneal injection of 20 mg/kg lipopolysaccharide (LPS). The control group was given normal saline only. In the ketamine group, the rats received intraperitoneal injection of 80 mg/kg ketamine 20 minutes before shock and 1 hour (ketamine 40 mg/kg) after shock. The survival time and survival rate were observed in each group. Serum tumor necrosis factor-alpha (TNF-alpha), myocardiac cyclic adenosine monophosphate (cAMP) were determined with radioimmunology assay, and expression of heat shock protein 70 (HSP70) was assessed by immunohistochemistry method. The survival rate was lower in the model group (0) compared with the control group (100%) and the ketamine group (70%), the differences were significant (both $P<0.05$). TNF-alpha was higher, while cAMP was lower in the model group compared with the control group and the ketamine group (all $P<0.01$). Positive expression of HSP70 in the model group was lower than the control group, while higher than the ketamine group (both $P<0.01$). There were no significant differences in TNF-alpha and cAMP between the control group and the ketamine group (both $P>0.05$). The authors conclude that serum TNF-alpha is increased and myocardiac cAMP is decreased in LPS-induced septic shock, whereas ketamine can inhibit the effect of LPS and protect myocardium against sepsis probably by stimulating the expression of myocardiac HSP70.

Value and Actuality of the Prescription Information for Therapeutic Drug Monitoring of Psychopharmaceuticals: A Comparison with the Medico-Scientific Evidence

Ulrich, S., Hiemke, C., Laux, G., Muller-Oerlinghausen, B., Havemann-Reinecke, U., Riederer, P., Zernig, G., and Baumann, P. Pharmacopsychiatry. May;40(3), pp. 121-127, 2007.

INVEST Fellow: Gerald Zernig, Austria, 1993-1994

Therapeutic drug monitoring (TDM) of psychopharmaceuticals, i.e., the assay of plasma concentrations, is a practical therapeutic application of

pharmacokinetic principles in psychiatry. The prescription information (summary of product characteristics, SPC) is provided by pharmaceutical companies according to the requirements of regulatory authorities. The present study investigated the degree of agreement of German SPCs for 48 psychopharmaceuticals with the existing medico-scientific evidence in the area of TDM. For this aim, an empirical summary score of SPC content related to TDM (SPCC (TDM)) was calculated and compared with the level of recommendation of TDM (LOR) of the AGNP-TDM expert group consensus guidelines. Considerable disagreement was found between the information on TDM in SPCs and existing medico-scientific evidence, e.g., in the case of antidepressant and antipsychotic drugs. Even for well studied compounds, such as amitriptyline and clozapine, insufficient information on TDM is included in German SPCs. Small differences existed in the TDM-related information in SPCs of generic drugs with, however, much variance between Germany, Austria and Switzerland. Generally, it must be concluded that deficits exist in the preparation of German SPCs for psychopharmaceutical drugs with respect to empirical pharmacokinetic data, i.e., TDM-relevant information. It is recommended that SPCs of psychopharmaceuticals should be improved in terms of TDM-related information and that target plasma concentrations be adjusted according to the guidelines of the AGNP-TDM expert group. A higher level of good pharmacokinetic practice may be thus achieved.

Phase 1A Safety Assessment of Intravenous Amitriptyline

Fridrich, P., Colvin, H.P., Zizza, A., Wasan, A.D., Lukanich, J., Lirk, P., Saria, A., Zernig, G., Hamp, T., and Gerner, P. J Pain. 2007 May 16; [Epub ahead of print].

INVEST Fellow: Gerald Zernig, Austria, 1993-1994

The antidepressant amitriptyline is used as an adjuvant in the treatment of chronic pain. Among its many actions, amitriptyline blocks Na+ channels and nerves in several animal and human models. As perioperative intravenous lidocaine has been suggested to decrease postoperative pain, amitriptyline, because of its longer half-life time, might be more useful than lidocaine. However, the use of intravenous amitriptyline is not approved by the US Food and Drug Administration. The authors therefore investigated the adverse effects of preoperative intravenous amitriptyline in a typical phase 1A trial. After obtaining written Food and Drug Administration and institutional review board approval, they obtained written consent for preoperative infusion of amitriptyline in an open-label, dose-escalating design (25, 50, and 100 mg, n=5 per group). Plasma levels of amitriptyline/nortriptyline were determined, and adverse effects were recorded in a predetermined symptom list. Infusion of 25 and 50 mg amitriptyline appears to be well tolerated; however, the study was terminated when 1 subject in the 100-mg group developed severe bradycardia. Intravenous infusion of amitriptyline (25 to 50 mg over 1 hour) did not create side effects beyond dry mouth and drowsiness, or dizziness, in 2 of our 10 otherwise healthy participants receiving the 25- to 50-mg dose. An appropriately powered future trial is necessary to determine a potential role of amitriptyline in decreasing postoperative pain. Amitriptyline potently blocks the persistently open Na+ channels, which are known to be instrumental in various pain states. As this occurs at very low plasma concentrations, a single preoperative intravenous infusion of amitriptyline could provide long-lasting pain relief and decrease the incidence of chronic pain.

Socioeconomic Inequality and Mental Health: A Latin American Literature Review

Ortiz-Hernandez, L., Lopez-Moreno, S., and Borges, G. Cad Saude Publica. Jun;23(6), pp. 1255-1272, 2007. Spanish.

INVEST Fellow: Guilherme Borges, Mexico, 1997-1998

[Article in Spanish]

This study provides a review of the scientific output in Latin America concerning the impact of socioeconomic status (SES) on mental disorders and drug use or addiction. International and regional databases were analyzed.

According to the majority of the studies, adults and adolescents with low SES showed increased risk of mental disorders, and alcohol consumption was higher among individuals with high SES, while low SES was associated with alcohol abuse and addiction, although the evidence was less conclusive. Smoking was more frequent among young people with high SES, but in adults it was more common with low SES. Illicit drug use was more frequent among adults (but not adolescents) with low SES. Prescription drugs tended to be consumed by adults and adolescents with higher SES. Use of solvents was more frequent among low SES adolescents. The studies' observed trends and methodological aspects are also discussed.

Activation of GABA(B) Receptors Reverses Spontaneous Gating Deficits in Juvenile DBA/2J Mice

Bortolato, M., Frau, R., Orru, M., Piras, A.P., Fa, M., Tuveri, A., Puligheddu, M., Gessa, G.L., Castelli, M.P., Mereu, G., and Marrosu, F. Psychopharmacology (Berl). 2007 Jun 29; [Epub ahead of print].

INVEST Fellow: Marco Bortolato, Italy, 2004-2005

Gamma-amino-butyric acid (GABA)(B) receptors play a key role in the pathophysiology of psychotic disorders. The authors previously reported that baclofen, the prototypical GABA(B) agonist, elicits antipsychotic-like effects in the rat paradigm of prepulse inhibition (PPI) of the startle, a highly validated animal model of schizophrenia. Authors studied the role of GABA(B) receptors in the spontaneous PPI deficits displayed by DBA/2J mice. Authors tested the effects of baclofen (1.25-5 mg/kg, intraperitoneal [i.p.]) in DBA/2J and C57BL/6J mice, in comparison to the antipsychotic drugs haloperidol (1 mg/kg, i.p.) and clozapine (5 mg/kg, i.p.). Furthermore, they investigated the expression of GABA(B) receptors in the brain of DBA/2J and C57BL/6J mice by quantitative autoradiography. Baclofen dose-dependently restored PPI deficit in DBA/2J mice, in a fashion similar to the antipsychotic clozapine (5 mg/kg, i.p.). This effect was reversed by pretreatment with the GABA(B) antagonist SCH50211 (50 mg/kg, i.p.). In contrast, baclofen did not affect PPI in C57BL/6J mice. Finally, quantitative autoradiographic analyses assessed a lower GABA(B) receptor expression in DBA/2J mice in comparison to C57BL/6J controls in the prefrontal cortex and hippocampus but not in other brain regions. These data highlight GABA(B) receptors as an important substrate for sensorimotor gating control in DBA/2J mice and encourage further investigations on the role of GABA(B) receptors in sensorimotor gating, as well as in the pathophysiology of psychotic disturbances.

Reference Concentrations of Antidepressants. A Compilation of Postmortem and Therapeutic Levels

Reis, M., Aamo, T., Ahlner, J., and Druid, H. J Anal Toxicol. Jun;31(5), pp. 254-264, 2007.

INVEST Fellow: Henrik Druid, Sweden, 2000-2001

In approximately 95% of all medicolegal autopsies performed in Sweden between 1992 and 2005, femoral blood samples were collected and screened for antidepressant drugs. A total of 8591 cases were identified and used for detailed analysis and interpretation. The present compilation provides information about 15 antidepressant drugs determined in femoral blood from certified fatal intoxications and in postmortem "control cases". The postmortem data were subjected to a previously proposed strategy, based on strictly standardized conditions regarding collection, handling and toxicological analysis of the samples. The postmortem data were compared with a therapeutic drug monitoring material (Group T; n = 16,809). The strict inclusion criteria meant that only 2737 postmortem cases were included in the survey. Accordingly, Group A (n = 330) were certified as deaths involving intoxication with a single antidepressant drug; Group B (n = 864) were deaths involving intoxication with more than one drug and/or with a significant concentration of ethanol; and Group C (n = 1800) were deaths under circumstances not involving incapacitation by drugs. In addition to providing reference levels for each drug, the results may also be used to assess risk of toxicity and supply

supplementary information to the standard fatal toxicity index.

Acute Stress Facilitates Hippocampal CA1 Metabotropic Glutamate Receptor-dependent Long-term Depression
Chaouloff, F., Hemar, A., and Manzoni, O. J Neurosci. Jul 4;27(27), pp.7130-7135, 2007.
INVEST Fellow: Olivier Manzoni, France, 1997-1998
Acute stress affects NMDA receptor (NMDAR)-dependent synaptic plasticity in the CA1 region of the hippocampus, with long-term potentiation and long-term depression (LTD) being, respectively, diminished and facilitated by acute exposure to stress. Here, the authors examined whether this facilitatory effect of stress on NMDAR-dependent LTD extends to metabotropic glutamate receptor (mGluR)-dependent LTD at Schaffer collateral-CA1 synapses. Application of a low dose (50 microM) of the selective group 1 mGluR agonist (RS)-3,5-dihydroxyphenylglycine (DHPG) promoted LTD in slices from stressed, but not from control, rats. Pretreatment of stressed rats with the glucocorticoid receptor (GR) antagonist RU38486 prevented the facilitation of DHPG-induced LTD (DHPG-LTD), indicating the involvement of corticosterone secretion and, in turn, stimulation of GRs. Finally, pretreatment of slices with an mGluR1, but not an mGluR5, antagonist blunted the sensitizing effect of stress on DHPG-LTD. These results indicate that acute stress, through corticosterone stimulation of GRs, facilitates the expression of mGluR1-dependent DHPG-LTD in the hippocampal CA1 region.

Role of the Cyclic-AMP/PKA Cascade and of P/Q-type Ca(++) Channels in Endocannabinoid-mediated Long-term Depression in the Nucleus Accumbens
Mato, S., Lafourcade, M., Robbe, D., Bakiri, Y., and Manzoni, O.J. Neuropharmacology. 2007 May 5; [Epub ahead of print].
INVEST Fellow: Olivier Manzoni, France, 1997-1998
Glutamate transmission between prefrontal cortex (PFC) and accumbens (NAc) plays a crucial role in the establishment and expression of addictive behaviors. At these synapses exogenous cannabinoid receptor 1 (CB1R) agonists reversibly inhibit excitatory transmission, and the sustained release of endogenous cannabinoids (eCB) following prolonged cortical stimulation leads to long-term depression (LTD). Activation of presynaptic K(+) channels mediates the effects of exocannabinoids, but the transduction pathway underlying the protracted phase of eCB-LTD is unknown. Here we report that the maintenance of eCB-LTD does not involve presynaptic K(+) channels: eCB-LTD was not affected by blockade of K(+) channels with 4-AP (100muM) and BaCl(2) (300muM) (fEPSP=78.9+/-5.4% of baseline 58-60min after tetanus, compared to 78.9+/-5.9% in control slices). In contrast, eCB-LTD was blocked by treatment of the slices with the adenylyl cyclase (AC) activator forskolin (10muM), and with the protein kinase A (PKA) inhibitor KT5720 (1muM) (fEPSP=108.9+/-5.7% in forskolin and 110.5+/-7.7% in KT5720, compared to 80.6+/-3.9% in control conditions). Additionally, selective blockade of P/Q-type Ca(2+) channels with omega-agatoxin-IVA (200nM) occluded the expression of eCB-LTD (fEPSP=113.4+/-15.9% compared to 78.6+/-4.4% in control slices), while blockade of N- with omega-conotoxin-GVIA (1muM) or L-type Ca(2+) channels with nimodipine (1muM), was without effect (fEPSP was 83.7+/-5.3% and 87+/-8.9% respectively). These data show that protracted inhibition of AC/PKA activity and P/Q-type Ca(2+) channels are necessary for expression of eCB-LTD at NAc synapses.

The Reperfusion Injury Model Improvement and the Tolerance Time Investigation of Rabbit Spinal Cord Ichemia Under Normothermia
Yao, J.Y., Weng, H., Zhang, L., Wang, Q.Y., Yuan, Y.Q., Tang, Y., and Li, J.S. Sichuan Da Xue Xue Bao Yi Xue Ban. Jun;38(3), pp. 497-500, 542, 2007. Chinese.
INVEST Fellow: Lan Zhang, China, 2004-2005
[Article in Chinese]

This study is designed to improve the rabbit model of ischemic- reperfusion injury and determine the safe clamping duration relevant to the spinal cord tolerance to ischemia at normothermia. 50 New Zealand white rabbits were assigned randomly to 5 groups (Group C20, C25, C30, C40 and C60, 10 rabbits in each group) according to different clamping durations, ranging from 20 min to 60 min. The rabbits were endotracheally intubated for ventilation, and their left ear arteries were catheterized for monitoring the mean artery pressure. The spinal cord ischemia was induced by infrarenal aorta occlusion. A catheter was inserted into the aorta distal clamped site for monitoring the distal artery pressure. The neurological functional status of animal was assessed with the Tarlov scale system (0 or 1 meaning the rabbit paraplegia), at the moment of revival, 6 h, 24 h, and 48 h after the reperfusion. After last scoring, the lumbar segments of spinal cord (L4-L6) were removed for pathological examination, and the normal motor neurons of anterior horn were counted. Forty-eight hours after the infusion, the severe neurological impairments were not detected in the rabbits whose aorta were only clamped for 20 min (Group C20). However, the rabbits in Group CSO became totally paraplegic, and the rabbits in Group C25 C30 or C40 developed the paraplegia at 30% , 80% or 90% respectively. The median number of normal motor neuron was 12. 5, 10 or 2 respectively in Group C20, C25 or C30, and 0 median number resulted in Group C40 and C60. The rabbit model of ischemic-reperfusion injury is successfully improved, of which the safe clamping duration without spinal cord injury is not more than 20 min at normothermia.

Explaining the Escalation of Drug Use in Substance Dependence: Models and Appropriate Animal Laboratory Tests

Zernig, G., Ahmed, S.H., Cardinal, R.N., Morgan, D., Acquas, E., Foltin, R.W., Vezina, P., Negus, S.S., Crespo, J.A., Stockl, P., Grubinger, P., Madlung, E., Haring, C., Kurz, M., and Saria, A. Pharmacology. Jun 14;80(2-3), pp. 65-119, 2007 [Epub ahead of print].

INVEST Fellow: Gerald Zernig, Austria, 1993-1994

Escalation of drug use, a hallmark of drug dependence, has traditionally been interpreted as reflecting the development of tolerance to the drug's effects. However, on the basis of animal behavioral data, several groups have recently proposed alternative explanations, i.e. that such an escalation of drug use might not be based on (1) tolerance, but rather be indicative of (2) sensitization to the drug's reinforcing effect, (3) reward allostasis, (4) an increase in the incentive salience of drug-associated stimuli, (5) an increase in the reinforcing strength of the drug reinforcer relative to alternative reinforcers, or (6) habit formation. From the pharmacological perspective, models 1-3 allow predictions about the change in the shape of drug dose-effect curves that are based on mathematically defined models governing receptor-ligand interaction and signal transduction. These predictions are tested in the present review, which also describes the other currently championed models for drug use escalation and other components of apparent 'reinforcement' (in its original meaning, like 'tolerance' or 'sensitization', a purely descriptive term). It evaluates the animal experimental approaches employed to support or prove the existence of each of the models and reinforcement components, and recapitulates the clinical evidence, which strongly suggests that escalation of drug use is predominantly based on an increase in the frequency of intoxication events rather than an increase in the dose taken at each intoxication event. Two apparent discrepancies in animal experiments are that (a) sensitization to overall reinforcement has been found more often for psychostimulants than for opioids, and that (b) tolerance to the reinforcing and other effects has been observed more often for opioids than for cocaine. These discrepancies are resolved by the finding that cocaine levels seem to be more tightly regulated at submaximum reinforcing levels than opioid levels are. Consequently, animals self-administering opioids are more likely to expose themselves to higher above-threshold doses than animals self-administering psychostimulants, rendering the development of tolerance to opioids more likely than tolerance to psychostimulants. The review concludes by making

suggestions on how to improve the current behavioral experimental approaches. Copyright (c) 2007 S. Karger AG, Basel.

Differential Effects of Intravenous R,S-(+/-)-3,4-Methylenedioxymethamphetamine (MDMA, Ecstasy) and its S(+)- and R(-)-enantiomers on Dopamine Transmission and Extracellular Signal Regulated Kinase Phosphorylation (pERK) in the Rat Nucleus Accumbens Shell and Core

Acquas, E., Pisanu, A., Spiga, S., Plumitallo, A., Zernig, G., and Chiara, G.D. J Neurochem. Jul;102(1), pp. 121-132, 2007.

INVEST Fellow: Gerald Zernig, Austria, 1993-1994

R,S(+/-)-3,4-methylenedioxymethamphetamine (R,S(+/-)-MDMA, 'Ecstasy') is known to stimulate dopamine (DA) transmission in the nucleus accumbens (NAc). In order to investigate the post-synaptic correlates of pre-synaptic changes in DA transmission and their relationship with MDMA enantiomers, the authors studied the effects of R,S(+/-)-MDMA, S(+)-MDMA, and R(-)-MDMA on extracellular DA and phosphorylated extracellular signal regulated kinase (pERK) in the NAc shell and core. Male Sprague-Dawley rats, implanted with a catheter in the femoral vein and vertical concentric dialysis probes in the NAc shell and core, were administered i.v. saline, R,S(+/-)-MDMA, S(+)-MDMA, or R(-)-MDMA. Extracellular DA was monitored by in vivo microdialysis with HPLC. Intravenous R,S(+/-)-MDMA (0.64, 1, and 2 mg/kg) increased dialysate DA, preferentially in the shell, in a dose-related manner. S(+)-MDMA exerted similar effects but at lower doses than R,S(+/-)-MDMA, while R(-)-MDMA (1 and 2 mg/kg) failed to affect dialysate DA. R,S(+/-)- and S(+)-MDMA but not R(-)-MDMA increased ERK phosphorylation (expressed as density/neuron and number of pERK-positive neurons/area) in both subdivisions of the NAc. The administration of the D1 receptor antagonist, SCH 39166, prevented the increase in pERK elicited by R,S(+/-)-MDMA and S(+)-MDMA, while the D2/3 receptor antagonist, raclopride, increased pERK in the NAc core per se but failed to affect the R,S(+/-)-MDMA-elicited stimulation of pERK. The present results provide evidence that the DA stimulant effects of racemic MDMA are accounted for by the S(+)-enantiomer and that pERK may represent a post-synaptic correlate of the stimulant effect of R,S(+/-)-MDMA on D1-dependent DA transmission.

Former HHH Drug Abuse Research Fellows

A Comparative Study of HIV/AIDS: The Knowledge, Attitudes, and Risk Behaviors of Schizophrenic and Diabetic Patients in Regard to HIV/AIDS in Nigeria

Ogunsemi, O.O., Lawal, R.A., Okulate, G.T., Alebiosu, C.O., and Olatawura, M.O. MedGenMed. Nov 29;8(4) p. 42, 2006.

HHH Fellow: Rahmaan Lawal, Nigeria, 1997-1998

Studies on knowledge and risk behaviors related to HIV/AIDS reported from developed countries have shown that people with psychiatric disorders constitute a special risk group. In Nigeria, although similar studies have been conducted on various population groups, there has, so far, been no reported study on people suffering from psychiatric disorders. The present study set out to compare knowledge, attitudes, and risk behaviors related to HIV/AIDS among schizophrenic patients and diabetic patients. Ninety-eight consecutive schizophrenic patients attending the outpatient clinics of a psychiatric hospital over a period of 8 weeks completed an interviewer's administered questionnaire. The interview covered demographics, risk behaviors, knowledge related to HIV/AIDS, and patients' attitudes toward people infected with HIV/AIDS. Their responses were compared with those of 56 diabetic patients who were similarly interviewed in a teaching hospital. Results: Compared with the diabetic patients, the schizophrenic patients were significantly less sexually active in the previous 12 months ($P < .05$). They had more misconceptions about HIV/AIDS and were less tolerant towards people living with HIV/AIDS

compared with the diabetic patients. They were also more likely to engage in high-risk behaviors. Mental health providers rarely educate psychiatric patients about HIV/AIDS and should be more involved in doing so. Despite being less sexually active, patients with schizophrenia engaged in risk behaviors as did the diabetic patients.

Brazilian Female Crack Users Show Elevated Serum Aluminum Levels
Pechansky, F., Kessler, F.H., Diemen, L., Bumaguin, D.B., Surratt, H.L., and Inciardi, J.A.
Rev Bras Psiquiatr. Mar;29(1), pp. 39-42, 2007.
HHH Fellow: Flavio Pechansky, Brazil, 1993-1994
There is no information in the literature on the impact of crack smoking using crushed aluminum cans as makeshift pipes, a common form of crack use in Brazil. Since aluminum intake is associated with neurological damage, the authors measured serum aluminum levels in crack smokers. The objective of this study was to ascertain the levels of aluminum in crack users who smoke on makeshift aluminum pipes. 71 female crack smokers, their mean age being 28.0 (+/- 7.7), provided information about their drug use, and had blood samples tested for serum aluminum level. 56 (79%) subjects smoked crack from crushed can pipes, while 15 (21%) smoked from other containers. Fifty-two (73.2%) out of the 71 subjects presented a serum aluminum level of 2 microg/l and 13 (18.3%) had a serum aluminum level of 6 microg/l cut-off point, which is above the reference value. When compared to non-drug users matched by their mean age and gender, they had similar median values and interquartile ranges for serum aluminum level [3 (2-4.6) for crack smokers; 2.9 (1.6-4.1) for controls], but with different means and standard deviations (4.7 +/- 4.9 and 2.9 +/- 1.7, respectively). Crack smokers have high serum aluminum level, but the authors are unsure of its complete association with aluminum cans. Further studies are needed. If such association is proven true in future research, further issues will be raised in dealing with this important disorder, including proper planning and evaluation of public health policies in this area.

Drug Consumption Among Sexual Offenders Against Females
Baltieri, D.A., and de Andrade, A.G. Int J Offender Ther Comp Criminol. 2007 Jul 5; [Epub ahead of print].
HHH Fellow: Arthur Guerra de Andrade, Brazil, 1991-1992
This article aims to evaluate the role of drug consumption among sexual offenders against females. Three groups of participants (N =133) comprising sexual offenders against girls, pubertal females, and women were examined with reference to history of drug and/or alcohol use, impulsivity level, sexual addiction, and recidivism risk. Sexual offenders against women were found to have significantly more difficulties with drug use, higher impulsivity level, and to be younger than the sexual offenders against girls and pubertal females. The combination of drug consumption and higher level of impulsivity may contribute to sexual aggression against adult females.

Alcohol and Drug Consumption Among Sexual Offenders
Baltieri, D.A., and de Andrade, A.G. Forensic Sci Int. 2007 Jun 12; [Epub ahead of print]
HHH Fellow: Arthur Guerra de Andrade, Brazil, 1991-1992
The purpose of this study was to evaluate the role of alcohol and drug consumption between sexual offenders against boys and girls. It was an observational, retrospective and cross-sectional study carried out by the Ambulatory for the treatment of sexual disorders of ABC Medical College, Santo Andre, Sao Paulo, Brazil (ABSex). The sample comprised 104 convicts, over 18 years old, sentenced only for sexual crimes against children (below 11 years old). Alcohol and drug consumption, sexual abuse history, sexual impulsivity, and risk of recidivism were evaluated. The sexual offenders against boys showed higher alcohol consumption problems than sexual offenders against girls ($chi(2)=19.76$, 1d.f., $p<0.01$). The severity of alcohol consumption was

also significantly higher in the sexual offenders against non-related boys than in the sexual offenders against non-related girls (p=0.037, ANOVA). After adjustment for other variables, such as monthly income before the penalty and alcohol consumption at the moment of the crime, the alcohol consumption severity in sexual offenders against boys was significantly higher than in sexual offenders against girls (OR=1.05, CI 1.01-1.08, p<0.01). Alcohol use or abuse is associated with the perpetration of sexual aggression. The role of alcohol consumption seems to be greater in sexual offenders against boys than in girls and this can contribute to criminal recidivism.

Is Attention-Deficit/Hyperactivity Disorder Associated with Illicit Substance Use Disorders in Male Adolescents? A Community-Based Case-Control Study

Szobot, C.M., Rohde, L.A., Bukstein, O., Molina, B.S., Martins, C., Ruaro, P., and Pechansky, F.

Addiction. Jul;102(7), pp. 1122-1130, 2007.

HHH Fellow: Flavio Pechansky, Brazil, 1993-1994

This study aims at evaluating the association between attention-deficit/hyperactivity disorder (ADHD) and illicit substance use disorders (SUD) (marijuana, cocaine and inhalants), controlling for the association with conduct disorder (CD), in a community-based sample of adolescents. Case-control, community-based study. The study was conducted in a delimited geographical area in the South of Brazil, served by four public health clinics. A total of 968 male adolescents (15-20 years of age) were screened for SUD in their households. Of the subjects who were screened positive, the authors selected 61 cases with illicit SUD. For each case selected, from the group which was screened negative, three controls without illicit or alcohol SUD, matched by age and proximity with the case's household. The screening instrument was the Alcohol Smoking and Substance Screening Test (ASSIST). SUD diagnoses were assessed by the drug section of the Mini International Neuropsychiatry Interview (MINI). Other psychiatric diagnoses were based on semistructured (Schedule for Affective Disorders and Schizophrenia for School-Age Children-epidemiological version; MINI) and clinical interviews. Adolescents with ADHD presented a significantly higher odds ratio (OR) for illicit SUD than youths without ADHD, even after adjusting for potential confounders (CD, ethnicity, religion and estimated IQ) (OR = 9.12; 95% CI = 2.84-29.31, P < 0.01). These results suggest an association between ADHD and illicit SUD in Brazilian adolescents that is not mediated by CD. These findings are potentially important from a prevention perspective because treatments are available for ADHD.

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

Research Findings - Intramural Research

Biomedical Informatics Section, Administrative Management Branch

An EHR-Based Multi-Site Recruiting System for Clinical Trials
Optimizing screening and evaluation process is essential in maximizing recruiting potential participants into clinical trials. IRP researchers developed a clinical recruiting system used in the management of human research studies whereby recruiting for various protocols is conducted at multiple sites by different groups with process interdependencies. The system is developed based on a multi-tier architecture with a series of real-time and on-demand decision support systems to increase the efficiency of screening and evaluation of participants during a recruiting process. It simulates various conditions by using derivation rules and recruiting templates for automatic generation of checklists in order to recommend the optimum selection rules based on existing participants' data and is seamlessly integrated into our large Human Research Information System, a comprehensive electronic health record (EHR) system for research participants. Vahabzadeh, M., Lin, J.-L., Mezghanni, M., Contoreggi, C., and Leff, M. Proc. 20th IEEE International Symposium on Computer-Based Medical Systems (CBMS 2007), pp. 331-336, 2007.

Computerized Contingency Management for Motivating Behavior Change: Automated Tracking and Dynamic Reward Reinforcement Management
Contingency management has been successfully used to reinforce abstinence in drug-dependent patients. The major challenge associated with this technique, however, is its likely prohibitive cost, especially when the reinforcement follows an escalating amount schedule. IRP investigators have implemented a less costly approach involving prize draws as the reinforcer. Workflow challenges of such an implementation are extensive considering varying conditions concurrently used in various protocols for meeting inclusion criteria, stratifying into various groups, tracking categories of prizes, determining eligibility for bonus draws based on laboratory results, etc. To address these challenges authors implemented the Automated Contingency Management (ACM) decision support system for dynamic reward reinforcement in the study of treatment of cocaine and opiates. Vahabzadeh, M., Lin, J.-L., Epstein, D.H., Mezghanni, M., Schmittner, J., and Preston, K.L. Proc. 20th IEEE International Symposium on Computer-Based Medical Systems (CBMS 2007), pp. 85-90, 2007.

Office of the Scientific Director

Cannabis Withdrawal among Non-Treatment-Seeking Adult Cannabis Users
Cannabis withdrawal occurs in animals and in heavy human cannabis users.

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However, its clinical significance has been doubted; it is not recognized in DSM-IV. This study evaluated cannabis withdrawal symptoms and subjects' response to them in a convenience sample of 104 adult cannabis smokers who reported a self-defined "serious" quit attempt without formal treatment. Ninety-eight percent experienced at least one withdrawal symptom; 49% experienced at least 4 symptoms. The three commonest withdrawal symptoms were craving for cannabis (66%), irritability (48%), and boredom (45%). Fifty-six percent of subjects experiencing withdrawal symptoms reported taking action to relieve their symptoms. The commonest action was substance use, reported by 77% of those taking action. This included 19% resuming cannabis use, 25% using alcohol, 23% using tobacco, and 23% using tranquillizers. These findings suggest that withdrawal symptoms are common among users to attempt to quit cannabis use, and that such symptoms can serve as a negative reinforcer for substance use, including relapse to cannabis use. These results therefore support the clinical significance of cannabis withdrawal. Copersino, M.L., Boyd, S.J., Tashkin, D.P., Huestis, M.A., Heishman, S.J., Dermand, J.C., Simmons, M.S., and Gorelick, D.A. American Journal on Addictions,15, pp. 8-14, 2006.

Bromocriptine Treatment for Cocaine Addiction: Association with Plasma Prolactin Levels

Bromocriptine is a dopamine (D2) receptor agonist that has been evaluated for the treatment of cocaine dependence, with inconsistent results. Prolactin is a circulating hormone whose plasma levels are reduced by activation of D2 receptors. Prolactin plasma levels have been proposed as a predictor of response to cocaine addiction treatment. This study evaluated the safety and efficacy of bromocriptine (2.5 mg orally thrice daily), along with drug abuse counseling, in 70 cocaine-dependent adult men participating in a 28-day inpatient treatment program followed by 26 weeks of outpatient treatment. Bromocriptine was given in a double-blind, placebo-controlled, randomized design. To maximize the opportunity for efficacy, medication was started during the last 2 weeks of the inpatient stay and continued as an outpatient. Both bromocriptine and placebo groups decreased their cocaine use, with no significant group differences in retention in treatment or proportion of cocaine-positive urine samples. There was no significant association between basal plasma prolactin concentrations or prolactin response to first bromocriptine dose and either outcome measure. These data do not support the efficacy of bromocriptine treatment for cocaine addiction nor a role for prolactin concentration in predicting treatment response. Gorelick, D.A., and Wilkins, J.N. Drug and Alcohol Dependence, 81, pp. 189-195, 2006.

Effect of Rate of Administration on Subjective and Physiological Effects of Intravenous Cocaine in Humans

The rate hypothesis of psychoactive drug action holds that the faster a drug is administered, gets to its site of action in the brain, and starts to act, the greater its rewarding effects and abuse liability. There is little confirmatory evidence for the rate hypothesis with cocaine in humans. This study evaluated the rate hypothesis in 17 experienced cocaine users (7 of whom completed all 10 sessions) by administering intravenous cocaine at each of 3 doses (10, 25, 50 mg) at each of 3 injection durations (10, 30, 60 seconds) in a double-blind, placebo-controlled, escalating dose design. Heart rate, blood pressure, and positive (e.g., rush, high) and negative (e.g., feel bad, anxious) subjects effects (100-mm visual analogue scales) were measured for 1 hour after dosing. Cocaine responses were evaluated with repeated measures mixed linear regression analyses, allowing use of data from all sessions for all subjects. Both dose and infusion rate (mg/sec) significantly influenced most subjective and cardiovascular variables. Analysis of the interaction suggested that dose had a stronger impact than rate. Rate had a stronger influence on positive subjective effects than on negative subjective effects or cardiovascular variables. These findings provide support for the rate hypothesis as it applies to effects of intravenous cocaine administration in humans. Nelson, R.A., Boyd, S.J., Ziegelstein, R.C., Herning, R., Cadet, J.L., Henningfield, J.E., Schuster,

C.R., Contoreggi, C., and Gorelick, D.A. Drug and Alcohol Dependence, 82, pp. 19-24, 2006.

The Cannabinoid CB1 Receptor Antagonist Rimonabant Attenuates the Hypotensive Effect of Smoked Marijuana in Male Smokers

Animal studies suggest that cannabinoid CB1 receptors play a role in regulating blood pressure. In human studies, activation of CB1 receptors by cannabis or THC has modest and inconsistent effects on blood pressure. This study evaluated the role of CB1 receptors in blood pressure in 63 male cannabis smokers (10.3 + 5.9 years of lifetime cannabis use) by administering escalating oral doses (1, 3, 10, 30, 90 mg) of the selective CB1 receptor antagonist rimonabant (or placebo) in a randomized, parallel-group, double-blind, placebo-controlled design. Subjects smoked an active (2.64% THC) or placebo marijuana cigarette 2 and 6 hours after rimonabant dosing. Blood pressure and symptoms were monitored for 90 minutes after smoking while subjects remained seated. Marijuana smoking after placebo rimonabant had no consistent effect on blood pressure, but 22% of subjects experienced symptomatic (dizziness, lightheadedness) hypotension, as did 20-33% of subject who received pretreatment with 1, 3, or 10 mg rimonabant. No subject receiving 30 or 90 mg rimonabant before marijuana smoking experienced symptomatic hypotension. The 7 subjects who experienced symptomatic hypotension had significantly higher mean (SD) peak plasma THC concentrations than did the 33 subjects who did not. Rimonabant by itself had no effects on blood pressure and did not alter THC pharmacokinetics. These findings indicate that CB1 receptors play a role in medicating effects of cannabis smoking on blood pressure in humans. Gorelick, D.A., Heishman, S.J., Preston, K.L., Nelson, R.A., Moolchan, E.T., and Huestis, M.A. American Heart Journal, 151, pp. 754.e1-754.e5, 2006.

Quitting among Non-Treatment-Seeking Marijuana Users: Reasons and Changes in Other Substance Use

Marijuana is the most widely used illegal drug in the world, yet relatively little is known about why adult users try to quit without formal treatment or whether they change use of other substances in response to quitting. This study examined the self-reported reasons for quitting marijuana use, changes in other substance use during the quit attempt, and reasons for resumption of use in 104 non-treatment-seeking adult marijuana smokers. Quitting was primarily motivated by concerns about the negative impact of marijuana on health and on self- and social-image. Spontaneous quitting of marijuana use was often associated with increased use of legal substances such as alcohol, tobacco, and sleeping aids, but not with initiation of new substance use. These findings suggest clinically relevant areas for further research on spontaneous recovery from marijuana use. Copersino, M.L., Boyd, S.J., Tashkin, D.P., Huestis, M.A., Heishman, S.J., Dermand, J.C., Simmons, M.S., and Gorelick, D.A. American Journal on Addictions,15, pp. 297-302, 2006.

Spending of Remuneration by Subjects in Non-Treatment Drug Abuse Research Studies

Research subjects are commonly paid for participation in non-treatment research studies, but relatively little is known about subject preferences or how they spend their payments. This study examined remuneration spending by 94 adult males who participated in residential, non-treatment drug abuse research studies. Subjects earned remuneration based on length of stay and specific research procedures. Remuneration could be used for in-kind purchases and bill payments, or taken as cash after discharge. Data on subject characteristics and spending of remuneration were extracted retrospectively from subjects' charts. The influence of subject characteristics on remuneration spending was evaluated with multivariate analyses. Participants received average remuneration of $1,454, taking 59% in cash. They received remuneration in a 3:1:1 ratio among cash, in-kind housing payments, and other in-kind categories. The four most popular spending categories were cigarettes (60.6%

of subjects), toiletries (60.6%), clothing (54.3%), and housing (52.1%). Primary drug of abuse, total remuneration, monthly income, length of stay on the residential research unit, age, and education were significantly associated with in-kind remuneration choices. Less total remuneration, intoxication in the month prior to study, higher IQ, and non-white race were associated with taking a greater percentage of remuneration in cash. These findings suggest that residential drug abuse research participants prefer cash to in-kind research remuneration, use in-kind spending predominantly for housing costs and personal items, and have remuneration choices influenced by drug use and economic status. These findings may help inform future research subject remuneration practices. Kurlander, J.E., Simon-Dack, S.L., and Gorelick, D.A. American Journal of Drug and Alcohol Abuse, 32, pp. 527-540, 2006.

Risk of Psychoactive Substance Dependence among Substance Users in a Trauma Inpatient Population

One measure of a substance's addictive risk is the proportion of users who become dependent. This study evaluated the lifetime and current risk of substance dependence among lifetime substance users' among trauma inpatients and provided a relative ranking of addictive risk among the substances. Data on use of 8 substance groups (alcohol, opiates, marijuana, cocaine, other stimulants, sedative-hypnotics, hallucinogens, other drugs) were obtained by interview (Structured Clinical Interview for the DSM-III-R) from 1,118 adult trauma inpatients. Prevalence of lifetime dependence among lifetime users ranged from 80.7% for opiates and 70.9% for cocaine to 33.3% for hallucinogens and 26.6% for sedative-hypnotics. The rank order of addictive risk was similar to that found in the general population. Trauma inpatients had a higher absolute addictive risk than the general population, comparable to the risk found in patients in treatment for substance use disorders. These findings suggest the importance of screening trauma inpatients for substance dependence. Martins, S.S., Copersino, M.L., Soderstrom, C.A., Smith, G.S., Dischinger, P.C., McDuff, D.R., Hebel, J.R., Kerns, T.J., Ho, S.M., Read, K.M., and Gorelick, D.A. Journal of Addictive Diseases, 26, pp. 71-77, 2007.

Sociodemographic Characteristics Associated with Substance Use Status in a Trauma Inpatient Population

Substance use is significantly associated with physical injury, yet relatively little is known about the prevalence of specific substance use disorders among trauma patients, or their associated sociodemographic characteristics. This study evaluated these issues in an unselected sample of 1,118 adult inpatients at the University of Maryland Shock Trauma Center, Baltimore, MD, who were interviewed with the psychoactive substance use disorder section of the Structured Clinical Interview for DSM-III-R. Among trauma inpatients, lifetime alcohol users (71.8% of subjects) were more likely male; users of illegal drugs (45.3%) were also more likely to be younger, unmarried, and poor. Patients with current drug abuse/dependence (18.8%) were more likely to be non-white, less educated, and poor; those with current alcohol abuse/dependence (32.1%) were also more likely male, unmarried, and older. These findings highlight the need for screening for substance use disorders in trauma settings and referral of patients to substance abuse treatment programs. Martins, S.S., Copersino, M.L., Soderstrom, C.A., Smith, G.S., Dischinger, P.C., McDuff, D.R., Hebel, J.R., Kerns, T.J., Ho, S.M., Read, K.M., and Gorelick, D.A. Journal of Addictive Diseases, 26, pp. 53-62, 2007.

Use of a "Microecology Technique" to Study Crime around Substance Abuse Treatment Centers

The issue of whether substance abuse treatment centers affect neighborhood crime is hotly debated. Empirical evidence on this issue would be useful to treatment providers, police agencies, policymakers, and community members, but is currently lacking. One reason for this lack is the difficulty of distinguishing the potential effect of a treatment center from the baseline crime

rate in the high crime areas in which they are often located. An appropriate control group is needed to distinguish whether crime appears to cluster around clinics only because they have higher foot traffic than nearby locations. This study presents a method to overcome these challenges using crime databases (arrests, 911 calls, and incidents) that are geocoded by street address (i.e., latitude and longitude of each event are assigned by computerized mapping). Events per unit area are calculated in concentric circular "buffers" drawn at 25-meter intervals around each site. A "crime slope" (slope estimate = _) comparing the crimes/area among the buffers is calculated using regression analysis for treatment centers and for three types of control sites: convenience stores and hospitals (socially acceptable high foot traffic sites) and residential points (low foot traffic). This technique controls for the high crime milieu of most treatment centers by comparing crime within rather than between neighborhoods and overcomes the lack of "before and after" crime data. Use of this innovative technique should provide valid empirical evidence on crime around substance abuse treatment centers, perhaps helping resolve a long debated public policy question. Boyd, S.J., Armstrong, K.M., Fang, L.J., Medoff, D.R., Dixon, L.B., and Gorelick, D.A. Social Science Computer Review, 25, pp. 163-173, 2007.

Neural Protection and Regeneration Section, Molecular Neuropsychiatry Branch

Bone Morphogenetic Protein 7 Has Neuroprotective Effects against Methamphetamine Toxicity

Methamphetamine (MA) is a drug of abuse and can have neurotoxic effects on dopaminergic neurons. NIDA IRP has previously found that bone morphogenetic protein 7 (BMP7) has neuroprotective and neuroregenerative properties (Chou, J. Harvey, B.K., Chang, C.F., Shen, H, Morales, M., and Wang, Y. J Neurol Sci. 240, pp. 21-29, 2006) and pretreatment with BMP7 reduced 6-hydroxydopamine-mediated neurodegeneration of dopaminergic neurons in a rodent model of Parkinson's disease (Harvey, B.K., Mark, A., Chou, J., Chen, G.J., Hoffer, B.J., and Wang, Y. Brain Res. 1022, pp. 88-95, 2004). Based on these findings, the neuroprotective effect of BMP7 against MA-mediated toxicity in dopaminergic neurons was evaluated. Primary rat dopaminergic neurons treated with MA (1 mM) decreased tyrosine hydroxylase immunoreactivity (THir) while increasing TUNEL staining. Pretreatment with BMP7 antagonized the effects of MA. The effects of BMP7 on MA toxicity were next examined in CD1 mice. High doses of MA (10 mg/kg x 4 s.c.) significantly reduced locomotor activity and THir in striatum. Intra-cerebroventricular administration of BMP7 attenuated these neurodegenerative changes. In BMP7 heterozygous knockout (BMP7+/-) mice, MA greatly suppressed locomotor activity and reduced TH immunoreactivity in nigra reticulata compared to wild type BMP7 +/+ mice, suggesting that deficiency in BMP7 expression increases vulnerability to MA insults. Since BMP7+/- mice carry a LacZ gene encoding the _-galactosidase (_-gal) protein at the BMP7 locus, the expression of BMP7 was indirectly measured through the enzymatic activity of _-gal in BMP7+/- mice. High doses of MA significantly suppressed _-gal activity in striatum, suggesting that MA may inhibit BMP7 expression at the terminals of nigrostriatal pathway. Overall, BMP7 reduced MA-related degeneration caused by high doses of methamphetamine. Chou, J., Luo, Y., Kuo, CC, Powers, K., Shen, H., Harvey, B.K., Hoffer, B. and Wang, Y. Poster. Society for Neuroscience Annual Meeting, Atlanta, GA, October 14-18, 2006.

Protective Effects of Astaxanthin against Ischemic Brain Injury

Astaxanthin (ATX) is a carotenoid pigment found in crustaceans and structurally similar to other dietary carotenoids such as beta-carotene, lutein and lycopene which are potent antioxidants. The ability of astaxanthin to act as neuroprotective agent against stroke was examined using the transient middle cerebral artery (MCA) ligation model in adult rats. Anesthetized animals were

given ATX or vehicle intracerebroventricularly 10-20 minutes prior to a 60 min MCA ligation. Astaxanthin did not alter blood gases (CO2 and O2), blood pH, blood pressure, body temperature, brain temperature and cerebral blood flow. Pretreatment with ATX significantly reduced ischemia -mediated glutamate release in cerebral cortex, measured by microdialysis and HPLC. ATX also antagonized ischemia/reperfusion - induced loss of aconitase activity, an indirect marker for oxidative damage, at 8 hours after stroke. At 2 days after stroke, rats that received ATX had a significant increase in locomotor activity and decrease in cerebral infarction volume compared to the vehicle controls. TUNEL labeling and cytochrome C release in the ischemic brain was suppressed by ATX. Collectively, astaxanthin has protective effects against ischemia-related injury in vivo through the inhibition of oxidative stress, inhibition of glutamate release, and anti-apoptosis. Wang, Y., Harvey, B.K., Shen, H. and Hoffer, B. Oral Presentation, 2007. American Society for Neural Transplantation and Repair, Clearwater, FL, May 3-6, 2007.

Tropism and Toxicity of Adeno-associated Viral Vectors on Neurons and Glia in vitro

To establish a platform for evaluating gene function and therapeutic potential against neurodegeneration, IRP scientists examined the infectivity (tropism) and toxicity associated with recombinant adeno-associated viral (rAAV) vectors. rAAV 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, 5, 6, 7 and 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 LDH and MTS 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. Use of cell-restricted promoters may be necessary to limit expression to neurons and reduce gliotoxicity in vitro. Howard, D.B, Powers, K., Wang, Y. and Harvey, B.K. Poster, 2007. American Society for Gene Therapy, Seattle, WA, May 30 - June 3, 2007.

Development and Plasticity Section, Cellular Neurobiology Research Branch

Increases in Expression of 14-3-3 Eta and 14-3-3 Zeta Transcripts during Neuroprotection Induced by Delta9-Tetrahydrocannabinol in AF5 Cells

The molecular mechanisms involved in N-methyl-D-aspartate (NMDA)-induced cell death and Delta9-tetrahydrocannabinol (THC)-induced neuroprotection were investigated in vitro with an AF5 neural progenitor cell line model. By microarray analysis, Ywhah, CK1, Hsp60, Pdcd 4, and Pdcd 7 were identified as being strongly regulated by both NMDA toxicity and THC neuroprotection. The 14-3-3 eta (14-3-3eta; gene symbol Ywhah) and 14-3-3 zeta (14-3-3zeta; gene symbol Ywhaz) transcripts were deceased by NMDA treatment and increased by THC treatment prior to NMDA, as measured by cDNA microarray analysis and quantitative real-time RT-PCR. Other 14-3-3 isoforms were unchanged. Whereas up-regulation of 14-3-3zeta expression was observed 30 min after treatment with THC plus NMDA, down-regulation by NMDA alone was not seen until 16 hr after treatment. By Western blotting, THC increased 14-3-3 protein only in cells that were also treated with NMDA. Overexpression of 14-

3-3eta or 14-3-3zeta by transient plasmid transfection increased 14-3-3 protein levels and decreased NMDA-induced cell death. These data suggest that increases in 14-3-3 proteins mediate THC-induced neuroprotection under conditions of NMDA-induced cellular stress. Chen, J., Lee, C.T., Errico, S.L., Becker, K.G., and Freed, W.J. Journal of Neuroscience Research, 85(8), pp. 1724-1733, 2007.

Microarray Analysis of Oxidative Stress Regulated Genes in Mesencephalic Dopaminergic Neuronal Cells: Relevance to Oxidative Damage in Parkinson's Disease

Oxidative stress and apoptotic cell death have been implicated in the dopaminergic cell loss that characterizes Parkinson's disease. While factors contributing to apoptotic cell death are not well characterized, oxidative stress is known to activate an array of cell signaling molecules that participate in apoptotic cell death mechanisms. IRP researchers investigated oxidative stress-induced cytotoxicity of hydrogen peroxide (H2O2) in three cell lines, the dopaminergic mesencephalon-derived N27 cell line, the GABAergic striatum-derived M213-20 cell line, and the hippocampal HN2-5 cell line. N27 cells were more sensitive to H2O2-induced cell death than M213-20 and HN2-5 cells. H2O2 induced significantly greater increases in caspase-3 activity in N27 cells than in M213-20 cells. H2O2-induced apoptotic cell death in N27 cells was mediated by caspase-3-dependent proteolytic activation of PKCdelta. Gene expression microarrays were employed to examine the specific transcriptional changes in N27 cells exposed to 100 microM H2O2 for 4 h. Changes in genes encoding pro- or anti-apoptotic proteins included up-regulation of BIK, PAWR, STAT5B, NPAS2, Jun B, MEK4, CCT7, PPP3CC, and PSDM3, while key down-regulated genes included BNIP3, NPTXR, RAGA, STK6, YWHAH, and MAP2K1. Overall, the changes indicate a modulation of transcriptional activity, chaperone activity, kinase activity, and apoptotic activity that appears highly specific, coordinated and relevant to cell survival. Utilizing this in vitro model to identify novel oxidative stress-regulated genes may be useful in unraveling the molecular mechanisms underlying dopaminergic degeneration in Parkinson's disease. Anantharam, V., Lehrmann, E., Kanthasamy, A., Yang, Y., Banerjee, P., Becker, K.G., Freed, W.J., and Kanthasamy, A.G. Neurochemistry International, 50(6), pp. 834-847, 2007.

Role of Heparin Binding Growth Factors in Nigrostriatal Dopamine System Development and Parkinson's Disease

The developmental biology of the dopamine (DA) system may hold important clues to its reconstruction. IRP scientists hypothesized that factors highly expressed during nigrostriatal development and re-expressed after injury and disease may play a role in protection and reconstruction of the nigrostriatal system. Examination of gene expression in the developing striatum suggested an important role for the heparin binding growth factor family at time points relevant to establishment of dopaminergic innervation. Midkine, pleiotrophin (PTN), and their receptors syndecan-3 and receptor protein tyrosine phosphatase beta/zeta, were highly expressed in the striatum during development. Furthermore, PTN was up-regulated in the degenerating substantia nigra of Parkinson's patients. The addition of PTN to ventral mesencephalic cultures augmented DA neuron survival and neurite outgrowth. Thus, PTN was identified as a factor that plays a role in the nigrostriatal system during development and in response to disease, and may therefore be useful for neuroprotection or reconstruction of the DA system. Marchionini, D.M., Lehrmann, E., Chu, Y., He, B., Sortwell, C.E., Becker, K.G., Freed, W.J., Kordower, J.H., and Collier, T.J. Brain Research, 25:1147, pp. 77-88, 2007.

Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Apoptotic and Behavioural Consequences of Mild Brain Trauma in Mice:

Markers for Prospective Intervention

Mild traumatic brain injury (mTBI) is a not uncommon event in adolescents and young adults, and although not resulting in clear morphological brain defects, it is associated with long-term cognitive, emotional and behavioural problems. The focus of the present study was to characterize the biochemical and behavioural changes associated with experimental mTBI in mice that may act as either targets or surrogate markers for interventional therapy. Specifically, mTBI was induced by 30 g and 50 g weight drop and, at 8 and 72 hr thereafter, markers of cellular apoptosis - caspase-3, Bax, apoptosis inducing factor (AIF) and cytochrome-c (Cyt-c) - were quantified by Western blot analysis in hippocampus ipsilateral to impact. Levels of amyloid- precursor protein (APP) were also measured, and specific behavioural tests, the passive avoidance, open field and forced swimming (Porsolt) paradigms, were undertaken to assess learning, emotionality and emotional memory. In the absence of hemorrhage or infarcts, as assessed by triphenyltetrazolium chloride staining, procaspase-3 and Bax levels were dramatically altered following mTBI at both times. No cleaved caspase-3 was detected, and levels of AIF and Cyt-c, but not APP, were significantly changed at 72 hr. Mice subjected to mTBI were indistinguishable from controls by neurological examination at 1 and 24 hr, and by passive avoidance/open field at 72 hr; but could be differentiated in the forced swimming paradigm. In general, this model mimics the diffuse effects of mTBI on brain function associated with the human condition, and highlights specific apoptotic proteins and a behavioural paradigm as potential markers for prospective interventional strategies. Tweedie, D., Milman, A., Holloway, H.W., Li, Y., Harvey, B.K., Shen, H., Pistell, P.J., Lahiri, D.K., Hoffer, B.J., Wang, Y., Pick, C.G., and Greig, N.H. Journal of Neuroscience Research, 85(4), pp. 805-815, 2007.

Proteomics Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

MALDI-Ion Mobility-TOFMS Imaging of Lipids in Rat Brain Tissue

While maintaining anatomical integrity, matrix assisted laser desorption/ionization mass spectrometry (MALDI-MS) has allowed researchers to directly probe tissue, map the distribution of analytes and elucidate molecular structure with minimal preparation. MALDI-ion mobility (IM)-orthogonal time-of-flight mass spectrometry (oTOFMS) provides an advantage by initially separating different classes of biomolecules such as lipids, peptides, and nucleotides by their IM drift times prior to mass analysis. In the present work, the distribution of phosphatidlycholine and cerebroside species was mapped from 16 microm thick coronal rat brain sections using MALDI-IM-oTOFMS. Furthermore, the use of gold nanoparticles as a matrix enables detection of cerebrosides, which although highly concentrated in brain tissue, are not easily observed as positive ions because of intense signals from lipids such as phosphatidlycholines and sphingomyelins. Jackson, S.N., Ugarov, M., Egan, T., Post, J.D., Langlais, D., Albert Schultz, J., and Woods, A.S. Journal of the American Society for Mass Spectrometry, 42(8), pp. 1093-1098, 2007.

Tag-Mass: Specific Molecular Imaging of Transcriptome and Proteome by Mass Spectrometry Based on Photocleavable Tag

MALDI tissue imaging of tissues has become a promising technique for tracking biomarkers while determining their location and structural characterization. IRP scientists have now developed specific targeting probes (oligonucleotides, antibodies), named Tag-Mass. This approach is based on probes modified with a photocleavable linker coupled with a tag cleaved and detected using mass spectrometry. Tag-Mass development is the key for a rapid, sensitive, and accurate approach to correlate levels of expression of different mRNA or proteins in diseases. Lemaire, R., Stauber, J., Wisztorski, M., Van Camp, C., Desmons, A., Deschamps, M., Proess, G., Rudlof, I., Woods, A.S., Day, R., Salzet, M., and Fournier, I. Journal of Proteome Research, 6(6), pp. 2057-

2067, 2007.

Molecular Neurobiology Research Branch

Molecular Genetics of Nicotine Dependence and Abstinence Genome Wide Association

Classical genetic studies indicate that nicotine dependence is a substantially heritable complex disorder. Genetic vulnerabilities to nicotine dependence largely overlap with genetic vulnerabilities to dependence on other addictive substances. Successful abstinence from nicotine displays substantial heritable components as well. Some of the heritability for the ability to quit smoking appears to overlap with the genetics of nicotine dependence and some does not. IRP researchers now report genome wide association studies of nicotine dependent individuals who were successful in abstaining from cigarette smoking, nicotine dependent individuals who were not successful in abstaining and ethnically-matched control subjects free from substantial lifetime use of any addictive substance. These data, and their comparison with data that the authors have previously obtained from comparisons of four other substance dependent vs. control samples support two main ideas: 1) Single nucleotide polymorphisms (SNPs) whose allele frequencies distinguish nicotine-dependent from control individuals identify a set of genes that overlaps significantly with the set of genes that contain markers whose allelic frequencies distinguish the four other substance dependent vs. control groups ($p < 0.018$). 2) SNPs whose allelic frequencies distinguish successful vs. unsuccessful abstainers cluster in small genomic regions in ways that are highly unlikely to be due to chance (Monte Carlo $p < 0.00001$). These clustered SNPs nominate candidate genes for successful abstinence from smoking that are implicated in interesting functions: cell adhesion, enzymes, transcriptional regulators, neurotransmitters and receptors and regulation of DNA, RNA and proteins. As these observations are replicated, they will provide an increasingly-strong basis for understanding mechanisms of successful abstinence, for identifying individuals more or less likely to succeed in smoking cessation efforts and for tailoring therapies so that genotypes can help match smokers with the treatments that are most likely to benefit them. Uhl, G.R., Liu, Q.R., Drgon, T., Johnson, C., Walther, D., and Rose, J.E. BMC Genetics, 8, pp. 10 - 15, 2007.

Molecular Genetics of Nicotine Dependence and Abstinence Genome Wide Association

Addictions are substantially heritable complex disorders. IRP investigatorsd report whole genome association studies that identify 89 genes likely to contain variants that contribute to addiction vulnerability, using previously- and newly-validated microarray based pooling assays. Each gene contains clustered single nucleotide polymorphisms (SNPs) that display significant allele frequency differences between abusers and controls in each of the two samples studied with 639,401 SNP arrays and confirmatory SNPs from each of two other abuser/control samples. These genes are implicated in interesting functions, including "cell adhesion" processes that help to establish and maintain neuronal connections of special relevance to addiction's memory-like features. Liu Q.R., Drgon T., Johnson C., Walther D., Hess J., and Uhl G.R. Am J Med Genet B Neuropsychiatr Genet. 141, pp. 918-925, 2006.

Medicinal Chemistry Section, Medications Discovery Research Branch

Novel Metabotropic Glutamate Receptor Subtype 5 Antagonists

The metabotropic glutamate receptor subtype 5 (mGluR5) has been implicated in drug abuse and other neuropsychiatric disorders. The lead compounds for this receptor subtype, MPEP and MTEP, have provided important tools with which to study the role these receptors play in the central nervous system, but have limited therapeutic application. In this report, IRP scientists followed a

lead from our previously described heterobicyclic amides by incorporating a heterobicyclic ring structure into the molecule. One novel quinoline analogue demonstrated high affinity for mGluR5 receptors (Ki=110 nM) and moderately potent antagonist activity (IC50 = 260 nM) in the functional assay measuring the hydrolysis of phosphoinositide at mGluR5 in CHO cells. Hence a new template for further structure-activity relationship investigation was discovered and the resulting compounds will provide new molecular tools with which to further study the mGluR5 and its role in CNS disorders. Kulkarni, S.S., and Newman A.H. Bioorganic Medicinal Chemistry Letters, 17, pp. 2987-2991, 2007.

Clinical Psychopharmacology Section, Chemical Biology Research Branch

Restoration of 3,4-methylenedioxymethamphetamine-induced 5-HT Depletion by the Administration of l-5-hydroxytryptophan

3,4-methylenedioxymethamphetamine (MDMA) causes persistent decreases in brain serotonin (5-HT) content and 5-HT transporter (SERT) binding, with no detectable changes in SERT protein. Such data suggest that MDMA impairs 5-HT transmission but leaves 5-HT nerve terminals intact. To further test this hypothesis, IRP researchers carried out two types of experiments in rats exposed to high-dose MDMA. First, they examined the effects of MDMA on SERT binding and function using different in vitro assay conditions. Next, they treated rats with the 5-HT precursor, L-5-hydroxytryptophan (5-HTP), in an attempt to restore MDMA-induced depletions of 5-HT. Rats received saline or MDMA injections (7.5 mg/kg ip, q 2 h x 3 doses); two weeks later, rats were allocated to groups. Rats in one group were decapitated, and brain tissue was assayed for SERT binding and [3H]5-HT uptake under conditions of normal (100 or 126 mM) and low (20 mM) NaCl concentration. Rats from another group received saline or 5-HTP/benserazide (5-HTP-B), each drug at 50 mg/kg ip, and were sacrificed 2 hr later. MDMA reduced SERT binding to 10% of control when assayed in 100 mM NaCl, but this reduction was only 55% of control in 20 mM NaCl. MDMA decreased immunoreactive 5-HT in caudate and hippocampus to about 35% of control. Administration of 5-HTP-B to MDMA-pretreated rats significantly increased the 5-HT signal towards normal levels in caudate (85 % of control) and hippocampus (66 % of control). Authors concluded that: 1) Following high-dose MDMA treatment sufficient to reduce SERT binding by 90%, a significant number of functionally intact 5-HT nerve terminals survive. 2) The degree of MDMA-induced decreases in SERT binding depends on the in vitro assay conditions. 3) 5-HTP-B restores brain 5-HT depleted by MDMA, suggesting that this approach might be clinically useful in abstinent MDMA users. Wang, X., Baumann, M.H., Dersch, C.M., and Rothman, R.B. J Pharmacol Exp Ther [2007 Jul 11, epub], 2007.

Amphetamine Analogs Increase Plasma Serotonin: Implications for Cardiac and Pulmonary Disease

Elevations in plasma serotonin (5-HT) have been implicated in the pathogenesis of cardiac and pulmonary disease. Normally, plasma 5-HT concentrations are kept low by transporter-mediated uptake of 5-HT into platelets and by metabolism to 5-hydroxyindoleacetic acid (5-HIAA). Many abused drugs (e.g., substituted amphetamines) and prescribed medications (e.g., fluoxetine) target 5-HT transporters and could thereby influence circulating 5-HT. IRP investigators evaluated the effects of amphetamines analogs [(+/-)-fenfluramine, (+/-)-3,4-methylenedioxymethamphetamine, (+)-methamphetamine, (+)-amphetamine, phentermine] on extracellular levels (i.e., plasma levels) of 5-HT and 5-HIAA in blood from catheterized rats. Effects of the 5-HT uptake blocker fluoxetine were examined for comparison. Drugs were tested in vivo and in vitro; plasma indoles were measured using a novel microdialysis method in whole blood. The authors found that baseline dialysate levels of 5-HT are approximately 0.22 nM, and amphetamine analogs

evoke large dose-dependent increases in plasma 5-HT ranging from 4 to 20 nM. The ability of drugs to elevate plasma 5-HT is positively correlated with their potency as 5-HT transporter substrates. Fluoxetine produced small, but significant, increases in plasma 5-HT. Although the drug-evoked 5-HT concentrations are below the micromolar levels required for contraction of pulmonary arteries, they approach concentrations reported to stimulate mitogenesis in pulmonary artery smooth muscle cells. Additional studies are needed to determine the effects of chronic administration of amphetamines on circulating 5-HT. Zolkowska, D., Rothman, R.B., and Baumann, M.H. J Pharmacol Exp Ther. 318, pp. 604-610, 2006.

Behavioral Neuroscience Section, Behavioral Neuroscience Research Branch

Stress-induced Relapse to Cocaine Seeking: Roles for the CRF(2) Receptor and CRF-binding Protein in the Ventral Tegmental Area of the Rat

Footshock reinstates cocaine seeking in cocaine-experienced rats by inducing corticotropin-releasing factor (CRF) and glutamate release in the ventral tegmental area (VTA) and thus activating VTA dopaminergic neurons. Footshock-induced VTA glutamate release, dopamine activation and reinstatements are blocked by VTA administration of an alpha-helical CRF, a nonselective CRF receptor antagonist. The effects of selective CRF antagonists have not yet been reported. The present studies were designed to explore the roles of VTA CRF receptor subtypes and CRF-BP in these effects induced by footshock. Rats were first trained to lever-press for intravenous cocaine (1 mg/infusion/0.13 ml, FR-1 schedule), and then tested under extinction conditions until response rates returned to the pretraining baseline. Reinstatements, VTA glutamate and dopamine levels [microdialysis with high performance liquid chromatography (HPLC)] were then assessed, under various pharmacological conditions, after mild inescapable footshock. Footshock-induced reinstatement of cocaine seeking and release of VTA glutamate and dopamine were blocked by selective blockade of VTA CRF(2) receptors (CRF(2)Rs) but not CRF(1)Rs. VTA perfusion of CRF or CRF(2)R agonists that have strong affinity for CRF-BP mimicked the effects induced by footshock while CRFR agonists that do not bind CRF-BP were ineffective. CRF(6-33), which competes for the CRF binding site on CRF-BP, attenuated the effects of CRF or urocortin I on VTA glutamate and dopamine release and on reinstatement of cocaine seeking. The present studies revealed a role of VTA CRF-BP and suggest an involvement of CRF(2)R in the effectiveness of stress in triggering glutamate and dopamine release and cocaine seeking in drug-experienced animals. Wang, B., You, Z.B., Rice, K.C., and Wise, R.A. Psychopharmacology, 193, pp. 283-294, 2007.

Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch

Blocking of Conditioning to a Cocaine-Paired Stimulus: Testing the Hypothesis that Cocaine Perpetually Produces a Signal of Larger-Than-Expected Reward

According to a recent account of addiction, dopaminergic effects of drugs like cocaine mimic the neuronal signal that occurs when a natural reward has a larger value than expected. Consequently, the drug's expected reward value increases with each administration, leading to an over-selection of drug-seeking behavior. One prediction of this hypothesis is that the blocking effect, a cornerstone of contemporary learning theory, should not occur with drug reinforcers. To test this prediction, two groups of rats were trained to self-administer cocaine with a nose-poking response. For 5 sessions, a tone was paired with each self-administered injection (blocking group), or no stimulus was paired with injection (non-blocking group). Then, in both groups, the tone

and a light were both paired with each injection for 5 sessions. In subsequent testing, the light functioned as a conditioned reinforcer for a new response (lever-pressing) in the non-blocking group, but not the blocking group. Thus, contrary to prediction, pre-training with the tone blocked conditioning to the light. Although these results fail to support a potentially powerful explanation of addiction, they are consistent with the fact that most conditioning and learning phenomena that occur with non-drug reinforcers can also be demonstrated with drug reinforcers. Panlilio, L.V., Thorndike, E.B. and Schindler, C.W. Pharmacology, Biochemistry and Behavior, 86, pp. 774-777, 2007.

Adenosine Receptor-Dopamine Receptor Interactions in the Basal Ganglia and Their Relevance for Brain Function

The dopamine D(1) and D(2) receptors are major receptors in the regulation of striatal function and striatal adenosine A(1) and A(2A) receptors are major modulators of their signaling. The evidence suggests the existence of antagonistic A(1)-D(1) heteromeric receptor complexes in the basal ganglia and prefrontal cortex and especially in the direct striatonigral-striatoentopeduncular GABA pathways. The neurochemical and behavioral findings showing antagonistic A(1)-D(1) receptor interactions can be explained by the existence of such A(1)-D(1) heteromeric receptor complexes and of antagonistic interactions at the level of the second messengers. In contrast, A(2A)-D(2) receptor heteromers may exist in the dorsal and ventral striato-pallidal GABA pathways, where activation of A(2A) receptors reduces D(2) receptor recognition, coupling and signaling. As a result of the A(2A) receptor-induced reduction of D(2) receptor signaling, the activity of these GABA neurons is increased resulting in reduced motor and reward functions mediated via the indirect pathway, causing a reduced glutamate drive to the prefrontal and motor areas of the cerebral cortex. Thus, A(2A) receptor antagonists and A(2A) receptor agonists, respectively, may offer novel treatments of Parkinson's disease (reduced D(2) receptor signaling) and of schizophrenia and drug addiction (increased D(2) receptor signaling). Fuxe, K., Ferre, S., Genedani, S., Franco, R. and Agnati, L.F. Physiol Behav, May 21, 2007, Epubmed ahead of print, PMID 17572452.

Adenosine A(2A) Receptors in Ventral Striatum, Hypothalamus and Nociceptive Circuitry: Implications for Drug Addiction, Sleep and Pain

Adenosine A(2A) receptors localized in the dorsal striatum are considered as a new target for the development of antiparkinsonian drugs. Co-administration of A(2A) receptor antagonists has shown a significant improvement of the effects of l-DOPA. The present review emphasizes the possible application of A(2A) receptor antagonists in pathological conditions other than parkinsonism, including drug addiction, sleep disorders and pain. In addition to the dorsal striatum, the ventral striatum (nucleus accumbens) contains a high density of A(2A) receptors, which presynaptically and postsynaptically regulate glutamatergic transmission in the cortical glutamatergic projections to the nucleus accumbens. It is currently believed that molecular adaptations of the cortico-accumbens glutamatergic synapses are involved in compulsive drug seeking and relapse. Here IRP scientists review recent experimental evidence suggesting that A(2A) antagonists could become new therapeutic agents for drug addiction. Morphological and functional studies have identified lower levels of A(2A) receptors in brain areas other than the striatum, such as the ventrolateral preoptic area of the hypothalamus, where adenosine plays an important role in sleep regulation. Although initially believed to be mostly dependent on A(1) receptors, here the authors review recent studies that demonstrate that the somnogenic effects of adenosine are largely mediated by hypothalamic A(2A) receptors. A(2A) receptor antagonists could therefore be considered as a possible treatment for narcolepsy and other sleep-related disorders. Finally, nociception is another adenosine-regulated neural function previously thought to mostly involve A(1) receptors. Although there is some conflicting literature on the effects of agonists and antagonists, which may

partly be due to the lack of selectivity of available drugs, the studies in A(2A) receptor knockout mice suggest that A(2A) receptor antagonists might have some therapeutic potential in pain states, in particular where high intensity stimuli are prevalent. Ferre, S., Diamond, I., Goldberg, S.R., Yao, L., Hourani, S.M., Huang, Z.L., Urade, Y. and Kitchen, I. Prog Neurobiol, May 1, 2007, Epubmed ahead of print, PMID 17532111.

5-HT(1B) Receptor-Mediated Serotoninergic Modulation of Methylphenidate-Induced Locomotor Activation in Rats

Previous studies have shown that the dopamine (DA) uptake blocker methylphenidate, a psychostimulant widely used for the treatment of attention-deficit hyperactivity disorder (ADHD), prevents the neurotoxic effects of the highly abused DA releaser methamphetamine. However, there is a lack of information about the pharmacological interactions of these two drugs at the behavioral level. When systemically administered within an interval of 2 h, previous administration of methylphenidate (10 mg/kg, intraperitoneal (i.p.)) did not modify locomotor activation induced by methamphetamine. On the other hand, previous administration of methamphetamine (1 mg/kg, i.p.) markedly potentiated methylphenidate-induced motor activation. With in vivo microdialysis experiments, methamphetamine and methylphenidate were found to increase DA extracellular levels in the nucleus accumbens (NAs). Methamphetamine, but not methylphenidate, significantly increased the extracellular levels of serotonin (5-HT) in the NAs. Methamphetamine-induced 5-HT release remained significantly elevated for more than 2 h after its administration, suggesting that the increased 5-HT could be responsible for the potentiation of methylphenidate-induced locomotor activation. In fact, previous administration of the 5-HT uptake blocker fluoxetine (10 mg/kg, i.p.) also potentiated the motor activation induced by methylphenidate. A selective 5-HT(1B) receptor antagonist (GR 55562; 1 mg/kg), but not a 5-HT(2) receptor antagonist (ritanserin; 2 mg/kg, i.p.), counteracted the effects of methamphetamine and fluoxetine on the motor activation induced by methylphenidate. Furthermore, a 5-HT(1B) receptor agonist (CP 94253; 1-10 mg/kg, i.p.) strongly and dose-dependently potentiated methylphenidate-induced locomotor activation. The 5-HT(1B) receptor-mediated modulation of methylphenidate-induced locomotor activation in rat could have implications for the treatment of ADHD. Borycz, J., Zapata, A., Quiroz, C., Volkow, N.D. and Ferre, S. Neuropsychopharmacology, May 9, 2007, Epubmed ahead of print, PMID 17487226.

Neurotransmitter Receptor Heteromers and Their Integrative Role in 'Local Modules': The Striatal Spine Module

'Local module' is a fundamental functional unit of the central nervous system that can be defined as the minimal portion of one or more neurons and/or one or more glial cells that operates as an independent integrative unit. This review focuses on the importance of neurotransmitter receptor heteromers for the operation of local modules. To illustrate this, IRP scientists use the striatal spine module (SSM), comprised of the dendritic spine of the medium spiny neuron (MSN), its glutamatergic and dopaminergic terminals and astroglial processes. The SSM is found in the striatum, and although aspects such as neurotransmitters and receptors will be specific to the SSM, some general principles should apply to any local module in the brain. The analysis of some of the receptor heteromers in the SSM shows that receptor heteromerization is associated with particular elaborated functions in this local module. Adenosine A(2A) receptor-dopamine D(2) receptor-glutamate metabotropic mGlu(5) receptor heteromers are located adjacent to the glutamatergic synapse of the dendritic spine of the enkephalin MSN, and their cross-talk within the receptor heteromers helps to modulate postsynaptic plastic changes at the glutamatergic synapse. A(1) receptor-A(2A) receptor heteromers are found in the glutamatergic terminals and the molecular cross-talk between the two receptors in the heteromer helps to modulate glutamate release. Finally, dopamine D(2) receptor-non-alpha(7) nicotinic acetylcholine receptor

heteromers, which are located in dopaminergic terminals, introduce the new concept of autoreceptor heteromer. Ferre, S., Agnati, L.F., Ciruela, F., Lluis, C., Woods, A. S., Fuxe, K. and Franco, R. Brain Res Rev, January 27, 2007, Epubmed ahead of print, PMID 17408563.

Striatal Adenosine A(2A) and Cannabinoid CB(1) Receptors Form Functional Heteromeric Complexes that Mediate the Motor Effects of Cannabinoids

The mechanism of action responsible for the motor depressant effects of cannabinoids, which operate through centrally expressed cannabinoid CB(1) receptors, is still a matter of debate. In the present study, IRP researchers report that CB(1) and adenosine A(2A) receptors form heteromeric complexes in co-transfected HEK-293T cells and rat striatum, where they colocalize in fibrilar structures. In a human neuroblastoma cell line, CB(1) receptor signaling was found to be completely dependent on A(2A) receptor activation. Accordingly, blockade of A(2A) receptors counteracted the motor depressant effects produced by the intrastriatal administration of a cannabinoid CB(1) receptor agonist. These biochemical and behavioral findings demonstrate that the profound motor effects of cannabinoids depend on physical and functional interactions between striatal A(2A) and CB(1) receptors. Carriba, P., Ortiz, O., Patkar, K., Justinova, Z., Stroik, J., Thermann, A., Muller, C., Woods, A.S., Hope, B.T., Ciruela, F., Casado, V., Canela, E.I., Lluis, C., Goldberg, S.R., Moratalla, R., Franco, R. and Ferre, S. Neuropsychopharmacology, Mar 14, 2007; Epubmed ahead of print, PMID 17356572.

Nicotinic Alpha 7 Receptors as a New Target for Treatment of Cannabis Abuse

Increasing use of cannabis makes the search for medications to reduce cannabis abuse extremely important. Here, IRP scientists show that homomeric alpha7 nicotinic receptors are novel molecular entities that could be targeted in the development of new drugs for the treatment of cannabis dependence. In rats, systemic administration of the selective alpha7 nicotinic acetylcholine receptor antagonist methyllycaconitine (MLA), but not the selective heteromeric non-alpha7 nicotinic acetylcholine receptor antagonist dihydrobetaerythroidine, (1) antagonized the discriminative effects of delta-9-tetrahydrocannabinol (THC), the main active ingredient in cannabis, (2) reduced intravenous self-administration of the synthetic cannabinoid CB1 receptor agonist WIN55,212-2 [(R)-(+)-[2,3-dihydro-5-methyl-3[(4-morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4-benzoxazinyl]-(1-naphthalenyl)methanone, mesylate salt], and (3) decreased THC-induced dopamine elevations in the shell of the nucleus accumbens. Altogether, these results indicate that blockade of alpha7 nicotinic receptors reverses abuse-related behavioral and neurochemical effects of cannabinoids. Importantly, MLA reversed the effects of cannabinoids at doses that did not produce depressant or toxic effects, further pointing to alpha7 nicotinic antagonists as potentially useful agents in the treatment of cannabis abuse in humans. Solinas, M., Scherma, M., Fattore, L., Stroik, J., Wertheim, C., Tanda, G., Fratta, W. and Goldberg, S.R. Journal of Neuroscience, 27, pp. 5615-5620, 2007.

Neurobiology of Relapse Section, Behavioral Neuroscience Research Branch

Systemic and Central Amygdala Injections of the mGluR(2/3) Agonist LY379268 Attenuate the Expression of Incubation of Sucrose Craving in Rats

IRP researchers previously reported that systemic or central amygdala injections of the mGluR(2/3) agonist LY379268 (which decreases glutamate release) prevented enhanced cue-induced cocaine seeking in extinction tests after prolonged withdrawal (incubation of cocaine craving). Here, authors report that systemic and central amygdala injections of LY379268 also

prevented the enhanced cue-induced sucrose seeking in extinction tests after prolonged sucrose-free period (incubation of sucrose craving). These findings suggest that central amygdala glutamate plays an important role in the incubation of reward craving after withdrawal from both drug and non-drug rewards. Uejima, J.L., Bossert, J.M., Poles, G.C., and Lu, L. Behavioral Brain Research, 181, pp. 292-296, 2007.

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

Consistency and Reliability of Subjective Responses to Imagery-induced Tobacco Craving

Although studies have demonstrated the validity of imagery procedures to elicit tobacco craving responses in single sessions, few studies have examined the consistency of responding in the same individuals over multiple experimental sessions. In this study, nondeprived smokers were presented with a randomized series of imagery scripts that varied in the intensity of smoking urge content. At each of five sessions spaced over several weeks, participants were exposed to six imagery trials (two each of no-, low-, and high-intensity imagery scripts). After each trial, participants completed subjective measures of tobacco craving and mood. Ratings of craving and negative mood significantly increased as a function of smoking-urge intensity, which was consistent across the five sessions. Further, significant intraclass correlations indicated that craving and mood responses were highly reliable over the five sessions, as well as across two, three, and four sessions. These results have practical implications for examining individual differences in sensitivity to smoking cues and for studies involving repeated measurement of elicited craving over time. Lee, D.C., Myers, C.S., Taylor, R.C., Moolchan, E.T. and Heishman, S.J. Addictive Behaviors, Epub ahead of print, 2007.

Tobacco Craving Predicts Lapse to Smoking in Adolescent Smokers

Previous research indicates that tobacco craving predicts relapse to smoking among adult smokers attempting to quit. IRP scientists hypothesized a similar relationship between craving and lapse among adolescent smokers during the treatment phase of a clinical trial. A visit was considered a lapse visit if the participant reported smoking or had a CO >= 7 ppm subsequent to an abstinent visit. Thirty-four participants (mean +/- SD, age 14.9 +/- 1.3 years, cigarettes per day 18.0 +/- 7.6, Fagerstroem Test for Nicotine Dependence 6.8 +/- 1.34, 65% female), were included in the current analysis of 167 treatment visits. Logistic regression analyses showed a positive relationship between degree of craving, measured by the Questionnaire on Smoking Urges, and lapse during smoking cessation treatment ($p = 0.013$). Additionally, linear regression analyses demonstrated a strong positive association between cigarettes smoked per day and craving scores ($p < 0.001$). Taken together with other data, these findings suggest that degree of craving might influence tobacco abstinence for adolescent smokers. Thus, monitoring and addressing craving appears useful to increase the success of adolescent smoking cessation. Bagot, K.S., Heishman, S.J. and Moolchan, E.T. Nicotine and Tobacco Research, 9, pp. 647-652, 2007.

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Program Activities

New NIDA PAs and RFAs

On April 24, 2007, NIDA issued two Program Announcements entitled **Medications Development for the Treatment of Cannabis-Related Disorders (R01) PA-07-365 and Medications Development for the Treatment of Cannabis-Related Disorders (R21) PA-07-366**. Through this FOA, NIDA solicits grant applications from institutions/organizations that propose to conduct preclinical and/or clinical research directed towards the identification, evaluation, and development of safe and effective medications for the treatment of Cannabis Related Disorders, and their medical and psychiatric consequences.

On July 13, 2007, NIDA issued an RFA entitled **Criminal Justice Drug Abuse Treatment Studies 2 (CJ-DATS 2) (U01) (RFA-DA-08-002)**. Through this RFA, NIDA invites cooperative agreement applications to participate as Research Centers in the second phase of the national Criminal Justice Drug Abuse Treatment Studies (CJ-DATS 2). The goal of this cooperative research program is to develop and test systems-level models that integrate public health and public safety approaches for criminal justice-involved adults and adolescents with drug abuse and addictive disorders. Letter of Intent Receipt Date for this RFA: September 26, 2007; Application Receipt Date: October 26, 2007.

PAs and RFAs with Other NIH Components/Agencies

On June 4, 2007, NIDA, in conjunction with the National Institute of Environmental Health Sciences (NIEHS) issued a Program Announcement entitled **Psychopharmacology of Widely Available Psychoactive Natural Products (R01) (PA-07-374)**. This Funding Opportunity Announcement (FOA) solicits research grant applications that characterize the chemistry, psychopharmacology, and/or toxicology of acute and chronic exposure to psychoactive natural products, as well as the transition in the use of these products to licit or illicit drugs of abuse.

On June 4, 2007, NIDA, in conjunction with the National Institute of Environmental Health Sciences (NIEHS) issued a Program Announcement entitled **Psychopharmacology of Widely Available Psychoactive Natural Products (R03) (PA-07-375)**. This Funding Opportunity Announcement (FOA) solicits research grant applications that characterize the chemistry, psychopharmacology, and/or toxicology of acute and chronic exposure to psychoactive natural products, as well as the transition in the use of these products to licit or illicit drugs of abuse.

On June 7, 2007, NIDA, in collaboration with numerous other NIH components,

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issued a PA entitled **Behavioral and Social Science Research on Understanding and Reducing Health Disparities (R01) (PAR-07-379)**. The Purpose of this PA is to encourage behavioral and social science research on the causes and solutions to health and disabilities disparities in the U. S. population. Health disparities between, on the one hand, racial/ethnic populations, lower socioeconomic classes, and rural residents and, on the other hand, the overall U.S. population are major public health concerns. Emphasis is placed on research in and among three broad areas of action: 1) Public policy, 2) health care, and 3) disease/disability prevention. Particular attention is given to reducing "health gaps" among groups. Proposals that utilize an interdisciplinary approach, investigate multiple levels of analysis, incorporate a life-course perspective, and/or employ innovative methods such as system science or community-based participatory research are particularly encouraged.

On June 7, 2007, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Behavioral and Social Science Research on Understanding and Reducing Health Disparities (R21) (PAR-07-380)**. The Purpose of this PA is to encourage behavioral and social science research on the causes and solutions to health and disabilities disparities in the U. S. population. Health disparities between, on the one hand, racial/ethnic populations, lower socioeconomic classes, and rural residents and, on the other hand, the overall U.S. population are major public health concerns. Emphasis is placed on research in and among three broad areas of action: 1) Public policy, 2) health care, and 3) disease/disability prevention. Particular attention is given to reducing "health gaps" among groups. Proposals that utilize an interdisciplinary approach, investigate multiple levels of analysis, incorporate a life-course perspective, and/or employ innovative methods such as system science or community-based participatory research are particularly encouraged.

On June 11, 2007, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Advancing Novel Science in Women's Health Research (ANSWHR) (R21) (PAS-07-381)**. The purpose of this Funding Opportunity Announcement (FOA), issued by the Office of Research on Women's Health (ORWH) and co-sponsoring NIH institutes and centers (ICs), is to promote innovative, interdisciplinary research that will advance new concepts in women's health research and the study of sex/gender differences. Recent research reports have established the importance of studying issues specific to women, including the scientific and clinical importance of analyzing data separately for females and males. ORWH is particularly interested in encouraging extramural investigators to undertake new interdisciplinary research to advance studies on how sex and gender factors affect women's health; however, applications in all areas of women's health and/or sex/gender research are invited.

On June 11, 2007, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Advancing Novel Science in Women's Health Research (ANSWHR) (R03) (PAS-07-382)**. The purpose of this Funding Opportunity Announcement (FOA), issued by the Office of Research on Women's Health (ORWH) and co-sponsoring NIH institutes and centers (ICs), is to promote innovative, interdisciplinary research that will advance new concepts in women's health research and the study of sex/gender differences. Recent research reports have established the importance of studying issues specific to women, including the scientific and clinical importance of analyzing data separately for females and males. ORWH is particularly interested in encouraging extramural investigators to undertake new interdisciplinary research to advance studies on how sex and gender factors affect women's health; however, applications in all areas of women's health and/or sex/gender research are invited.

Planned Meetings

Publications

Staff Highlights

Grantee Honors

On June 29, 2007, NIDA, in conjunction with a number of other NIH components, issued a PA entitled **Neurotechnology Research, Development, and Enhancement (SBIR [R43/R44]) PA-07-389**. Advances in the brain and behavioral sciences are being made rapidly, vastly improving our understanding of healthy brain function and offering promise to the millions suffering from brain and behavioral disorders. This Funding Opportunity Announcement (FOA) solicits Small Business Innovation Research (SBIR) grant applications from small business concerns (SBCs) that propose to enable neuroscience and behavioral research through the development of novel, or the significant enhancement or improvement of currently existing, tools and approaches to be used in brain and behavioral research. Such tools and approaches could include those used in basic or clinical research, or for clinical treatment and care (e.g., assessment, diagnosis, and treatment of brain disorders). Research solicited under this funding opportunity announcement is not limited to any particular type of technology, level of analysis, or approach. Multidisciplinary teams of researchers are especially encouraged to apply. Technologies appropriate for study, development and enhancement under this FOA include hardware, software, and wetware (and combinations thereof).

On June 29, 2007, NIDA, in conjunction with a number of other NIH components, issued a PA entitled **Neurotechnology Research, Development, and Enhancement (SBIR [R41/R42] PA-07-390)**. Advances in the brain and behavioral sciences are being made rapidly, vastly improving our understanding of healthy brain function and offering promise to the millions suffering from brain and behavioral disorders. This Funding Opportunity Announcement (FOA) solicits Small Business Innovation Research (SBIR) grant applications from small business concerns (SBCs) that propose to enable neuroscience and behavioral research through the development of novel, or the significant enhancement or improvement of currently existing, tools and approaches to be used in brain and behavioral research. Such tools and approaches could include those used in basic or clinical research, or for clinical treatment and care (e.g., assessment, diagnosis, and treatment of brain disorders). Research solicited under this funding opportunity announcement is not limited to any particular type of technology, level of analysis, or approach. Multidisciplinary teams of researchers are especially encouraged to apply. Technologies appropriate for study, development and enhancement under this FOA include hardware, software, and wetware (and combinations thereof).

On June 29, 2007, NIDA, in collaboration with NIMH and NIAAA, issued a PA entitled **Mentoring Programs to Diversify the Mental Health and Substance Abuse HIV/AIDS Workforce through Innovative Educational Initiatives (R25) (PAR-07-386)**. This funding opportunity announcement (FOA) was developed in response to: (i) simultaneous overrepresentation of individuals from racial and ethnic groups with HIV/AIDS, yet underrepresentation of individuals from racial and ethnic groups, individuals with disabilities, and individuals from disadvantaged backgrounds as HIV/AIDS researchers; (ii) insufficient scientific information about HIV/AIDS disparities experienced by members of underrepresented racial and ethnic groups; (iii) the paucity of HIV/AIDS mental health, and substance abuse research by investigators from underrepresented racial and ethnic groups; and (iv) the limited number of individuals from underrepresented racial and ethnic groups who are pursuing careers in HIV/AIDS mental health and/or substance abuse research. Through this PA participating Institutes encourage the development of research mentoring programs for graduate students, postdoctoral fellows, and early career faculty from underrepresented groups to improve the capacity for high quality HIV research and to facilitate the research career development of investigators in HIV/AIDS fields, particularly as they relate to mental health and substance abuse. This FOA solicits grant applications from applicant organizations that propose to: (i) develop a special summer institute for new

and improved research mentorship programs--targeting individuals from underrepresented racial and ethnic groups, individuals with disabilities, or individuals from disadvantaged backgrounds--relevant to the HIV/AIDS research missions of NIMH, NIAAA and NIDA and/or (ii) establish a central network of senior mentors in HIV/AIDS research for mentees from underrepresented groups (for the purpose of this FOA, "underrepresented groups" is defined as individuals from racial and ethnic groups, individuals with disabilities, and individuals from disadvantaged backgrounds). These mentoring programs should have a thematic focus on research/educational activities that relate to the mental health, substance abuse or CNS aspects of HIV infection (e.g., disparities, neuropsychiatry, neuropathogenesis, prevention, treatment, services).

On July 19, 2007, NIDA, in conjunction with several other NIH Institutes, issued a PA entitled **Health Research with Diverse Populations (R01) (PA-07-409)**. The purpose of this Funding Opportunity Announcement (FOA) is to invite grant applications for biological, behavioral, social, addictive, and mental health research related to the health of lesbian, gay, bisexual, transgender, intersex, and other diverse populations. Proposed research should be appropriate for the missions of one or more of the participating Institutes.

On July 24, 2007, NIDA and NIAAA jointly issued a PA entitled **Genetic Epidemiology of Substance Use Disorders (R01) (PA-07-413)**. This funding opportunity announcement (FOA) solicits research to expand the application of genetic epidemiologic methods to studies of substance and alcohol use disorders (SUDs/AUD, drug and alcohol abuse and dependence) by applying genetic epidemiologic approaches to advance our understanding of developmental trajectories of SUD/AUD, differentiate genetic and environmental factors in the development and maintenance of SUD/AUD, broaden and refine phenotypic definitions of SUDs/AUD, guide the translation of etiologic findings to treatment, prevention, gene-finding and molecular studies, and meet the methodologic challenges of the field.

On July 24, 2007, NIDA and NIAAA jointly issued a PA entitled **Genetic Epidemiology of Substance Use Disorders (R03) (PA-07-414)**. This funding opportunity announcement (FOA) solicits research to expand the application of genetic epidemiologic methods to studies of substance and alcohol use disorders (SUDs/AUD, drug and alcohol abuse and dependence) by applying genetic epidemiologic approaches to advance our understanding of developmental trajectories of SUD/AUD, differentiate genetic and environmental factors in the development and maintenance of SUD/AUD, broaden and refine phenotypic definitions of SUDs/AUD, guide the translation of etiologic findings to treatment, prevention, gene-finding and molecular studies, and meet the methodologic challenges of the field.

On July 24, 2007, NIDA and NIAAA jointly issued a PA entitled Genetic Epidemiology of Substance Use Disorders (R21) (PA-07-415). This funding opportunity announcement (FOA) solicits research to expand the application of genetic epidemiologic methods to studies of substance and alcohol use disorders (SUDs/AUD, drug and alcohol abuse and dependence) by applying genetic epidemiologic approaches to advance our understanding of developmental trajectories of SUD/AUD, differentiate genetic and environmental factors in the development and maintenance of SUD/AUD, broaden and refine phenotypic definitions of SUDs/AUD, guide the translation of etiologic findings to treatment, prevention, gene-finding and molecular studies, and meet the methodologic challenges of the field.

On July 24, NIDA, in collaboration with several other NIH Institutes, issued a PA entitled **Developmental Pharmacology (R01) (PAR-07-416)**. The purpose of this PA is to encourage multidisciplinary, investigator-initiated basic and translational research in developmental pharmacology with particular emphasis on the role of ontogeny on drug metabolizing enzymes, transporters,

receptors and signaling pathways activity across developmental periods from fetal life to adolescence.

On July 25, 2007, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Neuroimaging Informatics Software Enhancement for Improved Interoperability and Dissemination (R03) (PAR-07-417)**. This FOA intends to support modification and enhancement of existing neuroimaging informatics tools and resources that are hosted or being considered for inclusion into the NIH Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC, www.nitrc.org, public release scheduled for October 2007). Examples of such tools include image segmentation, image registration, image processing pipelines, statistical analysis packages, spatial alignment and normalization algorithms, and data format translators. Resources include well-characterized test datasets, data formats, and databases, among others. The proposed work shall significantly improve the interoperability and adoptability of neuroimaging informatics tools and resources and result in enhanced dissemination, adoption, and evolution of such tools and resources by the broader neuroimaging research community.

On August 3, 2007, NIDA, in collaboration with numerous other NIH components, issued a PA entitled Data Ontologies for Biomedical Research (R01) (PAR-07-425). The NIH Blueprint for Neuroscience Research is a framework to enhance cooperative activities among the NIH Office of the Director and 15 NIH Institutes and Centers that support research on the nervous system. This FOA is released in affiliation with the Neuroscience Blueprint, with Institutes and Centers participating independently, and with participation by Institutes that are not part of the Neuroscience Blueprint.

On August 3, 2007, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Sharing Data and Tools: Federation using the BIRN and caBIG Infrastructures (R01) (PAR-07-426)**. The NIH Blueprint for Neuroscience Research is a framework to enhance cooperative activities among the NIH Office of the Director and 15 NIH Institutes and Centers that support research on the nervous system. This FOA is released in affiliation with the Neuroscience Blueprint, with Institutes and Centers participating independently, and with participation by Institutes that are not part of the Neuroscience Blueprint. Sharing data and tools across a research community adds tremendous value to the efforts of that community. Search engines like Google show the power of sharing text based data. While strides have been made, the infrastructure necessary to share and query data sets that have more than just textual biomedical data is still under development. Examples of such heterogeneous data sets include those that contain images, clinical data, or genomic/gene expression data. Two large NIH supported infrastructure projects to allow data and tool sharing are the caBIG(TM) program and the Biomedical Informatics Research Network (BIRN). Many of the communities involved in neuroscience research embrace the data/tool sharing idea. Some communities, such as neuroimaging researchers, have seized it, and in so doing, have accrued scientific benefits that would have been otherwise out of reach. As a specific example, three neuroimaging research communities are serving as the biological test beds for the BIRN infrastructure (http://www.nbirn.net). The BIRN infrastructure has now matured to the point where it can serve as a platform for data sharing and informatics tool sharing that extends beyond the neuroimaging researchers involved in the test beds, to include other areas of neuroscience beyond imaging, and to include biomedical research beyond neuroscience. The caBIG(TM) program has goals that are related to those of the BIRN program, but has chosen a different development path. caBIG(TM) aims to develop applications and underlying architecture that connects data and tools in an open, federated environment. Interoperability in caBIG(TM) is based on standardizing interfaces and data, rather than on specific software systems used in BIRN. General information concerning caBIG can be found at cabig.nci.nih.gov.

On August 21, 2007, NIDA, in collaboration with other NIH components and with the Administration for Children and Families (ACF) and CDC and SAMHSA, issued a PA entitled **Research on Interventions for Child Abuse and Neglect (R01) (PA-07-437)**. This Funding Opportunity Announcement (FOA) solicits research project grant (R01) applications focused on conducting efficacy and effectiveness trials of child abuse and neglect interventions. Specifically, this FOA solicits grant applications that include various levels of interventions. For those interventions that need preliminary research, applicants should consider additional mechanisms, which are used to establish efficacy, including the R21 and R34, as appropriate. However, given the public health need for children and families who experience the negative effects of child abuse and neglect, interventions in which preliminary developmental/exploratory work has already been undertaken, and pilot studies, or in some cases efficacy trials, have demonstrated positive change are strongly encouraged for R01 grant applications under this FOA. Of particular interest is the development of large scale trials designed to target either or both the victims or perpetrators of child abuse and neglect, including preventive interventions. Child abuse and neglect is a complex public health issue likely caused by a myriad of factors, including individual-, family-, and community-level elements. Thus, a research program focused on understanding and addressing these problems must necessarily draw upon interdisciplinary theories and approaches. One of the goals of this FOA is to bring together multi-disciplinary and translational perspectives encompassing basic biomedical, behavioral and social science research in mental health, physical health, public health and prevention, alcohol and substance abuse, neurology, injury, trauma and child development, to advance our knowledge of child abuse and neglect. Only projects proposing rigorous scientific research designs will be considered; service demonstrations or other types of service programs are not eligible for funding under this FOA.

On July 18, 2007, NIDA, in collaboration with a number of other NIH components, issued an RFA entitled **U.S.-India Bilateral Collaborative Research Partnerships (CRP) on the Prevention of HIV/AIDS (R21) (RFA-AI-07-031)**. This Funding Opportunity Announcement (FOA) solicits Exploratory/Developmental (R21) applications from United States (U.S.)-funded institutions with an Indian-institution partner to establish Collaborative Research Partnerships (CRP) in the field of HIV/AIDS prevention with an emphasis on topical microbicides as well as other modes of HIV/AIDS prevention. The U.S.-India Bilateral CRP Program is designed to develop collaborations between scientists and institutions in the U.S. and India to conduct high quality HIV/AIDS prevention research of mutual interest and benefit to both countries while developing the basis for future institutional and individual scientific collaborations. This FOA will utilize the research capacity of the institutions and scientists in both countries to advance the field of HIV/AIDS prevention and develop preliminary data that may support a research proposal to test an HIV/AIDS prevention program with public health significance.

On July 17, 2007, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Tools and Techniques for Elucidating and Manipulating Neural Circuit Development (R21) (RFA-MH-08-060)**. The NIH Blueprint for Neuroscience Research is a framework to enhance cooperative activities among the NIH Office of the Director and 15 NIH Institutes and Centers that support research on the central and peripheral nervous systems. In fiscal year 2008, the Blueprint is emphasizing neural development. This Funding Opportunity Announcement (FOA) solicits applications directed toward the discovery of novel and/or improved means for precise spatiotemporal analysis or manipulation of circuit assembly in the developing central and peripheral nervous systems. For the purposes of this FOA, neural circuit development is defined as processes occurring during prenatal and postnatal development (through adolescence) that begin with axon and dendrite formation and continue through axon guidance and

pathfinding, myelination, synapse formation and synapse refinement. Tools and technologies for the study of invertebrates, vertebrates and/or humans are acceptable if the resulting resources will accelerate research in the area of neural circuit development.

On July 23, 2007, NIDA, in collaboration with several other NIH Institutes, issued an RFA entitled **Exceptional, Unconventional Research Enabling Knowledge Acceleration (EUREKA) (R01) (RFA-GM-08-002)**. This FOA solicits Research Project Grant (R01) applications from institutions/organizations proposing exceptionally innovative research on novel hypotheses or difficult problems, solutions to which would have an extremely high impact in biomedical or biobehavioral research that is germane to the mission of one or more of the participating NIH Institutes.

On August 8, 2007, NIDA, in collaboration with several other NIH Institutes, issued an RFA entitled **Collaborative Research to Explore New Uses for Existing Radioligands (R21/R33) (RFA-DA-08-001)**. Through the issuance of this RFA, participating Institutes seek 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. The primary focus of the proposal must be on human studies; animal studies are allowable only if required to obtain regulatory approval for the ligands.

On August 9, 2007, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Genome-wide Association Studies in the Genes, Environment, and Health Initiative - Study Investigators (U01) (RFA-HG-07-012)**. The purpose of this funding opportunity is to provide support for investigative groups to conduct genome-wide association (GWA) genotyping and/or replication studies, using data and specimens from human subjects on whom information is available for conditions/traits of public health importance and relevant environmental exposures. It includes support for sharing the specimens and data and analyzing the resulting data as part of the NIH-wide Genes, Environment, and Health Initiative (GEI).

On August 9, 2007, NIDA, in collaboration with a number of other NIH components, issued and RFA entitled **Clinical Research Education and Career Development (CRECD) in Minority Institutions (R25) (RFA-RR-07-005)**. This Funding Opportunity Announcement (FOA) is intended to encourage both current CRECD awardee institutions in the final year of funding and eligible institutions that have not received previous CRECD award to apply. These awards are intended to support development and implementation of curriculum-dependent programs in minority institutions to train selected doctoral and postdoctoral candidates in clinical research leading to a Master of Science in Clinical Research or Master of Public Health in a clinically relevant area. A successful program will result in an accredited master's degree program to produce trained clinical researchers who can become part of translational and/or patient-oriented research projects. This FOA has two phases: (1) an initial two-year Phase I to develop and offer a structured didactic course work and mentored clinical research training leading to a degree in Master of Science in Clinical Research or Master of Public Health for qualified and selected candidates; (2) Phase II of the program will provide continued mentoring and career development to the selected CRECD graduates

for up to three years in clinical research as part of their training and skill development to become independent clinical investigators.

NIDA has spearheaded, in conjunction with OBSSR, the RFA entitled **Facilitating Interdisciplinary Research via Methodological and Technological Innovation in the Behavioral and Social Sciences (R21)** http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-07-004.html, a trans-NIH Roadmap RFA intended to support new developments in methodologies and technologies that will facilitate interdisciplinary research involving the behavioral and social sciences. The applications received were reviewed on July 9-10, 2007.

Other Program Activities

Clinical Trials Network (CTN) Update

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

A total of 27 protocols have been initiated since 2001. Over 8,100 participants have enrolled in studies. Of these studies, 20 have completed enrollment and locked the data; one completed enrollment and is in the data-lock phase; and four are currently enrolling. Two new protocols are in the development phase.

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

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

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

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

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

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

The following protocols have locked the data:

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

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

Protocol CTN 0008, A Baseline for Investigating Diffusion of Innovation

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

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

Protocol CTN 0011, A Feasibility Study of a Telephone

Enhancement Procedure (TELE) to Improve Participation in Continuing Care Activities

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

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

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

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

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

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

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

Protocol CTN 0020, (Job Seekers Training for Substance Abusers). This study was also conducted in a Navajo American Indian site, the Na'nizhoozhi Center, Inc. in Gallup, New Mexico, the first CTN study to be conducted there.

Protocol CTN 0021, (Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome for Spanish-Speaking Individuals Seeking Treatment for Substance Abuse). This is the first Spanish-only protocol in the CTN.

The following protocol has ended new enrollment and is 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.

Four protocols are currently enrolling:

Protocol CTN 0027, Starting Treatment with Agonist Replacement Therapies (START) is a randomized, open-label, multi-center study that was developed in collaboration with the Division of Pharmacotherapies & Medical Consequences of Drug Abuse (DPMCDA). Enrollment began in April 2006. As of August 3, 2007, there were 408 randomized participants.

Protocol CTN 0028, Randomized Controlled Trial of Osmotic-Release Methylphenidate (OROS MPH) for Attention Deficit Hyperactivity Disorder (ADHD) in Adolescents with Substance Use Disorders (SUD). Enrollment is now open at 11 sites. As of August 3, 2007, 145 participants have been randomized.

Protocol CTN 0029, A Pilot Study of Osmotic-Release Methylphenidate (OROS MPH) in Initiating and Maintaining Abstinence in Smokers with Attention Deficit Hyperactivity Disorder (ADHD). This study is being carried out at six community treatment sites across five Nodes. There are a total of 226 randomized participants.

Protocol CTN 0030, Prescription Opioid Addiction Treatment Study (POATS) is a randomized 2-phase, open-label, multi-center study in outpatient treatment settings. Pre-screening began in May 2006. The study is being carried out in 11 sites. There are 217 randomized participants.

Two protocols are in the development phase:

Protocol CTN 0031, Stimulant Abuser Groups to Engage in 12-Step (STAGE-12): Evaluation of a Combined Individual-Group Intervention to Reduce Stimulant and Other Drug Use by Increasing 12-Step Involvement. On June 20-21, 2007, the protocol development team met with staff from the Data and Statistics Coordinating Center (Duke Clinical Research Institute) in Durham NC to discuss specific procedures for the Electronic Data Capture being utilized in this study. This face-to-face meeting was the first of its kind during protocol development in the CTN. 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) will take place in Bethesda, MD on December 3-5, 2007. The protocol development team is also collaborating with other CTN investigators (Dennis McCarty - Oregon/Hawaii Node and Joseph Guydish - California/Arizona Node) to incorporate an ancillary study on Health Services Research to be supported by supplementary funds from DESPR.

Protocol CTN 0032, HIV Rapid Testing and Counseling Protocol. This protocol is under development. This study seeks to evaluate the most effective strategy to ensure that persons in drug treatment programs are tested for HIV and receive their HIV test results. The Centers for Disease Control (CDC) have made a priority to bring HIV rapid testing and counseling into outpatient health care settings for high-risk populations. Protocol 0032 was approved for development late November, 2006, and the protocol team meets regularly by conference call. The DSMB met on July 13, 2007 to review and discuss the protocol, and made recommendations to NIDA

In addition to the primary CTN trials, there are currently 30 funded studies supported by independent grants that use CTN studies as a platform.

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 will be collecting data to assess the costs and benefits of the two treatment approaches EMM (Enhanced Medical Management) and SMM (Standard Medical Management).

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

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

Akins, Michael R. -- Brown University
Syncam Family Interactions in Synapse Formation

Alexandre, Pierre K. -- Johns Hopkins University
Economic Aspects of Ecstacy Use

Ambrose Lanci, Lisa M. -- Thomas Jefferson University
Anxiety in Females During Cocaine Withdrawal

Back, Sudie E. -- Medical University of South Carolina
Translational Research Training: Stress and Addiction

Baldwin, Gayle C. -- University of California Los Angeles
Cocaine Synergizes with T Cell Activation as a Cofactor for HIV Infection

Baumann, Steven -- Psychology Software Tools, Inc.
Stimulus Delivery and Response Hardware for FMRI Studies in Substance Abuse

Becker, Jill B. -- Gordon Research Conferences
2007 Catecholamines Gordon Research Conference

Beckwith, Curt G. -- Miriam Hospital
Comprehensive HIV Testing Strategies for Jails

Bickel, Warren K. -- University of Arkansas Medical Sciences Little Rock
The Behavioral Economics of Relapse

Bidlack, Jean M. -- International Narcotics Research Conference, Inc.
38th Annual International Narcotics Research Conference

Bidlack, Jean M. -- University of Rochester
Pharmacology of Drug Abuse

Bierut, Laura J. -- Washington University
Human Genetics of Addiction: A Study of Common and Specific Factors

Bogenschutz, Michael P. -- University of New Mexico Albuquerque
Clinical Trial Network: Southwest Node

Booth, Robert E. -- University of Colorado Denver/Health Sciences Center Aurora

Intervention to Reduce injection Drug Use

Boudreaux, Edwin D. -- University of Medicine/Dentistry of New Jersey-Robert Wood Johnson Medical School
Multicenter Pilot Studies for Educational Tobacco Interventions

Bowen, Anne M. -- University of Wyoming
Wyoming Meth Use and AIDS Risk: Exploring Rural Culture and Context

Braine, Naomi -- Beth Israel Medical Center, New York
MSM Communities in NYC Respond to HIV and Methamphetamine

Brigham, Gregory S. -- University of Cincinnati
Community Reinforcement and Family Training for Treatment Retention/HIV Risk

Britt, Jonathan P. -- University of Chicago
The Processing of Tonic and Burst Activity Patterns in DA Terminals in the Nacc

Bromberg, Jonas -- Inflexxion, Inc.
Internet Support for Self-Managing Neuropathic Pain

Brookshire, Bethany R. -- Wake Forest University Health Sciences
The Effects of Chronic Methylphenidate on Dopamine and Serotonin Interactions

Brown, Ana C. -- Arizona State University
Explaining Program Effects on Youth Substance Use: Role of Negative Cognitions

Brunzell, Darlene H. -- Yale University
nAChR Subunit Contributions to Nicotine Dependent Behaviors

Budney, Alan J. -- University of Arkansas Medical Sciences Little Rock
Behavioral Treatment of Adolescent Marijuana Use

Budney, Alan J. -- University of Arkansas Medical Sciences Little Rock
Development and Efficacy Test of Computerized Treatment for Marijuana Dependence

Cance, Jessica D. -- University of North Carolina Chapel Hill
Pubertal Timing and Adolescent Substance Use: Psychological and Social Mediators

Carelli, Regina M. -- University of North Carolina Chapel Hill
Neurophysiological Study: Cocaine and Natural Reinforcers

Cass, Wayne A. -- University of Kentucky
Calcitriol and Methamphetamine Neurotoxicity

Chawla, Neharika -- University of Washington
Experiential Avoidance and Substance Use Relapse

Childers, Steven R. -- Wake Forest University Health Sciences
Neuroscience of Drug Abuse Training Program

Chowdhury, Parimal -- University of Arkansas Medical Sciences Little Rock
Sixth Annual Meeting of the Internatioanl Society for the Prevention of Tobacco

Clark, David J. -- Palo Alto Institute for Research & Education, Inc.
Genetic Determinants of Opioid-induced Hyperalgesia

Cloak, Christine C. -- University of Hawaii at Manoa
Impact of Marijuana Exposure on Brain Maturation

Cole, Shannon H. -- Vanderbilt University
Identifying Dopamine Transporter Regulator Proteins in C. Elegans

Collins, Stephanie L. -- Columbia University Health Sciences
Sex Differences & Impulsivity: Effect of Drug History & Stimulant Administration

Cowan, Ronald L. -- Vanderbilt University
Genetic Factors in Human MDMA Toxicity: A PET Study

Cropsey, Karen L. -- Virginia Commonwealth University
Relapse Prevention to Reduce HIVAmong Women Prisoners

Czoty, Paul W. -- Wake Forest University Health Sciences
Cocaine Discrimination, Self-Administration and Microdialysis in Monkeys

Dalva, Matthew B. -- University of Pennsylvania
Cell-Contact Mediated Mechanisms Assembling Synapses

Davidson, Leslie L. -- Columbia University Health Sciences
Health & Psychosocial Need: Children with Developmental Disorder in a Time of HIV

De Wit, Harriet -- University of Chicago
Craving During Smoking Abstinence: Does It Abate Or incubate?

Deadwyler, Samuel A. -- Wake Forest University Health Sciences
Neuronal Analysis of Cocaine Effects on Cognition

Delisi, Lynn E. -- New York University School of Medicine
World Congress of Psychiatric Genetics with Emphasis on Genes for Drug Abuse

Dematteo, David S. -- Treatment Research Institute, Inc. (TRI)
Development of a Prevention Intervention for Low-Risk Drug Court Clients

Dewey, Stephen L. -- Brookhaven Science Assoc., Brookhaven National Laboratory
Treating Adolsecent and Adult Methamphetamine or Inhalant Abuse with S-(+)-GVG

Donny, Eric C. -- University of Pittsburgh at Pittsburgh
Are Some Regular Smokers Resistant to Nicotine Dependence?

Donovan, Dennis M. -- University of Washington
Clinical Trials Network: Pacific Northwest Node

D'souza, Deepak C. -- Yale University
Cannabinoids, Neural Synchrony and Information Processing

Du, Congwu -- State University New York Stony Brook
Optical and fMRI Studies of Cocaine in the Rat Brain

Dubocovich, Margarita L. -- Northwestern University
Modulation of Methamphetamine Actions in the CNS

Dymecki, Susan M. -- Harvard University Medical School
Developmental Genetics of Serotonin Neuron Subtypes in Brain Reward Circuits

Eiden, Rina D. -- State University of New York at Buffalo
Maternal Substance Use and Toddler Self-Regulation

Eisch, Amelia J. -- University of Texas Southwest Medical Center, Dallas
New Horizons in Adult Neurogenesis

Eldridge, Gloria D. -- University of Alaska Anchorage

HIV, Drugs, and Prisoners: Barriers to Epidemiologic and Intervention Research

Ernst, Thomas M. -- University of Hawaii at Manoa
Rgr-Based Motion Tracking for Real-Time Adaptive MRI and Spectroscopy

Evans, Christopher J. -- University of California Los Angeles
Center for Study of Opioid Receptors and Drugs of Abuse (CSORDA)

Evans, Suzette M. -- Columbia University Health Sciences
Sex Differences in Stress & Impulsivity in Cocaine Abusers

Evans, Suzette M. -- New York State Psychiatric Institute
Progesterone Treatment for Cocaine-Dependent Women

Evins, A. Eden -- Massachusetts General Hospital
Smoking Cessation and Smoking Relapse Prevention in Patients with Schizophrenia

Fawcett, Stephen B. -- University of Kansas Lawrence
Testing the Community Change Model with Substance Abuse Coalitions

Febo, Marcelo -- Northeastern University
Brain Imaging of Cocaine and Maternal Reward

Fiellin, David A. -- Yale University
Buprenorphine Maintenance Vs. Detoxification in Prescription Opioid Dependence

Filbey, Francesca -- The Mind Institute
The Effects of CNR1 on Brain Function in Cannabis Users

Foltin, Richard W. -- New York State Psychiatric Institute
Translational Approach to Models in Relapse

Frangakis, Constantine -- Johns Hopkins University
Statistical Designs and Methods for Partially Controlled HIV/AIDS Studies

Friedmann, Peter D. -- Association for Medical Education & Research in Substance Abuse
AMERSA Annual National Conference

Fuller, Crystal M. -- New York Academy of Medicine
Pharmacy Referral Intervention: IDU Access to Services

Gale, Michael J. -- University of Washington
Inate Immune Defense Against HCV and HIV: The Chimeric Mouse Model

Gauda, Estelle B. -- Johns Hopkins University
Immersion in Drug Abuse

Gillette, Rhanor -- University of Illinois Urbana-Champaign
Toggling a Switch for Appetance and Avoidance

Ginsburg, Brett C. -- University of Texas Health Science Center San Antonio
Age, Ethanol, and Strain Effects on the Behavioral Pharmacology of Cannabinoids

Gintzler, Alan R. -- Suny Downstate Medical Center
Adenylyl Cyclase Gbetagamma Stimulation and Opioid Tolerance

Go, Vivian F. -- Johns Hopkins University
Prevention for Positives: A Randomized Controlled Trial Among Vietnamese HIV

Golik, Jerzy -- Makscientific, LLC
New Drugs to Enhance Endocannabinoid Responses for Treating Excitotoxicity

Gorbach, Pamina M. -- University of California Los Angeles
Transmission Behavior in Partnerships of Newly HIV Infected Southern Californians

Gourevitch, Marc N. -- New York University School of Medicine
Substance Abuse Research Education and Training (SARET)

Griffiths, Roland R. -- Johns Hopkins University
Human Clinical Pharmacology of Emerging Drugs of Abuse (Club Drugs)

Grimm, Jeffrey W. -- Western Washington University
Incubation of Craving: Neural Substrates

Gruber, Staci A. -- Mc Lean Hospital, Belmont, MA
Marijuana and Mood: Frontal Predictors of Behavior

Grueter, Brad A. -- Stanford University
Role of Psd-95 in Synaptic and Drug induced Plasticity in Dopamine Neurons

Guo, Xiaohui -- University of Miami-Medical School
Measurement Invariance Analysis on ASI-Lite

Hagan, Holly C. -- National Development & Research Institutes
Reducing HIV Transmission By Promoting Sexual Health Among Drug Users

Hahn, Judith A. -- University of California San Francisco
Dynamic Modeling of the HCV Epidemic in IDU

Heimer, Robert -- Yale University
Environmental Factors in HIV Transmission Among Suburban IDUs

Henderson, Leslie P. -- Dartmouth College
Steroid Regulation of Ion Channels

Henry, Loren K. -- Vanderbilt University
Integration of Computational and Biological Analysis of Serotonin Transporters

Herin, David V. -- University of Texas Health Science Center Houston
Dextroamphetamine Treatment for Comorbid Cocaine Dependence and ADHD

Herrold, Amy A. -- Loyola University Chicago
Mglur5 Regulation of METH Reward and Sensorimotor Gating

Heslin, Kevin C. -- Charles R. Drew University of Medicine & Science
Racial/Ethnic Disparities in Mental Healthcare Use by Substance Abuse Clients

Ho, Wenzhe -- Children's Hospital of Philadelphia
Opioids, HIV/HCV and Host Cell Innate Immunity

Houghten, Richard A. -- Torrey Pines Institute for Molecular Studies
In Vivo Screening of Mixture-Based Combinatorial Libraries

Hoven, Christina W. -- New York State Psychiatric Institute
Maternal Incarceration and Course of Child Psychopathology in the South Bronx

Hurt, Hallam -- Children's Hospital of Philadelphia
In Utero Cocaine Use: Adolescent and Young Adult Neurocognitive Outcome

Inturrisi, Charles E. -- Weill Medical College of Cornell University
Pharmacology and Neuroscience of Drug Abuse

Jarbe, Torbjorn U. -- Northeastern University
Endogenous/Exogenous Cannabinoids: A Comparison

Jason, Leonard A. -- De Paul University
Evaluating Alternative Aftercare Models for Ex-offenders

Javitt, Daniel C. -- Nathan S. Kline Institute for Psychiatric Research
Phencyclidine Abuse & Psychosis: Biomedical Mechanisms

Johnson, Kenneth M. -- University of Texas Medical Branch Galveston
Neural and Pharmacological Mechanisms of Abused Drugs

Jones, Joshua L. -- University of North Carolina Chapel Hill
Amygdalar Regulation of Nucleus Accumbens Reward Signaling

Jones, Sara R. -- Wake Forest University Health Sciences
Dopamine Transporter Changes Following Cocaine Self-Administration

Kamarck, Thomas W. -- University of Pittsburgh at Pittsburgh
Psychosocial Stress Exposure: Real-Time and Structured Interview Technologies

Kandel, Denise B. -- Columbia University Health Sciences
Epidemiological/Familial Aspects of Drug Use

Kang, Sung-Yeon -- National Development & Research Institutes
Gender Differences in Healthcare and Drug Treatment Utilization among Drug Users

Keefe, Kristen A. -- University of Utah
Neural Substrates of Stimulus-Induced Drug Seeking

Kelly, Brian C. -- Purdue University West Lafayette
Emerging Trends of Tryptamine Use: Contexts & Risks

Kinlock, Timothy W. -- Friends Research Institute, Inc.
Buprenorphine for Prisoners

Kirk, Gregory -- Johns Hopkins University
Real Time Methods for Quantifying Exposure to Illicit Drugs & Psychosocial Stress

Kollins, Scott H. -- Duke University
Mechanisms of Nicotine Dependence in ADHD Adults

Korthuis, Philip T. -- Oregon Health & Science University
Quality Outcomes for Patients with Drug Abuse and HIV

Kral, Alexander H. -- Research Triangle Institute
Qualitative Exploration of Low-Frequency Heroin Injectors not in Drug Treatment

Kumar, Santosh -- University of Memphis
Autosense: Quantifying Exposures to Addictive Substances and Psychosocial Stress

Lachance, Heather R. -- National Jewish Medical & Research Center
Development of Behavioral Couples Treatment for Smoking Cessation

Lariviere, William R. -- University of Pittsburgh at Pittsburgh
Genetics of Neuropathic & Inflammatory Hypersensitivity

Ledgerwood, David M. -- Wayne State University
Prize Reinforcement for Smoking Cessation

Lee, Debora -- University of California Los Angeles
Long-Term Follow Up of Community Intervention in Yunnan, China

Leung, Hoi-Chung -- State University New York Stony Brook
The Role of Frontostriatal Circuits in Multimodal Response Inhibition

Levine, Allen S. -- University of Minnesota Twin Cities
Effect of Sweet Tastants on Opioid-Melanocortin Interactions

Levitt, Pat R. -- Vanderbilt University
Development of Reciprocal Neural Circuitry

Liberto, Joseph -- American Academy of Addiction Psychiatry
18th-22nd Annual Meetings and Symposium

Liberty, Hilary James -- Social Sciences Innovations Corporation
Using CAI to Enhance Drug Tx Staff HCV Knowledge and Communication Skills

Licata, Stephanie C. -- Mc Lean Hospital, Belmont, MA
FMRI Studies Investigating the Choice Effects of Sedative/Hypnotics

Lin, Zhicheng -- Mc Lean Hospital, Belmont, MA
Human Dopamine Transporter Gene: Variations and Transcriptional Regulation

Lindsey, Kimberly P. -- Mc Lean Hospital, Belmont, MA
FMRI of Cigarette Smoking: Effects of Dependence, Withdrawal, and Conditioned Reinforcement

Loh, Horace H. -- University of Minnesota Twin Cities
Structural and Functional Studies of Mu Opiate Receptors

Lowe, John R . -- Florida Atlantic University
Community Partnership to Affect Cherokee Adolescent Substance Abuse

Lukas, Scott E. -- Mc Lean Hospital, Belmont, MA
Training in Drug Abuse and Brain Imaging

Mackie, Kenneth P. -- Indiana University Bloomington
Cannabinoid Modulation of Cell Function

Mackie, Kenneth P. -- Indiana University Bloomington
2007 CB2 Cannabinoid Meeting

Mackler, Scott A. -- University of Pennsylvania
NaC1, A Cocaine Regulated mRNA in the Rat Brain

Makriyannis, Alexandros -- Northeastern University
Endocannabinoid Active Sites as Therapeutic Targets

Makriyannis, Alexandros -- Northeastern University
Training Program in Medications Development for Drugs of Abuse

Malison, Robert T. -- Yale University
Patient-Oriented Research and Mentoring in the Translational Neurobiology/Genetic

Mandyam, Chitra D. -- Scripps Research Institute
Regulation of Adult Neurogenesis by Methamphetamine

Markowitz, John S. -- Medical University of South Carolina
Drug Transporters and the Disposition of ADHD therapeutic Agents

Martin, Billy R. -- Virginia Commonwealth University
Center for Drug Abuse Research

Martin, Laura E. -- University of Kansas Medical Center
Nicotine Addiction and Reward Processing: An fMRI Investigation

Martins, Silvia Saboia -- Johns Hopkins University
Trends in Problems Related to Extramedical Use of Analgesics

Mason, Graeme F. -- Yale University

Neuroimaging Sciences Training Program

Mason, Michael J. -- Villanova University
Social Ecology of Urban Adolescent Substance Abuse: A Multiple Domain Approach

Mason, Peggy -- University of Chicago
Physiology of Raphe Magnus Cells During Wake and Sleep

Massey, Kerri A. -- University of California San Diego
Nicotinic and GABAergic Interactions in Hippocampal Development

Matell, Matthew S. -- Villanova University
Neuroanatomical Localization of the Dopaminergic Modulation of Clock Speed

Matsumoto, Rae R. -- University of Mississippi
Synthesis and Evaluation of Sigma-Active Cocaine Antagonists

Mayer, Andrew Robert -- The Mind Institute
Multimodal Imaging of the Sensory Gating Deficit in Chronic Cocaine Abusers

Mcginty, Jacqueline F. -- Medical University of South Carolina
Drug Abuse Training Program

Mechlin, M. Beth -- University of North Carolina Chapel Hill
Ethnicity and Pain: Psychosocial Stress and Stress Responses

Mendelson, Jack H. -- Mc Lean Hospital, Belmont, MA
Drug Abuse Research Training Program

Meng, Ian D. -- University of New England
Chronic Morphine-Induced Sensitization of Trigeminal Dura Sensitive Neurons

Mertens, Jennifer -- Kaiser Foundation Research Institute
Brief Intervention to Reduce Substance Use in South African Primary Care

Metrik, Jane -- Brown University
Marijuana's Acute Effects on Risk Taking, Sexual/HIV Risk, and Impulsivity

Midgley, A. Rees -- Indepthlearning
Drug Scene Investigators

Miech, Richard A. -- University of Colorado Denver/Health Sciences Center Denver
The Growing Disparity in Illegal Drug Use Across Socioeconomic Strata

Miller, Gregory M. -- Harvard University Medical School
Methamphetamine Effects Via Trace Amine Associated Receptor 1

Miller, Leslie M. -- Rice University
Web Adventures to Teach Adolescents About Inhalant Abuse

Miller, Matthew J. -- Harvard University School of Public Health
Prescription Opioid Use and the Risk of Injury Among Elderly Americans

Molitor, Thomas W. -- University of Minnesota Twin Cities
Training in Neuroimmune/Neurobehavior Addiction Research

Molitor, Thomas W. -- University of Minnesota Twin Cities
Opiate Modulates Lymphocyte Trafficking into the CNS in TB Meningitis

Monterosso, John R. -- University of California Los Angeles
Neural Recruitment During Self-Control of Smoking: An fMRI Paradigm

Morgan, Drake -- University of Florida
Chronic Opioids and Aging

Morgenstern, Jonathan -- National Center on Addiction/Substance Abuse
Disease Management for Chronic Drug Abuse

Moron-Concepcion, Jose A. -- University of Texas Medical Branch Galveston
Protein Expression in Extinction of Morphine-Dependent Conditioned Behavior

Moyers, Theresa B. -- University of New Mexico Albuquerque
Testing Theory-Based Training in Motivational Interviewing

Nation, Jack R. -- Texas A&M University System
Heavy Metal and Drug Self-Administration: Mechanisms

Nunes, Edward V. -- New York State Psychiatric Institute
Clinical Trials Network: Long Island Regional Node

O'Dell, Laura E. -- University of Texas El Paso
Nico-Teen: Mechanisms of Nicotine Reward and Withdrawal During Adolescence

Olsen, Dale E. -- Simmersion, LLC
Interactive Multimedia Simulation to Train Motivational Interviewing Skills

Ondersma, Steven J. -- Wayne State University
The WIDUs: Indirect Screening for Perinatal Drug Use

O'Neill, Joseph -- University of California Los Angeles
Magnetic Resonance Spectroscopic Imaging of the Brain in Methamphetamine Abuse

O'Phelan, Kristine Hazel -- Queen's Medical Center
Effects of Methamphetamine in Traumatic Brain injury

Oser, Carrie B. -- University of Kentucky
Rural Drug Abuse Treatment: Organizations, Counselors, and Client Outcomes

Osgood, D. Wayne -- Pennsylvania State University
Friendship Networks and Emergence of Substance Use

Overman, William H. -- University of North Carolina Wilmington
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Owens, Douglas K. -- Stanford University
Making Better Decisions: Policy Modeling for AIDS and Drug Abuse

Ozechowski, Timothy J. -- Oregon Research Institute
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Paulus, Martin P. -- University of California San Diego
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Petry, Nancy M. -- University of Connecticut School of Medicine and Dentistry
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Podus, Deborah L. -- University of California Los Angeles
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Polcin, Douglas L. -- Public Health Institute
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Poling, James C. -- Yale University
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Pollio, David E. -- Washington University
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Porreca, Frank F. -- University of Arizona

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Porrino, Linda J. -- Wake Forest University Health Sciences
Neurobiological Correlates of Cocaine Abuse

Portoghese, Philip S. -- University of Minnesota Twin Cities
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Rawls, Scott M. -- Temple University
Cannabinoid Regulation of Basal Ganglia Glutamate and GABA

Ray, Stuart C. -- Johns Hopkins University
Mechanisms of Hepatitis C Virus Evolution

Razdan, Raj K. -- Organix, Inc.
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Rea, Mark S. -- Rensselaer Polytechnic Institute
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Rende, Richard -- Butler Hospital, Providence, RI
Sibling Contagion for Smoking: Social & Genetic Influences in Early Adulthood

Renshaw, Perry F. -- Mc Lean Hospital, Belmont, MA
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Richter, Kimber P. -- University of Kansas Medical Center
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Rieger, Jayson Michael -- Adenosine Therapeutics, LLC
Adenosine A2a Receptor Antagonists for the Treatment of Cocaine Addiction

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

Robles, Rafaela R. -- Universidad Central Del Caribe
Puerto Rico Drug Abuse Research Development Program (PRDARDP II)

Roesch, Matthew R. -- University of Maryland Baltimore
Orbitofrontal-Accumbens Interactions, Dopamine Modulation and Impulsive Choice

Roiko, Samuel A. -- University of Minnesota Twin Cities
Effects of Passive Immunization on Nicotine Dependence in Rats

Roy, Sabita -- University of Minnesota Twin Cities
Role of Mu Opioid Receptor in Immune Function

Saldana, Lisa -- Oslc Community Programs
Integrating interventions for Maternal Substance Abuse and Child Neglect

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

Scavone, Jillian L. -- Thomas Jefferson University
Cannabinoid and Opioid Interactions in Noradrenergic Cells

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
Drug Counseling and Abstinent-Contingent Take Home Buprenorphine in 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

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

Seybold, Virginia S. -- University of Minnesota Twin Cities
Neuroscience Training in Drug Abuse Research

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

Sheth, Christopher M. -- Virginia Commonwealth University
Tolerance to the Immunosuppressive Effects of Delta-9 Tetrahydrocannabinol

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

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

Simmons, Janie E. -- National Development & Research 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

Snyder, Solomon H. -- Johns Hopkins University
Drug Abuse Research Center

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

Sorensen, James L. -- University of California San Francisco
California-Arizona Clinical Trials Network Node

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

Staley, Julie K. -- Yale University
Neuroreceptor Imaging of Tobacco Smokers

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

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

Stella, Nephi -- University of Washington
Novel CB Receptors

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

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

Strain, Eric C. -- Johns Hopkins University
Mentoring of Clinical investigators in Patient Oriented Research

Strathdee, Steffanie A. -- University of California San Diego
Training Program in Substance Use, HIV and Related Infections

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

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

Terrell, Heather K. -- Arizona State University
Substance Abuse in Women: the Role of Stressful Pregnancy Outcomes

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

Thomas, David M, -- Wayne State University
Molecular Mechanisms of Methamphetamine Neurotoxicity

Tolan, Patrick H. -- University of Illinois at Chicago
Developmental Evalulation of Prevention Effects of the Safe Children Intervention

Torres, Gonzalo E. -- University of Pittsburgh at Pittsburgh
Physical and Functional Link of the Dopamine Transporter with Synaptic Proteins

Traynor, John R. -- University of Michigan at Ann Arbor
Postdoctoral Training in the Biology of Drug Abuse

Traynor, John R. -- University of Michigan at Ann Arbor
Role of Lipid Rafts in Adenylyl Cyclase Sensitization

Ursu, Stefan -- University of California Davis
The Human PFC Response to Drug Cues: Outcome Representation Vs. Cognitive Control

Valdez, Avelardo -- University of Houston
Drug Abuse Research Development Program

Vezina, Paul R. -- University of Chicago
Neuropsychopharmacology Training for Drug Abuse Research

Waldron, Holly B. -- Oregon Research Institute

Adolescent Substance Abuse: Progressive Treatment

Waldron, Holly B. -- Oregon Research Institute
Development of A Family-Based Treatment for Adolescent Methamphetamine Abuse

Wang, Zuoxin -- Florida State University
Dopamine Regulates Drug and Social Reward interactions

Wasan, Ajay D. -- Brigham and Women's Hospital
Oral Opioid Treatment and Psychiatric Comorbidity

Wassum, Kate M. -- University of California Los Angeles
Opioid and Glutamate Modulation of Reward Value During Goal-Directed Behavior

Waterhouse, Barry D. -- Drexel University
Neurochemistry and Neurophysiology of MDMA (Ecstasy)

Weinstein, Harel -- Weill Medical College of Cornell University
Hallucinogens and 5-Ht Receptors: Mechanisms and Effects

Weiss, Roger D. -- Mc Lean Hospital, Belmont, MA
CTN: Northern New England Node

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

Wightman, Robert M. -- University of North Carolina Chapel Hill
Dynamics of In Vivo Dopamine Release

Winger, Gail D. -- University of Michigan at Ann Arbor
Behavioral Economic Analysis of Polydrug Abuse

Young, Paul A. -- Nova Research Company
Qds(Tm)-Web Interview Administering System

Yu, Aiming -- State University of New York at Buffalo
Pharmacogenetics in Indolealkylamine Metabolism and Drug interactions

Yudowski, Guillermo A. -- University of California San Francisco
Regulation of GPCR Recycling At the Plasma Membrane

Yurgelun-Todd, Deborah A. -- Mc Lean Hospital, Belmont, MA
Brain Changes with Cannabis and Methamphetamine

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

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

Extramural Policy and Review Activities

Receipt, Referral, and Review

NIDA received 1428 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 1163 applications.

OEA arranged and managed 32 grant review meetings in which 679 applications were evaluated. OEA's reviews included applications in chartered, standing review committees and Special Emphasis Panels (SEPs). In addition, OEA's Contracts Review Branch (CRB) arranged and managed 13 contract proposal 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 28 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)
Loan Repayment Program,br> Requests for Applications (RFA)

OEA managed the following RFA reviews:

- DA07-002/DA07-003: Mechanisms of Drug Abuse Interactions With HIV Neuropathogenesis (R01 & R03)
- DA07-004: Development of Immunotherapeutic Products for the Treatment of Methamphetamine Addiction (U01)
- DA07-006: Design, Synthesis, and Preclinical Testing of Potential Treatment Agents for Drug Addiction (R01)
- DA07-007: Brain Imaging Drug Use Prevention Messages (R21)
- DA07-008: Exploratory/Developmental Centers for Translational Research on the Clinical Neurobiology of Drug Addiction (P20)
- DA07-010/ DA07-011: Extinction and Pharmacotherapies for Drug Addiction (R01 & R03)
- DA07-012: The Genes, Environment, and Development Initiative (U01)

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- DA07-013: Joint NIDA-NIJ Initiative for Research on Retail Drug Markets (R21)
- RM07-004: Facilitating Interdisciplinary Research via Methodological and Technological Innovation in the Behavioral and Social Sciences (R21)

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

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

- N01DA-7-1130: International Collaboration Opportunities & Research Partnerships
- N01DA-7-1134: Blending Research and Practice

SBIR Phase I Concept Review

- N43DA-8-1135: Development of a Practical Tool Kit to Help Offerors Submit a Successful SBIR/STTR Proposal
- N43DA-8-1136: Building International Research Capacity
- N43DA-8-2213: Development of Website Training for Pain Specialists on Addiction Medicine
- N43DA-8-2214: Development of Web-based Skills Training for Primary Care Physicians on Screening, Brief Intervention, Referral and Treatment
- N43DA-8-5538: Drug Abuse Screening, Assessment, Patient-Treatment Matching Technologies for use in Primary Care
- N43DA-8-5539: Tools to Measure Cost- Cost Offsets of Prevention Interventions Cost Benefits, Cost Effectiveness Studies
- N43DA-8-7764: Nanoscience-based Design of Therapies for Substance Abuse
  Treatment
- N43DA-8-7765: Discovery and Study of Psychoactive Components of Botanicals
- N43DA-8-8874: Design and Synthesis of Treatment Agents for Drug Abuse

Phase II SBIR Contract Reviews

- N44DA-7-4404: Rehabilitation for Methamphetamine Induced Impulsivity
- N44DA-7-4407: E-Health Relapse Prevention for the Workplace

Certificates of Confidentiality

Between April 6 and July 31 2007, OEA processed 92 Certificate applications, including 23 for extension of expiration dates and 13 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 spring. Activities included open forums for discussions and presentations that included "NIDA's HIV/AIDS Research Program: The Evolving Scientific Agenda within a New Budget Era" by Dr. Jacques Normand and "Requirement for OMB Clearance for NIDA Contracts Involving Clinical Research and Seeking Exemption from It" by Dr. Charles MacKay.

CTN-Related Review Activities

The Data and Safety Monitoring Board(s) met:

- May 10, 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).
- June 20, 2007 via web conference to review an update report for study protocol CTN 0027 Starting Treatment with Agonist Replacement Therapies (START) implementation.
- July 13, 2007 to review and discuss study protocol CTN 0032, HIV Rapid Testing and Counseling Protocol.

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Congressional Affairs (Prepared August 31, 2007)

Appropriations

On July 19, 2007, the House passed H.R. 3043, the FY2008 Labor, HHS, Education Appropriations bill, which includes funding for NIH. The bill recommends $29,649,887,000 for NIH, which would be $750,000,000 above the FY 2007 appropriation and $1,028,646,000 above the President's request. In this bill, NIDA receives $1,015,559,000 -- $14,938,000 above the FY 2007 appropriation and $15,194,000 above the President's request.

The Senate's bill (S. 1710), as approved by the Appropriations Committee, would provide NIH with $1 billion over the FY 2007 enacted level or $29,899,887,000 ($1.3 billion over the FY 2008 President's Budget). NIDA receives $1,022,594,000 -- $21,973,000 above the FY 2007 appropriation and 22,229,000 above the President's request. Floor action is pending in the Senate.

HEARINGS, BRIEFINGS, AND EVENTS OF INTEREST

Capitol Hill briefing on Co-occurring Disorders -- On June 27, 2007, the Friends of NIDA sponsored the eighth in a series of educational briefings on Capitol Hill. The briefing, titled **"Double Jeopardy: When Addiction and Mental Illness Coexist"**, drew a standing-room-only crowd of nearly two hundred, including staff from a total of 60 different House and Senate offices. The event received tremendous support from the drug abuse, addiction, and mental health community on Capitol Hill, evident by the endorsement and cosponsorship of three relevant congressional caucuses: the Addiction, Treatment and Recovery Caucus, the Mental Health Caucus, and the newly-formed Drug Policy Caucus. Congresswoman Grace Napolitano (D-CA), co-chair of the Mental Health Caucus, spoke to the audience with conviction about her strong commitment to improving the lives of those struggling with mental disorders.

The focus of the briefing was co-occurring mental disorders and substance use, and the fact that research increasingly supports the benefit of studying and treating co-occurring disorders together, with both medication and behavioral therapies. Studies on the root causes of these disorders, common risk factors, and potential interventions will enable us to better serve the large population for whom substance use is only part of the problem.

NIDA Director Dr. Nora Volkow provided an overview of the Institute's work in this crucial area. Dr. Patrick Flynn, Professor of Psychology and Deputy Director of the Institute of Behavioral Research at Texas Christian University, shared information regarding the two distinct treatment systems for co-occurring substance use and mental disorders. The final, and very moving, speakers

were Brittany and Basil Calomeris, who courageously shared the story of their family's personal struggle with a co-occurring disorder and the arduous journey to treatment.

Senate staff briefing (7/13/07) -- At the request of Senator Tom Harkin's (D-IA) office, NIDA Deputy Director Dr. Tim Condon provided a staff briefing on "Methamphetamine, Emerging Drug Problems, and Blending Research and Practice." Dr. Condon briefed two dozen Senate staff from the Committee on Health, Education, Labor and Pensions.

House Crime Summit (6/22/07) - At the request of Representative Bobby Scott (D-VA), NIDA Deputy Director Dr. Tim Condon provided remarks on "Treatment is the Key: Providing Drug Abuse Services in Criminal Justice Settings." The event, "Violent Crime - Prevention and Solutions from the Experts, A Summit on Crime Policy" was held under the auspices of the House Judiciary Committee, Subcommittee on Crime, Terrorism and Homeland Security.

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, 2007, Senators Joseph Biden (D-DE), Edward Kennedy (D-MA) and Michael Enzi (R-WY) introduced S. 1011, the Recognizing Addiction as a Disease Act of 2007, which would make the same changes. In a press release, Senator Biden said the intent of the legislation is to recognize addiction as a preventable and treatable neurobiological disease, and to better identify the roles and missions of our research institutes. "Addiction is a neurobiological disease - not a lifestyle choice - and it's about time we start treating it as such," said Sen. Biden. "We must lead by example and change the names of our Federal research institutes to accurately reflect this reality. By changing the way we talk about addiction, we change the way people think about addiction, both of which are critical steps in getting past the social stigma too often associated with the disease." The House bill was referred to the Health Subcommittee of the Energy and Commerce Committee; the Senate bill was marked up and passed by the Health, Education, Labor and Pensions Committee on June 27. The bill has been placed on the Senate calendar under General Orders.

Stem Cells -- H.R. 3/S. 5 - On January 5, 2007, Representative Diana DeGette (D-CO) introduced H.R. 3, the Stem Cell Research Enhancement Act of 2007. The Senate companion, S. 5, was introduced on January 4, 2007, by Senate Majority Leader Harry Reid (D-NV). The bills would require the Secretary of HHS to conduct and support research using human embryonic stem cells regardless of the date on which such cells were derived. The House passed its bill on January 11, 2007, and the Senate passed its bill on April 11, 2007. The Senate bill was amended prior to floor consideration. As amended, the bill would also require the Secretary to conduct and support research involving methods of obtaining pluripotent stem cells that do not involve the use of human embryos. The 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.

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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 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 Wellston Mental Health and Addiction Equity Act of 2007, to amend section 712 of the Employee Retirement Income Security Act of 1974, section 2705 of the Public Health Service Act, and section 9812 of the Internal Revenue Code of 1986 to require equity in the provision of mental health and substance-related disorder benefits under group health plans. The Senate bill has been reported favorably from committee; there is currently a "hold" on further consideration of the bill. The House bill has been reported favorably by the Education and Labor Committee, and awaits further action by other committees of jurisdiction.

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. Both bills have been reported favorably by their respective committees and await 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, and further action is anticipated this fall. Further action is 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. 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.

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 introduced the Drug Endangered Children Act of 2007, to extend the grant program for drug-endangered children. The bill has been favorably reported by the Judiciary Committee, and awaits action by the Energy and Commerce Committee.

H.R. 1200 - On February 27, 2007, Representative Jim McDermott (D-WA) introduced H.R. 1200, the American Health Security Act of 2007. The purpose of the bill is "to provide for health care for every American and to control the cost and enhance the quality of the health care system." Of interest to NIH is section 722, which would establish the Office of Primary Care and Prevention Research within the Office of the Director; require the establishment of a data system of information regarding primary care and prevention research that is conducted or supported by the ICs; require the establishment of a clearinghouse to provide information on research and prevention activities of the ICs that relate to primary care and prevention research; require a biennial report on primary care and prevention research; and authorize $150 million for FY 2008, $180 million for FY 2009, and $216 million for FY 2010. In addition, the legislation would amend the authorities of the NIH Director to require that sufficient resources are sufficiently allocated for projects on primary care and prevention research. H.R. 1200 was jointly referred to the House Committees on Energy and Commerce; Ways and Means; Oversight and Government Reform; and Armed Services.

H.R. 1309 - On March 14, 2007, the House passed H.R. 1309, the Freedom of Information Act Amendments of 2007. Provisions of interest to NIH would shorten the time limits on which to act on requests, require agencies to establish a system to assign an individualized tracking number for each request for information, establish a telephone line or Internet service regarding the status of a request, institute additional reporting requirements regarding FOIA requests and processing times, and broaden "media status" to those who have "internet publications." The bill has been referred to the Senate. See S. 849.

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 was reported favorably by the Judiciary Committee, and further action is pending.

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. 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.

S. 849 - On April 30, 2007, the House Committee on the Judiciary reported (S. Rept. 110-59), without amendment, S. 849, the Openness Promotes Effectiveness in our National (OPEN) Government Act of 2007. This bill is similar to provisions in H.R. 1309, the Freedom of Information Act of 2007. Provisions in S. 849 of interest to NIH would shorten the time limits on which to act on requests, require agencies to establish a system to assign an individualized tracking number for each request for information, establish a telephone line or Internet service regarding the status of a request, institute additional reporting requirements regarding FOIA requests and processing times, and broaden "media status" to those who have "internet publications." S. 849 was placed on the Senate Legislative Calendar under General Orders. See H.R. 1309.

S. 884 - On March 14, 2007, Senator Richard Durbin (D-IL) introduced the Family-Based Meth Treatment Access Act of 2007, to amend the Public Health Service Act regarding residential treatment programs for pregnant and parenting women, a program to reduce substance abuse among nonviolent offenders, and for other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions.

S. 980 - On March 23, 2007, Senator Dianne Feinstein (D-CA) introduced the Online Pharmacy Consumer Protection Act of 2007, to amend the Controlled Substances Act to address online pharmacies. The bill was referred to the Judiciary Committee, which held a hearing in May.

S. 1082 - On May 9, 2007, the Senate passed 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. S. 1082 was introduced on April 10, by Senator Edward Kennedy (D-MA). See H.R. 2900.

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. 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. 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. 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 26, 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.

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International Activities

New Research Training Program

NIDA has created a new version of the INVEST Drug Abuse Research Fellowship, offering postdoctoral research training in clinical trials. In addition to the normal cohort of INVEST Fellows, the NIDA International Program and Clinical Trials Network (CTN) are offering INVEST/CTN Fellowships to non-U.S. scientists to work with a mentor affiliated with one of the 17 CTN Regional Research and Training Centers. Like the regular INVEST Fellowships, the INVEST/CTN Drug Abuse Research Fellowship combines postdoctoral research training in the United States with professional development activities and grant-writing guidance. Fellows may conduct their research in any aspect of the Clinical Trials Network research agenda on drug abuse and addiction, such as intervention research, clinical trials methodology, or drug abuse treatment as HIV/AIDS prevention. Fellows and their mentors are encouraged to develop jointly and seek funding for a collaborative research project to be conducted in the Fellow's home country. Fellows and their U.S. mentors are part of a network of international scientists who exchange information and collaborate on drug abuse research nationally, regionally, and globally.

Research Results

Research Team Supported by INVEST and DISCA Awards Finds Methamphetamine Neurotoxicity is Dose-Dependent and May Permanently Alter White Matter
Researchers from Seoul National University and Harvard University have concluded that altered concentrations of brain metabolites, including N-acetyl-aspartate (NAA) and myo-inositol (MI), may indicate neurotoxicity associated with drug abuse. Writing in Drug and Alcohol Dependence 88(1), pp. 28-35, 2007. the researchers describe proton magnetic resonance spectroscopy (MRS) studies that explored differences in brain metabolites between abstinent methamphetamine (MA) abusers and healthy comparison subjects, as well as the associations between metabolite concentrations and clinical characteristics. The research findings suggest that MA-induced metabolic alterations of frontal gray and white matter are dose-dependent, for primarily male subjects, and that the MA-related abnormalities in gray matter may, in part, recover with abstinence, but not those in the white matter. Lead author Young Hoon Sung was a 2005-2006 NIDA INVEST Fellow, working with co-author Perry F. Renshaw, Harvard University and McLean Brain Imaging Center. Another co-author, In Kyoon Lyoo, is a 2007 NIDA Distinguished International Scientist, also working with Dr. Renshaw.

Binational Research Team Supported by NIDA-Dutch Addiction Program Supplement Evaluates Effectiveness of Experimental Treatment

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A research team comparing the effectiveness of manualized behavior therapy on school-aged disruptive behavior disordered (DBD) children in everyday clinical practice to care as usual has concluded that the effect size of the experimental treatment was significantly larger when care as usual consisted of family therapy, but there was no significant difference when care as usual consisted of behavior therapy. Writing in Behavior Modification May 31(3), pp. 298-312, 2007, Drs. John E. Lochman, University of Alabama, and Walter Matthys, Utrecht, conclude that the comparison of an experimental treatment to care as usual depends on the type of usual treatment.

International Program's Bibliometric Study Identifies Countries, Funding Sources, and Trends in Drug Abuse Research Articles
In an effort to assess the involvement of the international research community, identify funding organizations, and describe the topics of drug abuse research being conducted, the International Program conducted a bibliometric study of articles published in Addiction and Drug and Alcohol Dependence from 1998 through 2004. The authors' institutions represented 60 countries, and 10 percent of the articles were cross-country collaborations. The authors credited 443 unique funding sources from 39 countries. Just 5 organizations constituted 60 percent of the funding sources, all of them U.S. government agencies. NIDA supported 41 percent of the research. Although more than 5,700 Medical Subject Heading categories were recorded in the more than 1,800 articles that met the inclusion criteria, 10 categories accounted for 50 percent of the total: psychology, epidemiology, therapeutic use, rehabilitation, pharmacology, administration and dosage, statistics and numerical data, drug effects, methods, and adverse effects.

FY 2006 Annual Report

A summary of the NIDA International Program's Fiscal Year 2006 activities demonstrates the broad range of activities NIDA supports to successfully develop new international scientific networks, encourage junior scientists to become drug abuse researchers, and engage experts from underrepresented geographic areas in international collaborative research.

NIDA International Forum

More than 260 registrants from 40 countries participated in the NIDA International Forum, which was held June 15-18, 2007 in Quebec City, Canada. The meeting was cosponsored by the NIDA International Program; the Institute of Neurosciences, Mental Health, and Addiction of the Canadian Institutes of Health Research; and the Canadian Centre on Substance Abuse. Introducing the meeting theme, Technological Innovations to Build International Research Capacity, Daniel Olguin Olguin of the MIT Media Lab described developmental projects where researchers use electronic or social sensor technologies to track social signals provided by speech and body gestures as well as physiological responses to track individual or group communication patterns, develop mathematical models of human behavior, identify individuals or groups with similar interests, and automatically record organizational interactions. Mr. Olguin Olguin reviewed Media Lab interventions designed to treat depression and diabetes, and invited Forum participants to suggest drug abuse research applications. Other plenary session speakers discussed high-tech tools - such as ecological momentary assessment, computerized intervention software, and automated clinical bookkeeping for contingency management programs - in drug abuse prevention and treatment research projects.

IP Director Dr. Steven W. Gust described how several years of flat or decreasing budgets have driven the Institute's interest in creating Web-based research and training tools. He also previewed an IP bibliographic study that identified 443 unique funding sources cited by drug abuse researchers who

published articles in Addiction and Drug and Alcohol Dependence between 1998 and 2004. Representatives from the Fogarty International Center and the Institute for International Education joined IP Program Analyst Dale Weiss to discuss funding opportunities for IP fellowship alumni. Dr. Flavio Pechansky, University of Porto Alegre, Brazil, discussed the individual and group actions necessary to build a regional research network.

During the poster session, more than 130 drug abuse scientists from around the world presented their research to NIDA Forum and CPDD participants while representatives from nine NIDA components and the NIH Fogarty International Center presented posters summarizing the units' goals, research interests, international focus, and international funding priorities. Concurrent workshops focused on ethnographic research in HIV/AIDS; international trends in inhalant abuse and a multinational effort to better define and classify inhalants; and web resources supported by NIDA and the National Institutes of Health. Working groups also met during the Forum, focusing on the Addiction Severity Index, the Clinical Trials Network, ethnography, HIV/AIDS in IberoAmerica and Central-Eastern Europe, inhalants abuse, and women, children, and families.

NIDA Components Outline International Focus
During the June 2007 NIDA International Forum poster session, nine NIDA components and the Fogarty International Center presented posters summarizing the units' goals, research interests, international focus, and international funding priorities. The posters were prepared for the Division of Basic Neuroscience and Behavioral Research; Division of Clinical Neuroscience and Behavioral Research; Division of Epidemiology, Services and Prevention Research; Division of Pharmacotherapies and Medical Consequences of Drug Abuse; International Program; Intramural Research Program; AIDS Research Program; Center for the Clinical Trials Network; Special Populations Office.

NIDA Presents International Awards of Excellence
The NIDA International Program Awards of Excellence recognize mentors, researchers, and binational collaborative teams who have demonstrated sustained support of the NIDA International Program mission through outstanding contributions to international cooperation in drug abuse research and training. The awards are presented each June at the NIDA International Forum; two-page written nominations may be submitted to the International Program by March. The 2007 NIDA International Program Awards of Excellence were presented to: Wallace Mandell, Johns Hopkins, Excellence in Mentoring; David S. Metzger, University of Pennsylvania, Excellence in International Leadership; and Richard S. Schottenfeld, Yale University and Mahmud Mazlan, Malaysian Substance Abuse Center Maur, Excellence in Collaborative Research.

NIDA-Supported Meetings

Satellite Examines Neurotoxicity
NIDA provided support for a satellite meeting, New Research Frontiers and Advances in Drug Addiction, at the International Society for Neurochemistry meeting held August 14-17, 2007 in Merida, Mexico. The satellite was cosponsored by the International Drug Abuse Research Society (IDARS), the International Society for Neurochemistry, and the American Society for Neurochemistry. Participants discussed the role of genomics, proteomics and metabonomics in drug-induced neurotoxicity; medication development; molecular biology and free radicals in drug-induced neurotoxicity; substituted amphetamines-induced neurochemical changes and relationship to neurotoxicity; imaging brain structure and function; and GHB, volatile solvent, and inhalant neurotoxicity.

ICADTS/TIAFT Meeting Focuses on Drugged and Drunk Driving
NIDA supported the joint meeting of the International Council on Alcohol, Drugs and Traffic Safety (ICADTS) and The International Association of

Forensic Toxicology (TIAFT) in Seattle, Washington, August 26 - 30, 2007. The three scientific tracks at the meeting examined driving under the influence of drugs; behavioral, post-mortem, and analytical toxicology; and road safety. A one-day pre-conference symposium for young scientists promoted networking, research skills, and career planning. The International Ignition Interlock Symposium was also held during the meeting. In addition to NIDA, meeting support was also provided by the U.S. National Highway and Traffic Safety Administration and Transport Canada. Dr. Marilyn A. Huestis, IRP, is past president of TIAFT, serves on the TIAFT Scientific Advisory Committee, and presented during the conference.

International Visitors

Dr. Jerry Flanzer, DESPR, arranged for a visit to NIDA from a delegation from China on May 7, 2007. Dr. Shenyang Guo, University of North Carolina lead the delegation. The delegation was here to learn more about the "Making Choices" program sponsored by NIDA. The Chinese government has provided seed funds to conduct a test of this program in China.

Under the auspices of the U.S. Department of State's International Visitor Leadership program, Dr. Vera Durisic, Head of the Department for Neurosis, Psychiatric Clinic in Montenegro visited NIDA on June 12, 2007. Meeting with Dr. Durisic from NIDA were, Dr. Vince Smeriglio and Debbie Grossman, DCNBR, and Carmen Rosa, CCTN.

On June 27, 2007 Dr. Gilberto Gerra, Director of the UNODC Global Challenges Program visited NIDA. Dr. Gerra was visiting Washington to discuss some of the new UNODC strategies in prevention and treatment as well as to learn more about U.S. Drug Demand Reduction programs. Dr. Gerra met with Dr. Tim Condon as well as representatives from DESPR, DPMCDA and CCTN.

A delegation of parliamentarians from the Australian Victorian Drugs and Crime Prevention Committee visited NIDA on July 30, 2007. The delegation was led by Deputy Chairman Mr. David Morris. The delegation was visiting Washington for the purpose of gathering evidence for the Committee's inquiry into the misuse/abuse of benzodiazepines and other forms of pharmaceutical drugs in Victoria. Representatives at the meeting from NIDA included Dr. Aria Crump and Moira O'Brien, DESPR, Geoffrey Laredo, OPSC and Dale Weiss, IP.

Other International Activities

Dr. Joseph Frascella, Director, DCNBR, gave a presentation entitled "Eating Addiction: Lessons Learned from Drug Addiction" at the 3rd European Association of Addiction Therapy Conference in Vienna, Austria on September 12, 2007.

Dr. Wilson Compton, Director, DESPR, presented a paper on the "Psychiatric Epidemiology of Pain" at the 11th Congress of the International Federation of Psychiatric Epidemiology in Goteborg, Sweden, May 4, 2007.

Dr. Wilson Compton presented a paper on "Reducing Opiate Analgesic Abuse" at the annual meeting of the College on Problems of Drug Dependence on June 18, 2007 in Quebec, Canada.

On June 26, 2007, Dr. Wilson Compton co-chaired and served as discussant on a panel addressing "Drug Addiction Treatment in Criminal Justice Settings" at the International Academy of Law and Mental Health, Padua, Italy.

Dr. Meyer Glantz, DESPR, represented NIDA at the 2007 World Mental Health Consortium annual meeting in Portsmouth, New Hampshire. The Consortium is a collaboration of the World Health Organization, NIMH and NIDA, and other

mental health institutions. The Consortium members sponsor and conduct the World Mental Health Survey, a multi-site investigation of the prevalence and concomitants of mental and substance use disorders 28 countries. The United States component of the survey, the National Comorbidity Survey-Replication, has completed data collection and is currently analyzing and publishing its findings.

Dr. Elizabeth Robertson, DESPR, gave a keynote address titled: Using Epidemiologic Data to Inform Prevention Programming at the 2007 National Anti-Drug Conference and International Anti-Drug Symposium which took place in Taipei, Taiwan from May 30th through June 3, 2007.

Dr. Yonette Thomas, DESPR, chaired a workshop on "Bringing the Social Environment into Focus in Drug Abuse Research" at the 11th Congress of the International Federation of Psychiatric Epidemiology in Goteborg, Sweden, May 3-6, 2007. Dr. Thomas' presentation addressed the importance of understanding and mapping the social environment in drug abuse research.

Dr. Peter Hartsock, DESPR, served on the organizing committee and organized and chaired a special symposium on AIDS modeling applications for understanding the Russian AIDS epidemic (fastest growing AIDS epidemic in the world; drug abuse has been the principal driver) and related interventions. Sixteenth International Conference on AIDS and Public Health, St. Petersburg, Russia, May 28-June1, 2007.

Dr. Augusto Diana, DESPR, served as a Task Force member for the International Task Force on Prevention Evaluation Measures, part of the Inter-American Drug Abuse Control Commission (CICAD) of the Organization of American States (OAS).

Dr. Diana presented the results of the Task Force, a compendium of prevention measures called the CICAD Toolkit for the Evaluation of Universal Substance Abuse Prevention Programs for Youth, to the VIII meeting of the Expert Group on Demand Reduction, held in Bogota, Columbia, February 13 - 15, 2007. The purpose of the meeting was to establish agreement on the use of a common set or measures for prevention programs across the participating member states.

Dr. Frank Vocci, Director, DPMCDA, spoke at the European Association of Addiction Treatment in Vienna on September 10, 2007 on New Pharmacological Development in the Treatment of Nicotine Dependence: Varenicline and More.

Drs. Ivan Montoya, Jag Khalsa, Ahmed Elkashef, and Frank Vocci presented a course on Addiction to Opiates at a pre-conference session of the II Latin American Congress on Addictions in Medellin, Colombia on July 25, 2007.

Dr. Frank Vocci spoke on the Neurobiology of Cocaine Addiction at the II Latin American Congress on Addictions. Dr. Jag Khalsa spoke on the Co-morbid Conditions and Infections Associated with Substance Abuse. Dr. Ahmed Elkashef spoke on the Development of Medications for the Treatment of Cocaine Dependence. Dr. Ivan Montoya spoke on the Development of Medications for the Treatment of Drug Dependencies.

Drs. Frank Vocci, Ivan Montoya, Ahmed Elkashef and Jag Khalsa, all of DPMCDA, met with the Dean of the School of Public Health and several faculty members of the University of Antioquia in Medellin, Columbia on July 25, 2007. Discussions were held regarding technical assistance needs for the assessment of drug abuse incidence, prevalence, and its consequences; and development of a research agenda in drug use and dependence in the Colombian population.

Dr. Jag Khalsa, Dr. Frank Vocci, Dr. Ahmed Elkashef, and Dr. Ivan Montoya also met with various clinicians/researchers from the School of Public Health at the University in Medellin, Colombia, and exchanged research findings on drugs

of abuse. The Colombian hosts were extremely impressed by NIDA's accomplishments and asked for assistance in setting up similar research and administrative infrastructure in Colombia where drug abuse and infections related problems are becoming a significant problem.

Dr. Jag Khalsa, DPMCDA, gave invited talks on medical consequences of drug abuse and infections, clinical consequences of marijuana, and drug-drug interactions at the Mariaberocentrum (Drug Treatment Center) in Stockholm, Sweden, and at the Helsinki University, Finland, June 1-4, 2007.

Dr. David Gorelick, IRP, gave the invited plenary lecture on addiction at the 2nd International Congress on Biological Psychiatry, Santiago, Chile, April 20, 2007. His topic was Neurobiology and Treatment of Cannabis Dependence.

Dr. Yavin Shaham, IRP, presented a seminar entitled "Relapse to Drug and Food Seeking: Recent Findings" on June 8, 2007 at the Free University in Amsterdam, Netherlands.

Dr. Mu-Fa Zou, IRP, gave invited lectures at Hubei University, Wuhan Institute of Science and Technology, both in Wuhan, and East China University of Science and Technology, in Shanghai, during his recent visit to China.

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Meetings/Conferences

NIDA, in collaboration with NIAAA and the **American Psychological Association** (APA) Divisions 28 (Psychopharmacology and Substance Abuse) and 50 (Addictions) organized a large program of research symposia and other events which were held as part of the APA annual meeting in San Francisco, August 17-20, 2007. In addition to these presentations of NIDA supported research made by NIDA staff and researchers in the field, NIDA, NIAAA and Divisions 28 and 50 sponsored an Early Career Investigators Poster Session and Social Hour. This event provided the opportunity for approximately 65 early career researchers to travel to the conference and present their work to the members of the Divisions and to interact with senior researchers in the field. The program was organized at NIDA by Meyer Glantz, Minda Lynch, Cora Lee Wetherington, Jane Smither, Melissa Racioppo, David Shurtleff, Lula Beatty, Teresa Levitin, Carol Myers, Harold Perl, Paul Schnur, Belinda Sims, and Aria Crump.

The National Institute on Drug Abuse (NIDA), in collaboration with the Center for Substance Abuse Treatment (CSAT), and the National Association of State Alcohol and Drug Abuse Directors (NASADAD) held a meeting **"Translating the Science of Addiction to Clinical Practice: The Challenge of Change"** on June 10, 2007 at the Wyndham Hotel in Burlington, Vermont. NIDA's Deputy Director, Dr. Timothy P. Condon, presented new research findings in addiction science and Dr. Cindy Miner, OSPC's Deputy Director, provided an update on recently released Blending Team Products including Motivational Interviewing (MIA:STEP) and Motivational Incentives (PAMI).

NIDA awarded 29 Director's Travel Awards for the 69th annual meeting of the College on Problems of Drug Dependence (CPDD) on June 16-21, 2007, in Quebec City, Canada. These awards are designed to enhance the opportunity for junior investigators to attend and present at the CPDD meeting, as well as to broaden their exposure to different disciplines of drug abuse and addiction research via the NIDA Tutorials Workshop. Drs. Mimi Ghim and Susan Weiss, OSPC, with the logistical support provided by Ms. Usha Charya, OSPC, coordinated the following activities at CPDD: (1) NIDA Tutorials Workshop, chaired by Dr. Ghim, which introduced trainees and fellows to different areas of drug abuse and addiction research in the course of presentations from three NIDA Training Directors; (2) NIDA Grant-Writing Workshop, chaired by Dr. Cindy Miner, where Drs. Cindy Miner, David Shurtleff, Mark Swieter, and Scott Lukas provided an overview on NIDA research training opportunities, program interests, review procedures, and grantsmanship to prospective candidates.

NIDA awarded 30 Women & Gender Junior Investigator Travel Awards for the annual meeting of the College on Problems of Drug Dependence (CPDD), June 15-21, 2007, Quebec City, Canada. These $750 awards, which have been made annually beginning in 2000, are designed to promote entry of junior

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investigators into drug abuse research on women and sex/gender differences. To further promote research in this field, NIDA published a mini-program book, *Focus on Women & Sex/Gender Differences*, for the CPDD meeting. Excerpted from the CPPD program book, it contains only those program listings related to women and sex/gender differences. It also contains the CPDD abstracts on women and sex/gender differences, information about the Women & Gender Junior Investigator Travel Awardees, announcement of the travel award program for CPDD 2008, and information on current NIDA program announcements in this area.

The **Screening and Brief Intervention for Drug Abuse in Health Care Settings: Building the Evidence Base Through Provider-Researcher Collaborations** Meeting took place in Rockville on July 19-20, 2007, in collaboration with SAMHSA's Center for Substance Abuse Treatment. The meeting was organized by NIDA's OSPC, DESPR and DCNBR. Screening and brief intervention for substance use has the potential to significantly alleviate an enormous national public health burden, yet little research has been conducted for drugs other than tobacco and alcohol. Thus, there is a need for data and research in this area. This meeting convened researchers and practitioners to review the state of the science and practice in the area of screening, brief intervention and referral to treatment (SBIRT) for illicit drug use in order to identify promising and important targets for additional research development.

A NIDA-sponsored workshop entitled **Developing a Testing Battery for Cognitive Dysfunction in Substance Abuse**, organized by Dr. Steven Grant, DCNBR, was held in Chevy Chase, Maryland, on July 12-13, 2007. The goal of the meeting was to determine the need for and scope of a standardized set of cognitive tasks that would be useful in substance abuse research.

A NIDA-sponsored workshop entitled **Using Real Time fMRI for Neurofeedback Control of Craving**, organized by Dr. Steven Grant, was held in Chevy Chase, Maryland on July 25-26, 2007 to explore how presenting subjects with real time displays of regional brain activity could be used in either research or treatment settings for substance abuse.

A NIDA-sponsored workshop entitled **Neuroimaging Research: Implications for the Treatment of Substance Abuse**, was part of the annual meeting of the American Psychological Association, was organized and co-chaired by Dr. Steven Grant and Dr. Meyer Glantz of DESPR and held in San Francisco, California, August 17-20, 2007.

NIDA's Special Populations Office (SPO), in conjunction with the American Psychological Association, held a **Research Development Seminar** on May 9-10, 2007 in Bethesda, Maryland. The two-day workshop, coordinated by Pamela Goodlow, SPO, provided scholars underrepresented in the field of drug abuse and addiction with technical assistance on proposal development skills in drug abuse research.

Dr. Timothy P. Condon, Deputy Director, NIDA, presented "It's a Brain Disease: Beyond a Reasonable Doubt--The Neuroscience of Addiction" at the 2007 Florida Drug Court Training Conference, Sixth Florida Statewide Drug Court Conference on April 26, 2007, in Orlando, Florida.

Dr. Timothy P. Condon presented "National Institute on Drug Abuse: Institute Update" at the American Society of Addiction Medicine's 38th Annual Medical Scientific Conference on April 27, 2007, in Miami, Florida.

Dr. Timothy P. Condon presented "Addiction as a Brain Disease: Implications for Health Professionals" at the Federation of State Physician Health Program's Annual Meeting on May 2, 2007, in San Francisco, California.

Dr. Timothy P. Condon chaired the "Testing and Counseling Policy" session at the Drug Abuse and Risky Behaviors: The Evolving Dynamics of HIV/AIDS conference on May 9, 2007, in Bethesda, Maryland.

Dr. Timothy P. Condon presented "Advances in Drug Abuse and Addiction from NIDA: Implications for Treatment" at the 6th Annual Chief Resident Immersion Training (CRIT) Program on May 14, 2007, in Cape Cod, Massachusetts.

Dr. Timothy P. Condon presented "Drug Abuse Treatment Within the Criminal Justice System: Addressing Our Nation's Public Health Needs" and co-chaired a symposium by the same name, at the NIDA/APA research-based program track, "The Science of Addiction: Translating New Insights Into Better Psychiatric Practice," part of the American Psychiatric Association 160th Annual Meeting on May 23, 2007 in San Diego, California.

Dr. Timothy P. Condon presented "The Science of Addiction: What We Have Learned" at the National Association of State Alcohol and Drug Abuse Directors' 2007 Annual Conference, "Translating the Science of Addiction to Clinical Practice: The Challenge of Change," on June 10, 2007, in Burlington, Vermont.

Dr. Timothy P. Condon presented "It's a Brain Disease: Beyond a Reasonable Doubt - The Neuroscience of Addiction" at the 2007 Florida Conference of Circuit Judges' Annual Business Program, on June 11, 2007, in Marco Island, Florida.

Dr. Timothy P. Condon presented "NIDA Networking Project, News and Updates" at the NIDA Genetics Consortium, on June 13, 2007, in Rockville, Maryland.

Dr. Timothy P. Condon presented "Addressing the Linkages between HIV/AIDS and Drug Abuse" to the Presidential Advisory Council on HIV/AIDS on June 13, 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 National Association of Drug Court Professionals on June 14, 2007, in Washington, D.C.

Dr. Timothy P. Condon provided remarks on "Treatment is the Key: Providing Drug Abuse Services in Criminal Justice Settings" before Congressman Bobby Scott (D-VA; Chairman, United States House of Representatives Committee on the Judiciary, Subcommittee on Crime, Terrorism, and Homeland Security) at the Violent Crime - Prevention and Solutions from the Experts; A Summit on Crime Policy, on June 22, 2007, in Washington, D.C.

Dr. Timothy P. Condon presented "Principles of Drug Abuse Treatment for Criminal Justice Populations" at the National Center for Community Corrections on June 29, 2007, in Washington, D.C.

Dr. Timothy P. Condon presented "Methamphetamine, Emerging Drug Problems, and Blending Research and Practice" to the U.S. Senate Committee on Health, Education, Labor and Pensions on July 13, 2007, in Washington, D.C.

Dr. Cindy Miner, Deputy Director, OSPC, presented "Neurobiology of Addiction" at the Southern West Virginia Coalfields Tobacco Prevention and Cessation Training Meeting on May 17, 2007 in Beckley, West Virginia.

Dr. Cindy Miner presented an "Overview of Blending Initiative" at Translating the Science of Addiction to Clinical Practice: The Challenge of Change, a NIDA-SAMHSA Meeting in Collaboration with NASADAD on June 10, 2007 in Burlington, Vermont.

Dr. Cindy Miner presented "Blending Team Product: Promoting Awareness of Motivational Incentives (PAMI)" at Translating the Science of Addiction to

Clinical Practice: The Challenge of Change, a NIDA-SAMHSA Meeting in Collaboration with NASADAD on June 10, 2007.

Dr. Cindy Miner presented "Highlighting NIDA Research Priorities and Funding Opportunities" at the American Academy of Child and Adolescent Psychiatry K12 Retreat on June 14-16, 2007 in Quebec City, Canada.

Dr. Cindy Miner chaired a Grantwriting Workshop at the College on Problems of Drug Dependence (CPDD) 69th Annual Meeting on June 19, 2007 in Quebec City, Canada.

Dr. Susan Weiss, Chief, Science Policy Branch, OSPC, participated in the Research Colloquium for Junior Investigators, sponsored by the American Psychiatric Institute for Research and Education (APIRE) in San Diego on May 20, 2007. She presented information on research training and funding opportunities available at NIDA to encourage psychiatrists to pursue research careers and become independent investigators.

Dr. Gayathri J. Dowling, Deputy Chief, Science Policy Branch, OSPC, NIDA, delivered the Banquet Address entitled "The Science of Addiction," at the Annual Wisconsin State Prevention Conference on July 25th, 2007, in Stevens Point, Wisconsin.

Dr. Gayathri J. Dowling, Deputy Chief, Science Policy Branch, OSPC, NIDA, gave a presentation entitled "The Science of Addiction" at the National Network for Safe and Drug-Free Schools and Communities Semi-Annual Professional Development Conference on August 1, 2007, in Washington, D.C.

Dr. Nicolette Borek, DCNBR, moderated a symposium on "Prenatal Nicotine Exposure: How Does it Relate to Developmental Vulnerabilities?" at the 160th Annual Meeting of the American Psychiatric Association in San Diego, CA, May 19-24, 2007.

Dr. Nicolette Borek moderated the session "Prenatal Drug Abuse and Adolescent Developmental Trajectories" at the 31st Annual Meeting of the Neurobehavioral Teratology Society in Pittsburgh, PA, June 23-27, 2007.

Dr. Wilson Compton, Director, DESPR, presented to the SAMSHA Screening, Brief Interventions and Referral to Treatment (SBIRT) grantees on "Developing a Research Agenda for SBIRT", May 10, 2007.

Dr. Wilson Compton presented on "Drug Abuse and Addiction: Preventable and Treatable Diseases" at the Wisconsin state substance abuse provider meeting in Madison, May 14, 2007.

At the annual meeting of the American Psychiatric Association in San Diego, Dr. Wilson Compton presented on "Methamphetamine Epidemiology" and "Dimensional Approaches to Nicotine, Marijuana and Alcohol Use Disorders" as well as serving as discussant in a panel on adolescent substance abuse treatment.

At the annual meeting of the Society for Prevention Research in Washington, District of Columbia, Dr. Wilson Compton co-chaired a panel on "Measurement of Community-Level Change Processes" on May 31, 2007.

Dr. Wilson Compton presented in sessions on "National Prevention and Treatment Best Practices" and "The NIATx Action Campaign" at the State Associations of Addiction Services National Conference for Executive and Senior Managers in Addiction Services held in Chicago, Illinois on July 9, 2007.

On July 24, 2007, Dr. Compton participated in the American Psychiatric Association DSM-V Task Force meeting, Arlington, Virginia.

On August 3, 2007, Dr. Wilson Compton presented "Drug Abuse Epidemiology"

at the meeting of the Safe and Drug Free Schools program in Washington, DC.

Dr. Redonna Chandler, DESPR, co-chaired a symposium "Drug Abuse Treatment within the Criminal Justice System: Addressing Our Nation's Public Health Needs" at the American Psychiatric Association 160th Annual Meeting, San Diego, CA, May 19-24, 2007.

Dr. Redonna Chandler, DESPR presented, "It's a Brain Disease beyond a Reasonable Doubt" at the National Association of Drug Court Professional's 13th Annual Drug Court Training Conference held in Washington, DC, June 13-16, 2007.

In June 2007 Dr. Yonette Thomas, DESPR, presented a poster at CPDD on "Trajectories of Drug Use and Contextual Factors among Minority Youth" based on data from the National Survey of Parents and Youth (NSPY). Her co-authors were Drs. Marsha F. Lopez, DESPR, Zhiqun Tang and Robert G. Orwin, WESTAT.

Dr. Elizabeth Robertson, DESPR, presented a session on the NIH grants process at the 2007 W. T. Grant Foundations Summer Scholars meeting, in Snowbird, UT on June 23, 2007.

Dr. Elizabeth Robertson participated in a two day meeting of the Basic Career Knowledge Taskforce of the Society for Prevention Research on July 10 and 11, 2007 in Arlington, VA.

Dr. Elizabeth Robertson participated on the Technical Consultation Group for the Substance Abuse and Mental Health Service Administration's National Outcome Measures (NOMs) and Evidence Based Practices (EBPs) Workgroup on August 1st and 2nd, 2007 in Bethesda, MD.

Dr. Redonna Chandler, Ph.D., DESPR, participated in the 7th Annual Meeting for Substance Abuse Treatment (CSAT) Science to Services and Services to Science: The Identification & Adoption of Effective Practices for Substance Abuse Treatment pre-meeting satellite session of the CPDD 69th Annual Scientific Meeting, Quebec City, Quebec, CA, July 16-21, 2007.

Dr. Elizabeth Ginexi, DESPR, and Dr. Eve Moscicki of NIMH helped to plan and participated in a Pre-conference Workshop at the Annual Meeting for the Society for Prevention Research titled "Underlying Mechanisms in Liability for Dysregulatory Behaviors." The focus of the workshop, which took place on May 29, 2007, was on clarifying how genetic and environmental factors operate together and to discuss the relevance to prevention research. NIDA/NIMH Travel awards were offered to 14 Early Career investigators to attend the meeting. Presenters included Jenae Neiderhiser (George Washington University), Diana Fishbein (RTI), Michael Vanyukov (University of Pittsburgh), Leslie Leve (Oregon Social Learning Center), Joan Kaufman (Yale University), Sara Jaffee (University of Pennsylvania), and Ken Dodge (Duke University).

Dr. Jessica Chambers, DESPR, chaired a scientific symposium on children of drug abusers at the Society for Prevention Science Meeting held in May 2007 in Washington, DC.

Dr. Augusto Diana, DESPR, delivered a keynote address entitled "Prevention and Methamphetamine What Do We Know?" to the 2nd Annual Drug Endangered Child Conference held from February 21-23, 2007, at Stephen F. Austin State University in Nacogdoches, Texas. Dr. Diana also facilitated a series of follow-up workshops at the conference, focused on the same topic.

Dr. Aria Crump, DESPR, represented NIDA/NIH at the HHS-sponsored Native Hawaiian and Pacific Islanders' Consultation Meeting in Carson, CA on April 23-24, 2007.

Dr. Aria Crump presented on DESPR research priorities at the NIDA Special Populations Office Research Development Seminar Series Meeting co-sponsored by the American Psychological Association that was held on May 9-10, 2007.

Drs. Aria Crump and Belinda Sims, DESPR, co-chaired a session entitled "Spotlight on Data Sharing: New Opportunities for Advancing Research with Existing Data Sets" for the Annual Meeting of the Society for Prevention Research on May 30, 2007.

Dr. Aleta Meyer, DESPR, chaired an organized paper symposium titled "Thinking about the Role of Peer Norms in School-Based Interventions to Prevent Aggression and Violence" at the 15th Annual Society for Prevention Research meeting in Washington DC on May 30, 2007.

Dr. Elizabeth Ginexi, DESPR, served as the Discussant for a Paper Symposium at the annual meeting for the Society for Prevention Research in Washington, DC on May 31, 2007 titled "The Role of Peers in Substance Use Risk and Substance Use Prevention." Drs. Philip Costanzo of Duke University, Thomas Valente of the University of Southern California, and Valerie Johnson of Rutgers University presented papers.

Drs. Aria Crump, Belinda Sims, and Richard Jenkins organized and participated in a multi-IC update on NIH policy and programmatic priorities for the Annual Meeting of the Society for Prevention Research on May 31, 2007.

Drs. Belinda Sims and Aria Crump co-chaired a Poster Forum entitled "At the Intersection of Health Disparities in Drug Abuse and the Research Pipeline: Minority Researchers Advancing the Science," at the May/June 2007 Society for Prevention Research Meeting in Washington, DC, which included presentations from researchers at various levels of early career development--undergraduate through assistant professor/research scientist.

Dr. Belinda Sims participated in a roundtable discussion on "Integrating and Coordinating Care across Levels of Intervention in School-Based Services: Research Strategies and Practical Considerations," during the May/June 2007 Society for Prevention Research annual meeting, in Washington, DC.

Drs. Eve Reider and Belinda Sims co-chaired a symposium "Is Early Prevention Intervention Later AIDS Prevention?" at the American Psychological Association annual meeting in San Francisco, CA on August 20, 2007. The panel of presenters included David Olds, University of Colorado, Karl Hill, University of Washington, and Kenneth Griffin, Weill Medical College of Cornell University. Deborah Capaldi, Oregon Social Learning Center, was the discussant for the symposium.

Dr. Richard Denisco, DESPR, served on the planning committee and was the contact person for the Pain, Opioids, and Addiction: An Urgent Problem for Doctors and Patients, March 5-6, 2007 at Natcher Auditorium NIH, Bethesda, MD.

Dr. Richard Denisco represented NIDA at The Tufts Health Care Institute Program on Opioid Risk Management on March 29-30, 2007 in Boston, MA.

Dr. Dionne Jones, DESPR, presented on a Panel "Drugs, African Americans and Criminal Justice Research: Implications for Career Choices and Job Excellence" at the Lonnie Mitchell Annual Conference, Washington, DC. March 29-31, 2007.

Dr. Richard Denisco presented an abstract "Effect of 12-Step Meeting Attendance on Drug Positive Status at One Year" at the College on Problems of Drug Dependency, in Quebec City on June 21, 2007.

Dr. Dionne Jones organized and chaired a panel presentation, "Drug Abuse and

Homelessness Among Women at Risk for HIV" at the American Psychological Association Annual Meeting, San Francisco, CA, August 17-20, 2007.

Dr. Peter Hartsock, DESPR, moderated a session titled "Drug Abuse in South African Youth Research Panel" at the NIDA-sponsored conference, "Southern Africa Initiative: Research Progress and Perspectives," Bethesda, MD, April 17, 2007.

Derrick Prather, SPO, presented a talk on "Substance Abuse; Risk Factors and the Social Impact" to teens attending the Health Education Camp at Howard University in Washington, D.C. on August 1, 2007.

Flair Lindsey, Program Analyst, Special Populations Office, coordinated the 11th annual Summer Research with NIDA program, which enabled high school and undergraduate students to engage in drug abuse research with various NIDA grantees for 8-10 weeks over the summer. This year, 52 students and 30 investigators participated.

Dr. Mark Swieter, OEA, made the presentation, "Update on Electronic Grant Submission and Process for Foreign Investigators" on June 16, 2007 at the NIDA International Forum in Quebec City, Canada.

Dr. Mark Swieter made the presentation, "Research Grants and the Peer Review Process" on June 19, 2007 at the Grant Writing Workshop at CPDD in Quebec City, Canada.

Dr. Meena Hiremath and Dr. Mark Swieter both of OEA and Dr. Gail Boyd from the Center for Scientific Review Co-chaired a workshop entitled "What's New at NIDA and NIH: Electronic Submission of Applications and More" on June 17, 2007 at CPDD in Quebec City, Canada.

Dr. Mark Green, OEA, conducted a mock grant application review training session for new investigators at the Society for Prevention Research on May 31, 2007.

Dr. Teri Levitin, Director, OEA, co-organized and co-presented with other NIDA staff a grant writing workshop at the American Psychiatric Association's annual meeting in May 2007. The purpose of the workshop was to help participants become more familiar with the research funding process at the NIH and to learn how to be more proactive in the preparation and submission of their own applications.

Dr. Teri Levitin participated as an invited panelist in a workshop called "Show Me the Money: Grant-getting for Graduate Students and New Faculty" at the Association for Psychological Science in May. Her presentation focused on opportunities for psychologists at NIDA.

Dr. Teri Levitin has been on the planning committee for NIDA activities at the American Psychological Association's annual meeting, and, with Dr. Harold Perl, co-organized and co-taught a continuing education course on grant writing at that meeting in August 2007. This four-hour workshop provided an overview of NIH extramural policies and procedures as well as NIDA and NIAAA program areas.

Dr. David Thomas, DBNBR, chaired a session titled, Mechanisms and Management of Neuropathic Pain, at the NIH Pain Consortium's 2nd annual meeting, Advances in Pain Research, held at the NIH main Campus Masur Auditorium, May 1, 2007.

Dr. David Thomas co-chaired a workshop titled, "Bridging Basic Pain Research, Conventional Pain Treatments and VR Pain Treatments" at the Cybertherapy 2007 meeting held in Alexandria, VA on June 11, 2007.

Dr. David Thomas chaired a session titled, "Pain" at the Cybertherapy 2007

meeting held in Alexandria, VA on June 12, 2007.

Dr. David Thomas made a presentation on the NIH grant process at a session titled, New Investigator Guide to the NIH Grant Process, Training Programs, and Funding Opportunities, at the American Pain Society meeting May 4, 2007, in Washington, DC.

Dr. David Thomas co-chaired and made a presentation at a session titled, "Alternative and Complementary Medicine," held June 28, 2007 at the American Peptide Society annual meeting in Montreal, Canada.

Dr. Rao S. Rapaka, DBNBR, co-organized a symposium on "Epigenetic Applications to Drug Development" at the Annual Meeting for the National Biotechnology Conference (NBC) of the American Association of Pharmaceutical Scientists (AAPS), San Diego, June 2007.

Dr. Rao S. Rapaka co-organized a symposium on "Alternative and Complementary Medicine: Applications to Peptide Research" at the 20th American Peptide Symposium, Montreal, June 28, 2007.

Drs. Hari Singh and David Shurtleff, both of DBNBR, organized and co-chaired a workshop session on "An Overview of NIDA Drug Supply & Analytical Services Program" at the 2007 CPDD meeting in Quebec, Canada on June 19, 2007.

Dr. Christine Colvis and David Shurtleff, DBNBR, organized and co-chaired a symposium entitled: "On the Road to Chemical Ligand Development for Drug Abuse Research" at the 2007 CPDD meeting in Quebec, Canada on June 17, 2007.

Drs. Paul Schnur and David Shurtleff, DBNBR, organized and co-chaired a NIDA sponsored symposium entitled "Extinction Learning: Application to Drug Addiction" at the 2007 annual meeting of the American Psychological Association, San Francisco CA on August 19, 2007.

Dr. David Shurtleff gave a Division 28 Fellow presentation entitled "A Role for Psychopharmacology in Understanding Individual and Genetic Vulnerability to Drug Addiction" at the 2007 meeting of the American Psychological Association, San Francisco CA on August 18, 2007.

Drs. Allison Chausmer and Cora Lee Wetherington, DBNBR, co-organized and co-chaired the symposium, "A Translational Approach to Understanding Gender, Adolescence and Vulnerability to Nicotine Addiction," at the Society for Research on Nicotine & Tobacco, February 21-24, 2007, Austin, TX.

Dr. Cora Lee Wetherington presented the workshop, "Sex/Gender Matters in Drug Abuse," at the Virginia Summer Institute for Addiction Studies, July 16-20, 2007, Williamsburg, VA.

Dr. Susan Volman, DBNBR, participated in an NIH funding workshop with representatives from other NIH ICs, at University of Maryland on May 3, 2007.

Dr. John Satterlee, DBNBR, gave a presentation describing the major aspects of the Epigenetics Roadmap Initiative to the trans-NIH Genomics Workgroup June 7, 2007.

Dr. John Satterlee attended and participated in the NCI-sponsored "ChIP-chip Workshop" on Chromatin Immunoprecipitation, Bethesda, MD July 9, 2007 and the NCI-sponsored workshop "Innovative Research at NIH: Finding What Works" on methods for identifying and fostering innovative research, Bethesda, MD June 21, 2007.

Drs. Jonathan Pollock and John Satterlee, both of DBNBR, co-chaired "Genes, Microarrays and Addiction Workshop", Bethesda, MD May 31-June 1, 2007.

Drs. Frank Vocci and Ahmed Elkashef, DPMCDA, co-chaired two workshops at the American Psychiatric Association meeting in San Diego in May 2007. The first workshop was entitled Promising Medications for the Treatment of Cocaine Addiction. Drs. Ahmed Elkashef, Kyle Kampman, Bankole Johnson, and George Koob presented at the workshop. The second workshop was entitled: Methamphetamine Abuse and Addiction: Prevalence and Treatment. Drs. Wilson Compton, William Haning and Trevor Robbins spoke at the workshop.

Drs. Ivan Montoya and Frank Vocci, DPMCDA, co-chaired a symposium at the CPDD meeting in Quebec, Canada in June 2007 entitled: Where there's smoke there's fire: Understanding vulnerability to tobacco and marijuana use in schizophrenia. Drs. Danielle Piomelli, Sherry Leonard, Cyril D'Souza, and Ivan Montoya made presentations at the symposium. Dr. Tony George was the discussant.

Drs. Ahmed Elkashef and Frank Vocci co-chaired a workshop at CPDD entitled: Pharmacotherapies for Stimulant Addiction. Drs. Eklashef, Kimmo Kopppasalmi, and Jason White presented. Dr. Frank Vocci was the workshop discussant.

Dr. Frank Vocci spoke on Cognitive Deficits Produced by Stimulants at the University of Arkansas on August 13, 2007.

On June 19, 2007, at the College on Problems of Drug Dependence 67th Annual Scientific Meeting, Drs. Ahmed Elkashef and David McCann, DPMCDA, chaired a workshop entitled "Issues in Medications Development for Relapse Prevention." Presentation were as follows: Dr. Charles O'Brien presented "The Importance of Relapse Prevention in Drug Addiction Treatment;" Dr. Jane B. Acri, DPMCDA, presented "Animal Models of Relapse: An Overview;" Dr. McCann presented "Use of Extinction/Reinstatement Rat Models of Relapse in Medications Discovery; " Dr. Anna Rose Childress presented "Human Laboratory Models of Relapse: Approaches, Pitfalls and a View to the Future;" and Dr. Elkashef presented "Considerations in the Design of Clinical Trials for Assessing the Efficacy of Relapse Prevention Medications." Dr. Frank Vocci served as the discussant. A brief summary of the presentations and discussions will be published in Drug and Alcohol Dependence.

On June 12, 2007, at the 12th Annual CyberTherapy Conference, "Transforming Health Care through Technology," Dr. Nathan M. Appel, DPMCDA, co-chaired the symposium entitled, "Addictions." Presentations were as follows: B. Girard and V. Turcotte, "A Virtual Arm to Stop Smoking, A Perceptual Learning Experiment;" R. Astur et al., "Establishing Preferences to Virtual Environments using Cocaine;" S-M. Kwak and J-H Lee, "Avoiding Coping Strategy User's Attentional Bias and Emotional Change to Appearance-Related Stimuli;" H.L. Copp et al., "Using Virtual Reality to Investigate Cross-Cue Reactivity and Environmental Cues in Nicotine Dependent Problem Drinkers;" and M.Z. Rosenthal et al., "Virtual Reality for Cue Exposure and Cell Phones as Cue Extinction Reminders in Treatment for Crack Cocaine Dependence." Dr. Appel was the symposium discussant. Dr. Appel also served on the Conference Program Committee.

Kevin Conway and Ivan Montoya co-chaired a symposium at the APA meeting in San Diego about the directionality of substance use disorders and mental disorders in May 2007.

Ivan Montoya and Frank Vocci co-chaired a symposium 'Comorbidity of Nicotine and Cannabis Use Disorders and Schizophrenia' at the CPDD meeting in Quebec City. Ivan Montoya made a presentation about the development of medications for the treatment of that triple comorbidity in June 2007.

Ivan Montoya participated in the NIDA International Satellite meeting and met with Hispanic investigators to discuss the development of an international web portal.

Dr. Nora Chiang, DPMCDA, and Dr. Michael Owens, University of Arkansas co-organized and co-chaired a symposium entitled "Newly Engineered Antibodies and Enzymes Therapies for Treating Drug Abuse" at the CPDD annual meeting in Quebec City, Canada, June 2007.

On June 18, 2007, at the College on Problems of Drug Dependence 67th Annual Scientific Meeting, Dr. Jane B. Acri presented in a workshop entitled "Computational Modeling of Complex Systems in Problems of Drug Dependence: A New Research Solution." Her presentation was entitled "The Complexities of Drug Dependence: Why We Might Need Computational Models." A brief summary of the presentations and discussions will be published in Drug and Alcohol Dependence.

Dr. Joseph Frascella, Director, DCNBR, co-chaired with Dr. Nora Volkow a symposium entitled "Insights on Obesity and Drug Addiction from Brain Imaging" held at the American Psychiatric Association in San Diego, CA on May 21, 2007.

Dr. Laurence Stanford, DCNBR, presented a talk on grant writing strategies at the NIDA Special Populations Office Research Development Seminar Series in May, 2007.

Dr. Laurence Stanford co-chaired a symposium at the 160th Annual Meeting of the American Psychiatric Association in San Diego, CA in May, 2007 entitled "A Picture of the Development of the Adolescent Brain: A Structural and Functional Assessment".

Dr. Joseph Frascella gave a presentation at the National Hispanic Science Network Summer Research Training Institute on Hispanic Drug Abuse entitled "NIH Proposal Writing and Research Mechanisms" at the University of Houston in Houston, Texas on June 6, 2007.

Drs. Laurence Stanford, Joseph Frascella, and Steven Grant, all of DCNBR, participated in an Association of American Medical Colleges Symposium on the Scientific Basis of Influence and Reciprocity in June, 2007.

Dr. Joseph Frascella attended a meeting hosted by the Rudd Center at Yale University on Food and Addiction in New Haven, Connecticut on July 9-10, 2007.

Dr. Woody Lin, DCNBR, represented NIDA at the annual meeting of the American Psychological Association held in San Francisco, California, August 17-20, 2007.

Dr. Petra Jacobs, CCTN, participated in the AATOD Workshop Committee Meeting on April 13, 2007.

CCTN staff/contractors participated in the 28th annual meeting of the Society for Clinical Trials that was held in Montreal, Canada, May 20-23, 2007 as follows:

> Dr. Paul Wakim chaired an Invited Session on "Effect Size in Sample Size Determination: Clinical versus Statistical Significance". The session included three speakers: Gordon Lan, Johnson & Johnson Pharmaceutical R&D, Carl Pieper, Duke University Medical Center and Christopher Coffey, University of Alabama at Birmingham, and a discussant (Paul Wakim).
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> Carmen Rosa chaired a symposium titled, "Safety Monitoring in Behavioral Trials: Challenges and Opportunities" that presented an overview of the design and safety monitoring of behavioral trials, a discussion of adverse events, and a discussion of challenges from the perspective of the principal investigator. The session included

four speakers: Kathleen Carroll, Yale University, New England Node, Greg Brigham, Maryhaven Inc., Ohio Valley Node, Felix Gyi, CEO, Chesapeake Research Review, Inc., and Kenzie Preston, Acting Chief, Clinical Pharmacology and Therapeutic Research Branch, National Institute on Drug Abuse.

Jeng-Jong (JJ) Pan and David Liu, presented a poster entitled, "Analysis of Adverse Events in Clinical Trials Using Data Mining."

DCRI, the Data and Statistics Center for CTN, presented a paper titled "Challenges of Establishing a Public Share Data Web Site", in the contributed paper session.

Janet Levy delivered an oral presentation entitled "Sizing Simple Trials to Develop Adaptive Treatment Strategies". Coauthors included Susan Murphy of the University of Michigan and Carl Pieper of the Duke Clinical Research Institute.

At the College on Problems of Drug Dependence (CPDD) annual meeting in Quebec City, June 17-21, 2007, Don Calsyn and other CTN members presented a symposium on the results of three HIV protocols completed in the CTN in 2006. There were other CTN presentations by Drs. Maxine Stitzer, George Woody, Dan Polsky, and other CTN members.

CCTN-Related participation in the 115th annual convention of the American Psychological Association (APA) held August 17-20 in San Francisco, CA included the following:

The CTN Gender Special Interest Group (SIG) presented a symposium entitled, "Women's Issues in Substance Abuse Treatment." The symposium was co-chaired by Susan Gordon (Delaware Valley) and Carmen Rosa (NIDA). Participants were Theresa Winhusen (Ohio Valley Node), Susan Tross (Long Island Node), and Denise Hien (Long Island Node); Kathleen Brady (Southern Consortium) was the discussant.

The CTN HIV Special Interest Group presented a symposium on the past and present HIV related studies conducted in the CTN. Dr. Don Calsyn (Lead Investigator CTN 0018) chaired the session entitled, "HIV/AIDS Related Research in the NIDA Clinical Trials Network." The session included five speakers: Robert Booth (Lead Investigator CTN 0017), Susan Tross (Lead Investigator CTN 0019), Don Calsyn, James Sorensen (California/Arizona Node PI), and Lisa Metsch (Lead Investigator CTN 0032). Presenters discussed the primary outcome findings from their trials and challenges involved in conducting HIV risk reduction research protocols in community treatment programs, many who have not previously been involved in research studies.

Member and affiliates of the CTN presented a symposium entitled, "Practical Challenges Integrating Evidence-Based Practices Into Addiction Treatment Programs." Participants included Joan Zweben (California/Arizona Node), Greg Brigham (Ohio Valley Node), Michael Levy (Northern New England Node), Dan Kivlahan (Washington Node), and Harold Perl (NIDA) and Dean Fixsen (consultant to the RUC).

Harold Perl (with Teresa Levitin [NIDA OEA]) taught a half-day technical assistance workshop titled, "Inside the Black Box at NIH (NIDA & NIAAA): Grant Writing Tips They Didn't Teach You in Graduate School," on August 15, 2007.

Dr. Peter Grundt, IRP, gave the NIDA-IRP Seminar series lecture on April 17,

2007 and was invited to give a lecture at the University of Minnesota, Duluth, in June 2007.

Drs. Peter Grundt, Noel Paul and George Cyriac, IRP, were invited to participate in the NIH Chemistry-Biology Interface Training Summit on June 21, 2007, in Bethesda, MD.

Dr. Roy Wise, IRP, presented a seminar entitled "Conditioned and Unconditioned Reward-related Input to the Dopamine System" at the Neural Pathways Reward Symposium at the Columbia University, Manhattan, New York on May 10, 2007.

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

Media and Education Activities

Press Releases

June 14, 2007 - HBO Producers win NIDA/CPDD Media Award for Documentary series "Addiction."
The National Institute on Drug Abuse and the College on Problems of Drug Dependence jointly presented the 2007 Media Award to John Hoffman, Vice President, Home Box Office (HBO) Documentary, for his role in co-producing the groundbreaking HBO documentary series "Addiction."

May 31, 2007 - NIDA Announces New Tools for Drug Abuse Treatment.
Two new products designed to speed the adoption of science-based interventions into clinical practice are now available from the National Institute on Drug Abuse. These new "Blending Team" products are part of an expanding portfolio that includes the latest research findings on drug abuse approaches and interventions. Blending Teams are composed of NIDA researchers, community-based substance abuse treatment practitioners, and trainers from the Substance Abuse and Mental Health Services Administration's Addiction Technology Transfer Center Network. In addition to the Blending Teams, NIDA sponsors a number of Blending conferences which are held periodically around the country to facilitate communication between researchers and treatment providers.

May 21, 2007 - NIDA Offers Psychiatrists a Look at State-of-the-Science on Addiction and Mental Illnesses.
The Director of the National Institute on Drug Abuse challenged psychiatrists to learn more about the importance of substance abuse as a factor in the diagnosis and treatment of mental illnesses. At the American Psychiatric Association Annual Meeting, Dr. Nora Volkow spoke at a three-day NIDA-sponsored research program track, "The Science of Addiction: Translating New Insights Into Better Psychiatric Practice." The program included a look at the interplay between genes and the environment, and closed with a discussion on the challenges of addiction and co-occurring mental illnesses.

May 8, 2007 - NIDA Looks at Non-Injection Drug Use and Spread of HIV/AIDS.
More than 500 scientists, clinicians and public health specialists met at the NIH to discuss the latest research on drug abuse and the evolving epidemic of HIV/AIDS. This was the first-ever two-day public meeting at NIH to include a focus on non-injection drug use and HIV transmission.

May 8, 2007 - NIDA NewsScan #50 - HIV/AIDS Issue

- HIV/STI Risk Behaviors in Delinquent Youth: A Community Health Problem
- Many Male Inmates Willing To Undergo Rapid HIV Testing

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- Study Shows Value of HIV Screenings in Virtually All Health Settings
- HBCU Students Willing To Accept Rapid HIV Testing; Those Most Likely To Consent Have a High Perceived Risk of Infection
- First Molecular Examination of HIV in High-Risk People Along U.S.-Mexico Border
- Adding HIV Risk Reduction Strategies to Drug Abuse Treatment Has Favorable Outcomes for Pregnant Women at Risk of Infection
- Study Investigates Impact of Partner HIV Status, Sexuality on Sex Practices of Methamphetamine- Abusing, HIV+ Men
- Minority Women with Dysthymia, a Form of Depression, May Be Less Likely To Receive HAART
- Managing Substance Abuse and HIV in Malaysia

May 7, 2007 - NIDA Survey Shows Most People with Drug Use Disorders Never Get Treatment.
Only 8 percent of people identified as drug abusers, and fewer than 40 percent of those diagnosed with drug dependence, have ever gotten any kind of intervention or treatment, according to the National Epidemiologic Survey on Alcohol and Related Conditions.

April 3, 2007 - NIDA Supported Study Shows Significant Association between Smoking, Mental Disorders in Pregnant Women.
New research has identified an association between mental disorders and nicotine dependence among pregnant women in the United States, not unlike what has been reported in the general population. The presence of these mental disorders in nicotine addicted pregnant women may make quitting smoking more difficult. This study supported in part by NIDA, was published in the April 2007 issue of Obstetrics and Gynecology.

April 2, 2007 - NIDA Survey Shows Lack of Substance Abuse Treatment Options for Offenders.
Substance abuse treatment services for offenders are not widely available in all phases of the correctional system, according to the first set of findings from a national survey funded by the National Institute on Drug Abuse. The National Criminal Justice Treatment Practices Survey (NCJTPS) provides a picture of existing treatment programs across all correctional settings, including prison, jails, probation and parole offices, and local community correction agencies for juvenile and adult offenders. The survey findings were published in a special issue of the Journal of Substance Abuse Treatment.

April 2, 2007 - NIDA Study Identifies Genes That Might Help Some People Abstain From Smoking.
Scientists supported by the National Institute on Drug Abuse have for the first time identified genes that might increase a person's ability to abstain from smoking. The breakthrough research was conducted by Dr. George Uhl at NIDA's Intramural Research Program and a team led by Dr. Jed Rose at the Center for Nicotine and Smoking Cessation Research at Duke University Medical Center.

March 3, 2007 - NIDA NewsScan #49 - Pain Opioids and Addiction Issue

- Physician Concerns Regarding Prescribing Opiates for Chronic Pain
- Researchers Assess Adolescents' Motivations To Abuse Prescription Medications
- Study Reveals a New Cellular Adaptation that Contributes to Opiate Tolerance
- URB597 Relieves Pain in Rats Without Cannabinoid-Associated Side Effects
- Managing the Impact of Pain: Antidepressants May Be Useful Part of Pain

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Articles of Interest

July 16, 2007, *TIME Magazine*—"How We Get Addicted"—Interview with Nora D. Volkow, M.D., Joseph Frascella Ph.D., and Frank Vocci, Ph.D.

July 10, 2007, *USA Today*—"Does Food 'Addiction' Explain Explosion of Obesity?"—Interview with Nora D. Volkow, M.D.

May/June, 2007, *Bethesda Magazine*—"This is Your Kid's Brain on..."—Interview with Susan Weiss, Ph.D.

Other Interviews

Dr. George R. Uhl, IRP, gave numerous US and international interviews in conjunction with publication of the first genome- wide association study for human genetic variations that underlie the ability to successfully quit smoking.

July 18, 2007, *ReachMD*, an XM Radio channel that covers a wide spectrum of medical issues. Dr. Joseph Frascella was interviewed on the topic of the science of addiction.

August 2007, *Women's Health Magazine*. Dr. Joseph Frascella was interviewed for an article on the topic of food addiction.

May 2007, *Teen Vogue*. Dr. Steven Grant was interviewed for an article on the resurgence of cocaine use.

June 2007, *Daily Health News*. Dr. Steven Grant was interviewed for an article on advances in brain imaging in substance abuse research.

Dr. Frank Vocci, Director, DPMCDA, was interviewed by the following people:

- Ben Merrens of Wisconsin NPR on Addiction.
- Dr. Larry Kashel of XM radio on the nicotine vaccine and other new medications to aid smoking cessation.
- Yvonne Wenger of the Charleston Post and Courier on cocaine dependence.
- Alaric De Arment of the Michigan City News Dispatch on abuse of methadone and its consequences.

Educational and Outreach Activities

Heads Up: Real News About Drugs and Your Body
Through a continuing partnership, the National Institute on Drug Abuse and SCHOLASTIC INC, the global children's publishing and media company, distribute 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®*. Student and Teacher compilations were completed for the 2006/07 school year, covering The Science of Addiction, Tobacco Addiction and Secondhand Smoke, Stress and Drug Abuse, and Health Literacy and Drug Abuse. NIDA is unique in that *Heads Up* is the only regular "run-of-book" insert included in any Scholastic magazine. In addition, the first article for the 2007/08 school year was completed for distribution in September 2007. This article covers the less obvious consequences of drug abuse, affecting perception, cognition, motor skills, and is the first of two articles this year focusing on decision making.

Brain Awareness Week Activities
On March 14 and 16, 2007, the National Institute on Drug Abuse once again

participated in Brain Awareness Week at the National Museum of Health and Medicine. Sponsored by the Dana Alliance, this event has taken place for 12 years. This year, NIDA scientists played "Brain Game Challenge" with 6-8th grade students. The students had the opportunity to learn new information about drug abuse, the brain and the body. They also received numerous publications, pencils and other handouts. As an indication of the popularity of the game, the students often did not want to leave when it was time to rotate to another station.

Take Your Child to Work Day
On April 26, 2007, the National Institute on Drug Abuse participated in the NIH sponsored Take Your Child to Work day. During this event, children of NIH staff circulate to stations set up by the various institutes. NIDA played "Brain Game Challenge," which gave the children the opportunity to learn facts about their brains as well as drug abuse and addiction. The children also received numerous NIDA publications, pencils, erasers, and other handouts. As with Brain Awareness Week, the game was very popular and the children frequently wanted to continue playing at the end of the game.

NIDA Physician's Outreach Project
The purpose of NIDA's Physician Outreach Project is to increase primary care physicians' awareness of NIDA-funded research, the medical consequences of drug abuse and addiction and to provide physicians with the information and resources they need to incorporate research findings into clinical practice. As part of this physician outreach project, NIDA is collaborating with the American Medical Association, other physician specialty organizations, and State, county, and local medical societies. An overview of this project's key activities is provided below. The NIDA Centers of Excellence for Physician Information (CoEs), designed to reach physicians-in-training in medical schools, have come in from the field on surveys related to core competencies and the most effective means and products to reach medical students. Pilot products are being developed and the CoEs involved have committed to including the eventual final products in the required curricula. These include:

- Creighton University School of Medicine in Omaha, NE
- University of Pennsylvania School of Medicine (in collaboration with Drexel University College of Medicine)
- University of North Dakota School of Medicine and Health Sciences
- Massachusetts Consortium of Medical Schools (which includes the University of Massachusetts Medical School, Tufts University School of Medicine, Boston University School of Medicine, and Harvard Medical School/Cambridge Health Alliance)

Recent and Upcoming Confernences/Exhibits

NAADAC The Association for Addiction Professionals Annual Conference Nashville, TN	September 5-8, 2007
National Prevention Network 20th Annual Prevention Research Conference Portland, OR	September 16-19, 2007
Latino Behavioral Health Institute 13th Annual Conference Los Angeles, CA	October 2-4, 2007
American Association for the Treatment of Opioid Dependence National Conference	October 20-24, 2007

San Diego, CA	
American Academy of Child and Adolescent Psychiatry 54th Annual Meeting Boston, MA	October 23-28, 2007
National Conference on Tobacco or Health Minneapolis, MN	October 24-26, 2007
American Academy of Pediatrics National Conference and Exhibition San Francisco, CA	October 27-30, 2007
American Public Health Association 135th Annual Meeting and Exposition Washington, DC	November 3-7, 2007
National Middle School Association 34th Annual Conference and Exhibit Houston, TX	November 8-10, 2007

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Drs. Belinda Sims, Elizabeth Robertson, Eve Reider, and Aria Crump, all of DESPR, are collaborating with staff from the National Institute on Child Health and Human Development, the National Institute on Mental Health, the NIH Office of Behavioral and Social Sciences Research, the Administration for Children and Families, and the Substance Abuse Mental Health Services Administration to plan a meeting entitled **Intervening Early: Progress and Opportunities in Child Service Settings**, scheduled for September 18-19, 2007. This meeting is being supported through NIDA's Office of Science Policy and Communications. The purpose of this meeting is to review existing prevention programs for children 0-5 and their families that are designed to improve child, parent and family outcomes in a variety of domains (e.g., social and emotional development, mental health, education, parenting, substance use, family functioning), with a particular focus on programs delivered within child service settings. Goals of this meeting include identifying critical research gaps that need to be addressed to 1) foster novel program development through the translation of basic research on self-regulatory processes, and 2) increase the uptake and implementation of effective preventive interventions for young children and their families within child service settings, including setting characteristics.

A meeting on the social neuroscience and the development of treatment and prevention interventions is being planned by Drs. Lisa Onken, Steve Grant, Nicolette Borek, Cecelia Spitznas and Melissa Riddle of NIDA's Division of Clinical Neuroscience and Behavioral Research, with Dr. Elizabeth Ginexi from NIDA's Division of Epidemiology, Services, and Prevention Research. The meeting will be held October 1 & 2, 2007 in Bethesda, Maryland.

Dr. Harold Gordon, DCNBR, organized and will chair a mini-symposium titled **Understanding the Neurobiology of Drug Addiction by studying Sleep Disturbances and Circadian Rhythms** at the upcoming Annual Meeting of the Society for Neuroscience to be held in San Diego, November 3-7, 2007.

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 next **National CTN Steering Committee Meeting** is planned for September 23-28, 2007 in Rockville, Maryland.

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NIDA Publications

Research Report Series: Tobacco Addiction (Spanish)
NIH Pub. No. 07-4342(S)
Describes what tobacco is, presents current epidemiological research data regarding its use, and reports on the medical consequences of tobacco use. Emphasizes the effects on the brain as well as current research findings about use during pregnancy. Includes treatment approaches.

Research Report Series: Anabolic Steroids (Spanish Revision)
NIH Pub. No. 07- 3721
Provides an authoritative, unbiased overview of anabolic steroid use and its effects. Brings together most recent findings from drug research and surveys on drug abuse by youth.

College on Problems of Drug Dependence
NIH Pub. No. 07-6201
This publication is more than just a "proceedings" from a meeting--it is valued as one of the only research tools and references for scientists and other professionals in the drug abuse field. It is the most comprehensive gathering of scientific information on all aspects of substance abuse and is invaluable to researchers and other scientists.

Brain Power! Challenge
NIH Pub. No. 07-5181
NIDA has recently completed *Brain Power! Challenge* for middle school students. This is the continuation of the *Brain Power!* series that now spans from kindergarten through middle school. The materials include six lessons as well as student activities and handouts. Students have the opportunity to learn about their brain, how it works, and the impact that various drugs have on the brain and body. The materials that were developed for kindergarten through fourth grade have been extremely popular and it is anticipated that the middle school version will be even more popular. NIDA is currently conducting a formal evaluation of the entire set of materials.

Heads Up: Real News About Drugs and Your Body: Student Compilation
This booklet is a collection of articles designed to teach youth in grades 6-12 about how drugs of abuse affect the brain and body. Topics covered are The Science of Addiction, Tobacco Addiction and Secondhand Smoke, Stress and Drug Abuse, and Health Literacy and Drug Abuse. These articles were distributed in Scholastic magazines nationwide during the 2006/2007 school year.

Heads Up: Real News About Drugs and Your Body: Teacher's Compilation

This booklet provides skill-building extension activities and further resources to those included for students. Topics covered are The Science of Addiction, Tobacco Addiction and Secondhand Smoke, Stress and Drug Abuse, and Health Literacy and Drug Abuse. These "teacher editions" were distributed nationwide during the 2006/2007 school year with Scholastic student magazines containing Heads Up articles.

Marijuana: What Parents Need to Know (Rev. 2007)
NIH Pub. No. 07-4036
Provides research-based information on the dangers of marijuana. Gives parents explanations of the latest scientific information about the drug and suggestions on how to talk to teenagers about this drug.

NIDA NOTES

***NIDA NOTES*: Collection of Articles That Address Drugs & AIDS (Rev. 2007)**
Presents 40 articles from 1995 to 2006. Includes titles such as "Drug Abuse Treatment Programs Make Gains in Methadone Treatment and HIV Prevention," "Prevention Programs for HIV-Positive Youths Reduces Risks of Further HIV Transmission," "NIDA Launches HIV/AIDS Public Awareness Campaign" and "Expanded HIV Testing: Benefits May Warrant Costs."

NEW! WEB
A Collection of *NIDA NOTES* Articles that Address Research on Drug Abuse Treatment
Revised 2007 * NCADI #NN0026
This updated collection includes articles published in *NIDA NOTES* from 1997 through February 2007. These articles discuss behavioral and medications treatment for drug abuse and addiction, benefits and efficacy evaluations of treatment strategies and components, and ancillary services.

NEW! WEB
A Collection of *NIDA NOTES* Articles that Address Research on Cocaine
Revised 2007 * NCADI #NN0066
This revised collection features *NIDA NOTES* articles originally published from 1995 through April 2007. It includes titles such as "Behavioral Response to Novelty Foreshadows Neurological Response to Cocaine;" "Cocaine Abusers' Pretreatment Cue Responses Predict Recovery Success;" "Brain Changes Accompany Cocaine Withdrawal;" and "Serotonin System May Have Potential as a Target for Cocaine Medications."

A Collection of *NIDA NOTES* Articles that Address Research on Heroin
Revised 2007 * NCADI #NN0023
This collection of *NIDA NOTES* includes research-based articles on heroin that were published from 1998 through 2006. Topics range from office-based buprenorphine treatment to HIV risk prevention programs for IV drug users.

A Collection of *NIDA NOTES* Articles that Address Research on Marijuana
Revised 2007 * NCADI #NN0058
This revised collection features *NIDA NOTES* articles originally published from 1995 through 2007. Topics include long-term cognitive impairments in heavy marijuana users, evidence that chronic marijuana users experience withdrawal upon quitting, the influence of genes and the environment on drug abuse vulnerability, the body's natural THC-like compounds, epidemiology, prevention, and treatment.

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 Program **E-News Letter**
The NIDA International Program issues an *E-News Letter* every other month to inform the international drug abuse research community about recent events, funding opportunities, NIDA's research training and exchange programs for international scientists, and forthcoming meetings. The June 2007 edition announced the newly created INVEST/CTN Drug Abuse Research Fellowships and reported on the NIDA International Forum, 2007 Awards of Excellence, and the United Nations Office on Drugs and Crime 2007 *World Drug Report*.

NIH Record *Highlights Fellows' Orientation*
The NIDA International Program orientation for INVEST and Hubert H. Humphrey Drug Abuse Research Fellows was featured in the May 4, 2007, *NIH Record*, the biweekly newsletter for employees of the National Institutes of Health.

Other Publications

Bukoski, W.J., and Compton, W.M. Drug Abuse Research Collaboration in the 21st Century. In: Scheier, L. M., & Dewey, W. L. (2007). The Complete Writing Guide to NIH Behavioral Science Grants. New York: Oxford University Press.

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Newman, A.H., Grundt, P., Cyriac, G.C., and Luedtke, R. 4-Phenylpiperazine Derivatives with Functionalized Linkers as Dopamine D3 Receptor Selective Ligands and Methods of Use. U.S. Provisional Patent Application filed June 15, 2007.

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Staff Honors and Awards

Dr. Christine Colvis, DBNBR, was awarded the NIH Directors award as part of the Molecular Libraries Roadmap project "for extraordinary leadership of the molecular libraries and imaging roadmap to enable research on new pathways to discovery in health and disease."

Dr. Colvis has been selected to be featured in an upcoming publication by the NIH Office of Research on Women's Health (ORWH). The featured women are to chosen based on achievements in their field, leadership positions, ability to combine family and career, and/or efforts as a mentor.

Dr. David Shurtleff, Director, DBNBR, was awarded the NIH Director's Award "for outstanding contributions to the development and advancement of diverse programs in basic neuroscience and behavioral research."

Dr. David Shurtleff was awarded NIH Director's Award "for extraordinary scientific leadership of the molecular libraries and imaging roadmap to enable research on new pathways to discovery in health and disease."

Dr. David Shurtleff was elected to Fellow American Psychological Association through APA Division 28.

Drs. Karen Skinner, Jonathan Pollock and David Shurtleff, all of DBNBR, as part of the Neuroscience Information Framework team, were recognized with the NIH Blueprint for Neuroscience Research Directors award "For significant administrative contributions and oversight to redirect the NIF project for successful Phase II implementation.

Dr. Joni Rutter, DBNBR, has been selected to be featured in an upcoming publication by the NIH Office of Research on Women's Health (ORWH). The featured women are to chosen based on achievements in their field, leadership positions, ability to combine family and career, and/or efforts as a mentor.

Dr. Cora Lee Wetherington, DBNBR, has been selected to be featured in an upcoming publication by the NIH Office of Research on Women's Health (ORWH). The featured women are to chosen based on achievements in their field, leadership positions, ability to combine family and career, and/or efforts as a mentor.

Dr. Da-Yu Wu, DBNBR, as part of the Neurodevelopment Workshop Project Team, was awarded NIH Blueprint for Neuroscience Research Directors award "for their expertise, dedication in planning the NIH Neuroscience Blueprint workshop on Neurodevelopment."

Dr. Laurence Stanford, DCNBR, received the Blueprint for Neuroscience

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Research Directors Award as a member of the Neurodevelopment Project Team in July, 2007.

Dr. Peter Hartsock, DESPR, was awarded the Meritorious Service Medal at the NIH Director's Ceremony, June 13, 2007. Dr. Hartsock's award was "For meritorious accomplishments in the field of advanced AIDS modeling with major and rapid impact upon U.S. Public Health Policy."

Dr. Peter Hartsock was awarded the first-ever Presidential Platinum Medal for Fitness by the President's Council on Physical Fitness and Assistant Secretary for Health Dr. John O. Agwunobi, Washington, D.C. May 3, 2007. The President's program on fitness was initiated in 1956 by President Dwight Eisenhower and has been supported by every president since. For the past 50 years, the Gold Medal was the highest award possible through the program.

In June 2007, **Drs. Betty Tai, Mary Ellen Michel** and **Paul Wakim** received the NIH Director's Award "for outstanding contributions leading to the successful launch of the Clinical and Translational Science Award Program". Dr. Tai is co-chair of the CTSA Community Engagement subcommittee; Dr. Michel is co-chair of the CTSA Clinical Research Ethics subcommittee; and Dr. Wakim is co-chair of the CTSA Biostatistics, Epidemiology and Research Design subcommittee. Carmen Rosa serves on the CTSA Public-Private Partnerships subcommittee.

Dr. Jag Khalsa, DPMCDA, received the prestigious NIH Director's Award for developing the domestic and international program of medical consequences of drug abuse and infections at NIDA. This was his second award from the NIH Director in two years.

Dr. Kenner Rice, Chief of the Chemical Biology Research Branch, IRP, was seleted to receive the 2007 Smissman Award presented by the American Chemical Society (ACS). The Bristol-Myers Squibb Smissman Award, established by the American Chemical Society in honor of Professor Edward E. Smissman of the University of Kansas, is given to a living scientist whose research, teaching or service has had a substantial impact on the intellectual and theoretical development of the field of medicinal chemistry. Dr. Rice, whose research has led to the development of compounds or medications that have the potential to treat or prevent drug addiction, was recognized at the ACS national meeting in August.

Staff Changes

Dr. Jose Ruiz has joined the Office of Extramural Affairs as a Scientific Review Administrator. Dr. Ruiz is an experienced NIH science policy analyst with an academic background that includes a doctorate in genetics and exploration of biochemical research questions of ligand-receptor interactions pertinent to Alzheimer's disease, atherosclerosis, and coagulation. Before joining NIDA, Dr. Ruiz was a science policy analyst for the National Institute of Nursing Research (NINR), where he used his knowledge of the NINR research portfolio in addressing a wide-range of requests and reporting requirements as well as in creating communication products on behalf of the Institute and facilitating strategic planning processes. Prior to joining NINR, Dr. Ruiz served as a science policy analyst for the NIH Government Performance and Results Act (GPRA) Office within the NIH Office of the Director. Dr. Ruiz managed the GPRA planning and reporting requirements across a number of NIH Institutes. Jose holds a Bachelor's degree in Biochemistry and Molecular Biology from Boston University, and a Ph.D. in Genetics from The George Washington University.

Dr. Nadine Rogers has joined the Office of Extramural Affairs as a Scientific Review Administrator. Nadine comes to NIDA from the Office of the U.S. Global AIDS Coordinator (OGAC), the office with responsibility for managing the

President's Emergency Plan for AIDS Relief (PEPFAR). As part of the Strategic Information Unit in OGAC, Nadine was the administrator of the scientific steering committee that advised the office. She also served as the liaison to the Institute of Medicine and led the team responsible for the annual meeting of HIV/AIDS program implementers. Prior to joining OGAC, she consulted with the U.S. Centers for Disease Control and Health Resources Services Administration in the creation and implementation of standardized guidelines for the development of HIV/AIDS epidemiologic profiles for prevention and care. She has helped NGOs to build their capacity in program design and evaluation, and her work has included the design and development of education materials, testing of technology-based HIV prevention messages, and promotion of the use of culture to influence social norms around HIV/AIDS. Nadine was a National Research Service Award Pre-Doctoral Fellow funded by the National Institute of Child Health and Human Development (NICHD) and was the recipient of the 2002 Johns Hopkins University, Charles D. Flagle Award for research examining the use of computer technology in public health. Nadine, who is a native of Trinidad and Tobago and a graduate of the University of the West Indies at Cave Hill, holds a Master of Science in Communications from The Clarion University of Pennsylvania and a doctorate in Health Policy & Management with a focus in the Social and Behavioral Sciences from The Johns Hopkins University, Bloomberg School of Public Health.

Dr. Bryan Fantie joined the Division of Clinical Neuroscience and Behavioral Research in the Behavioral and Brain Development Branch in July 2007. Dr. Fantie came to NIDA from American University, where he was a faculty member in the Department of Psychology since 1989, was Director of the Human Neuropsychology Laboratory, and also was Founding Director of the Behavioral Neuroscience Doctoral Program. During his tenure at American University, Dr. Fantie also was involved in conducting research in NIH intramural programs at NIMH, NCI, and NINDS. His published work includes chapters and articles on brain development, assessment of attention across the lifespan, attentional capacities and deficits, affective processes, and memory.

Dr. Melissa Riddle, formerly Deputy Chief of the Behavioral and Integrative Treatment Branch, DCNBR, left NIDA for a position at the National Institute of Dental and Craniofacial Research. As a Branch Chief at NIDCR, she will be responsible for administering a behavioral and social science research program.

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Dr. Richard Catalano is receiving the 2007 August Vollmer award from the American Society of Criminology, recognizing a criminologist whose research scholarship has contributed to justice or to the treatment of prevention of criminal or delinquent behavior.

Dr. Patricia Chamberlain of the Oregon Social Learning Center received the Science to Practice Award at the 15th Annual Meeting of the Society for Prevention Research Conference in Washington, D.C. on May 31, 2007. This award is given to an individual or a team of individuals in recognition of continued support of the implementation of research based prevention practices in real world settings.

Dr. Thomas Dishion received a 2006 American Psychological Association award for distinguished contributions to family psychology and the University of Oregon Research Innovation Award.

Dr. Mary Jeanne Kreek, Rockefeller University, received an honorary doctorate, *Doctor Philosophiae Honoris Causa*, of the University of Tel Aviv.

Dr. Philip Palmgreen and the SENTAR group of the University of Kentucky were awarded the 2007 Prevention Science Award at the 15th Annual Meeting Awards Presentation for the Society for Prevention Research. The Prevention Science Award is given to an individual or a team of individuals for a significant body of research that has applied scientific methods to test one or more preventive interventions or policies. This award recognizes individuals for the work of developing and testing prevention strategies.

Dr. Gerald Patterson is the 2007 recipient of the American Psychological Association, Division 7, Urie Bronfenbrenner Lifetime Award in Developmental Psychology.

Dr. Guillermo J. Prado of Florida International University was awarded the 2007 ECPN Early Career Award at the 15th Annual Meeting Awards Presentation for the Society for Prevention Research. This award is presented to a person early in their career in prevention. This award is bestowed on someone who has shown a commitment to prevention science through outstanding contributions to research, policy or practice.

Drs. Edward Smith and Linda Caldwell received the 2007 Society for Prevention Research International Collaboration Award. This award is given to an individual or a team of individuals for contributions to the field of prevention science in the area of international collaboration.

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