Director's Report to the National Advisory Council on Drug Abuse - September, 2009

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Research Findings - Basic Neuroscience Research

Toll-Like Receptor-3 Activation in Human Neuronal Cells Induces Interferon-λ Expression

Interferon lambda (IFN-λ) belongs to the type III family of IFNs which when activated exerts antiviral, antitumor and immunoregulatory activities. Toll-like receptors (TLRs) are a family of receptors that mediate innate immune responses to stimuli from pathogens and endogenous signals. It has been shown that agonists of TLR-3 can induce IFN-λ production in macrophages or plasmacytoid dendritic cells. Little is known about IFN-λ expression in human neuronal cells and whether IFN-λ expression in human neuron relies on the TLR ligand activation. Human neuronal cells expressed endogenous IFN-λ1, but not IFNλ2/3, however upon activation of TLR-3 in neuronal cells all three structurally related cytokines were significantly induced. Activation of TLR-3 also exhibited antiviral activity against pseudotyped HIV-1 infection of the neuronal cells. Human neuronal cells also expressed functional IFN-λ receptors which when activated inhibited pseudotyped HIV-1 infection and induced APOBEC 3G/3F, anti-HIV-1 cellular factors. This paper provides compelling evidence that there is intracellular expression and regulation of IFN-λ in human neuronal cells, which may have a major role in the innate neuronal protection against viral infections in the CNS. Zhou L, Wang X, Wang YJ, Zhou Y, Hu S, Ye L, Hou W, Li H, Ho WZ. Activation of Toll-Like receptor-3 induces interferon-λ expression in human neuronal cells. Neuroscience. 2009 Mar 17;159(2):629-637.

Chronic Cocaine Enhances Stress-Induced Potentiation of Excitatory (Glutamatergic) Neurotransmission in Dopamine Neurons within the VTA

Current concepts suggest that stress-induced release of neuromodulators such as corticotropin-releasing factor (CRF) can drive drug-dependent behaviors. Furthermore, prior drug exposure can enhance behavioral and neurochemical responses to stress. Previously, it had been shown that CRF can enhance NMDA-type glutamatergic transmission. This paper now shows that after repeated cocaine exposure, the magnitude and duration of the CRF-induced potentiation of NMDA receptor-mediated neurotransmission is significantly increased within ventral tegmental area (VTA) dopamine neurons, a key locus of drug- and stress-induced neuroadaptation. Furthermore, although CRF itself does not enhance AMPA-type glutamatergic transmission, CRF did enhance AMPA receptor-mediated transmission in mice that were exposed to chronic cocaine. Importantly, pharmacological experiments revealed that CRF receptor 1 and protein kinase A pathways were newly recruited after repeated cocaine for the enhancement of CRF-induced NMDAR potentiation and the appearance of AMPAR potentiation. Thus, enhanced CRF-induced potentiation of excitatory

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synaptic transmission onto VTA dopamine neurons after cocaine preexposure is likely to produce an abnormal increase in dopamine release during stressful events and could augment activation of addictive behaviors in response to stress. Hahn J, Hopf FW, Bonci A. Chronic cocaine enhances corticotropin-releasing factor-dependent potentiation of excitatory transmission in ventral tegmental area dopamine neurons. J Neurosci. 2009 May 20;29(20):6535-6544.

Impaired Synaptic Plasticity Following Chronic Cocaine

Dr. Peter Kalivas and colleagues have been providing novel evidence that chronic drug abuse results in future deficits in the ability to generate synaptic plasticity (for review, see Kalivas PW. Nat Rev Neurosci. 2009 Aug;10(8):561-572). In the present study, his group sought to determine whether withdrawal from repeated cocaine administration can alter the capacity of a subsequent cocaine injection to elicit morphological, biochemical, and physiological plasticity. Three weeks after termination of chronic daily cocaine or saline administration, the researchers filled neurons in the nucleus accumbens with the lipophilic dye, DiI. They observed a shift to larger diameter spines in the daily cocaine-pretreated rats. During the first 2 hours after an acute cocaine challenge, a bidirectional change in spine head diameter and increase in spine density was measured in the daily cocaine-pretreated animals. In contrast, no change in spine diameter or density was elicited by a cocaine challenge in daily saline animals during the first 2 hours after injection. However, spine density was elevated at 6 hours after a cocaine challenge in daily saline-pretreated animals. The time-dependent profile of proteins in the postsynaptic density subfraction of neurons elicited by a cocaine challenge in daily cocaine-pretreated subjects indicated that the changes in spine diameter and density were associated with a deteriorating actin cytoskeleton and a reduction in glutamate signaling-related proteins. Correspondingly, the amplitude of field potentials in accumbens evoked by stimulating prefrontal cortex was reduced for up to 6 hours after acute cocaine in daily cocaine-withdrawn animals. These data indicate that daily cocaine pretreatment dysregulates dendritic spine plasticity elicited by a subsequent cocaine injection. In humans, the altered drug experience caused by previous drug abuse may underlie diminishing behavioral control and contribute to a progressively deteriorating disorder. Shen H, Toda S, Moussawi K, Bouknight A, Zahm DS, Kalivas PW. Altered dendritic spine plasticity in cocaine-withdrawn rats. J Neurosci. 2009 Mar 4;29(9):2876-2884.

Optical Fluorescent Tool Monitors Dopamine Release From Single Presynaptic Terminals

Investigators at Columbia University have designed optical tracers of monoaminergic neuro-transmitters, or false fluorescent neurotransmitters, which are taken up by secretory vesicles (VMAT2) and released after stimulation as if they were native transmitters. This has allowed the researchers to examine transmitter accumulation and exocytosis from single presynaptic terminals in the striatum and to make observations relevant to stimulation-dependent synaptic plasticity. They found a relatively low percentage of vesicles fusing to the plasma membrane with each stimulus, and that the release of transmitter differed across separate terminals. That is, some terminals were more active than others; additionally, transmitter release from each terminal also depended on the frequency of stimulation. Further, when the presynaptic autoreceptors on neurons were blocked, release was inhibited from two-thirds of the terminals, which were the terminals that were least active. Thus, activity-dependent terminal heterogeneity is associated with receptor-mediated responses and underscores the presence of frequency-dependent coding that may determine how particular synapses are activated during important functions such as decision-making and learning. Gubernator

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NG, Zhang H, Staal RGW, Mosharov EV, Pereira DB, Yue M, Balsanek V, Vadola PA, Mukerjee B, Edwards RH, Sulzer D, Sames D. Fluorescent false neurotransmitters visualize dopamine release from individual presynaptic terminals. Science. 2009;324:1441-1444.

Genome-wide Analysis of Chromatin Regulation by Cocaine Reveals a Role for Sirtuins

Long lasting changes in gene expression lead to changes in the reward systems of the brain. Normally investigators measure steady state mRNA levels to assess gene expression. However, advances in chromatin immunoprecipitation technology have enabled analysis of histone modifications which regulate chromatin structure at specific genomic locations. Chromatin structure is highly predictive for gene activation or repression. In initial experiments, Dr. Nestler and co-workers characterized genome wide levels of histone acetylation and methylation from the nucleus accumbens (NAc) brain region of rats treated chronically with cocaine. These studies revealed that many genes previously known to be up regulated by cocaine exposure also have additional acetylation of histone H3 and H4. Dr. Nestler then looked genome wide to see where the cocaine-induced transcription factors deltaFosB and CREB bound in the NAc of cocaine treated animals. Cross comparison of these data sets identified many genes that had not previously been implicated in response to cocaine, including the Sirtuin genes (Sirt1 and Sirt2) which function as NAD-dependent histone deacetylases. These genes function in many biological processes, including aging; however their role in the nervous system is poorly understood. Dr. Nestler used pharmacological activators and inhibitors of sirtuins to look at their function in cocaine responses. Interestingly, activation of sirtuins dramatically enhanced the rewarding effect of cocaine, while inhibition of sirtuins had the opposite effect. Thus genome wide chromatin immunoprecipitation strategies enabled Dr. Nestler and co-workers to identify a number of new genes likely to be in chronic cocaine responses. Two of these, Sirt1 and Sirt2, were functionally validated using pharmacological agents. Pharmaco-logical modulation of sirtuin function may be a fruitful future avenue to explore in the development of therapeutic agents to treat cocaine addiction.
Renthal W, Kumar A, Xiao G, Wilkinson M, Covington HE, Maze I, Sikder D, Kodadek TJ, Stack A, Kabbaj M, and EJ Nestler. Genome-wide analysis of chromatin regulation by cocaine reveals a role for sirtuins. Neuron. 2009; 62:335-348.

Genetically Determined Interaction Between the Dopamine Transporter and the D2 Receptor on Prefronto-Striatal Activity and Volume in Humans

Dopamine modulation of neuronal activity during memory tasks identifies a nonlinear inverted-U shaped function. Both the dopamine transporter (DAT) and dopamine D(2) receptors (encoded by DRD(2)) critically regulate dopamine signaling in the striatum and in prefrontal cortex during memory. Moreover, in vitro studies have demonstrated that DAT and D(2) proteins reciprocally regulate each other presynaptically. Therefore, Dr. Sadee and his colleagues have evaluated the genetic interaction between a DRD(2) polymorphism (rs1076560) causing reduced presynaptic D(2) receptor expression and the DAT 3'-VNTR variant (affecting DAT expression) in a large sample of healthy subjects undergoing blood oxygenation level-dependent (BOLD)-functional magnetic resonance imaging (MRI) during memory tasks and structural MRI. They found a significant DRD(2)/DAT interaction in prefrontal cortex and striatum BOLD activity during both working memory and encoding of recognition memory. The differential effect on BOLD activity of the DAT variant was mostly manifest in the context of the DRD(2) allele associated with lower presynaptic expression. Similar results were also evident for gray matter volume in caudate. These interactions describe a nonlinear relationship

between compound genotypes and brain activity or gray matter volume. Complementary data from striatal protein extracts from wild-type and D(2) knock-out animals (D2R(-/-)) show that DAT and D(2) proteins interact in vivo. Together, these data demonstrate that the interaction between genetic variants in DRD(2) and DAT critically modulates the nonlinear relationship between dopamine and neuronal activity during memory processing. Bertolino A, Fazio L, Di Giorgio A, Blasi G, Romano R, Taurisano P, Caforio G, et al., Genetically determined interaction between the dopamine transporter and the D2 receptor on prefronto-striatal activity and volume in humans. J Neurosci. 2009 Jan 28;29(4):1224-1234.

Mammalian Par3 Regulates Notch Signaling During Cortical Neurogenesis

Proper formation of the cerebral cortex depends on the orderly production of a large number of neurons during embryonic development. Radial glial cells spanning the primitive stages of developing cortex are a major population of neuronal progenitor cells during cortical development, in addition to their well-characterized role in guiding radial migration of newly born neurons generated in the ventricular zone. Radial glial cells divide to generate either a neuron or a new glial cell. The precise control of radial glial cell division in the developing cortex is likely a major factor in controlling the number of neurons in the mature cerebral cortex. While the asymmetric cell division of radial glial progenitors produces neurons as well as allowing self-renewal, little is known about the mechanism that generates asymmetry in daughter cell fate specification. A group of NIDA researchers at the Memorial Slone Kettering Cancer Center, led by Songhai Shi, found that mammalian partition defective protein 3 (mPar3), a key cell polarity determinant, exhibits dynamic distribution in radial glial progenitors. While it is enriched at the lateral membrane domain in the ventricular endfeet during interphase, mPar3 becomes dispersed and shows asymmetric localization as cell cycle progresses. Either removal or ectopic expression of mPar3 prevents radial glial progenitors from dividing asymmetrically yet generates different outcomes in daughter cell fate specification. Furthermore, the expression level of mPar3 affects Notch signaling, and manipulations of Notch signaling or the expression of Numb, a mediator of Notch, suppress mPar3 regulation of radial glial cell division and daughter cell fate specification. These results reveal a critical molecular pathway underlying asymmetric cell division of radial glial progenitors in the mammalian neocortex. These studies add to our understanding of normal and abnormal cortical development and may yield insights into developmental causes of pathological conditions such as seen in mental health disorders or mental retardation. Bultje RS, Castaneda-Castellanos DR, Jan LY, Jan YN, Kriegstein AR, Shi SH. Mammalian Par3 regulates progenitor cell asymmetric division via notch signaling in the developing neocortex. Neuron. 2009 July 30; 63:189-202.

Striatal Specific Rhes Mediates Mutant-Huntingtin Cytotoxicity in HD

Huntington's disease is an inherited neurodegenerative disease that typically appears in middle age that is characterized by jerky movements (chorea), abnormal posturing, sleep disturbance, seizure, and dementia. In addition, anxiety, depression, and the worsening of substance abuse are frequently seen in these patients. Wood Guthrie, the famous American folksinger, who wrote "This Land is Your Land" suffered from Huntington's disease. The disease is caused by a polyglutamine repeat in the huntingtin protein. While the nature of the genetic mutation has been known for 15 years, scientists have been puzzled by the fact that neurodegeneration happens only in the striatum of the brain despite the fact that the mutation is expressed everywhere in the body. In a recent paper in Science, Dr. Solomon Snyder, funded by NIDA, has solved

this puzzle. The Snyder lab shows that the selective cytotoxicity is caused by Rhes, a small GTP binding protein that is specifically expressed in the striatum. The Rhes protein binds more readily to the normal Huntingtin protein than the mutant huntingtin protein. Meanwhile the mutant Hungtintin protein but not the normal protein forms aggregates or clumps. When the mutant Huntingtin protein is expressed together with Rhes there is an increase in the amount of soluble mutant protein and a decrease in the number of aggregates that is associated with increased cytotoxicity. Depletion of the Rhes protein in cell lines decreased the cytotoxicity when the mutant huntingtin protein is expressed. The Snyder lab then showed that SUMOylation, the covalent attachment of the small ubiquitin-like modifier (SUMO) at lysine at residues 15 and 91 of Huntingtin protein is responsible for the increased solubility of the mutant huntingtin protein and cytotoxcity. Altering the Lys-residues to arginine and depleting the SUMOylation enzyme SUMO1 prevented cytotoxcity. Although, Dr. Snyder and his colleagues show that the SUMOylation of the huntingtin protein is not dependent on the GTPase activity of Rhes, the effect of Rhes on SUMOylation is dependent on the attachment of Rhes through farnesylation. Thus, farnesylation inhibitor Lonafarnib (SCH66336) is being tested in phase II clinical trials for progeria and may be useful for the prevention and treatment of Huntington's disease. Subramaniam S, Sixt KM, Barrow R, Snyder SH. Rhes, a striatal specific protein, mediates mutant-huntingtin cytotoxicity. Science. 2009 Jun 5;324(5932):1327-1330.

Carbon Nanotube Membranes for Active Transdermal Drug Delivery of Nicotine and Other Compounds

Cigarette smoking continues to be the leading cause of premature death and illness in every industrialized country in the world, and in the U.S. alone leads to more than 400,000 deaths each year. Quitting smoking leads to immediate health benefits, but is difficult because people become addicted to nicotine, the active ingredient in tobacco. The nicotine patch is a widely recognized over-the-counter treatment device for use in smoking cessation that delivers a constant dose of nicotine through the skin to help relieve the symptoms associated with withdrawal. Success rates for smokers using the patch to quit, while better than those who try to quit by cessation alone, have been less than optimal (<20%). Some have proposed that this may be due to the constant steady-state pattern of nicotine delivered by the patch does not match the intra-day peaks and valleys of nicotine blood levels associated with smoking each cigarette through the day. Dr. Bruce Hinds and his colleagues at the University of Kentucky have developed a novel skin patch device for delivering nicotine based on an active layer of aligned carbon nanotubes (CNT) approximately 1.5-7 nanometers in diameter crossing through a solid polymer film. The openings of the CNTs are modified chemically so that they can be opened or closed at any time by applying or removing a small electric current, respectively. Dr. Hinds has shown that in the open state, small molecules are actively pumped across the membrane five times faster than simple diffusion. In other words, the CNT patch is a programmable system that can be controlled by the physician or the patient to mimic the rapid attainment of high nicotine plasma levels similar to those associated with smoking a cigarette, and then closed to allow a slow return to normal. The usefulness of the CNT patch is not limited to nicotine; many other skin absorbable compounds could be used as well. For example, Dr. Hinds has now demonstrated current modulated transport of the alpha-adrenergic agonist clonidine in therapeutically useful doses through the CNT patch on human skin. He and his colleagues have proposed that opioid withdrawal symptoms could be relieved in a similar manner by the use of clonidine in the CNT patch. Presently, such treatment requires multiple injections per day over the 3-5 day opioid withdrawal syndrome in sick and often uncooperative patients. The CNT patch device represents a major step forward in developing a programmable, transdermal drug delivery system that can be useful to treat a variety of syndromes and

that can be tailored to an individual patient's needs in a manner that will improve therapy and likely increase patient compliance. Majumder M, Stinchcomb A, Hinds BF. Towards mimicking natural protein channels with aligned carbon nanotube membrans for active drug delivery. Life Sci 2009 Apr 18 [E-pub ahead of print].

High Specific Activity (+)-Amphetamine and (+)-Methamphetamine

In general, the (S)-(+)-enantiomers of amphetamine and methamphetamine have been demonstrated to have about five times greater psychostimulant activity than their respective (R)-forms. In a recent study of the effects of (S)- and (R)- methamphetamine in humans, the pharmacokinetic parameters for the enantiomers administered separately were found to be similar, but the elimination half-life was longer for (R)-methamphetamine, it did not increase the systolic pressure like (S)-methamphet-amine. Interestingly, (R)-methamphetamine was psychoactive producing intoxication and drug-liking ratings similar to those for (S)-methamphetamine at the same dose. However, despite the longer half- life of (R)-methamphetamine, its effects were dissipated twice as fast as those of (S)-methamphetamine. Investigation of amphetamine binding sites has been hindered by the lack of the separate antipodes, (S)- and (R)-, of amphetamine and methamphetamine with high specific activity. Thus, it has been reported that, using (+)-tritiated amphetamine (specific activity 15.7 Ci/mmol), binding site with apparent affinity constants of 96 and 279 nM were detected in hypo-thalamic membrane preparations from rat brain, but has been challenged as artefactual, resulting from inadequate filtration technique. Data obtained using both filtration and centrifugation techniques in a follow up investigation were consistent with the presence of a binding site for (S)-amphetamine, but could neither confirm nor exclude the presence of a second binding site. As part of a NIDA supported program to provide useful biochemical tools to researchers, the PI and coworkers have synthesized higher specific activity (>30 Ci/mmol) (S)-amphetamine and (S)-meth-amphetamine by reductive dechlorination of (S)-(3',5'-dichlorophenyl-2-propylazide and (S)-2',6'-dichloro-methamphetamine, respectively, while the latter was readily obtained by resolution of racemic 2',6'-dichloromethamphetamine using (+)-dibenzoyltartaric acid, the analogous amphetamine resisted all efforts to resolve it. Hence, the required chiral precursor was prepared by stereospecific total synthesis following methodology that had been previously been developed in authors' laboratories. Lamb PB, McElhinny CJ, Sninski T, Purdom H, Carroll FI, Lewin AH. High specific activity (+)-amphetamine and (+)-methamphetamine, J. Label Compd. Radiopharm. (E-pub) July 15, 2009.

Morphine Enhances Tat-induced Activation in Murine Microglia

Increasing evidence suggests that opiates accelerate the pathogenesis and progression of acquired immunodeficiency syndrome (AIDS), as well as the incidence of human immunodeficiency virus (HIV) encephalitis (HIVE), a condition characterized by inflammation, leukocyte infiltration, and microglial activation in the brain. The mechanisms, by which the HIV-1 transactivating protein Tat and opioids exacerbate microglial activation, however, are not fully understood. In the current study, researchers explored the effects of morphine and HIV-1 Tat(1-72) on the activation of mouse BV-2 microglial cells and primary mouse microglia. Both morphine and Tat exposure caused up-regulation of the chemokine receptor CCR5, an effect blocked by the opioid receptor antagonist naltrexone. Morphine in combination with Tat also induced morphological changes in the BV-2 microglia from a quiescent to an activated morphology, with a dramatic increase in the expression of the microglial activation marker CD11b, as compared with cells exposed to either agent alone. In addition, the mRNA expression of inducible nitric oxide synthase

(iNOS), CD40 ligand, Interferon-gamma-inducible protein 10 (IP-10), and the proinflammatory cytokines tumor necrosis factor alpha (TNFalpha), interleukin (IL)-1beta, and IL-6, which were elevated with Tat alone, were dramatically enhanced with Tat in the presence of morphine. In summary, these findings shed light on the cooperative effects of morphine and HIV-1 Tat on both microglial activation and HIV coreceptor up-regulation, effects that could result in exacerbated neuropathogenesis. Bokhari SM, Yao H, Bethel-Brown C, Fuwang P, Williams R, Dhillon NK, Hegde R, Kumar A, Buch SJ. Morphine enhances Tat-induced activation in murine microglia. Journal of Neurovirology. 2009 May 22; 15:219-228.

Evidence for HIV Tat-Induced Dopamine System Dysfunction

Individuals infected with human immunodeficiency virus (HIV) may develop neuropsychological impairment, and a modest percentage may progress to HIV-associated dementia (HAD). Research using human and nonhuman, in vitro and in vivo models, demonstrates that subcortical dopamine (DA) systems may be particularly vulnerable to HIV-induced neuro-degeneration. In this study, Booze and colleagues examined how the HIV-1 protein Tat altered brain striatal DA transmission; her approach involved in vivo brain microdialysis in rats. The current study investigated Tat-induced neuronal dysfunction between 24-h and 48-h post-Tat administration, and demonstrates a reduction in evoked DA for the Tat-treated group relative to vehicle-treated group at 24 and 48 h. The Tat-induced reduction of DA overflow by 24 h suggests dysfunction of nerve terminals, and a compromised DA system in Tat-treated animals. Furthermore, the current study provides direct support for HIV-associated decline of DA function at a systemic level, helping to characterize the functional outcome of the relatively large amount of research on the molecular and behavioral levels of HIV-induced neurotoxicity. This initial study may provide additional characteristics of Tat-induced neuronal dysfunction to inform research on therapeutic intervention, and it provides a springboard for future in vivo research currently needed in the field. Ferris MJ, Frederick-Duus D, Fadel J, Mactutus CF, Booze RM. In vivo microdialysis in awake, freely moving rats demonstrates HIV-1 Tat-induced alterations in dopamine transmission. Synapse. 2009 Mar;63(3):181-185.

NOP Ligand Activity

The "orphan" receptor NOP (nociceptin opioid peptide) is found in the forebrain and spinal cord of animals and humans. Its distribution can be measured by the binding of its natural ligand, known as nociceptin, in radiolabeled form. As an endogenous ligand, nociceptin may affect a range of neuronal circuits and brain regions. When administered to animals by an icv route it can display a pronociceptive effect, and when given intrathecally, an antinociceptive effect. Synthetic ligands for the NOP have been discovered since nociceptin was identified, both peptides and heterocyclic non-peptides, having a range of activities from partial agonism to full antagonism. These determinations are based largely on cell membrane and tissue in-vitro binding, and on the degree of stimulation of radiolabeled GTPgammaS binding, and the degree of cellular calcium stimulation or inhibition measured in electrophysio-logical studies. Recently, Dr. Nurulain Zaveri of the Molecular Medicine Research Institute and collaborators at SRI International have been examining NOP ligands with "mixed" properties: NOP agonist/MOP (mu opioid receptor) agonist, and NOP antagonist/MOP agonist. For this work, a chronic neuropathic pain model in rats was used. This work has shown that compound SR 16435 (a ligand with high affinity for both the NOP and MOP receptors) exhibited anti-allodynic effects at 3 or 10 mg/kg by i.p. administration, and this effect was largely blocked by naloxone co-administration at 1 mg/kg. This suggests the effect on the MOP predominates in this case. In another example, the researchers found that NOP antagonists SR 16430 and SR 14148 (having partial MOP agonism) co-

administered at 3 or 10 mg/kg with morphine at 3 or 10 mg/kg could significantly enhance the anti-allodynic effect of morphine. Further experiments are planned with additional ligands intended to optimize the balance between opioid (MOP) and non-opioid (NOP) effects on neuropathic pain. Khroyan TV, Polgar WE, Orduna J, Jiang F, Olsen, C, Toll, L, Zaveri NT. Activity of new NOP receptor ligands in a rat peripheral mononeuropathy model: potentiation of morphine anti-allodynic activity by NOP receptor antagonists. Eur J Pharmacol May 21 2009;610(1-3):49-54.

The Biosynthesis of N-arachidonoyl Dopamine (NADA), A Putative Endocannabinoid and Endovanilloid, Via Conjugation of Arachidonic Acid with Dopamine

N-arachidonoyl dopamine (NADA) is an endogenous ligand that activates the cannabinoid type 1 receptor and the transient receptor potential vanilloid type 1 channel. Two potential biosynthetic pathways for NADA have been proposed, though no conclusive evidence exists for either. The first is the direct conjugation of arachidonic acid with dopamine and the other is via metabolism of a putative N-arachidonoyl tyrosine (NA-tyrosine). In the present study, Walker and colleagues, investigated these biosynthetic mechanisms and report that NADA synthesis requires tyrosine hydroxylase in dopaminergic terminals; however, NA-tyrosine, which is identified here as an endogenous lipid, is not an intermediate. The investigators show that NADA biosynthesis primarily occurs through an enzyme-mediated conjugation of arachidonic acid with dopamine. While this conjugation likely involves a complex of enzymes, their data suggests a direct involvement of fatty acid amide hydrolase in NADA biosynthesis either as a rate-limiting enzyme that liberates arachidonic acid from AEA, or as a conjugation enzyme, or both. Hu SS, Bradshaw HB, Benton VM, Chen JS, Huang SM, Minassi A, Bisogno T, Masuda K, Tan B, Roskoski R, Cravatt BF, Di Marzo V, Walker JM. The biosynthesis of N-arachidonoyl dopamine (NADA), a putative endocannabinoid and endovanilloid, via conjugation of arachidonic acid with dopamine. Prostaglandins Leukot Essent Fatty Acids, 2009, Jun 28, [E-pub ahead of print].

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Research Findings - Multi-Division Research

Injection Drug Use Associated with Increased Multiplicity of HIV Infection in Women

Genetic recombination of multiple viruses at the cellular level within a single host is believed to contribute to HIV-1 diversity and escape from host immunity and antiviral therapies. Multiple infection rates calculated from observed inter- or intra-subtype recombinants in individual patients are estimates of the cumulative multiple infection rates over the evolutionary history of the viral strains involved; however these estimates can be influenced by factors other than recombination. If selection over time either favors or acts against multiple infection recombinants, the estimated multiple infection rates will be biased. Therefore, one must characterize a population of infected individuals directly to truly assess the rate and dynamics of multiple infection. In this prospective longitudinal study of 58 HIV-1 positive participants from The Women's Interagency HIV Study (WIHS), Dr. Markham and colleagues estimated the incidence of multiple infection and the impact of the risk factor of injection drug use (IDU) on multiple infection by including both IDUs and non-IDUs in the sample. By using an analytical technique developed specifically to detect intra-strain recombination in singly infected hosts that can yield a statistically significant inference of recombination with as few as six nucleotide differences between the parental genomes, the role of recombination at all these biological levels could be examined with much greater resolution than previous studies. The study found that 40% of the samples had multiple HIV-1 infections. Injection drug use significantly increased the incidence of multiple infections and significantly increased the rate of observed recombinants. Multiple infection and recombination significantly add to the genetic diversity of HIV-1 and its evolutionary potential, and injection drug use significantly increased both. Templeton AR, Kramer MG, Jarvis J, Kowalski J, Gange S, Schneider MF, et al., Multiple-infection and recombination in HIV-1 within a longitudinal cohort of women. Retrovirology. 2009 Jun 3;6:54.

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Research Findings - Basic Behavioral Research

Cue-Induced Craving in Smokers: Real-time Monitoring in Naturalistic Settings

Laboratory investigations have documented self-reported craving when individuals are exposed to stimuli previously paired with drugs. Cue-induced cravings have been the target of extinction-based therapies but these treatment approaches show limited effectiveness in a laboratory setting. NIDA supported researchers are working to develop cues that better resemble those addicts encounter in the real world (for examples, personalized or social stimuli). Another approach has been to deliver drug-related cues in a real world setting using remote technology. Drs. Stephen Tiffany and Matthew Warthen recently completed a study in heavy smokers, wherein cues were provided via hand-held personal digital assistants (PDAs). Using a newly developed "CREMA" procedure, the investigators couple cue reactivity (CR) with ecological momentary assessment (EMA) to both deliver cues and record real-time subject reactions (such as mood rating, cravings, and latency to smoke). Parallel studies were conducted with the same subjects in a laboratory setting, comparing cue presentation of smoking-related cues versus non-smoking cues. Cues were both visual Ð photographs Ð and imagery in the form of written scripts (for subjects to read and then actively imagine). Over an 8-day study period, subjects recorded responses for 24 h/day, including cigarettes smoked and reactions to cue presentations on a subscale from the Questionnaire of Smoking Urges and mood questions. Subjects were prompted for CREMA sessions four times per day during a 12 h window that was set by the participant. Results reveal completion of 29.07 (average) of 32 CREMA trials in 43 smokers. Post-cue craving ratings were significantly greater following smoking stimuli than non-smoking stimuli, (as has been reliably demonstrated in previous laboratory studies). Craving ratings were also significantly higher following imagery than following photographs. Similar data were derived from analogous laboratory trials given before and after the CREMA procedure. Overall this study supports the viability of using experimental CR procedures in naturalistic environments that allow data collection for context, social and individual subject variables. Future studies might target these variables in interventions that can be delivered along with experimental data collection in real time. Tiffany ST, Warthen MW. Evaluation of cue reactivity in the natural environment of smokers using ecological momentary assessment. Exper Clin Psychopharmacol. 2009;17(2):70-77.

Naltrexone Attenuates the Incentive Motivational Effects of Nicotine-Associated Cues

While the direct reinforcing effect of nicotine (NIC) contributes to human smoking, environmental stimuli paired with this drug effect and smoking

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behavior are potent motivators for continued use and relapse. Animal models can mimic these relapse effects by demonstrating that NIC-associated cues presented after extinction prompt drug-seeking behavior in an i.v. self-adminstration paradigm. This, and many other studies, suggest that NIC associated cues acquire incentive motivational properties. It is of interest to determine the neurobiological mechanisms through which these incentive cues activate behavior. Endogenous opioid systems have been implicated in the conditioned incentive effects of environmental stimuli associated with a number of drugs of abuse. Conditioned place preference with NIC is blocked in preproenkephalin knock-out mice and in those with reduced expression of opioid receptors in the ventral tegmental area Ð the location of dopamine cells important in central reinforcing effects of drugs of abuse. In fact, endogenous opioid systems modulate central dopaminergic activity. However, inconsistent effects have been reported with the opiate antagonist, naltrexone, in smoking cessation efforts, and pre-treatment with this antagonist is without effect on i.v. NIC self-administration in animal studies. Recently Dr. Xiu Liu and his colleagues at the University of Pittsburgh assessed naltrexone effects on (1) NIC's direct reinforcing properties, and (2) incentive motivational effects of cues paired with NIC. In this study, rats self-administered i.v. NIC with paired presentation of a tone+light (conditioned stimuli) over 30 sessions. For one group (cue-induced reinstatement) operant responding was then extinguished by placing rats in the experimental chambers without NIC-associated stimuli, and delivering saline instead of NIC for each bar press. Then, reinstatement tests were conducted wherein the conditioned stimuli were re-introduced and operant responses elicited by these stimuli were measured, again in the absence of NIC delivery. Half of these animals were pretreated with naltrexone before reinstatement, and half received saline instead. For the second group (cue-maintained lever pressing), responding during extinction resulted in the presentation of conditioned stimuli (also with saline infusions instead of NIC). Thus, for this group, the conditioned stimuli reinforced operant responding during extinction. Animals in this second group were also divided into those receiving pretreatment with naltrexone during extinction, and controls who received saline. Additional control groups were tested to examine the effects of acute and chronic naltrexone on operant responding for i.v. NIC. Group comparisons revealed that naltrexone dose dependently blocked cue-induced reinstatement in group one, and suppressed cue-maintained lever responding during extinction in group two. By contrast, the same doses of naltrexone that blocked cue-induced reinstatement and cue-maintained operant responding were without effect on operant responding for NIC, whether naltrexone was given acutely or chronically for seven days. Taken together, these findings suggest that endogenous opioid systems may have an important role in the incentive motivational properties of NIC-associated cues and that these systems may be a target for interventions directed at associative influences on smoking behavior. Xiu L, Palmatier MI, Caggiula AR, Sved AF, Donny EC, Gharib M, Booth S. Naltrexone attenuation of conditioned but not primary reinforcement of nicotine in rats. Psychopharmacol. 2009; 202:589-598.

Different Neurobiological Substrates for Aversive Versus Reinforcing Effects of Cocaine

Cocaine has strong reinforcing properties and also induces anxiogenic effects that can be measured in an animal behavioral assay. In Dr. Aaron Ettenberg's runway procedure, rats run along a straight alley (in a non-drugged state) to receive an i.v. cocaine infusion in the goal box at the end. In this paradigm, "retreats" away from the goal box provide a quantitative measure of the aversive properties of the drug. Thus, the procedure provides a model of the approach-avoidance conflict that typifies human drug seeking. Retreats have also been measured in rats trained to run for intracerebroventricular cocaine infusions, and Dr. Ettenberg is interested in determining the neurobiological circuits responsible for the drug's aversive properties. While prior research has

indicated importance of the mesocorticolimbic dopamine system (including the prefrontal cortex, PFC) in cocaine's rewarding effects, it is not known if aversive properties arise from this, or a different, brain system. In a recent study, rats were trained to run for bilateral cocaine infusion into the medial PFC. Training began with an acclimation phase with the goal box closed. On the following 15 daily trials rats were placed in the start box and a guillotine door to the goal box was opened. Movement through the runway was recorded and bilateral cocaine infusions, (three doses or vehicle, administered to separate groups), were delivered upon entry into the goal area. Rats were removed 5-min after cocaine delivery. Dependent measures included run times and retreats, providing behavioral assessments of reinforcing and aversive drug effects, respectively. The investigator found that all doses of cocaine were associated with faster running speeds in the apparatus, as has previously been observed with i.v. cocaine delivery. However, unlike previous studies with this procedure, mPFC cocaine infusions were not associated with retreats. Since these behaviors are measured prior to drug delivery (in the goal box), they are believed to index the animal's memory for the drug effects Ð positive or negative. The findings indicate that while PFC is an important substrate for positive effects, aversive properties of this drug arise from neurotransmitter activation in some other part of the central dopamine system. Guzman D, Moscarello JM, Ettenberg A. The effects of medial prefrontal cortex infusions of cocaine in a runway model of drug self-administration: Evidence of reinforcing but not anxiogenic actions. Eur J Pharmacol. 2009; 605:117-122.

Drug-Conditioned Place Preference in Human Subjects

Animal behavioral models that mimic human drug abuse include those that directly measure reinforcing properties of drugs (such as i.v. self-administration) and those that measure a drug's ability to impart reinforcing properties to stimuli associated with the drug's effects. The latter can be assessed using conditioned place preference procedures (CPP) where rats are placed in a particular environment, repeatedly after drug administration, so that the drug-induced subjective experience becomes associated with discrete stimuli in that environment. Subsequently, on tests of CPP expression, animals will spend more time on the drug-associated side of a test chamber, than a side previously paired with only saline, suggesting these drug- related-stimuli elicit approach behavior by virtue of their acquired motivational properties. Investigators infer that the drug induces a positive subjective state, much like those reported when human subjects are queried for their subjective ratings of drug effects in a laboratory. However, there has yet to be an empirical demonstration of CPP in human subjects. Drs. Emma Childs and Harriet de Wit undertook a study to establish amphetamine induced CPP with 20 mg oral d-amphetamine in healthy, adult volunteers. The study involved two pairings with drug and a test room, and two pairings of placebo with a different test room. Each pairing lasted four hours, during which time subjective drug effects (Profile of Mood States, the Addiction Research Centre Inventory Ð ARCI, and Drug Effects Questionnaire) were measured. A separate control group experienced drug and placebo in both rooms (unpaired condition). During the test for CPP, rather than assess subject's choice of room, subjects completed a room preference questionnaire while in a new setting. Results showed a significantly higher rating for the drug-associated room in the paired condition (i.e., amphetamine-paired-room only), suggesting establishment of a CPP. Subsequent regression analysis revealed that room liking negatively correlated with POMS anxiety; and that overall, POMS anxiety, "drug liking", the hallucinogen-like scale of the ARCI, and positive mood, accounted for 43% of the variance in room liking. Thus, there was an orderly relationship between the CPP and subjective effects of d-amphetamine; thus, both negative subjective effects and drug liking contributed to the establishment of the CPP to amphetamine. This study validates a common procedure used to study drug effects in animal models and supports the underlying assumption that CPP

expression can be related to subjective effects. Childs E, de Wit H. Amphetamine-induced place preference in humans. Biol Psychiat. 2009; 65:900-904.

New Mouse Self-Administration Procedure for Genetics Studies in Nicotine Addiction

Supported in part by a NIDA grant to Dr. Rafael Maldonado, in Barcelona, Spain, a new procedure has been developed to establish i.v. nicotine (NIC) self-administration in C57BL/6 mice. The investigators note that nicotine intake is difficult to establish in laboratory animals and that previously there has only been one demonstration of nicotine relapse using laboratory models. Human smokers relapse during abstinence for a number of difference reasons, and these paths to relapse can be modeled in animal 'reinstatement' paradigms. In these paradigms, animals are extinguished from i.v. self-administration and then, later, given a drug-associated cue, with a priming dose of the drug, or with a stressor. Under all three conditions, animals show a reinstatement of drug seeking behavior, resembling the human condition of relapse. In the Maldonado study, mice make nose-poke responses for i.v. NIC (0.03mg/kg/infusion), paired with pump noise and cue lights. After stable responding was established, extinction was conducted without cues, and saline was delivered instead of NIC. During reinstatement, nose pokes were measured in response to cue presentation, 0.18 mg/kg s.c. NIC, or a mild foot shock stressor, in different groups of subjects. Cue induced reinstatement was robust, and observed in 90% of the animals, whereas only 30% reinstated following the priming dose of NIC. Stress with mild shock induced drug-seeking in 50% of the animals. These results appear to mimic the powerful effects of conditioned stimuli in human relapse to smoking, even after prolonged abstinence. Martin-Garcia E, Barbano MF, Galeote L, Maldonado R. New operant model of nicotine-seeking behaviour in mice. Int J Neuropsychopharm. 2009;12:343-356. Moreover, establishment of this procedure allowed the researchers to investigate the genetic basis of NIC reinforcement using a mouse model. Morphine and opioid peptides derived from pre-proenkephalin (which bind to mu opioid receptors) have been demonstrated to participate in NIC reward and in NIC withdrawal symptoms. However, the dynorpyhin/kappa-opioid receptor system is also implicated in the reinforcing effects of several drugs of abuse, and activating this system decreases drug reward. Dr. Maldonado and colleagues trained wild-type, and prodynorpyhin knock-out mice, for NIC induced conditioned place preference, and for i.v. self-administration of NIC. They also measured NIC induced locomotion, antinociception and precipitated withdrawal. Knock-out mice were no different on any measures, with the exception of i.v. NIC self-administration: knock-out mice self-administered doses that were sub-threshold for wild-type animals (5.2 ug/kg/infusion) and would not take higher doses that were readily self-infused by the wild type group (21.3 to 85.5 ug/kg/infusion), indicating a shift to the left in the dose-response curve. This is the first study to reveal opioid peptide modulation of nicotine intake, possibly via the mediation of NIC's aversive effects, and suggests that NIC's subjective properties can be separated neurochemically from psychomotor stimulation, associative effects, and ability to induce physical dependence and antinociception. Galeote L, Berrendero F, Bura SA, Zimmer A, Maldonado R. Prodynorphin gene disruption increases the sensitivity to nicotine self-administration in mice. Int J Neuropsychopharm. 2009; 12:615-625.

Genetic Differences Play a Role in Sensitivity to Delayed Rewards

Emerging evidence suggests a genetic component to addiction, which is characterized by heightened impulsivity. Comparisons of multiple inbred mouse strains reveal significant differences in delay discounting (DD, a measure of impulsivity). However, findings from mouse and rat models do not always

correspond, and although there have been several studies of DD comparing two inbred rat strains, calculation of strain differences requires more than two lines. NIDA grantees Drs. Wilhelm and Mitchell compared 6 rat strains (Brown Norway [BN], Copenhagen [C], Fischer [F], Lewis [L], Noble [N] and Wistar Furth [WF]) that, with the exception that L rats were derived from Wistar stock over 50 years ago, are genetically unrelated. Although primarily interested in potential differences in DD behavior, they also measured sucrose preferences, sucrose consumption, and locomotor activity. Using 10% sucrose solution as a reinforcer, rats received training in a 3-lever paradigm where responding on the middle lever "activated" the outer levers for a period of time. During the activated period, responding on one of the outer levers resulted in an adjusting sucrose reinforcer. Responding on the other outer lever delivered a standard (150ul) sucrose reinforcer. The volume of the adjusted reinforcer started at 75% sucrose and increased or decreased by 10%, depending on whether the rat chose the standard, or the adjusting lever, on the previous trial, respectively. During a DD session, responding on the standard lever resulted in delivery of 150ul following a delay of 0, 2, 4, 8 or 16 seconds. This delay didn't change within a session, but did vary between sessions. With all rat strains, the "indifference points" Ð that is, the point at which rats select from each end lever with roughly equal frequency, decreased as time to reward increased. Strain differences were most apparent at the longer delays, with N rats having significantly higher indifference points as compared to 4 of the 5 other strains. This suggests that N rats were more adverse to delay of reinforcement, and also suggests a heritability component in DD behavior. After the DD procedure, rats were given two-bottle sucrose preference tests to evaluate potential differences in baseline preferences that may affect interpretation of the DD data. For example, if a lower preference for sucrose were detected, there may appear to be an increase in impulsivity that may actually be the result of a faster devaluation of sucrose reward. During 50 minute test sessions, rats were given access to two bottles offering water or varied percents of sucrose. Significant strain differences were seen in the choice of water versus 10% sucrose, with N rats selecting more sucrose than all but the C strain. C rats also drank significantly more sucrose than F and WF rats. The researchers concluded that heredity also influences sucrose preference. Given this finding, results from the DD task cannot be attributed to differential reward preferences (or reward sensitivity) in the N rat strain. Next, animals were tested for locomotor activity in two 30-min test sessions. WF and L rats were significantly less active than most other rat strains, however activity was not correlated with DD or sucrose preference. Taken together, these data suggest that there is a heritability component in aversion to delayed reinforcement. This may have significant implications for disorders that are characterized by heightened aversion to delayed rewards. Understanding the role of specific genes and gene combinations may provide viable targets for the development of pharmacotherapies for disorders characterized by heightened impulsivity including drug addiction. Wilhelm CJ, Mitchell SH. Strain differences in delay discounting using inbred rats. Genes Brain Behav. 2009; 8:426-434.

Increased Sensitivity to Methamphetamine Following Prenatal Exposure to Lead

Children who live in inner cities have increased risk of exposure to lead above the "safe" range of less than 10ug/dl. Even when blood lead levels are within this so-called "safe" range, exposure to lead is known to be associated with neurobehavioral impairment and disturbed cognitive function. Additionally, lead exposure may also be associated with an enhanced vulnerability for drug abuse. Given a rise in methamphetamine (METH) use among people in low socioeconomic status, NIDA investigator Paul Wellman and colleagues were interested in the effects of prenatal lead exposure on response to METH. In these studies they employed an animal model of behavioral sensitization, which reveals the enhanced behavioral activation over repeated METH administration

(as compared to initial, acute response). Female rats were administered either lead-free vehicle or 16 mg lead for 30 days prior to breeding. Once pregnant, they continued to receive either vehicle or lead treatment until the pups were weaned. After weaning, offspring were given no experimental treatment until post-natal day 70, when they were assigned to one of four test groups: no lead/10 days of systemic vehicle, no lead/10 days systemic METH (1 mg/kg/day), lead/10 days of systemic vehicle, or lead/10 days systemic METH (1 mg/kg/day). On days 1-10, animals were placed in locomotor activity (LMA) chambers, and LMA was monitored 15 minutes prior to treatment and for 45 min. post-treatment. On days 11-14, a dose-effect relationship was established in all animals given daily systemic injections of 0, 1, 2 and 4 mg/kg METH. For the first two exposures to METH (days 1 and 2), there were no differences in METH-induced LMA when comparing lead versus no lead exposure. However, with repeated METH treatment, animals exposed to lead showed significantly more LMA--an effect that lasted until day 6 when response levels of the two groups converged. Animals receiving vehicle treatments showed no increase in LMA. Dose-response testing indicated that METH produced an inverted U-shaped curve, with 1 and 2 mg/kg producing peak elevations in LMA. Prenatal treatment did not affect this dose-response relationship. Blood samples at breeding, postnatal day 2, and postnatal day 21, verified lead exposure of the dams and the pups. However, by the end of the experiment, there were no differences in the blood levels of lead in the exposed versus the non-exposed rats, indicating that the lead had been cleared from the blood. Therefore, increased sensitization of lead-exposed animals given METH challenges was due to residual effects of the lead and not a direct interaction between lead and METH. These results indicate increased behavioral responsiveness to METH if animals are exposed to lead during the prenatal and weaning period. These findings may have significant public health implications, as lead also affects cognitive development. Since lead affects both behavioral response to chronic psychostimulant administration (results of the present study) and impairs cognition, children exposed to lead during development may be particularly vulnerable for problems of drug abuse. Clifford PS, Hart N, Thompson J, Buckman S, Wellman PJ, Bratton GR, Nation JR. Prenatal lead exposure enhances meth-amphetamine sensitization in rats. Pharm Biochem Behav. 2009;93:165-169.

Blockade of Hypocretin Neurons in the Insula Decreases Nicotine Reinforcement

Damage to the insula from stroke has been associated with spontaneous tobacco cessation and reductions in urge to smoke, and imaging studies in smokers have shown that abstinence-induced cigarette craving is associated with activation of this cortical region. These findings suggest a role for the insula in nicotine reinforcement. In a recent study, NIDA grantees Paul Kenny, Jonathan Hollander and colleagues studied hypocretin (Hcrt) peptides (also known as orexins) in the insula, as these peptides have been implicated as potential regulators of reward and motivation. To investigate hypocretin's role in nicotine reinforcement, they first trained rats to self-administer intravenous nicotine. Rats were then pretreated with the Hcrt-1 receptor antagonist, SB-334867, and nicotine self-administration was assessed. Responding to receive nicotine decreased following Hcrt-1 blockade. This was due to a nonspecific response suppression, as responding for food was not similarly reduced. They next tested animals in an ICSS (intra-cranial self-stimulation) paradigm in which an animal lever-presses to receive rewarding electrical stimulation. Typically, nicotine lowers the current threshold that maintains self-stimulation, indicating reward enhancement. Administra-tion of the Hcrt-1 antagonist attenuated reward-enhancing effects of nicotine, supporting a role for Hcrt-1 receptors nicotine's rewarding properties. Next the investigators infused SB-334867 directly into the insular cortex. Infusion here, but not the somatosensory cortex control region, reduced responding for nicotine. Taken

together, these data support a significant role for insular hypocretin receptors in nicotine reward and suggest that Hcrt-1 receptors may be a viable new target for tobacco cessation pharmacotherapies. Hollander JA, Lu Q, Cameron MD, Kamenecka TM, Kenny PJ. Insular hypocretin transmission regulates nicotine reward. PNAS. 2008;105(49):19480-19485.

Anxiety and Dysphoria During Spontaneous Withdrawal from Acute Morphine Exposure

Negative motivational states induced by drug withdrawal contribute to the pattern of addiction with drugs that induce physical dependence, such as the opiates. Withdrawal from chronic exposure to heroin or morphine includes symptoms of both anxiety and depression. Such negative emotional states can be induced by acute drug exposure and researchers have studied precipitated withdrawal after single drug treatments to study somatic and affective components of withdrawal from drugs like the opiates. The influence of withdrawal states induced by each individual opiate experience, over the course of morphine or heroin addiction, has not been studied. In animal behavioral models, anxiety can be indexed validly and reliably by elevated acoustic startle reflex, whereas conditioned place aversion is used to assess dysphoria or anhedonia associated with depression. The present study investigated the effects of spontaneous and naloxone precipitated withdrawal from one or two morphine injections using acoustic startle and place aversion. Results indicated that anxiety-like behavior (startle potentiation) emerges spontaneously after a single exposure to morphine and seems to be related to a decrease in opiate receptor occupancy. Moreover, it shares a pharmacological profile with naloxone precipitated opiate withdrawal, in that both can be blocked by anxiolytic drugs such as the benzodiazepines. They also found that during spontaneous withdrawal, startle potentiation develops before the rewarding effects of morphine have subsided (i.e., during the post-drug interval when conditioned place preference can be established). In contrast to these spontaneous withdrawal effects, naloxone potentiated startle and conditioned place aversion develop concurrently. Thus, increased anxiety-like behavior develops independently from decreased reward system activity. Furthermore, anxiogenic and dysphoric manifestations of opiate withdrawal may be mediated by distinct neural mechanisms, which may be progressively engaged during withdrawal after individual acute exposures to morphine during addiction. In conclusion, negative emotional states accompany the earliest stages of drug exposure, are likely a recurrent feature of intermittent drug use in humans, and thus may contribute significantly to the development of addiction. Rothwell PE, Thomas MJ, Gewirtz JC. Distinct profiles of anxiety and dysphoria during spontaneous withdrawal from acute morphine exposure. Neuropsychopharmacol. published online, June 10, 2009.

Learning Deficits Associated with Adolescent Cocaine in the Rat

Since previous epidemiological and preclinical research have suggested that the consequences of cocaine consumption may be different depending upon age of the individual, the present study investigated the effects of self-administered and passively administered cocaine, on odor-reward learning in adult rats exposed to cocaine either during adolescence or adulthood. Odor-reward learning was chosen as a task mediated by orbitofrontal cortex. Over 18 training days, rats were exposed to cocaine during adolescence or adulthood and tested during adulthood. The exposure conditions used a three group yoked design, with one-third self-administering cocaine, one-third yoked and receiving cocaine passively and one-third yoked and receiving saline. Following drug exposure, all rats were returned to their home cages for an 18 day drug free period. Then they were trained in two spatial maze-learning tasks. In the first task (easy) they learned to find food in four distinctive-odor arms of the maze. In the second task (difficult), they learned to find food in four

distinctive-odor arms of the maze, but the maze had eight arms, four of which had the previous odors and now had to be avoided (so-called win-shift task). Results indicated that cocaine self-administration behavior was similar in adolescent and adult rats. However, despite similarities in the amount of cocaine consumed in adult and adolescent rats, subsequent learning was affected differentially after the drug-free period. On the difficult test, adolescent and adult rats exposed to cocaine both showed learning deficits compared to saline controls, but adolescents were somewhat more impaired, which was evident on the trials to criterion measure. Rats self-administering cocaine were also more impaired than those receiving cocaine passively, indicating that the observed deficits were not due exclusively to the pharmacological effects of cocaine, but may be related also to the expectancy and/or controllability of cocaine delivery. These findings support a view that similar intakes of cocaine can have difference consequences when drug use begins during adolescence vs. adulthood. Harvey RC, Dembro KA, Rajagopalan K, Mutebi MM, Kantak KM. Effects of self-administered cocaine in adolescent and adult male rats on orbitofrontal cortex-related neurocognitive functioning. Psychopharmacol, published online, June 10, 2009.

Coexpression of Alpha 2-Adrenergic and Opioid Receptors on Primary Afferent Nociceptive Fibers Which May Represent An Anatomical Substrate for Analgesic Synergy

Agonists acting at alpha 2-adrenergic and opioid receptors (alpha 2ARs and ORs, respectively) inhibit pain transmission in the spinal cord. When coadministered, agonists activating these receptors interact in a synergistic manner. Although this interaction is well established, its mechanism remains poorly understood. In the present study, NIDA-grantee Dr. George Wilcox and colleagues (University of Minnesota) used immunohistochemistry to investigate the spatial relationship between alpha 2ARs and ORs in the rat spinal cord. They observed extensive colocalization between alpha 2A-adrenergic and delta-opioid receptors (DOR) on substance P (SP)-immunoreactive (-ir) varicosities in the superficial dorsal horn of the spinal cord and in peripheral nerve terminals in the skin. Furthermore, coincubation of isolated synaptosomes with alpha 2AR and DOR agonists resulted in a synergistic increase in the inhibition of potassium-stimulated neuropeptide release. These findings suggest that coexpression of 2AAR-DOR on primary afferent nociceptive fibers represent an anatomical substrate for analgesic synergy. Riedl MS, Schnell SA, Overland AC, Chabot-Dore AJ, Taylor AM, Ribeiro-Da-Silva A, Elde RP, Wilcox GL, Stone LS. Coexpression of alpha 2A-adrenergic and delta-opioid receptors in substance P-containing terminals in rat dorsal horn. J Comp Neurol. 2009;513:385Ð398.

Contribution of CD14 for Glial Mediated Neuropathic Pain

The CNS toll-like receptor 4 (TLR4) plays a key role in the development of behavioral hypersensitivity in the neuropathic pain spinal nerve L5 transection (L5Tx) model in rats. The TLR4 is a well-known receptor for lipopolysaccharide (LPS) in innate immune responses. NIDA-grantee Dr. Joyce Deleo and colleagues (Dartmouth Medical School) investigated the role of CD14, an accessory molecule in the LPSÐTLR4 signaling pathway, in the development of L5Tx-induced neuropathic pain. CD14 knockout mice displayed significantly decreased behavioral sensitivity as early as day 1 post-L5Tx, indicating a nociceptive role of CD14. By flow cytometric analyses, they found elevated microglial surface CD14 expression in the ipsilateral lumbar spinal cord 3 days post-L5Tx, as well as substantial increases in microglial size. Further, intrathecal injection of soluble CD14 induced significantly greater mechanical hypersensitivity in wild type (C3H/HeN) mice compared with TLR4-deficient (C3H/HeJ) mice. Together, these data demonstrate that CD14 plays a role in TLR4-dependent nerve injuryÐinduced neuropathic pain. Cao L, Tanga FY and DeLeo JA. The contribu-ting role of CD14 in toll-like receptor 4 dependent

neuropathic pain. Neurosci. 2009; 158:896Ð903.

The Glutamate Transport Protein GLT1 is a Potential New Target for Treating Cocaine Addiction

A variety of studies in animal models indicate that increased glutamate transmission in several brain regions is a key neuroadaptation that promotes relapse to cocaine-seeking behavior. Therapeutic agents that can decrease glutamate transmission are therefore possible candidates for treatment of cocaine addiction. In this study, Dr. George Rebec and his colleagues tested the hypothesis that decreasing glutamate transmission by upregulation of a glutamate transporter would attenuate cocaine relapse. They targeted GLT1, which is expressed on astrocytes and is responsible for taking up most extracellular glutamate released by synaptic activation. Rats were trained to self-administer cocaine in sessions where lever pressing delivered intravenous cocaine paired with presentation of a combined light and tone cue. After learning to self-administer, the rats went through five days of extinction training, where the lever was present, but pressing it delivered neither cocaine nor the cue. At the end of each extinction session, they received an injection of 50, 100, or 200 mg/kg ceftriaxone, a β-lactam antibiotic, believed to increase GLT1 expression. Control animals received injections of saline vehicle. By the end of these five sessions, none of the rats was pressing the lever previously associated with cocaine more than a few times. On the sixth day, they were tested for reinstatement of cocaine-seeking with presentation of the cue. During reinstatement testing, lever presses delivered the cue, but not cocaine and the number of lever presses was used to assess reinstatement of cocaine-seeking behavior. Animals that had received saline or the lowest does of ceftriaxone pressed the lever significantly more than those who had received either of the two higher doses, indicating that ceftriaxone treatment at these doses significantly attenuated relapse behavior. Ceftriaxone at the highest dose had no effect on reinstatement of food seeking in similar experiments in which animals were trained to respond for food, indicating that the effect was specific for cocaine and not a general enhancement of extinction. Western blot analysis showed that GLT1 protein levels were significantly increased in both the prefrontal cortex and nucleus accumbens of rats treated with the highest dose of ceftriaxone compared to those treated with saline or the 50 mg/kg dose (brains of animals treated with 100mg/kg were not used in this analysis). The results implicate GLT1 as a potential target for treatment of cocaine addiction, and may be an attractive target for translational research because ceftriaxone is an approved drug commonly used to treat postoperative infections. Sari Y, Smith KD, Ali PK, Rebec GV. Upregulation of GLT1 attenuates cue-induced reinstatement of cocaine-seeking behavior in rats. J Neurosci. 2009; Jul 22;29(29):9239-9243.

Individual Rats with Higher Addiction Liability Show More Persistent Neuroadaptations in Ventral Tegmental Dopamine Neurons Following Cocaine Self-Administration

Studies in animal models have shown that addictive drugs produce neuroadaptations in dopamine neurons of the ventral tegmental area (VTA) that are critical for certain features of drug addiction. This study asked whether individual differences in these neuroadaptive responses are correlated with naturally occurring individual differences in drug addiction liability. To study this question, the investigators took advantage of high-responder (HR) and low-responder (LR) rats, which are distinguished on the basis of how much they move around in a novel environment. These spontaneous differences have been associated with increased addiction liability for HR over LR rats in several models of addiction. They first trained HR and LR rats to self-administer cocaine, using a dosing regimen that equalized drug intake across individuals. They then recorded the activity of VTA neurons at various periods of

withdrawal. Withdrawal from cocaine self-administration increased VTA dopamine cell firing and bursting in all animals. However, these changes in firing rates and patterns were more persistent in HR than in LR rats. In the LR rats, elevated firing rats persisted for only one day, and then declined to baseline levels, whereas in the HR rats, the increase in firing was apparent at both withdrawal days 1 and 3 and then declined to baseline by withdrawal day 10. These results demonstrate individual differences in the duration of drug-induced neuroadaptations in dopamine neurons of the VTA. More persistent elevation of dopamine cell activity and reduced capacity to return to baseline levels may be an important factor contributing to the development of addiction in "at-risk" individuals. McCutcheon JE, White FJ, Marinelli M. Individual Differences in Dopamine Cell Neuroadaptations Following Cocaine Self-Administration. Biol Psychiatry. 2009; Jun 16. [E-pub ahead of print].

Prenatal Exposure to Cocaine Increases Dopamine Release Induced by Chronic Exposure to Cocaine in Adulthood

Studies in rodents have shown that prenatal exposure to cocaine can increase the rewarding potency of cocaine on operant or instrumental learning, e.g., in drug self-administration paradigms. Conversely, the potency of cocaine on Pavlovian learning seen in conditioned place preference, appears to be decreased in adult rodents after exposure in utero. The investigators current research focuses on cellular mechanisms underlying the adaptation of mesolimbic brain reward circuitry in response to adult drug exposure, and understanding how these mechanisms differ between developmentally exposed and non-exposed offspring, in a model of prenatal cocaine exposure. Previously, they have demonstrated increased cocaine sensitivity in operant tasks, and decreased sensitivity in classical Pavlovian tasks, upon cocaine challenge. Here, they studied the effects of prenatal cocaine exposure on dopamine (DA) levels in the nucleus accumbens (NAcc) of mice subjected to chronic non-contingent cocaine administration in adulthood using in vivo microdialysis. The mice were injected with cocaine every other day for a total of seven doses, withdrawn for 21 days, and then challenged with an additional injection. Microdialysis samples obtained after the first, seventh challenge doses showed increasing cocaine-stimulated DA release in the nucleus accumbens, which was significantly enhanced after prenatal cocaine exposure. Interestingly, the same dosing regimen that produces reduced levels of locomotor sensitization in prenatally exposed animals produced augmented DA release at days 7 and 21, compared to non-exposed controls. This sensitized DA release may therefore reflect the enhanced rewarding effects of cocaine in prenatally exposed animals rather than locomotor stimulating effects. The results show that early developmental cocaine exposure can alter adapta-tion of brain reward systems to chronic psychostimulant exposure in adulthood. Malanga CJ, Ren JQ, Guerriero RM, Kosofsky BE. Augmentation of cocaine-sensitized dopamine release in the nucleus accumbens of adult mice following prenatal cocaine exposure. Dev Neurosci. 2009;31(1-2):76-89.

Emotional Arousal in Cocaine Exposed Toddlers: Prediction of Behavior Problems

A recent study by Dr. Linda Mayes and colleagues at Yale University School of Medicine examined the relationship between prenatal cocaine exposure and agitated emotional arousal, self-regulation, and references to caregivers during a toy-wait task. The study involved 225 2½ year-old toddlers (including 129 Prenatally Cocaine and Other Drug Exposed [PCE], 30 Non Cocaine but other drug Exposed [NCE], 66 Non Drug Exposed [NDE]). Children's behaviors in the toy-wait task were coded for emotional arousal and regulation behaviors. The findings revealed a non-significant trend for PCE toddlers to exhibit greater agitated emotional arousal than NCE and NDE toddlers. In addition, PCE boys made significantly more references to their caregivers during the task than

NDE boys; however, PCE boys did not differ from NCE suggesting that the effect was not cocaine-specific, but rather related to other drug exposures. Among girls, there were no differences in reference to caregivers as a function of drug exposure status. References to caregivers during the task included such behaviors as looking to, approaching, reaching and making physical contact, behaviors interpreted by the authors as reflecting "an attempt to regulate emotion by drawing in the caregiver." Results also suggested that higher agitated arousal at age 2½ years was related to greater decreases in externalizing behaviors through age 5½ years, but did not predict change changes in internalizing symptoms. Neither of these outcomes was affected by drug exposure status. Drug exposure status also did not predict externalizing or internalizing problems over time. In sum, the results of this study suggest a possible link between drug exposure and emotional arousal and emotional regulation. This finding is important because of possible implications for risk for or protection from later psychopathology. Outcomes showing no relationship between drug exposure status and externalizing and internalizing problems over time can be viewed as an encouraging finding regarding drug-exposed children given the historical concerns about possible adverse consequences of prenatal exposure to drugs of abuse. Chaplin TM, Fahy T, Sinha R, Mayes LC. Emotional arousal in cocaine exposed toddlers: Prediction of behavior problems. Neurotoxicol Teratol. 2009; May 21 [E-pub ahead of print].

The Changing Role of the Medial Preoptic Area in the Regulation of Maternal Behavior Across the Postpartum Period

Maternal behavior in rats undergoes considerable plasticity in parallel to the developmental stage of the pups, resulting in distinct patterns of maternal behavior and care at different postpartum time points. For example, Dr. Morrell and her colleagues have shown that rat mothers prefer their pups over cocaine through the first 8 days postpartum, but their preference begins to switch to a preference for drug at PPD10. In the current study, they investi-gated a neural substrate that may be involved in this change in preference. The medial preoptic area (mPOA) of the hypothalamus is one critical neural substrate underlying the onset and early expression of maternal behavior in rats, but little is known about its specific functional role in the evolving expression of maternal behavior across the postpartum period. To study this question, the investigators used a reversible local neural inactivation method to examine the role of the mPOA in the regulation of maternal behavior throughout the postpartum period. This approach avoids the compensatory plasticity in CNS that occurs after permanent lesions and allows repeated testing of the same individuals. Early (PPD7Ð8) and late (PPD13Ð14) postpartum maternal behavior was evaluated in female rats following infusions of bupivacaine or vehicle into the mPOA or into control areas. Consistent with the study's hypotheses, mPOA inactivation severely, but transiently, disrupted early postpartum maternal behavior, whereas infusion of vehicle or inactivation of adjacent control sites was without effect. Later in the postpartum period, however, transient mPOA inactivation facilitated the expression of maternal behaviors, in clear contrast with the lower level of expression of these behaviors characteristic of this later period. The results demonstrate that the mPOA is differentially engaged throughout the entire postpartum period in orchestrating appropriate maternal responses with the developmental stage of the pups. Further, the results suggest that the mPOA may be part of the neural circuit involved in the changing preference for cocaine over maternal care shown in the earlier experiments. Pereira, M, Morrell, JI. The changing role of the medial preoptic area in the regulation of maternal behavior across the postpartum period: Facilitation followed by inhibition. Behav Brain Res. 2009; June 21. [E-pub ahead of print].

Sex and Ovarian Hormones Influence Vulnerability and Motivation for Nicotine During Adolescence in Rats

In animal models of nicotine self-administration in adult rats, several sex differences have been observed. For example, a greater percentage of females acquire self-administration under low dose conditions and females show higher progressive ratio responding, suggesting greater motivation to obtain nicotine. In human laboratory studies, subjective responses to nicotine have been shown to vary with the menstrual cycle and to be affected by exogenous delivery of the ovarian hormone progesterone. Research has not examined whether these nicotine effects observed in adults occur also in adolescents. Thus, in the present study, Dr. Wendy Lynch of the University of Virginia sought to determine whether sex differences in nicotine self-administration are also seen in adolescent rats and if this difference is modulated by ovarian hormones. Nicotine self-administration training began on postnatal day 30 with either 5 or 10 microg/kg/infusion followed by testing on a progressive ratio schedule. Dr. Lynch found that under the lower nicotine dose, a greater percentage of females than males acquired self-administration. Early in adolescence, there were no sex differences in progressive ratio responding, but differences emerged in late adolescence in that females had higher break points; thus, they were willing to make more operant responses to obtain drug. Progressive ratio responding in females also was correlated with estrogen and progesterone levels, varying negatively with progesterone and positively with the ratio of estradiol to progesterone. Overall, these data indicate that sex differences in nicotine self-administration reported adult rats have their origin in adolescence and, as in humans, nicotine's effects are modulated by ovarian hormones. Lynch WJ. Sex and ovarian hormones influence vulnerability and motivation for nicotine during adolescence in rats. Pharmacol Biochem Behav. 2009; Jul 17. [E-pub ahead of print].

Housing Conditions Affect Conditioned Place Preference and Dopamingeric Markers in Adolescent Male Rats

Dr. Sari Izenwasser and colleagues at the University of Miami Miller School of Medicine assessed whether cocaine reward during early adolescence, in male rats, is affected by social and environmental housing conditions. She also examined the relation between cocaine reward outcomes and dopaminergic proteins that mediate drug reward. Social conditions were manipulated by housing rats either alone or with two or three conspecifics per cage. Environmental conditions were manipulated by housing rats either with toys (enrichment) or without toys (impoverishment). These conditions, which began on postnatal day (PND) 23, constituted six experimental conditions: socially isolated rats housed alone, either impoverished with no toys (II) or enriched with toys (IE); and social rats housed two/cage either with no toys (SI2) or with toys (SE2), or three/cage with (SE3) or without (SI3) toys. Cocaine reward was determined through use of the cocaine conditioned place preference (CPP) procedure conducted on PND 43-47 using either 5 or 10 mg/kg cocaine. Results indicated that CPP was established in the II rats (isolated, no toys) under both doses of cocaine. With additional cage mates or toys, CPP was decreased. Rats housed three/cage, either with (SE3) or without (SI3) toys, did not exhibit CPP with either cocaine dose. Thus, both social housing and toys diminished CPP, and housing with two cage mates prevented CPP. Further, there were correlations between these housing conditions and markers of dopaminergic transmission. In the nucleus accumbens increased dopamine transporter (DAT) protein was observed in rats housed three/cage with toys (SE3) compared to those housed alone without toys (II). Administration of cocaine also increased tyrosine hydroxylase and DAT in the II rats, but not in the SE3 rats. Zakharova E, Miller J, Unterwald E, Wade D, Izenwasser S. Social and physical environment alter cocaine conditioned place preference and dopaminergic markers in adolescent male rats. Neurosci. 2009; Jul 3. [E-pub ahead of print].

Hedonic Sensitivity in Adolescent and Adult Rats: Taste Reactivity and Voluntary Sucrose Consumption

In her 2000 article, "The adolescent brain and age-related manifestations," Dr. Linda Spear at Binghamton University suggested that adolescents may have a partial anhedonia, that leads them to seek out natural and drug rewards as compensation for this attenuation in hedonic sensitivity. She and colleague Carrie Wilmouth recently tested this hypothesis by assessing hedonic reactions to sucrose using a well-established taste-reactivity (TR) test, which measures oral-facial appetitive and aversive reactions to tastants. Contrary to their prediction, results suggested greater hedonic sensitivity in adolescents. They found that appetitive taste responses to 10% sucrose solution were nearly three times higher in adolescent than adult rats. Further evidence for greater hedonic sensitivity in adolescents was seen the concentration-effect curves, as well as more pronounced paw licking in adolescents in response to a 34% sucrose solution. In response to quinine, adolescents exhibited fewer negative oral-facial responses. In a two-bottle taste test, adolescents consumed more sucrose than adults; however, adolescents and adults equally preferred sucrose over water. The authors conclude that these results do not support the hypothesis that adolescents exhibit an age-related, partial anhedonia.
Wilmouth CE, Spear LP. Hedonic sensitivity in adolescent and adult rats: Taste reactivity and voluntary sucrose consumption. Pharmacol Biochem Behav. 2009 Jun;92(4):566-573.

Nicotine and Social Interaction Interact to Enhance Reward in an Adolescent Rodent Model

NIDA grantee Dr. Janet Neisewander has been using the conditioned place preference paradigm (CPP) to study drug, and social interaction, rewards in adolescent rats. She has demonstrated that cocaine, and time with "play partners" independently can induce a CPP during adolescence. She also reported that doses of both, which are sub-threshold for inducing CPP alone, can summate to induce CPP when conditioned together. This suggests that inherently rewarding properties of social interaction might increase cocaine's reinforcing value, or that cocaine may enhance the reward value of social activities. In the new study she established nicotine (nic) CPP in adolescent rats, using either the s.c or i.v. route of administration. Using a biased CPP design, where drug is paired with the initially non-preferred side of a two-sided test box, she exposed rats to two times per day pairings Ð once per day when nic was paired with the non-preferred side, and once per day where vehicle was paired with the preferred side. Different groups were conditioned with .01, .03 or .06 i.v. nic, and 0.1, 0.3 or 0.6 s.c nic, in 10-min sessions over four days. In studies where social interaction was paired with nic during conditioning sessions, only two 10-min conditioning sessions were conducted, to test sub-threshold doses of reward. Social conditions included isolation versus conditioning with one playmate. In the final study, the investigator sought to determine if social and drug variables interact in an additive, or synergistic, manner. In this study, she eliminated the associative strength of nic alone, as a contributing factor to CPP, by pairing nic with both sides of the apparatus (thus negating the conditioned rewarding effects of the drug). Social reward continued to be paired with only the conditioning side, and groups receiving nic (both sides) + social reward were compared with groups receiving nic (paired side only) + social reward. Results of the studies revealed dose-orderly CPP with both routes of nic administration. She also replicated the original CPP finding that was established with social interaction, in that rats conditioned with a playmate showed greater preference for the paired side than isolates. Also similar to the results with cocaine, rats conditioned with a drug+social interaction combination (0.1 s.c. nic + playmate) exhibited significantly more time on the paired side during the test for CPP than those conditioned with nic or playmate alone. (This interaction could be

demonstrated only with the s.c. route of administration). The final study replicated this finding, even though the nic was paired with both sides, suggesting nic enhancement of the playmate CPP. These findings suggest that nic administration, via smoking in adolescents, may enhance the rewarding effects of social interaction during a developmental period when these interactions are highly valued and influential. This interaction may contribute to the development and maintenance of smoking in teens. Thiel KJ, Sanabria F, Neisewander JL. Synergistic interaction between nicotine and social rewards in adolescent male rats. Psychopharm. 2009; 204:391-402.

Varenicline Both Mimics and Blocks Nicotine's Discriminative Stimulus Effects

Varenicline is an alpha4beta2 (a4b2) partial agonist that acts as an agonist with partial efficacy, but also acts as a functional competitive antagonist because occupying the receptor makes it unavailable for full agonist binding. Varenicline is the newest pharmacotherapy for smoking cessation available in the United States, but little is known about its ability to attenuate behavioral effects of nicotine in animal models outside of the self-administration model. NIDA grantee Mark LeSage and colleagues therefore used drug discrimination methodology to investigate varenicline's partial agonist effects. Rats trained to discriminate nicotine from saline were challenged with varenicline or cytisine (an older a4b2 partial agonist used as control). While varenicline partially generalized to nicotine (up to 63% responding on nicotine-paired lever), cytisine only marginally generalized (max of 23% responding on nicotine-paired lever). Similarly, when given prior to nicotine, varenicline significantly attenuated responding on the nicotine-paired lever while cytisine only slightly reduced responding on the nicotine-paired lever. Given these data, varenicline's behavioral profile in drug discrimination is consistent with its label as a partial agonist. Furthermore, drug discrimination appears to be a more sensitive paradigm for differentiating between a4b2 partial agonists. LeSage MG, Shelley D, Ross JT, Carroll FI, Corrigall WA. Effects of the nicotine receptor partial agonists varenicline and cytisine on the discriminative stimulus properties of nicotine in rats. Pharm Biochem Behav. 2009; 91:461-467.

Director's Report to the National Advisory Council on Drug Abuse - September, 2009

Research Findings - Brain and Behavioral Development Research

fMRI and the Effects of Prenatal Methamphetamine Exposure on Verbal Memory

Efforts to understand specific effects of prenatal methamphetamine (MA) exposure on cognitive processing are hampered by high rates of concomitant alcohol use during pregnancy. Dr. Elizabeth Sowell and her colleagues at UCLA examined whether neurocognitive systems differed among children (ages 7-15) with differing prenatal teratogenic exposures when they engaged in a verbal paired associate learning task while undergoing functional magnetic resonance imaging. Groups did not differ in age, gender, or socioeconomic status. Participants' IQ and verbal learning performance were measured using standardized instruments. The MA group activated more diffuse brain regions, including bilateral medial temporal structures known to be important for memory, than both the alcohol-exposed only and the CON groups. These group differences remained after IQ was covaried. More activation in medial temporal structures by the MA group compared with the alcohol-exposed only group cannot be explained by performance differences because both groups performed at similar levels on the verbal memory task. More diffuse activation in the MA group during verbal memory may reflect recruitment of compensatory systems to support performance of the verbal memory network. Differences in activation patterns between the MA and alcohol-exposed only groups suggest that prenatal MA exposure influences the development of the verbal memory system above and beyond effects of prenatal alcohol exposure. Lu LH, Johnson A, O'Hare ED, Bookheimer SY, Smith LM, O'Connor MJ, Sowell ER. Effects of prenatal methamphetamine exposure on verbal memory revealed with functional magnetic resonance imaging. J Dev Behav Pediatr. 2009 Jun;30(3):185-192.

Early Parental Care Important for Hippocampal Maturation

The effects of early life experience on later brain structure and function have been studied extensively in animals, yet the relationship between childhood experience and normal brain development in humans remains largely unknown. Dr. Hallam Hurt and her colleagues used data from a study on prenatal cocaine exposure to examine this question. The data set included ecologically valid in-home measures of early experience during childhood (at age 4 and 8 years) and high-resolution structural brain imaging during adolescence (mean age 14 years) and examined the effects on later brain morphology of two dimensions of early experience: parental nurturance and environmental stimulation. Parental nurturance at age 4 predicted the volume of the left hippocampus in adolescence, with better nurturance associated with smaller hippocampal volume. In contrast, environmental stimulation did not correlate with

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hippocampal volume. Moreover, the association between hippocampal volume and parental nurturance disappeared at age 8, supporting the existence of a sensitive developmental period for brain maturation. These findings suggest that variation in normal childhood experience is associated with differences in brain morphology, and hippocampal volume is specifically associated with early parental nurturance. The results provide neuroimaging evidence supporting the important role of warm parental care during early childhood for brain maturation. Rao H, Betancourt L, Giannetta JM, Brodsky NL, Korczykowski M, Avants BB, et al., Early parental care is important for hippocampal maturation: Evidence from brain morphology in humans. Neuroimage 2009 Jul 9. [E-pub ahead of print].

Response Inhibition among Early Adolescents Prenatally Exposed to Tobacco: An fMRI Study

Children prenatally exposed to tobacco have been found to exhibit increased rates of behavior problems related to response inhibition deficits. The present study compared the brain function of tobacco-exposed and unexposed 12-year-olds during a Go/No-Go response inhibition task using an event-related functional MRI (fMRI) design. Prenatal alcohol exposure, neonatal medical problems, environmental risk, IQ, current environmental smoke exposure, and handedness were statistically controlled. Tobacco-exposed children showed greater activation in a relatively large and diverse set of regions, including left frontal, right occipital, and bilateral temporal and parietal regions. In contrast, children unexposed to tobacco showed activation in the cerebellum, which prior research has indicated is important for attention and motor preparation. The diversity of regions showing greater activation among tobacco-exposed children suggests that their brain function is characterized by an inefficient recruitment of regions required for response inhibition. Bennett DS, Mohamed FB, Carmody DP, Bendersky M, Patel S, Khorrami M, Faro SH, Lewis M. Response inhibition among early adolescents prenatally exposed to tobacco: An fMRI study. Neurotoxicol Teratol. 2009 Apr 5. [E-pub ahead of print].

Maternal Smoking During Pregnancy and Newborn Neurobehavior: Effects at 10 to 27 Days

Dr. Laura Stroud and her colleagues examined effects of maternal smoking during pregnancy on newborn neurobehavior at 10 to 27 days. Participants were 56 healthy infants (28 smoking-exposed, 28 unexposed) matched on maternal social class, age, and alcohol use. Maternal smoking during pregnancy was determined by maternal interview and maternal saliva cotinine. Postnatal smoke exposure was quantified by infant saliva cotinine. Infant neurobehavior was assessed through the NICU Network Neurobehavioral Scale. Smoking-exposed infants showed greater need for handling and worse self-regulation and trended toward greater excitability and arousal relative to matched, unexposed infants (all moderate effect sizes). In contrast to prior studies of days 0 to 5, no effects of smoking-exposure on signs of stress/abstinence or muscle tone emerged. In stratified, adjusted analyses, only effects on need for handling remained significant. Effects of maternal smoking during pregnancy at 10 to 27 days are subtle and consistent with increased need for external intervention and poorer self-regulation. Along with parenting deficits, these effects may represent early precursors for long-term adverse outcomes from maternal smoking during pregnancy. That signs of abstinence shown in prior studies of 0- to 5-day-old newborns did not emerge in older newborns provides further evidence for the possibility of a withdrawal process in exposed infants. Stroud LR, Paster RL, Papandonatos GD, Niaura R, Salisbury AL, Battle C, Lagasse LL, Lester B. Maternal smoking during pregnancy and newborn neurobehavior: Effects at 10 to 27 days. J Pediatr. 2009 Jan;154(1):10-16.

Planned Meetings

Publications

Staff Highlights

Grantee Honors

A Methodological Study of Maternal Recall of Smoking in Pregnancy

Retrospective recall of smoking during pregnancy is assumed to be substantially biased, but this has rarely been tested empirically. Dr. Lauren Wakschlag and her colleagues examined the validity of an interview-based retrospective recall more than a decade after pregnancy, in a cohort with repeated, multimethod characterization of pregnancy smoking (N = 245). Retrospective smoking patterns were examined in relation to prospective reported and biological estimates of overall and trimester-specific smoking status and intensity. Characteristics of women whose smoking status was misclassified by either prospective or retrospective measures were compared with women whose status was congruent for nonsmoking across timepoints. In general, sensitivity and specificity of recalled smoking were excellent relative to both prospective self-reported and cotinine-validated smoking status and trimester-specific intensity. However, measures were less congruent for amount smoked for women who recalled being heavy smokers. Further, retrospective measures captured some smokers not identified prospectively due to smoking that occurred prior to assessments. Women who would have been misclassified as nonsmokers based on either prospective or retrospective assessment differed significantly from congruently classified nonsmokers in a number of maternal, family, and neighborhood, but not child behavior, characteristics. When epidemiological studies of the impact of smoking in pregnancy use retrospective methods, misclassification may not be a significant problem if prenatal smoking is assessed in terms of the pattern across pregnancy. This type of interview-based recall of pregnancy smoking may be relatively accurate, although optimal measurement should combine retrospective and prospective self-report and biological assays, as each provide unique information and sources of error. Pickett KE, Kasza K, Biesecker G, Wright RJ, Wakschlag LS. Women who remember, women who do not: A methodological study of maternal recall of smoking in pregnancy. Nicotine Tob Res. 2009 Jul 28. [E-pub ahead of print].

Developmental Consequences of Prenatal Tobacco Exposure

This paper exhaustively reviews results from published, in press, and conference proceedings from 2007 and 2008 that link in-utero tobacco exposure to neurodevelopmental outcomes in exposed offspring. Prenatal tobacco exposure (PTE) affected speech processing, levels of irritability and hypertonicity, attention levels, ability to self-regulate, need to be handled, and response to novelty preference in infants. In early childhood, PTE effects were mostly behavioral outcomes including activity and inattention and externalizing behaviors, including conduct disorder and antisocial behavior. In adolescents, PTE predicted increased attention deficit hyperactivity disorder, modulation of the cerebral cortex and white matter structure, and nicotine addiction. Several studies found moderating effects with PTE and genetic susceptibilities including dopamine transporter, serotonergic synaptic function, and monoamine oxidase pathways. Other studies suggested that environmental and genetic factors might be more important than the direct teratological effects of PTE. The majority of studies reviewed were prospective and tobacco exposure was quantified biologically. Most demonstrated a direct association between PTE and neurodevelopmental outcomes. More work is needed to examine multifactorial influences. Effects of PTE on offspring appear to be moderated by genetic variability, neurobehavioral disinhibition, and sex. Cornelius MD, Day NL. Developmental consequences of prenatal tobacco exposure. Curr Opin Neurol. 2009 April;22(2):121-125.

Allelic Variation of Calsyntenin 2 (CLSTN2) Modulates the Impact of Developmental Tobacco Smoke Exposure on Mnemonic

Processing in Adolescents

Deficits in attention and mnemonic processing and to abnormal function of medial temporal lobe structures that support mnemonic processing have been linked to exposure to tobacco smoke during development. The purpose of this study was to test whether genetic variation may mediate individual differences in vulnerability to the effects of developmental exposure to tobacco smoke. The impact of allelic variation within CLSTN2 was examined in 101 adolescents who were systematically characterized for prenatal and adolescent exposure to tobacco smoke. While subjects performed an encoding and retrieval task, verbal and visuospatial memory was assessed and functional magnetic resonance imaging data were acquired. The results replicated prior findings of a beneficial effect of the CLSTN2 C allele on verbal memory. This beneficial effect was eliminated by adolescent exposure to tobacco smoke and was associated with increased activation of entorhinal/perirhinal cortex during early and delayed retrieval in CLSTN2 C allele carriers. These findings extend previous work demonstrating that calsyntenins play an essential role in learning and indicate that this role is modulated both by CLSTN2 genotype and, during adolescent development, by exposure to tobacco smoke. Jacobsen LK, Picciotto MR, Health CJ, Mencl WE, Gelernter J. Allelic variation of calsyntenin 2 (CLSTN2) modulates the impact of developmental tobacco smoke exposure on mnemonic processing in adolescents. Biol Psychiatry. 2009 Apr 15; 65(8):671-679.

Effects of Alcoholism Severity and Smoking on Executive Neurocognitive Function

Prior research has revealed neurocognitive deficits in chronic alcoholic men. The causes of these deficits may be due to the direct effects of alcohol toxicity; however, other factors that include pre-existing cognitive deficits, comorbid psychiatric disorders or other substances of abuse cannot be ruled out. Cigarette smoking is often comorbid with alcoholism, but the combined effects of smoking and alcohol toxicity have yet to be determined. The purpose of this study was to examine the effects of combined chronic alcoholism and chronic smoking on neuropsycho-logical measures of a broad range of executive measures including reaction-time. The sample was recruited from a community and consisted of 240 alcoholic and non-alcoholic men. The results revealed that both alcoholism and smoking are correlated negatively with executive function. However, alcoholism revealed a more generalized effect in that alcoholism severity did not predict executive function when IQ was included in the regression analyses. In contrast, chronic smoking was related to processing speed deficits, irrespective of IQ, suggesting the deficits caused by chronic smoking are more specific. The current results reinforce the importance of smoking when considering cognitive function in alcoholism. Glass JM, Buu A, Adams KM, Nigg JT, Puttler LI, Jester JM, Zucker RA. Effects of alcoholism severity and smoking on executive neurocognitive function. Addiction 2009 Jan; 104(1):38-48.

Heritability and a Genome-Wide Linkage Analysis of a Type II/B Cluster Construct for Cannabis Dependence in an American Indian Community

Prior research has indicated a moderate genetic influence on cannabis dependence. The investigators of the current study investigated whether it is possible to use hierarchical average linkage and K means-cluster analysis to subtype individuals with cannabis dependence into a dichotomous construct. Using a community sample of 606 American Indians, a genetic linkage analyses was utilized to also examine the heritability of this construct and its behavior. Ninety-one per cent of cannabis-dependent partici-pants fell into one of the two

subtypes: Type A/I cluster (n = 114, 56%) and Type B/II cluster (n = 70, 35%). Heritability was significant for the Type B/II cluster (versus no diagnosis) and evidence for linkage was found on chromosome 16 and on chromosome 19. Regions of interest for this phenotype were also located on chromosomes 14, 21, 22. Other studies have identified these same areas of the genome for drug dependence phenotypes. The findings of this study provide a useful approach to characterize heritable versus non-heritable subtypes of cannabis dependence. The results may have important implications in characterizing clinical course and in matching treatment strategies. Ehlers C, Gilder D, Gizer I, Wilhelmsen K. Heritability and a genome-wide linkage analysis of a type II/B cluster construct for cannabis dependence in an American Indian community. Addict Biol. 2009;3:338-348.

Cognitive Development and Lead Exposure in Poly-Drug Exposed Children

The impact of early postnatal lead exposure measured at age 4 on children's IQ and academic achievement at 11 years of age was examined. The sample consisted of 278 inner-city, primarily African American children who were polydrug exposed prenatally. Regression analyses indicated a linear effect of lead exposure on outcomes and no moderating effects of polydrug exposure. An IQ loss of about 4.1-5.4 Full Scale IQ points was estimated for each 10 microg/dL increase in blood lead level at ages 4, 9, and 11 years as a function of blood lead level at age 4. Decrements in scores on tests of non-verbal reasoning were consistently associated with higher lead levels at age 4, while verbal decrements became apparent only at age 11. Lower reading summary scores at 9 and 11 years were consistently associated with higher lead exposure, while decrements in mathematics were not apparent until 11 years. Subgroup analyses on children with blood lead levels <10 microg/dL showed detrimental lead effects even at the 5 microg/dL level, providing additional evidence of adverse effects occurring at blood lead levels below the current 10 microg/dL public health blood lead action level. Min MO, Singer LT, Kirchner HL, Minnes S, Short E, Hussain Z, Nelson S. Cognitive development and low-level lead exposure in poly-drug exposed children. Neurotoxicol Teratol. 2009 Jul-Aug;31(4):225-231.

Intrauterine Cocaine Exposure and Executive Functioning in Middle Childhood

This longitudinal study by Dr. Deborah Frank and her colleagues evaluated whether the level of intrauterine cocaine exposure (IUCE) or the interaction between IUCE and contextual variables was related during middle childhood to executive functioning, as assessed with the Stroop Color-Word and Rey Osterrieth Complex Figure tests. The Stroop Interference score measures verbal inhibitory control while the Rey Osterrieth Organizational score evaluates skills such as planning, organization and perception. Examiners assessed children at 9.5 and 11 years of age. Level of IUCE (Unexposed; Lighter, and Heavier) was documented by positive postpartum maternal reports and infant meconium assays. In covariate-controlled regressions, level of IUCE was not significantly associated with Stroop Interference or Rey Osterrieth Organization scores. However, in covariate controlled post-hoc tests comparing the "Heavier" exposed group to the combined "Lighter/ Unexposed" group, children in the Heavier group had significantly poorer Stroop Interference scores, but there was no significant group difference for Rey Osterrieth Organizational scores. Children's average Organization scores in "Unexposed", "Lighter," and "Heavier" exposed groups were well below the test norm means. Results of this study indicate that heavier IUCE may be associated with mild compromise on school-aged children's ability to inhibit prepotent verbal responses. Rose-Jacobs R, Waber D, Beeghly M, Cabral H, Appugleise D, Heeren T, Marani J, Frank DA. Intrauterine cocaine exposure and executive

functioning in middle childhood. Neurotoxicol Teratol. 2009 May-Jun;31(3):159-168.

Cocaine-Exposed Infant and Caregiver Behavior: Gender Differences

Prenatal cocaine exposure and the role of gender were evaluated by Dr. Michael Lewis and his colleagues using risk factor analyses to determine whether 6-month-old cocaine-exposed male infants demonstrated greater disruptions in infant-caregiver socioemotional interactions during a Still-Face test. Overall, non-cocaine-exposed infants spent more time looking at toys, compared with cocaine-exposed infants; nonexposed female infants spent more time scanning the environment, compared with nonexposed male infants. When female caregiver behavior during the Still-Face was evaluated, differences emerged in amount of time the caregiver spent vocalizing to the infant. She vocalized more to a cocaine-exposed infant compared with a nonexposed one; she reduced vocalizing more during the test if the cocaine-exposed infant was female. An exposure by gender interaction emerged in the amount of change in caregiver vocalizations; however, the overarching hypothesis that male cocaine-exposed infants are at higher risk than nonexposed male, nonexposed female, and cocaine-exposed female infants was not supported. Because this interaction was evident in this cohort at 24 months, future research is needed to determine at what age an interaction begins to emerge in this cohort. Lewis MW, Phillips G, Bowser M, DeLuca S, Johnson HL, Rosen TS. Cocaine-exposed infant behavior during still-face: Risk factor analyses. Am J Orthopsychiatry. 2009 Jan;79(1):60-70.

Prenatal Cocaine Exposure and Infant Cortisol Reactivity and Regulation

In these two studies by Dr. Rina Eiden, the role of prenatal cocaine exposure on infant hypothalamic-pituitary-adrenal axis activity, infant reactivity and regulation were examined at 7 months of infant age. Participants were 168 caregiver-infant dyads (87 cocaine exposed, 81 not cocaine exposed; 47% boys). In the first study, maternal behavior, caregiving instability, and infant growth and behavior were assessed and children's saliva was sampled before, during, and after standardized procedures designed to elicit emotional arousal. Results revealed cocaine-exposed infants had greater cortisol reactivity compared to non-cocaine-exposed infants. Infant gender and caregiving instability moderated this association. The findings support a dual hazard vulnerability model and have implications for evolutionary-developmental theories of individual differences in biological sensitivity to context. In the second study, it was hypothesized that cocaine exposed infants would display higher arousal or reactivity and lower regulation during a procedure designed to arouse anger/frustration. Results indicated that cocaine exposed infants were more reactive to increases in the level of stress from trial 1 to trial 2 but, unlike the control group infants, exhibited no change in the number of regulatory strategies as stress increased, Infant birth weight moderated the association between cocaine exposure and infant regulation; among cocaine exposed infants, those with lower birth weight displayed higher reactivity compared to those with higher birth weight. Contrary to expectations, there were no indirect effects between cocaine exposure and infant reactivity/ regulation via environmental risk, parenting, or birth weight. Results are supportive of a terato-logical model of prenatal cocaine exposure for infant reactivity/regulation in infancy. Eiden RD, Veira Y, Granger DA. Prenatal cocaine exposure and infant cortisol reactivity. Child Dev. 2009 Mar-Apr;80(2):528-543 and Eiden RD, McAuliffe S, Kachadourian L, Coles C, Colder C, Schuetze P. Effects of prenatal cocaine exposure on infant reactivity and regulation. Neurotoxicol Teratol. 2009 Jan-Feb;31(1):60-68.

ERP Study of Risk-Taking and the Feedback Negativity Response to Loss among Adolescents with Prenatal Drug Exposure

Dr. Linda Mayes and Dr. Carl Lejuez examined event-related brain potentials in a high-risk sample of 32 adolescents (50% Female) who were exposed to cocaine and other drugs prenatally. Adolescents were selected for extreme high- or low-risk behavior on the Balloon Analog Risk Task, a measure of real-world risk-taking propensity. The feedback error-related negativity (fERN), an event-related potential (ERP) that occurs when an expected reward does not occur, was examined in a game in which choices lead to monetary gains and losses with feedback delayed 1 or 2 s. Feedback type, feedback delay, risk status, and sex were all associated with fERN variability. Monetary feedback also elicited a P300-like component, moderated by delay and sex. Delaying reward feedback may provide a means for studying complementary functioning of dopamine and norepinephrine systems. Crowley MJ, Wu J, Crutcher C, Bailey CA, Lejuez CW, Mayes LC. Risk-taking and the feedback negativity response to loss among at-risk adolescents. Dev Neurosci. 2009;31(1-2):137-148.

Inhibitory Deficits in Children with Attention-Deficit/HyperactivityDisorder: Intentional versus Automatic Mechanisms of Attention

Prior research has shown that children with attention deficit hyperactivity disorder (ADHD) present with deficits of intentional inhibitory mechanisms; however, the literature is lacking on whether automatic (reflexively controlled) inhibitory mechanisms are impaired in these children. The present study compared deficits in intentionally and reflexively controlled inhibition of attention in two subtypes of children with ADHD. Fifty children with ADHD were classified into one of three subtypes: predominantly inattentive (ADHD/PI), combined (ADHD/C), and those children with ADHD/C who also met criteria for comorbid oppositional defiant disorder (ADHD/C + ODD). A countermanding task was used to examine a deficit of intentionally controlled inhibition and an inhibition of return (IOR) task was chosen to examine deficits in reflexively controlled inhibition. Compared to a group of 21 children without a diagnosis of ADHD, children with ADHD required more time to inhibit responses on the countermanding tasks and the subtypes did not differ. Children with ADHD/C and ADHD/C + ODD showed substantial impairment as evidenced by a complete absence of reflexive inhibition, whereas the children with ADHD/PI were considerably less impaired on this task. The findings indicate that distraction by external stimuli may be less related to the attention problems of children in the ADHD/PI subtype. Future research is needed that specifically examines the developmental course of automatic and intentional inhibitory control among both typical and at-risk populations in that these findings would have implications for assessing the clinical efficacy of treatments for ADHD. Fillmore M, Milich R, Lorch E. Inhibitory deficits in children with attention-deficit/ hyperactivity disorder: Intentional versus automatic mechanisms of attention. Dev and Psychopathol. 2009 Spring;21(2):539-554.

Increased Sensitivity to the Disinhibiting Effects of Alcohol in Adults with ADHD

Disinhibi-tory psychopathology is believed to play an important role in the development of drug abuse disorders. Individuals with attention deficit hyperactivity disorder (ADHD) are often characterized as having behavior that is undercontrolled. In order to better understand inhibitory control as it relates to substance abuse, Dr. Mark Fillmore and his colleagues at the University of Kentucky tested the sensitivity to alcohol in individuals who have established deficits in inhibitory control; adults with ADHD. The present study used a cued go/no-go task to measure inhibitory control in ten adults with ADHD with a

mean age of 23 years compared to the performance of twelve aged matched normal controls. Information was provided during the task to alert the subjects as to the probability that a go or no-go target would be presented. Given the known impairing effects alcohol has on inhibitory control, it was predicted that alcohol would produce even greater inhibitory impairment in individuals with preexisting deficits in behavioral control. The results revealed that when valid cues were used to aid a subjects' performance on the cued no-go task, controls did not demonstrate inhibitory failures. In contrast, alcohol impaired those with ADHD, regardless of cue condition (i.e. valid versus invalid). Further research is needed to better understand how the disinhibiting effects of alcohol are related to risky behavior while intoxicated. Weafer J, Fillmore M, Milich R. Increased sensitivity to the disinhibiting effects of alcohol in adults with ADHD. Exp Clin Psychopharmacol. 2009 April: 17(2):113-121.

Youth Living with HIV and Partner-Specific Risk for Secondary Transmission of HIV

Secondary transmission remains a significant concern among HIV-infected youth. Little is known, however, about how partner-specific sexual risk behaviors for the secondary transmission of HIV may differ between the 2 largest subgroups of HIV-positive youth, women-who-have-sex-with-men (WSM) and men-who-have-sex-with-men (MSM), During 2003-2004, a convenience sample of HIV-infected youth, 13 to 24 years of age, were recruited from 15 Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) clinical sites. Approximately 10 to 15 youth were recruited at each site. Participants completed an ACASI survey including questions about sex partners in the past year. Cross-sectional data analyses, including bivariate and multivariable regressions, using generalized estimating equations, were conducted during 2008 to compare recent partner-specific sexual risk behaviors between WSM and MSM. There were significant differences between the 2 groups in recent partner-specific sexual risk behaviors including: lower rates of condom use at last sex among WSM; a larger proportion of the sex partners of MSM reported as concurrent; and greater use of hard drugs at last sex by MSM and/or their partner. When measuring risk as a composite measure of sexual risk behaviors known to be associated with HIV transmission, both groups had high rates of risky behaviors. These data suggest that recent partner-specific sexual risk behaviors for HIV transmission are high among young infected MSM and WSM. These findings suggest the need to offer interventions to reduce the secondary transmission of HIV to all HIV-positive youth in care. However, differences in risk behaviors between young MSM and WSM support population-specific interventions. Jennings JM, Ellen JM, Deeds BG, Harris DR, Muenz LR, Barnes W, Lee SS, Auerswald CL, Adolescent Trials Network for HIV/AIDS Interventions. Youth living with HIV and partner-specific risk for the secondary transmission of HIV. Sex Transm Dis. 2009 Jul;36(7):439-444.

Risks for Non-adherence to Antiretroviral Therapy among HIV-Infected Youth

Adherence continues to be a major barrier to successful treatment with highly active antiretroviral therapy (HAART) for HIV-infected individuals. HIV-infected adolescents and young adults face a lifetime of treatment with HAART. Often, individuals who struggle with adherence to HAART face multiple barriers that impact on the success of any single modality intervention. The Adolescent Trials Network for HIV/AIDS Interventions (ATN) conducted a cross-sectional, observational study to determine the prevalence of personal barriers to adherence and to identify associations between these barriers in HIV-infected subjects aged 12 to 24. The ATN studied the following personal barriers to adherence: mental health barriers, high/low self-efficacy and outcome expectancy, and the presence of specific structural barriers. There were 396

subjects recruited from sites from the ATN or the Pediatric AIDS Clinical Trials Group, 148 of which self-identified as non-adherent. No significant differences were found between adherent and non-adherent subjects for the presence of mental health disorders. Adherence was significantly associated with all but one structural barrier. Both self-efficacy and outcome expectancy were higher among adherent versus non-adherent subjects. Grouping subjects according to low self-efficacy and outcome expectancy for adherence, adherence differed according to the presence or absence of mental health disorders and structural barriers. The data suggest that adolescents have significant rates of non-adherence and face multiple personal barriers. Rudy BJ, Murphy DA, Harris DR, Muenz L, Ellen J. Adolescent Trials Network for HIV/AIDS Interventions. Patient-related risks for non-adherence to antiretroviral therapy among HIV-infected youth in the United States: A study of prevalence and interactions. AIDS Patient Care STDS. 2009 Mar;23(3):185-194.

Transgender Female Youth and HIV Risk

This Adolescent Trials Network for HIV/AIDS Interventions (ATN) study examined the HIV risk behaviors and life experiences of 151 transgender female youth, ages 15-24, in Los Angeles and Chicago. Descriptive analyses and logistic regression modeling were used to identify life factors associated with ever having engaged in sex work. Sixty-seven percent of participants had ever engaged in sex work and 19% self-reported being HIV positive. Many factors were significantly associated with sex work for this sample population. A final multivariate logistic regression model found that lower education status, homelessness, use of street drugs, and perceived social support remained significantly associated with sex work when controlling for other factors. Findings highlight the complex HIV risk environment and suggest a need for sex work initiation research for transgender female youth. HIV prevention efforts for this population need to include broad-based approaches that take into account individual, social, and community-level factors relevant to the lives of transgender female youth. Wilson EC, Garofalo R, Harris RD, Herrick A, Martinez M, Martinez J, Belzer M. The Transgender Advisory Committee, The Adolescent Medicine Trials Network for HIV/AIDS Interventions. Transgender female youth and sex work: HIV risk and a comparison of life factors related to engagement in sex work. AIDS Behav. 2009 Feb 6. [E-pub ahead of print].

Recruitment Venues for At-Risk Young Males and Females from Urban Neighborhoods: Findings from the Adolescent Trials Network for HIV/AIDS Interventions

Finding and accessing members of youth subpopulations, such as young men who have sex with men (YMSM) of color or young females of color, for behavioral or disease surveillance or study recruitment, pose particular challenges. Venue-based sampling strategies--which hinge on where individuals congregate or "hang out" rather than where they live--appear to be effective alternatives. Methods used to identify venues focus on engaging members of social networks to learn where targeted populations congregate. However, it is not always clear if and how these methods differ according to gender, whether the youth accessed at a venue are actually from neighborhoods in which the venues are found, and whether the location of venues relative to neighborhoods of residence is different for young men and young women. This study by the Adolescent Trials Network for HIV/AIDS interventions (ATN) illustrates the gender differences in venue type and venue location where eligible youth study participants from high-risk neighborhoods could be accessed for HIV research across 15 research sites. The findings indicate that the study's method led to identifying venues where one quarter or more of the youth were eligible study participants and from the high-risk neighborhoods. Sites targeting young women of color had a higher proportion of eligible study participants who were also from the high-risk neighborhoods than sites

targeting YMSM. Clubs were most commonly identified by sites targeting YMSM as recruitment venues, whereas neighborhood-based service or commercial centers were more common venues for young women of color. This study reveals how venue-based recruitment strategies can be tailored and resources maximized by understanding the key differences in the types of venues preferred by males and females. Chutuape KS, Ziff M, Auerswald C, Castillo M, McFadden A, Ellen J, Adolescent Trials Network for HIV/AIDS Interventions. Examining differences in types and location of recruitment venues for young males and females from urban neighborhoods: Findings from a multi-site HIV prevention study. J Urban Health. 2009 Jan;86(1):31-42.

An HIV Prevention Protocol Reviewed at 15 National Sites: How do Ethics Committees Protect Communities?

This study examined whether ethics committees reviewing community-based participatory research concentrate on the protection of communities, in addition to individual participants, using data from 15 Adolescent Trials for HIV/AIDS Intervention (ATN) sites. Eighty-two ethics committee concerns related to consent (35%), protocol procedures (49%), data collection (17%), and HIPAA (6%) were identified. Concerns generally involved individual level subject issues; only 17% were related to community issues. To improve community-level protections in research, the ATN authors recommend that both ethics committee members and research staff receive education concerning protection and respect for communities, that a community member group be established to advise researchers throughout the planning and implementation of community-level studies and that local ethics committee boards include members with community-level experience. Deeds BG, Castillo M, Beason Z, Cunningham SD, Ellen JM, Peralta L and the Adolescent Trials Network for HIV/AIDS Interventions. An HIV Prevention Protocol Reviewed at 15 National Sites: How do ethics committees protect communities? J Empir Res Hum Res Ethics. 2009 Jun;3(2):77-86.

Clear and Independent Associations of Several HLA-DRB1 Alleles with Differential Antibody Responses to Hepatitis B Vaccination in Youth

To confirm and refine associations of human leukocyte antigen (HLA) genotypes with variable antibody (Ab) responses to hepatitis B vaccination, the Adolescent Trials Network for HIV/AIDS Interventions (ATN) analyzed 255 HIV-1 seropositive (HIV+) youth and 80 HIV-1 seronegatives (HIV-) enrolled into prospective studies. In univariate analyses that focused on HLA-DRB1, -DQA1, and -DQB1 alleles and haplotypes, the DRB1*03 allele group and DRB1*0701 were negatively associated with the responder phenotype. Collectively, DRB1*03 and DRB1*0701 were found in 42 out of 78 non-responders, 65 out of 160 medium responders, and 27 out of 97 high responders. Meanwhile, DRB1*08 was positively associated with the responder phenotype, mostly due to DRB1*0804. These immunogenetic relationships were all independent of non-genetic factors, including HIV-1 infection status and immunodeficiency. Alternative analyses confined to HIV+ youth or Hispanic youth led to similar findings. In contrast, analyses of more than 80 non-coding, single nucleotide polymorphisms within and beyond the three HLA class II genes revealed no clear associations. Overall, several HLA-DRB1 alleles were major predictors of differential Ab responses to hepatitis B vaccination in youth, suggesting that T-helper cell-dependent pathways mediated through HLA class II antigen presentation are critical to effective immune response to recombinant vaccines. Li Y, Ni R, Song W, Shao W, Shrestha S, Ahmad S, Cunningham CK, Flynn PM, Kapogiannis BG, Wilson CM, Tang J. Clear and independent associations of several HLA-DRB1 alleles with differential antibody responses to Hepatitis B vaccination in youth. Hum Genet. 2009 Jul 14. [E-pub ahead of print].

Short-Cycle Therapy in Adolescents after Continuous Therapy with Established Viral Suppression: The Impact on Viral Load Suppression

This was a proof-of-principle study to evaluate the impact of short cycle therapy (SCT; 4 days on/3 days off) in HIV+ adolescents and young adults with good viral suppression on a protease inhibitor-based antiretroviral regimen. Subjects were recruited by the Adolescent Trials Network for HIV/AIDS Interventions (ATN) and the Pediatric AIDS Clinical Trials Group. Subjects were infected either through perinatal/early childhood transmission or later via risk behaviors. All subjects were required to have at least 6 months of documented viral suppression below 400 copies/ml plus a preentry value below 200 copies/ml and an entry CD4+ T cell count above 350 cells/mm3. Of the 32 subjects enrolled, 37.5% had confirmed viral load rebound >400 copies, with 56% coming off for any reason. The majority of subjects resuppressed when placed back onto continuous therapy using the same agents. Although no difference was found in virologic rebound rates between the early and later transmission groups, those infected early in life had higher rates of coming off SCT for any reason. There was no impact of SCT on the CD4+ T cell counts in those who remained on study or those who came off SCT for any reason. Subjects demonstrated good adherence to the SCT regimen. This study suggests that further evaluation of SCT may be warranted in some groups of adolescents and young adults infected with HIV. Rudy BJ, Sleasman J, Kapogiannis B, Wilson CM, Bethel J, Serchuck L, Ahmad S, Cunningham CK, Adolescent Trials Network for HIV/AIDS Interventions. Short-cycle therapy in adolescents after continuous therapy with established viral suppression: The impact on viral load suppression. AIDS Res Hum Retroviruses. 2009 Jun;25(6):555-561.

Director's Report to the National Advisory Council on Drug Abuse - September, 2009

Research Findings - Clinical Neuroscience Research

Brain Response to Drug Prevention Messages

Dr. Daniel Langleben and colleagues at University of Pennsylvania used functional brain imaging to resolve a fundamental debate regarding the processing of information in drug prevention messages. Some communication theories propose that higher message sensation value (MSV), a measure of sensory intensity of audio, visual, and content features of an ad, brings increased attention and cognitive processing, leading to higher ad impact. Others argue that the attention-intensive format result in reduced processing of PSA content and reduced overall effectiveness. In this study, fMRI and recognition memory measures were used to compare high and low MSV, anti-tobacco PSAs and neutral videos. In a short-delay, forced-choice memory test, frames extracted from PSAs were recognized more accurately than frames extracted from the neutral videos (NV). Frames from the low MSV PSAs were better recognized than frames from the high MSV PSAs. The accuracy of recognition of PSA frames was positively correlated with the prefrontal and temporal, and negatively correlated with the occipital cortex activation. The low MSV PSAs were associated with greater prefrontal and temporal activation than the high MSV PSAs. The high MSV PSAs produced greater activation primarily in the occipital cortex. These findings support the "dual processing" and "limited capacity" theories of communication that postulate a competition between ad's content and format for the viewers' cognitive resources and suggest that the "attention-grabbing" high MSV format could impede the learning and retention of an ad. These findings also demonstrate the potential value of using neuroimaging in the design and evaluation of mass media public health communications. Langleben D, Loughead J, Ruparel K, Hakun J, Busch-Winokur S, Holloway M, Strasser A, Cappella J, Lerman C. Reduced prefrontal and temporal processing and recall of high "sensation value" ads. Neuroimage. 2009 May 15;46(1):219-225.

Hijacking the Attentional Network

Dr. Daniel Weissman and colleagues at the University of Michigan used fMRI to investigate whether consciously perceived, irrelevant instructional cues can hijack the attentional network, leading to an enhancement of the perceptual processing of irrelevant stimuli. Using a cross-modal attentional cueing task during fMRI scans, they found that such irrelevant cues increased activity in frontal regions that control attention and sensory cortices that underlie the perceptual processing of task-irrelevant stimuli. Furthermore, in left ventrolateral (but not dorsolateral) prefrontal regions, the magnitude of this increased activity varies with whether an irrelevant instructional cue is presented simultaneously with (versus after) a relevant instructional cue. These findings show that consciously perceived, irrelevant instructional cues

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can activate inappropriate task objectives in working memory, resulting in a hijacking of the attentional network. Moreover, they reveal different time courses of hijacking effects in ventrolateral and dorsolateral prefrontal regions, consistent with models in which these regions make distinct contributions to cognitive control. These results may provide a foundation for understanding the ability of drug-related stimuli to capture attention. Moore KS, Porter CB, Weissman DH. Made you look! Consciously perceived, irrelevant instructional cues can hijack the attentional network. Neuroimage. 2009 May 15;46(1):270-279.

Enhanced Choice for Viewing Cocaine Pictures in Cocaine Addiction

Dr. Rita Goldstein and colleagues at Brookhaven National Laboratories used two newly designed laboratory tasks with pictures to investigate the bias people with cocaine use disorders (CUD) have to choose cocaine over nondrug rewards. Choice for viewing cocaine, pleasant, unpleasant, or neutral pictures, under explicit contingencies (choice made between two fully visible side-by-side images) and under more implicit contingencies (selections made between pictures hidden under flipped-over cards), was examined in 20 CUD and 20 matched healthy control subjects. Subjects also provided self-reported ratings of each picture's pleasantness and arousal. Under both contingencies, CUD subjects chose to view more cocaine pictures than control subjects, group differences that were not fully explained by the self-reported picture ratings. Healthy control subjects avoided viewing cocaine pictures as frequently as, or even more than, unpleasant pictures. In contrast, CUD subjects' choice for viewing cocaine pictures exceeded choice for viewing unpleasant pictures (but did not exceed choice for viewing pleasant pictures, in contrast to their self-reported ratings). CUD subjects with the most cocaine viewing selections, even when directly compared with selections of the pleasant pictures, also reported the most frequent recent cocaine use. Enhanced drug-related choice in cocaine addiction can be demonstrated even for nonpharmacologic (pictorial) stimuli. This choice, which is modulated by alternative stimuli, partly transcends self-reports (possibly indicative of a discordance in cocaine addiction between self-reports and objective behavior) to provide an objective marker of addiction severity. Moeller S, Maloney T, Parvaz M, Dunning J, Alia-Klein N, Woicik P, Hajcak G, Telang F, Wang G, Volkow N, Goldstein R. Enhanced choice for viewing cocaine pictures in cocaine addiction. Biological Psychiatry. 2009 Jul;66(2):169-176.

Cannabinoid Receptor 1 (CNR1) Gene Haplotype Linkages to Cocaine Disorder in European-Americans Verified in Multiple Sites

Joel Gelernter and colleagues aimed to replicate the association between CNR1 and cocaine disorder (CD) in four independent samples. They examined eight markers across the 45 kb CNR1 region and four large samples, family-based European-American (EA) sample (n=734), case-control EA sample (n=862), family-based African-American (AA) sample (n=834) and case-control AA sample (n=619) . They reported that the interaction between two independent CNR1 variants significantly increased risk for CD in the EA family and EA case-control samples. EA subjects with SNP3(G+) and SNP8(T)/T had higher risk to develop CD than those EA subjects with the other genotypes for these two SNPs. The SNP3(G)-SNP8(T) haplotype also showed significant association with CD in the EA case-control sample. In the AA family sample, SNP8(T)/T significantly conferred higher risk for CD. The authors conclude that two independent CNR1 variants have significant interaction effects on risk for CD in EAs; they may also have effects on risk for CD in AAs. Zuo L, Kranzler HR, Luo X, Yang BZ, Weiss R, Brady K, Poling J, Farrer L, Gelernter J. Interaction between two independent CNR1 variants increases risk for cocaine dependence in European Americans: A replication study in family-based sample and

population-based sample. Neuropsychopharmacology. 2009 May;34(6):1504-1513.

Relationship Between Cerebral Morphology and the Expression of Dopamine Receptors in Humans

Drs. David Zald, Ron Cowan and colleagues at Vanderbilt University examined the association between cerebral morphology and dopamine receptor distribution in 45 healthy subjects using structural MRI and PET scanning with the D-2/D-3 ligand [F-18] fallypride. Using voxel-based morphometry, grey matter volume and density images were correlated with binding potential images on a voxel-by-voxel basis. Associations between cerebral morphology and DA receptor binding potential were also examined for selected regions-of-interest (ROIs) after spatial normalization. They found that cerebral morphology, particularly grey matter density, correlated with [F-18] fallypride binding potential in a regionally specific manner. Voxel-wise analyses indicated that grey matter volume and density positively correlated with DA receptor binding throughout the midbrain, including the substantia nigra. Positive correlations were observed in medial cortical areas, including anterior cingulate and medial prefrontal cortex, and circumscribed regions of the temporal, frontal, and parietal lobes. ROI analyses revealed significant positive correlations between DA receptor binding potential and cerebral morphology in the caudate, thalamus, and amygdala. Overall, grey matter density appeared more strongly correlated with DA receptor binding potential than grey matter volume. Woodward N, Zald D, Ding Z, Riccardi P, Ansari M, Baldwin R, Cowan R, Li R, Kessler R. Cerebral morphology and dopamine D-2/D-3 receptor distribution in humans: A combined [F-18] fallypride and voxel-based morphometry study. Neuroimage. 2009 May 15;46(1):31-38.

Dopamine D1 Receptor Availability and Cocaine Self-Administration in Humans

Dr. Diane Martinez and colleagues at Columbia University used PET ligand imaging to determine D(1) receptor availability in human cocaine-dependent (CD) subjects and matched healthy controls (HCs). In addition, the study determined the association between D(1) receptor availability and cocaine-seeking behavior. Twenty-five CD subjects and 23 matched HCs were scanned using the D1 Dopamine receptor PET radiotracer [(11)C]NNC 112. During separate cocaine self-administration sessions, CD volunteers were given the choice to self-administer cocaine (0, 6, and 12 mg) or to receive a monetary voucher worth $5. D(1) receptor availability was measured in the limbic, associative, and sensorimotor striatum in addition to cortical brain regions. No difference in D(1) receptor availability was seen between the two groups. A negative association was seen between D(1) receptor binding potential in the limbic striatum and the choice for the 6 mg dose of cocaine. These results do not support the hypothesis that cocaine dependence is associated with a reduction in D(1) receptor availability in the striatum. However, within the CD subjects, low D(1) receptor availability in the ventral striatum was associated with the choice to self-administer cocaine, suggesting that low D(1) receptor availability may be associated with an increased risk of relapse in cocaine dependence. Martinez D, Slifstein M, Narendran R, Foltin RW, Broft A, Hwang D, Perez A, Abi-Dargham A, Fischman MW, Kleber HD, Laruelle M. Dopamine D1 Receptors in Cocaine Dependence Measured with PET and the Choice to Self-Administer Cocaine. Neuropsychopharmacology. 2009 Jan 28;34(7):1774-1782.

Acute Dopamine Agonist Impairs Reinforcement Learning in Humans

Diane Santesso and colleagues at Harvard demonstrated that a single low dose of a D2/D3 agonist (pramipexole) impaired reward learning in healthy subjects performing a probabilistic reward task, ostensibly by activating DA autoreceptors to reduce phasic DA bursts linked to instrumental learning. This group recently extended these behavioral findings using event-related potentials and computational modeling. Compared with the placebo group, participants receiving pramipexole showed increased feedback-related negativity to probabilistic rewards and decreased activation in dorsal anterior cingulate regions previously implicated in integrating reinforcement history over time. Additionally, findings of blunted reward learning in participants receiving pramipexole were simulated by reduced presynaptic DA signaling in response to reward in a neural network model of striatal-cortical function. These preliminary findings offer important insights on the role of phasic DA signals on reinforcement learning in humans and provide initial evidence regarding the spatiotemporal dynamics of brain mechanisms underlying these processes. Santesso DL, Evins AE, Frank MJ, Schetter EC, Bogdan R, Pizzagalli DA. Single dose of a dopamine agonist impairs reinforcement learning in humans: Evidence from event-related potentials and computational modeling of striatal-cortical function. Hum Brain Mapp. 2009 Jul;30(7):1963-1976.

Brain Response to Drug Words

Dr. Rita Goldstein and colleagues at Brookhaven National Laboratories used functional brain imaging to test the hypothesis that drug-related words can trigger activation in the mesencephalon, where dopaminergic cells are located. Fifteen individuals with cocaine use disorders and 15 demographically matched healthy control subjects pressed buttons in response to drug-related versus neutral words during fMRI scanning. Drug words, but not neutral words, activated the mesencephalon in the cocaine users only. In the cocaine users only, these increased drug-related mesencephalic responses were associated with enhanced verbal fluency specifically for drug words. The correlation between the brief verbal fluency test, which can be easily administered (crucial for clinical studies), and fMRI cue reactivity could be used as a biomarker of neurobiological changes in addiction. Goldstein R, Tomasi D, Alia-Klein N, Carrillo J, Maloney T, Woicik P, Wang R, Telang F, Volkow N. Dopaminergic response to drug words in cocaine addiction. Journal of Neuroscience. 2009 May;29(18):6001-6006.

Effects of Insula Damage on Risky Decision-Making

Dr. Antoine Bechara and colleagues at the University of Southern California used a risky decision-making task with lesion patients and healthy controls to investigate whether the insula is necessary for advantageous decision-making under risk, specifically decisions involving uncertain gains and losses. Compared to healthy controls, insula lesion patients showed an altered decision-making pattern in domains involving both risky gains and risky losses. Specifically, insula damage was associated with insensitivity to differences in expected value between choice options. Additionally, patients made significantly fewer risky choices than healthy adults in the gain domain. In conjunction with earlier findings, these results suggest that risky decision-making is dependent on the integrity of a neural circuit that includes several brain regions known to be critical for the experience and expression of emotions, namely the insula, amygdala, and ventromedial prefrontal cortex. However, each neural region seems to provide a distinct contribution to the overall process of decision-making. Weller J, Levin I, Shiv B, Bechara A. The effects of insula damage on decision-making for risky gains and losses. Social Neuroscience. 2009;4(4):347-358.

Differential Processing of Risk and Reward in Medial Prefrontal

Cortex

Antoine Bechara and associates at University of Southern California used functional magnetic resonance imaging (fMRI) and investigated functional specificity in the medial prefrontal cortex regarding decision-making. Using a task that simulates risky decisions, they found that the dorsal region of the medial prefrontal cortex (MPFC) was activated whenever a risky decision was made, but the degree of this activity across subjects was negatively correlated with their risk preference. In contrast, the ventral MPFC was parametrically modulated by the received gain/loss, and the activation in this region was positively correlated with an individual's risk preference. These results demonstrate that the dorsal and ventral MPFC convey different decision signals (i.e., aversion to uncertainty vs. approach to rewarding outcomes), where the relative strengths of these signals determine behavioral decisions involving risk and uncertainty. Xue G, Lu Z, Levin I, Weller J, Li X, Bechara A. Functional dissociations of risk and reward processing in the medial prefrontal cortex. Cerebral Cortex. 2009 May;19(5):1019-1027.

Cocaine Abusers Show Abnormalities in Dorsal Striatum Recruitment by Motor Tasks

Colleen Hanlon and colleagues at Wake Forest scanned non-treatment seeking chronic cocaine users and matched controls during performance of two finger-sequencing paradigms that differentially activate the caudate nucleus (internally-guided) and the putamen (externally-guided) interleaved with blocks of rest. They reported significant deficits in sensorimotor control in cocaine users for both motor tasks, with the most severe impairments present during internally-guided movements dependent on the caudate nucleus. Cocaine users lacked the typical functional segregation observed in the dorsal striatum of the control subjects. The total percent signal change in the dorsal striatum was not significantly different between the groups, but cocaine users activated significantly less contralateral caudate and putamen for internally-guided versus externally-guided movements, respectively. These data provide clear evidence that chronic cocaine users have significant motor performance deficits that are accompanied by altered processing within the dorsal striatum. These data suggest the effects of cocaine extend beyond the confines of the motivational domains of the ventral striatum. Hanlon CA, Wesley MJ, Porrino LJ. Loss of functional specificity in the dorsal striatum of chronic cocaine users. Drug Alcohol Depend. 2009 Jun 1;102(1-3):88-94.

Cocaine Abusers Show Blunted Anterior Cingulate Cortex Recruitment by an Emotional Conflict Task

Rita Goldstein and colleagues at Brookhaven compared individuals with current cocaine use disorders (CUD) and matched healthy controls as they underwent functional magnetic resonance imaging during performance of a rewarded drug cue-reactivity task previously shown to engage the anterior cingulate cortex (ACC). Despite the lack of group differences in task performance, individuals with CUD showed more ACC hypoactivations. Nevertheless, intensity of emotional salience contributed to the results: (1) CUD individuals with the largest rostroventral ACC [Brodmann Area (BA) 10, 11, implicated in default brain function] hypoactivations to the most salient task condition (drug words during the highest available monetary reward) and had the least task-induced cocaine craving; (2) CUD individuals with the largest caudal-dorsal ACC (BA 32) hypoactivations especially to the least salient task condition (neutral words with no reward) had the most frequent current cocaine use; and (3) responses to the most salient task condition in both these ACC major subdivisions were positively intercorrelated in the controls only. ACC hypoactivations in drug users, therefore, cannot be attributed to task difficulty or disengagement.

Nevertheless, emotional salience modulates ACC responses in proportion to drug use severity. Interventions to strengthen ACC reactivity or interconnectivity may be beneficial in enhancing top-down monitoring and emotion regulation as a strategy to reduce impulsive and compulsive behavior in addiction. Goldstein RZ, Alia-Klein N, Tomasi D, Carrillo JH, Maloney T, Woicik PA, Wang R, Telang F, Volkow ND. Anterior cingulate cortex hypoactivations to an emotionally salient task in cocaine addiction. Proc Natl Acad Sci U S A. 2009 Jun 9;106(23):9453-9458.

Conflict Effects Without Conflict in the Anterior Cingulate

Dr. Joshua Brown of Indiana University used fMRI to test a computational model of anterior cingulate function that accounts for error likelihood effects, risk prediction effects, and how individual differences in conflict and error likelihood effects vary with trait differences in risk aversion. This study tested the prediction that apparent conflict effects in anterior cingulate cortex (ACC) may result in part from an increasing number of simultaneously active responses, regardless of whether or not the cued responses are mutually incompatible. In Experiment 1, the model prediction was tested with a modification of the Eriksen flanker task, in which some task conditions require two otherwise mutually incompatible responses to be generated simultaneously. In that case, the two response processes are no longer in conflict with each other. The results showed small but significant medial prefrontal cortex (PFC) effects in the incongruent vs. congruent contrast, despite the absence of response conflict, consistent with the multiple response effect of the model. Nonetheless, actual response conflict led to greater ACC activation, suggesting that conflict effects are specific to particular task contexts. In Experiment 2, results from a change signal task suggested that the context dependence of conflict signals does not depend on error likelihood effects. Instead, inputs to ACC may reflect complex and task specific representations of motor acts, such as bimanual responses. Overall, the results suggest the existence of a richer set of motor signals monitored by medial PFC and are consistent with distinct effects of multiple responses, conflict, and error likelihood in medial PFC. These results form the foundation for a better understanding of anterior cingulate dysfunction that has been repeatedly demonstrated in substance abusers. Brown JW. Conflict effects without conflict in anterior cingulate cortex: Multiple response effects and context specific representations. Neuroimage. 2009 Aug;47(1):334-341.

Brain Serotonin Transporter Binding in Former Users of MDMA ('Ecstasy')

Dr. Ronald Cowan at Vanderbilt University used PET ligand brain imaging to determine the status of brain serotonin transporters (SERT) in a group of abstinent MDMA (3,4-methylenedioxy-methamphet-amine) users using [C-11]DASB. Subjects were former MDMA users, polydrug users who had never taken MDMA and controls who reported no history of illicit drug use. There was no significant difference in the binding potential of [C-11]DASB between the groups in any of the brain regions examined. To the extent that [C-11]DASB binding provides an index of the integrity of serotonin axons, these findings suggest that MDMA use may not result in long-term damage to axons when used recreationally in humans. Selvaraj S, Hoshi R, Bhagwagar Z, Murthy N, Hinz R, Cowen P, Curran H, Grasby P. Brain serotonin transporter binding in former users of MDMA ('Ecstasy'). British Journal of Psychiatry. 2009 Apr;194(4):355-359.

Ecstasy Users Require Increased Recruitment of the Basal Ganglia to Accomplish a Motor Performance Task

Dr. Ronald Cowan and colleagues at Vanderbilt used functional brain imaging to determine if MDMA users would show altered activation in motor system brain regions. This hypothesis was based on prior research demonstrating that MDMA (Ecstasy) produces changes in serotonin (5-hydroxytryptamine) terminals, and 5-HT innervates cortical and subcortical brain regions mediating motor function. They used functional magnetic resonance imaging (fMRI) to assay motor task performance-associated brain activation changes in MDMA and non-MDMA users. Fourteen MDMA users and 10 controls performed an event-related motor tapping task during fMRI. Regions of interest analyses were used to measure percent signal change (PSC) and percent activated voxels (PAV) in bilateral motor cortex, sensory cortex, supplementary motor area (SMA), caudate, putamen, pallidum and thalamus. Statistical Parametric Mapping 5 was used to measure brain activation via three methods: T-maps, PSC and PAV. There was no statistically significant difference in reaction time between the two groups. For the Tap 4 condition, MDMA users had more activation than controls in the right SMA for T-score, PSC and PAV. Lifetime episodes of MDMA use were positively correlated with PSC for the Tap 4 condition on the right for putamen and pallidum and with PAV in the right motor and sensory cortex and bilateral thalamus. In conclusion, group differences in the right SMA and positive dose-response association between lifetime exposure to MDMA and signal magnitude and extent were found in several brain regions. This is consistent with MDMA-induced alterations in basal ganglia-thalamocortical circuit neurophysiology and is potentially secondary to neurotoxic effects on 5-HT signaling. Further studies examining behavioral correlates and the specific neurophysiological basis of the observed findings are warranted. Karageorgiou J, Dietrich MS, Charboneau EJ, Woodward ND, Blackford JU, Salomon RM, Cowan RL. Prior MDMA (Ecstasy) use is associated with increased basal ganglia-thalamocortical circuit activation during motor task performance in humans: An fMRI study. Neuroimage. 2009 Jul 1;46(3):817-826.

Stress and HPA Axis Activity Interact to Create Risk For Drug Abuse

Uma Rao and colleagues at UT-Southwestern Medical Center examined whether hypothalamic-pituitary-adrenal (HPA) activity and stressful life experiences are related to the development of substance use disorder in depressed and nondepressed adolescents, and whether substance use disorder predicts a worsening course of depression. They measured urinary free cortisol for 3 nights in adolescents with no prior history of substance use disorder and collected information on recent stressful life experiences. They followed these adolescents for up to 5 years to assess the onset of substance use disorder, course of depression, and stressful experiences. They found that elevated cortisol was associated with onset of substance use disorder and that stressful life experiences moderated this relationship. Cortisol and stress accounted for the effects of a history or risk of depression on the development of substance use disorder. Substance use disorder was associated with higher frequency of subsequent depressive episodes. They concluded that higher cortisol prior to the onset of substance use disorder may indicate vulnerability to substance use disorder and that stressful experiences increase the risk for substance use disorder in such vulnerable youth. The high prevalence of substance use disorders in depressed individuals may be explained, in part, by high levels of stress and increased HPA activity. Rao U, Hammen CL, Poland RE. Mechanisms underlying the comorbidity between depressive and addictive disorders in adolescents: Interactions between stress and HPA activity. Am J Psychiatry. 2009 Mar;166(3):361-369.

PET Studies of Nicotine Effects on Dopamine Turnover

Dr. Edward Domino and colleagues at University of Michigan used PET ligand imaging using L-[beta-(11)C]DOPA to determine the effects of nicotine on

regional brain dopamine (DA) utilization. Eight young nonhuman primates were given nicotine in small doses for 9 days to produce minimal dependence. On the tenth day, PET measurements were repeated before and after nicotine administration. PET studies were done in habituated, trained, and fully conscious animals. Acute nicotine administered as a bolus plus infusion for 30 min in similar doses to maintain a steady-state level for 30 min did not affect the utilization rate constant in dorsal or ventral striatum as measured by L-[beta-(11)C]DOPA. When animals were given nicotine repeatedly after overnight nicotine abstinence, DA utilization was reduced. A subsequent nicotine dose normalized utilization to slightly above control levels. Changes in ventral striatum were similar to those in dorsal striatum. The reduced rate of utilization demonstrated with L-[beta-(11)C]DOPA after overnight nicotine abstinence and its reversal by nicotine the next day provides an important PET measure of brain nicotine dependence and withdrawal. Domino EF, Tsukada H, Harada N. Positron emission tomographic measure of brain dopamine dependence to nicotine as a model of drugs of abuse. Psychopharmacology. (Berl.). 2009 May;204(1):149-153.

Nicotine Receptor Changes During Acute and Prolonged Cigarette Abstinence

Dr. Kelly Cosgrove and colleagues at Yale School of Medicine used SPECT ligand imaging to characterizes changes in beta(2)* nicotinic acetylcholine receptor (-nAChR) availability during acute and prolonged abstinence from tobacco smoking. They also investigated how changes in beta(2)*-nAChR availability related to clinical features of tobacco smoking. Participants were tobacco smokers (n = 19) and an age-matched nonsmoker comparison group (n = 20). Tobacco smokers participated in up to 4 single-photon emission computed tomography (SPECT) scans during abstinence at 1 day, and 1, 2 , 4, and 6 to 12 weeks. Age-matched nonsmokers participated in a single SPECT scan. Compared with nonsmokers, beta(2)*-nAChR availability in the striatum, cortex, and cerebellum of smokers was not different at 1 day of abstinence, was significantly higher at 1 week of abstinence, and was not different at 4 or at 6 to 12 weeks of abstinence. In smokers, beta(2)*-nAChR availability was significantly lower in the cortex and cerebellum at 6 to 12 weeks compared with 1 week of abstinence. In addition, cerebellar beta(2)*-nAChR availability at 4 weeks of abstinence was positively correlated with craving on the day of the SPECT scan. These data suggest that higher beta(2)*-nAChR availability persists up to 1 month of abstinence and normalizes to nonsmoker levels by 6 to 12 weeks of abstinence from tobacco smoking. These marked and persistent changes in beta(2)*-nAChR availability may contribute to difficulties with tobacco cessation. Cosgrove KP, Batis J, Bois F, Maciejewski PK, Esterlis I, Kloczynski T, Stiklus S, Krishnan-Sarin S, O'Malley S, Perry E, Tamagnan G, Seibyl JP, Staley JK. Beta2-Nicotinic acetylcholine receptor availability during acute and prolonged abstinence from tobacco smoking. Arch. Gen. Psychiatry. 2009 June;66(6):666-676.

PET Study of Dopaminergic Activity in Depressed Smokers

Dr. Ursula Busto and colleagues at the University of Toronto used PET ligand imaging to assess changes in Dopamine D2 receptors in healthy controls and unmedicated patients with current depression with and without current tobacco dependence. Over a single study day, 2 [(11)C]-raclopride positron emission tomography scans were taken at baseline and 2 h following oral d-amphetamine 30 mg. Striatal [(11)C]-raclopride binding potential was measured before and after d-amphetamine administration. Depressed smokers had a lower baseline [(11)C]-raclopride binding potential compared with both control non-smokers and depressed non-smokers. There was an effect of smoking status on amphetamine-induced change in [(11)C]-raclopride binding potential, but no effect of depression. This may be due to a floor effect because

of the low BP at baseline. Depressed subjects reported a significant increase of positive mood after d-amphetamine administration compared with controls (depressed smokers vs. control smokers, and depressed non-smokers vs. controls). Comorbid major depression and tobacco dependence therefore exacerbates tobacco dependence related decreases in d-amphetamine-induced changes in [(11)C]-raclopride binding potential. These results suggest the presence of an altered dopamine system in comorbid patients. Dopaminergic activity in depressed smokers: A positron emission tomography study. Busto UE, Redden L, Mayberg H, Kapur S, Houle S, Zawertailo LA. Synapse. 2009 Aug;63(8):681-689.

Tobacco Abstinence and Brain Responses to Smoking Cues

Dr. Joseph McClernon used fMRI to evaluate the effect of 24-h smoking abstinence on brain responses to smoking-related cues. Adult smokers (N=18) underwent fMRI scanning following smoking as usual (satiated condition) and following 24-h abstinence (abstinent condition). During scanning, they viewed blocks of photographic smoking and control cues. Following abstinence, greater activation was found in response to smoking cues compared to control cues in parietal, frontal, occipital, and central cortical regions and in dorsal striatum (putamen) and thalamus. In contrast, no smoking cue greater than control cue activations were observed following smoking as usual. Direct comparisons between conditions (satiated vs. abstinent) showed greater brain reactivity in response to smoking cues following abstinence. In addition, positive correlations between pre-scan craving in the abstinent condition and smoking cue activation were observed in right dorsomedial prefrontal cortex (dmPFC) including superior frontal gyrus, anterior cingulate gyrus, and supplementary motor area. These findings indicate that smoking abstinence significantly potentiates neural responses to smoking-related cues in brain regions subserving visual sensory processing, attention, and action planning. Moreover, greater abstinence-induced craving was significantly correlated with increased smoking cue activation in dmPFC areas involved in action planning and decision making. These findings suggest that drug abstinence can increase the salience of conditioned cues, which is consistent with incentive-motivation models of addiction. McClernon FJ, Kozink RV, Lutz AM, Rose JE. 24-h smoking abstinence potentiates fMRI-BOLD activation to smoking cues in cerebral cortex and dorsal striatum. Psychopharmacology (Berl). 2009 May;204(1):25-35.

Childhood Experience of ADHD May Predict Adulthood Smoking Behavior

In this large sample study involving over 1100 new mothers, Dr. Kollins and colleagues found self-reported personal history of childhood experience of attention-deficit/hyperactivity disorder (ADHD) associated with five cigarette smoking-related outcomes in adulthood. Women with a history of intermediate levels of hyperactive-impulsive symptoms during their childhood reported smoking more cigarettes per day than women with low or high levels of childhood ADHD symptoms. Past history of hyperactive-impulsive symptoms is linked with the number of cigarettes smoked per day during the pregnancy period, and inattentive behavior was similarly linked to the number of cigarettes currently smoked per day. Childhood inattentive behaviors were predictive of an earlier age onset of smoking only when hyperactive-impulsive behaviors were low, with a stronger association for Black women compared to White females. These findings represent a potential, indirect means through which women with even a moderate childhood history of ADHD symptomatology may create circumstances that compromise the health and well-being of their own children. Willoughby MT, Kollins SH, McClernon FJ; Family Life Investigative Group. Association between smoking and retrospectively reported attention-deficit/hyperactivity disorder symptoms in a large sample of new mothers. Nicotine Tob Res. 2009 Mar;11(3):313-322.

Postnatal Parental Smoking Effects on the Development of ADHD Symptoms and Oppositional Behavior in Children

In addition to genetic determinants, environmental factors such as mothers who smoke during pregnancy are linked to child ADHD. In this study Dr. Kollins and colleagues evaluated the effects of postnatal maternal smoking on ADHD symptoms that were divided into inattentive and hyperactive-impulsive domains and oppositional behavior in a group of 5- to 12-year-old children, ascertained on the basis of an ADHD diagnosis, and their healthy siblings, while controlling for a range of important covariates, including prenatal smoking and self-reported maternal ADHD symptoms. Parents and teachers were asked to complete the DSM-IV ADHD evaluation as outcome of the disruptive behaviors. The study found that postnatal smoke exposure (from either mothers or fathers) was associated with higher ratings of ADHD and oppositional defiant disorder. The findings suggest both prenatal and postnatal maternal smoking impact ADHD development in children. Kollins SH, Garrett ME, McClernon FJ, Lachiewicz AM, Morrissey-Kane E, FitzGerald D, Collins AL, Anastopoulos AD, Ashley-Koch AE. Effects of postnatal parental smoking on parent and teacher ratings of ADHD and oppositional symptoms. J Nerv Ment Dis. 2009 Jun;197(6):442-449.

Risk/Reward Decision-Making in Schizophrenia: The Influence of Tobacco Smoking

Dr. Marc Potenza and his colleagues at Yale University examined the relationship between the deficits in cognitive functioning, and the mixed results previously found from studies of risk/reward decision-making, shown in individuals with schizophrenia. Thirty-two smokers with schizophrenia, ten non-smokers with schizophrenia, nine non-psychiatric non-smokers and ten non-psychiatric smokers were administered computerized versions of the Iowa Gambling Task (IGT) and the Wisconsin Card Sorting Task (WCST). Smokers were allowed to smoke ad libitum during designated breaks in order to prevent deprivation. Subjects with schizophrenia performed significantly worse than non-psychiatric controls on both the IGT and the WCST, and performance on these tasks was significantly correlated across subject groups. Among women with schizo-phrenia, smokers performed significantly better than non-smokers on the IGT. Individuals with schizophrenia performed worse than controls on the IGT, suggesting impairments in risk/reward decision-making. Correlations between IGT and WCST performance suggest a shared element underlying task performance, such as a deficit in set-shifting or perseverance. Further research is needed to establish the relationship between cigarette smoking and IGT performance in schizophrenia. Risk/reward decision-making in schizophrenia: A preliminary examination of the influence of tobacco smoking and relationship to Wisconsin Card Sorting Task performance. Yip SW, Sacco KA, George TP, Potenza MN. Schizophr Res. 2009 May;110(1-3):156-164.

Relationship of Nicotine Dependence, Subsyndromal and Pathological Gambling, and Other Psychiatric Disorders

Dr. Marc Potenza and his colleagues at Yale University used nationally representative data from the National Epidemiologic Survey on Alcohol and Related Conditions to examine the influence of DSM-IV nicotine dependence on the association between pathological gambling severities and other psychiatric disorders. Face-to-face interviews were conducted with 43,093 adults living in households and group-quarters in the United States. The main outcome measure was the co-occurrence of current nicotine dependence and Axis I and II disorders and severity of gambling based on the 10 inclusionary diagnostic criteria for pathological gambling. Among non-nicotine-dependent respondents,

increasing gambling severity was associated with greater psychopathology for the majority of Axis I and II disorders. This pattern was not uniformly observed among nicotine-dependent subjects. Significant nicotine-by-gambling-group interactions were observed for multiple Axis I and II disorders. All significant interactions involved stronger associations between gambling and psychopathology in the non-nicotine-dependent group. Additional research is needed to examine specific prevention and treatment for individuals with problem/pathological gambling with and without nicotine dependence. Grant JE, Desai RA, Potenza MN. Relationship of nicotine dependence, subsyndromal and pathological gambling, and other psychiatric disorders: Data from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2009 Mar;70(3):334-343.

Hybrid SVM-GLM Approach for fMRI Data Analysis

Dr. Ze Wang at University of Pennsylvania developed an optimized method for exploratory analysis of fMRI data. Hypothesis-driven fMRI data analysis methods, represented by the conventional general linear model (GLM), have a strictly defined statistical framework for assessing regionally specific activations but require assumptions about the shape of hemodynamic brain responses that may not be accurate. Exploratory methods, like the support vector machine (SVM), are independent of prior hemodynamic response function (HRF), but generally lack a statistical inference framework. To take the advantages of both kinds of methods, this study describes a composite approach through combining conventional GLM with SVM. This hybrid SVM-GLM concept is to use the power of SVM to obtain a data-derived reference function and enter it into the conventional GLM for statistical inference. The data-derived reference function was extracted from the SVM classifier using a new temporal profile extraction method. In simulations with synthetic fMRI data, SVM-GLM demonstrated a better sensitivity and specificity of performance for detecting the synthetic activations, as compared to the conventional GLM. With real fMRI data, SVM-GLM showed better sensitivity than regular GLM for detecting the sensorimotor activations. Wang Z. A hybrid SVM-GLM approach for fMRI data analysis. Neuroimage. 2009 Jul 1;46(3):608-615.

Selective Dopamine D3 Radioligand

Dr. Robert Mach and colleagues at Washington University performed in vitro evaluation of radiolabled 4-(Dimethylamino)-N-(4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)benzamide (WC-10), a N-phenyl piperazine analog, which has been shown to have high affinity and selectivity for dopamine D(3) receptors versus dopamine D(2) receptors. In this study, WC-10 was radiolabeled with tritium and [(3)H]WC-10 binding to genetically cloned dopamine D(2L) and D(3) receptors was evaluated in vitro. [(3)H]WC-10 binds with a 66-fold higher affinity to human D(3) than D(2L) receptor. However, [(3)H]WC-10 binds to rat Sf9 rD(3) receptors with a lower affinity than it binds to human HEK D(3) receptors and binds with a higher affinity to rat Sf9 rD(2L) receptors. The pharmacologic profiles of a series of dopaminergic drugs for inhibiting the binding of [(3)H]WC-10 to D(3) receptors was in agreement with previously reported data. In vitro autoradiography studies of rat and non-human primate brains show that [(3)H]WC-10 labeled D(3) sites in the striatal region. Xu J, Chu W, Tu Z, Jones LA, Luedtke RR, Perlmutter JS, Mintun MA, Mach RH. [(3)H]4-(Dimethylamino)-N-[4-(4-(2-methoxyphenyl)piperazin- 1-yl)butyl]benzamide, a selective radioligand for dopamine D(3) receptors. I. In vitro characterization. Synapse. 2009 Sep;63(9):717-728.

Neuronal Mechanism of Anger Regulation

Dr. Alia-Klein and colleagues at Brookhaven National Laboratories examined the influence of the monoamine oxidase A (MAOA) gene (low vs. high transcription variants) on brain response to the emotional word ÒNoÓ (as an emphatic prohibition of behavior) and in relationship to trait anger reactivity and control. Orbitofrontal activation did not differ as a function of the genotype. Instead, carriers of the low-MAOA genotype had reduced left middle frontal gyrus activation to ÒNoÓ compared with the high variant. Furthermore, left amygdala and posterior thalamic activation to ÒNoÓ increased with anger reactivity only for carriers of the low-MAOA genotype. Thus, decreased middle frontal response to No and the unique amygdala/thalamus association pattern in this group with anger reactivity but not anger control may underlie the vulnerability to aggression in carriers of the low-MAOA genotype. Alia-Klein N, Goldstein R, Tomasi D, Woicik P, Moeller S, Williams B, Craig I, Telang F, Biegon A, Wang G, Fowler J, Volkow N. Neural Mechanisms of Anger Regulation as a Function of Genetic Risk for Violence. Emotion. 2009 Jun;9(3):385-396.

Acute Topiramate Exerts Biphasic Dose-Dependent Effects on Laboratory Aggression in Subjects at High Risk for Violent Behavior

Gerry Moeller and colleagues at UT-Houston examined the acute effects of topiramate on aggression using a laboratory model of human aggression in individuals on parole/probation and with an Axis-II personality disorder and/or a substance use disorder. Subjects received 100, 200, 300, and 400 mg in an ascending sequence, with intervening placebo doses. Topiramate produced an inverted U-shaped dose response curve, with increases in aggression peaking at 200 mg and a modest decrease at 400 mg. The pattern in aggressive responding is consistent with non-human aggression studies of GABA-A modulators. Acute topiramate doses >400 mg may have anti-aggressive effects, but dose levels in the 200-300 mg range may produce increases in aggression and side effects. Lane SD, Gowin JL, Green CE, Steinberg JL, Moeller FG, Cherek DR. Acute topiramate differentially affects human aggressive responding at low vs. moderate doses in subjects with histories of substance abuse and antisocial behavior. Pharmacol Biochem Behav. 2009 Apr;92(2):357-362.

White Matter Integrity Predicts Delay Discounting Behavior in 9- to 23-Year-Olds

Dr. Kelvin Lim and colleagues at the University of Minnesota used structural brain imaging to determine whether rapid prefrontal lobe development during adolescence would be associated with alterations in delayed discounting, a measure of impulsivity related to the risk of substance abuse. Healthy participants, aged 9-23, completed a delay discounting task assessing the extent to which the value of a monetary reward declines as the delay to its receipt increases. Diffusion tensor imaging (DTI) was used to evaluate how individual differences in delay discounting relate to variation in fractional anisotropy (FA) and mean diffusivity (MD). The analyses revealed a number of clusters where less impulsive performance on the delay discounting task was associated with higher FA and lower MD. The clusters were located primarily in bilateral frontal and temporal lobes and were localized within white matter tracts, including portions of the inferior and superior longitudinal fasciculi, anterior thalamic radiation, uncinate fasciculus, inferior fronto-occipital fasciculus, corticospinal tract, and splenium of the corpus callosum. FA increased and MD decreased with age in the majority of these regions. Some, but not all, of the discounting/DTI associations remained significant after controlling for age. Olson E, Collins P, Hooper C, Muetzel R, Lim K, Luciana M. White matter integrity predicts delay discounting behavior in 9-to 23-year-olds: A diffusion tensor imaging study. Journal of Cognitive Neuroscience. 2009 Jul;21(7):1406-1421.

Twin Study Suggests Lack of Adolescent Drug Use Specificity in Conferring Risk for Adult Drug Abuse

Past studies have demonstrated the existence of a shared etiology across substances of abuse; however, few have tested developmental models using longitudinal data. Palmer, Crowley and colleagues utilized the longitudinal Colorado twin sample of 1733 respondents to assess: 1) the rates of multiple substance use and disorders at each developmental stage, and the likelihood of a substance use disorder (SUD; i.e., abuse or dependence) diagnosis in young adulthood based on adolescent drug involvement, 2) whether the pattern of multiple substance use and disorders and likelihood ratios across substances support a model of generalized risk, and 3) whether the ranked magnitudes of substance-specific risk match the addiction liability ranking. This analysis provided further evidence that substance use and SUDs are developmental phenomena, which increase from adolescence to young adulthood with few and inconsistent gender differences. Moreover, they reported that adolescents and young adults are not specialized users, but rather tend to use or abuse multiple substances increasingly with age. Risk analyses indicated that progression toward a SUD for any substance was increased with prior involvement with any substances during adolescence. Despite the high prevalence of alcohol use, tobacco posed the greatest substance-specific risk for developing subsequent problems. These data also confirm either a generalized risk or correlated risk factors for early onset substance use and subsequent development of SUDs. Palmer RH, Young SE, Hopfer CJ, Corley RP, Stallings MC, Crowley TJ, Hewitt JK. Developmental epidemiology of drug use and abuse in adolescence and young adulthood: Evidence of generalized risk. Drug Alcohol Depend. 2009 Jun 1;102(1-3):78-87.

Therapeutic Dose of Zolpidem Reduces Thalamic GABA in Healthy Volunteers

Dr. Stephanie Licata and her colleagues at the McLean Hospital/Harvard Medical School evaluated the effects of acute administration of zolpidem on levels of GABA, glutamate, glutamine, and other brain metabolites using magnetic resonance spectroscopy (MRS). Proton MRS ((1)H MRS) was employed to measure the effects of zolpidem on brain chemistry. Participants underwent scanning following acute oral administration of a therapeutic dose of zolpidem (10 mg) in a within-subject, single-blind, placebo-controlled, single-visit study. In addition to neurochemical measurements from single voxels within the anterior cingulate (ACC) and thalamus, a series of questionnaires was administered periodically throughout the experimental session to assess subjective mood states. Zolpidem reduced GABA levels in the thalamus, but not the ACC. There were no treatment effects with respect to other metabolite levels. Self-reported ratings of "dizzy," "nauseous," "confused," and "bad effects" were increased relative to placebo, as were ratings on the sedation/intoxication and psychotomimetic/dysphoria scales of the Addiction Research Center Inventory. Moreover, there was a significant correlation between the decrease in GABA and "dizzy." Zolpidem engendered primarily dysphoric-like effects and the correlation between reduced thalamic GABA and "dizzy" may be a function of zolpidem's interaction with alpha1GABA(A) receptors in the cerebellum, projecting through the vestibular system to the thalamus. Licata SC, Jensen JE, Penetar DM, Prescot AP, Lukas SE, Renshaw PF. A therapeutic dose of zolpidem reduces thalamic GABA in healthy volunteers: A proton MRS study at 4 T. Psychopharmacology (Berl). 2009 May;203(4):819-829.

Behavioral and Neurological Foundations for the Moral and Legal Implications of Intoxication, Addictive Behaviors and Disinhibition

Dr. Marc Potenza and his colleagues at Yale University addressed how disinhibition and addictive behaviors are related and carry moral implications. Both typically involve diminished consideration of negative consequences, which may result in harm to oneself or others. Disinhibition may occur on state and trait levels, and addictive substances may elicit disinhibitory states, particularly when intoxication is reached. Data suggest that trait disinhibition and addictions may be conceptualized as involving misdirected motivation with underlying biological bases including genetic factors, alterations in neurotransmitter systems and differences in regional brain function. The influences of intoxication on the brain share similarities with cognitive impairments in individuals with chronic substance abuse and those with trait disinhibition related to frontal lobe injuries. These findings raise questions about volitional impairment and morality. Although impaired volition related to disinhibition and addictive behaviors has been studied from multiple perspectives, additional research is needed to further characterize mechanisms of impairment. Such findings may have important implications in multiple legal and psychiatric domains. Leeman RF, Grant JE, Potenza MN. Behavioral and neurological foundations for the moral and legal implications of intoxication, addictive behaviors and disinhibition. Behav Sci Law. 2009;27(2):237-259.

Poor Blood-Brain Barrier Penetration of Drugs Continues to Obstruct Effective Anti-HIV Treatment

HIV Protease inhibitors have been the leading effective agent in anti-HIV treatment. A major obstacle for effectively managing the ongoing HIV replication in the brain, with associated neural complications, is that protein inhibitors may not penetrate the central nervous system to achieve therapeutic concentrations. In a multicenter, observational cohort study, Dr. Igor Grant and his group determined the effective penetration of atazanavir, one of the most frequently prescribed antiretrovirals, into cerebrospinal fluid (CSF). It was found that atazanavir concentrations in CSF samples were highly variable and were often 100-fold lower than plasma concentrations. The concomitant administration of ritonavir competitively binding to the host metabolizing enzyme cytochrome P450-3A4, boosted and doubled plasma concentration of atazanavir. However, it failed to significantly elevate CSF concentrations of atazanavir. CSF concentrations were less than one percent of plasma concentration. The study concludes that atazanavir may not protect against HIV replication in the CSF. Best BM, Letendre SL, Brigid E, Clifford DB, Collier AC, Gelman BB, McArthur JC, McCutchan JA, Simpson DM, Ellis R, Capparelli EV, Grant I; CHARTER Group. Low atazanavir concentrations in cerebrospinal fluid. AIDS. 2009 Jan 2;23(1):83-87.

Beta-Adrenergic Activity as a Biomarker for Severity of Chronic, Clinical Pain?

In patients with fibromyalgia syndrome (FMS) and temporomandibular disorder (TMD), stress and pain may chronically enhance sympathetic activity, altering cardiovascular responses and worsening pain. In this study, Dr. Girdler and colleagues examined the association of beta-adrenergic activity and clinical pain responses. The data suggested that beta-adrenergic tone is higher in patients under the influence of these painful episodes than in control patients. With the challenges of experimental stress (e.g. postural alteration, speech and ischemic pain), greater changes in beta-adrenergic activity, including heart rate, blood pressure, and total vascular resistance, was evident in these patients, along with lowered levels of epinephrine and norepinephrine. The beta-antagonist propranolol reversed these symptoms but changes in blood pressure, CO and total vascular resistance persisted. The number of painful body sites and ratings of total clinical pain were also significantly lower after beta-blockade versus placebo tests. These findings indicate that both FMS and

TMD may involve dysregulation of beta-adrenergic activity that contributes to altered cardiovascular and catecholamine responses and to the severity of clinical pain. Light KC, Bragdon EE, Grewen KM, Brownley KA, Girdler SS, Maixner W. Adrenergic dysregulation and pain with and without acute beta-blockade in women with fibromyalgia and temporomandibular disorder. J Pain. 2009 May;10(5):542-552.

Higher Sensitivity to Heat Pain, but Not Cold Pain in Patients under Opioid Therapy

Preclinical studies suggest that opioid exposure may induce a paradoxical decrease in the nociceptive threshold, commonly referred to as opioid-induced hyperalgesia. In this study, Dr. Jianren Mao addressed its clinical implications and significance in chronic pain management. Patients with chronic pain and under sustained opioid therapy displayed higher sensitivity to heat pain and exacerbated experimental hyperalgesia (pain windup upon temporal summation of the second pain to thermal stimulation) in comparison to those with no history of opioid use. In contrast, no changes in cold-induced pain or warm sensation were observed. The patients requiring higher doses of opioid for daily pain management were more sensitive to pain and suffered from more severe hyperalgesia, indicating that higher vulnerability to pain and hyperalgesia under quanti-tative thermal testing can be characteristic of subjects with sustained ongoing opioid therapy. The data suggest that quantitative thermal testing may be a useful tool in the clinical assessment of opioid-induced hyperalgesia. Chen L, Malarick C, Seefeld L, Wang S, Houghton M, Mao J. Altered quantitative sensory testing outcome in subjects with opioid therapy. Pain. 2009 May;143(1-2):65-70.

A Potential Marker for Identification of Individuals at Risk for Opioid Medication Misuse

Dr. Ajay Wasan examined the relationship between self-reported cravings for prescription medication and subsequent opioid misuse among chronic pain patients who were prescribed opioids for pain. Six hundred thirteen patients taking opioid medication for chronic noncancer pain were asked to scale how often they have felt a craving for their medication. All participants completed a series of baseline questionnaires. After 6 months the participants were administered the Prescription Drug Use Questionnaire, a structured prescription drug use interview, and submitted a urine sample for toxicology assessment. Their treating physicians also completed a substance misuse behavior checklist (Prescription Opioid Therapy Questionnaire). The study revealed that about 55 percent of participants reported that they never felt a craving for their medication, whereas 45 percent reported some degree of craving their medication. Those who reported craving their medication were significantly more often male, unmarried, had lower scores on social desirability, and had been prescribed opioids for a longer time than those who did not report similar cravings. At a 6-month follow-up, those who reported craving their medication showed higher scores on the Prescription Drug Use Questionnaire, had a higher incidence of physician-rated aberrant drug behavior on the Prescription Opioid Therapy Questionnaire, showed a higher frequency of abnormal urine toxicology screens, and more often had a positive Aberrant Drug Behavior Index. These results suggest that self-reported craving is a potential marker for identification of those at risk for opioid medication misuse. Wasan AD, Butler SF, Budman SH, Fernandez K, Weiss RD, Greenfield SF, Jamison RN. Does report of craving opioid medication predict aberrant drug behavior among chronic pain patients? Clin J Pain. 2009 Mar-Apr;25(3):193-198.

Psychiatric Comorbidity is Associated with Diminished Pain Relief

Comorbid psychopath-ology is an important predictor of poor outcomes in many types of back or neck pain treatments. In this study, Dr. Ajay Wasan explored whether high levels of psychopathology are predictive of pain relief after medial branch block injections in the lumbar or cervical spine. The Low Psychopath-ology (LP) group reported a mean improvement in pain after one month treatment, while the average pain score was worse in High Psychopathology group. Using an analysis of covariance, no baseline demographic, social, or medical variables were significant predictors of pain improvement, nor did they mitigate the effect of psychopathology on the outcome. It was concluded that psychiatric comorbidity is associated with diminished pain relief. Wasan AD, Jamison RN, Pham L, Tipirneni N, Nedeljkovic SS, Katz JN. Psychopathology predicts the outcome of medial branch blocks with corticosteroid for chronic axial low back or cervical pain: A prospective cohort study. BMC Musculoskelet Disord. 2009 Feb 16;10:22.

Neural Bases of Empathic Accuracy

Dr. Kevin Ochsner and colleagues at Columbia University used a functional imaging paradigm to test the hypothesis that an accurate understanding of another's emotions should depend on affective, motor, and/or higher cognitive brain regions. Using fMRI in healthy subjects, empathically accurate, as compared with inaccurate, judgments depended on (i) structures within the human mirror neuron system thought to be involved in shared sensorimotor representations, and (ii) regions implicated in mental state attribution, the superior temporal sulcus and medial prefrontal cortex. These data demonstrate that activity in these two sets of brain regions tracks with the accuracy of attributions made about another's internal emotional state. Taken together, these results provide both an experimental approach and theoretical insights for studying empathy and its dysfunction, such as between drug abusers and therapists. Zaki J, Weber J, Bolger N, Ochsner K. The neural bases of empathic accuracy. Proc. Natl. Acad. Sci. U.S.A. 2009 Jul;106(27):11382-11387.

Brain Responses to AnotherÕs Mistakes

Dr. Mathew Shane and colleagues at the Mind Institute at the University of New Mexico used fMRI to determine the functional role of specific brain areas activated when viewing another personÕs mistakes. Previous work identified several regions, including inferior parietal cortex and rostral/ventral anterior cinguli (r/vACC), that show unique sensitivity to the observation of another's errors. The current results found that participants' level of self-reported perspective-taking (but not empathic concern) correlated with fMRI signal changes in inferior parietal cortex (IPC), while participants' level of self-reported empathic concern (but not perspective taking) correlated with fMRI signal changes in r/vACC. This functional dissociation provides strong evidence for separate roles for IPC and r/vACC in the processing of observed errors. IPC may foster a sense of agency by distinguishing self- from other-performed actions; r/vACC may, in turn, promote a more contextually-mediated understanding of the other's failed goal-attainment. These studies provide a foundation for investigating how social interactions may influence drug use, such as seeing positive or negative consequences of drug use by peers. Shane M, Stevens M, Harenski C, Kiehl K. Double dissociation between perspective-taking and empathic-concern as predictors of hemodynamic response to another's mistakes. Social Cognitive and Affective Neuroscience. 2009 Jun;4(2):111-118.

Director's Report to the National Advisory Council on Drug Abuse - September, 2009

Research Findings - Epidemiology and Etiology Research

Effect of Early Versus Deferred Antiretroviral Therapy for HIV on Survival

The optimal time for the initiation of antiretroviral (ARV) therapy for asymptomatic individuals with HIV infection is uncertain. For this study, researchers conducted two parallel analyses involving a total of 17,517 asymptomatic individuals with HIV infection in the U.S. and Canada who received medical care during the period 1996 through 2005. None of the participants had undergone previous ARV therapy. In each group, they stratified individuals according to the CD4+ count (351 to 500 cells per cubic millimeter or >500 cells per cubic millimeter) at the initiation of ARV therapy. In each group, they compared the relative risk of death for those who initiated therapy when the CD4+ count was above each of the two thresholds of interest (early-therapy group) with that of those who deferred therapy until the CD4+ count fell below these thresholds (deferred-therapy group). In the first analysis, which involved 8,362 subjects, 2,084 (25%) initiated therapy at a CD4+ count of 351 to 500 cells per cubic millimeter, and 6,278 (75%) deferred therapy. After adjustment for calendar year, cohort, and demographic and clinical characteristics, among persons in the deferred-therapy group there was an increase in the risk of death of 69%, as compared with that in the early-therapy group (relative risk in the deferred-therapy group, 1.69; 95% confidence interval [CI], 1.26 to 2.26; P<0.001). In the second analysis involving 9,155 subjects, 2,220 (24%) initiated therapy at a CD4+ count of more than 500 cells per cubic millimeter and 6,935 (76%) deferred therapy. Among those in the deferred-therapy group, there was an increase in the risk of death of 94% (relative risk, 1.94; 95% CI, 1.37 to 2.79; P<0.001). These findings show that early initiation of ARV therapy before the CD4+ count fell below two prespecified thresholds significantly improved survival, as compared with deferred therapy. Kitahata M, Gange S, Abraham A, Merriman B, Saag M, Justice A, et al., Effect of early versus deferred antiretroviral therapy for HIV on survival. N Engl J Med. 2009; 360(18):1815-1826.

Genetics of Nicotine Dependence (NICSNP) in an Adoption Sample

Nicotine dependence results from a complex interplay of genetic and environmental factors. Over the past several years, a large number of studies have been performed to identify distinct gene loci containing genetic vulnerability to nicotine dependence. Two of the most prominent studies were conducted by the Collaborative Study of the Genetics of Nicotine Dependence (NICSNP) Consortium using both candidate gene and high-density association approaches. In this publication, the investigators attempted to confirm and extend the most significant findings from the high-density association study and the candidate gene study using the behavioral and genetic resources of the

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Staff Highlights

Grantee Honors

Iowa Adoption Studies (N= 516); phenotypic data were drawn from follow up interviews conducted between 199 and the present. Mean age of males and females were 47 and 45 respectively. The investigators found evidence that genetic variation at CHRNA1, CHRNA2, CHRNA7, and CHRNB1 alters susceptibility to nicotine dependence, but did not replicate any of the most significant single nucleotide polymorphism associations from the NICSNP high-density association study. Further examination of the NICSNP findings in other population samples is indicated. Philibert R, Todorov A, Andersen A, Hollenbeck N, Gunter T, Heath A, Madden P. Examination of the Nicotine Dependence (NICSNP) Consortium findings in the Iowa Adoption Studies Population. Nicotine Tob Res. 2009;11(3):286-292.

Genetic Influences on Young Black Women Using Drugs

This study assessed overlap in heritable and environmental influences on the timing of initiation for alcohol, cigarettes, and cannabis in African-American women, using a sample of 462 female twins (100 monozygotic and 131 dizygotic pairs) from wave 5 (begun in 2005) or wave 4 (begun in 2002) of the Missouri Adolescent Female Twin Study. Mean age at the time of interview was 25.1 years. Ages at first use of alcohol, cigarettes, and cannabis were gathered in diagnostic interviews administered over the telephone. Standard genetic analyses were conducted with substance use initiation variables categorized as never, late, and early onset. Variance in the timing of first use was attributable in large part to genetic sources: 44% for alcohol, 62% for cigarettes, and 77% for cannabis. Genetic correlations across substances ranged from 0.25 to 0.70. Shared environmental influences were modest for alcohol (10%) and absent for cigarettes and cannabis. Findings contrast with reports from earlier studies based on primarily Caucasian samples, which have suggested a substantial role for shared environment on substance use initiation when measured as lifetime use. By characterize-ing onset as timing of first use, this study may be tapping a separate construct. Differences in findings may also reflect a distinct etiological pathway for substance use initiation in African-American women that could not be detected in previous studies. Sartor C, Agrawal A, Lynskey M, Bucholz K, Madden P, Heath A. Common genetic influences on the timing of first use for alcohol, cigarettes, and cannabis in young African-American women. Drug Alc Dep. 2009;102(1-3):49-55.

Longitudinal Community Plasma HIV-1 RNA Concentrations and Incidence of HIV-1 Among Injecting Drug Users: Prospective Cohort Study

Researchers examined the relationship between plasma HIV-1 RNA concentrations in the community and HIV incidence among injecting drug users. They used data from a prospective cohort study of injection drug users (IDUs) living in an inner-city community of Vancouver, Canada. The IDU, with and without HIV, were followed up every six months between 1 May 1996 and 30 June 2007. Estimated community plasma HIV-1 RNA was measured in the six months before each HIV negative participant's follow-up visit as well as associated HIV incidence. Among 622 IDU with HIV, 12,435 measurements of plasma HIV-1 RNA were obtained. Among 1429 injecting drug users without HIV, there were 155 HIV seroconversions, resulting in an incidence density of 2.49 (95% confidence interval 2.09 to 2.88) per 100 person years. In a Cox model that adjusted for unsafe sexual behaviors and sharing used syringes, the estimated community plasma HIV-1 RNA concentration remained independently associated with the time to HIV seroconversion (hazard ratio 3.32 (1.82 to 6.08, P<0.001), per log(10) increase). When the follow-up period was limited to observations after 1 January 1988 (when the median plasma HIV RNA concentration was <20 000 copies/ml), the median viral load was no longer statistically associated with HIV incidence (1.70 (0.79 to 3.67, P=0.175), per log (10) increase). A longitudinal measure of community plasma

HIV-1 RNA concentration was correlated with the community HIV incidence rate and predicted HIV incidence independent of unsafe sexual behaviors and sharing used syringes. These findings have importance for informing both HIV prevention and treatment interventions. Wood E, Kerr T, Marshall B, Li K, Zhang R, Hogg R, Harrigan P, Montaner J. Longitudinal community plasma HIV-1 RNA concentrations and incidence o HIV-1 among injecting drug users: prospective cohort study. BMJ. 2009;338:1191-1195.

Features of Men With Anabolic-Androgenic Steroid Dependence: A Comparison With Nondependent AAS Users and With AAS Nonusers

The authors note that anabolic-androgenic steroid (AAS) dependence has been a recognized syndrome for some 20 years, but remains poorly understood. To better understand this syndrome, this study evaluated three groups of experienced male weightlifters: (1) men reporting no history of AAS use (N=72); (2) nondependent anabolic-androgenic steroid (AAS) users reporting no history of AAS dependence (N=42); and (3) men meeting adapted DSM-IV criteria for current or past AAS dependence (N=20). Data assessed include demographic indices, lifetime history of psychiatric disorders by the Structured Clinical Interview for DSM-IV, variables related to AAS use, and results from drug tests of urine and hair. Analysis revealed that nondependent AAS users showed no significant differences from AAS nonusers on any variable assessed. Dependent AAS users, however, differed substantially from both other groups on many measures. Notably, they reported a more frequent history of conduct disorder than nondependent AAS users (odds ratio [95% CI]: 8.0 [1.7, 38.0]) or AAS nonusers (13.1 [2.8, 60.4]) and a much higher lifetime prevalence of opioid abuse and dependence than either comparison group (odds ratios 6.3 [1.2, 34.5] and 18.6 [3.0, 116.8], respectively). Men who exhibited AAS dependence, unlike nondependent AAS users or AAS nonusers, showed a distinctive pattern of comorbid psychopathology, overlapping with that of individuals with other forms of substance dependence. AAS dependence showed a particularly strong association with opioid dependence. The authors note that this observation recalls recent animal data suggesting similarities in AAS and opioid brain reward mechanisms. The study findings provide support for the existence of AAS dependence and suggest that individuals with AAS dependence and individuals with "classical" substance dependence may possibly harbor similar underlying biological and neuropsychological vulnerabilities. Kanayama G, Hudson J, Pope H. Features of men with anabolic-androgenic steroid dependence: A comparison with nondependent AAS users and with AAS nonusers. Drug Alcohol Depend. 2009;102(1-3):130-137.

Elevated HIV Risk Behavior Among Recently Incarcerated Injection Drug Users In A Canadian Setting: A Longitudinal Analysis

While incarceration has consistently been associated with a higher risk of HIV infection for individuals who use injection drugs (IDU), the effect of incarceration on the post-release risk environment remains poorly described. Researchers sought to assess the impact of incarceration on risk factors for HIV infection after release from prison in a sample of active IDU in Vancouver, Canada. Using a prospective cohort of community-recruited IDU followed from May 1, 1996 to November 30, 2005, they examined contingency tables and performed linear growth curve analyses to assess changes in the prevalence of independent risk factors for HIV infection from before to after a period of incarceration among participants reporting incarceration and a matched control group. Of the 1603 participants followed-up over the study period, 147 (9.2%) were eligible for an analysis of post-incarceration risk behaviors and 742 (46.3%) were used as matched controls. Significant differences were found in one or both groups for the prevalence of frequent cocaine injection, requiring

help injecting, binge drug use, residence in the HIV outbreak epicenter, sex-trade participation, and syringe sharing (all $p < 0.05$) after incarceration. In linear growth curve adjusted for age, gender and ethnicity, syringe sharing was significantly more common in those recently released from prison ($p = 0.03$) than in the control group. In a sample of Canadian IDU, any effect of incarceration was observed on the prevalence of several behaviors that are risk factors for HIV infection, including intensity of drug use or participation in the sex trade. However, those recently released from prison were more likely to report syringe sharing than those in a matched control group. Milloy M, Buxton J, Wood E, Li K, Montaner J, Kerr T. Elevated HIV risk behavior among recently incarcerated injection drug users in a Canadian setting: A longitudinal analysis. BMC Public Health. 2009;9:156-163.

Measuring the Risk for Substance Abuse Disorders

The inability to quantify the risk for disorders, such as substance use disorders (SUD), hinders etiology research and the development of targeted and effective interventions. Based on the concept of common transmissible liability to SUD related to illicit drugs, a method enabling quantification of this latent trait has been developed, utilizing high-risk design and item response theory. This study examined properties of a SUD transmissible liability index (TLI) derived using this method. Sons of males with or without SUD were studied longitudinally from preadolescence to young adulthood. The properties of TLI, including its psychometric characteristics, longitudinal risk assessment and ethnic variation, were examined. A pilot twin study was conducted to analyze the composition of TLI's phenotypic variance. The data suggest that TLI has concurrent, incremental, predictive and discriminant validity, as well as sensitivity to ethnic differences. The data suggest a high heritability of the index in males. The results also suggest applicability of the method for genetic and other etiology-related research, and for evaluation of individual risk. Vanyukov M, Kirisci L, Moss L, Tarter R, Reynolds M, Maher B, et al., Measurement of the risk for substance use disorders: Phenotypic and genetic analysis of an index of common liability. Behav Genet. 2009;39(3):233-244.

Neighborhood Quality and Development of Cannabis Use Disorder In Boys

This prospective investigation examined the contribution of neighborhood context and neurobehavioral disinhibition to the association between substance use disorder (SUD) in parents and cannabis use disorder in their sons. It was hypothesized that both neighborhood context and son's neurobehavioral disinhibition mediate this association. Two hundred and sixteen boys were tracked from ages 10-12 to age 22. The extent to which neighborhood context and neurobehavioral disinhibition mediate the association between parental SUD and son's cannabis use disorder was evaluated using structural equation modeling. The best fitting model positioned neighborhood context and neurobehavioral disinhibition as mediators of the association between parental SUD and cannabis use disorder in sons. Neurobehavioral disinhibition also was a mediator of the association between neighborhood context and son's cannabis use. The implications of this pattern of association between parental SUD, neighborhood context, and individual risk for SUD for improving prevention are discussed. Ridenour T, Tarter R, Reynolds M, Mezzich A, Kirisci L, Vanyukov M. Neurobehavioral disinhibition, parental substance use disorder, neighborhood quality and development of cannabis use disorder in boys. Drug Alcohol Depend. 2009;102(1-3):71-77.

Clarifying the Phenotype and Environtype of Cannabis Use Disorder In Boys To Young Adults

Employing a prospective paradigm, this investigation derived the childhood phenotype and the environtype associated with risk for cannabis use disorder. Two hundred and sixteen boys were evaluated between age 10-12 on a comprehensive protocol using self, mother, and teacher reports, and later followed up at ages 19 and 22 to determine the presence of cannabis use disorder. The Transmissible Liability Index (TLI) and Non-Transmissible Liability Index (NTLI) were derived using item response theory. Logistic regression was conducted to evaluate the accuracy of the indexes, singly and in combination, to predict cannabis use disorder. The TLI and NTLI together predicted with 70% and 75% accuracy cannabis use disorder manifest by age 19 and age 22. Sensitivity was 75% at both ages 19 and 22, whereas specificity was respectively 51% and 64%. The findings pertaining to sensitivity indicate that SUD risk for cannabis use disorder can be screened in childhood; however, the specificity scores demonstrate that a low score on the TLI does not inevitably portend a good prognosis up to 10 years later. Kirisci L, Tarter R, Mezzich A, Ridenour T, Reynolds M, Vanyukov M. Prediction of cannabis use disorder between boyhood and young adulthood: Clarifying the phenotype and environtype. Am J Addict. 2009;18(1):36-47.

Gender Differences In Risk Factors of HIV In South African Drug Users

South Africa continues to be the global epicenter of HIV infection. Further, extensive gender disparities in HIV infection exist with females four times as likely to be infected with HIV/AIDS as males. A cross-sectional collection of drug users recruited in the Pretoria region of South Africa (N = 385) was used to model HIV infection as a function of sexual risk behaviors and drug use as modified by gender. Receiving money from illicit sources and knowing someone with AIDS were loosely associated with HIV. Gender interactions were observed for age, cocaine use and condom use. Gender stratified analyses revealed that males who used condoms, were younger and tested negative for cocaine use were less likely to test positive for HIV. Findings suggest that males may have more control of risk behaviors and support the need for gender specific prevention strategies. Hedden S, Whitaker D, Floyd L, Latimer W. Gender differences in the prevalence and behavioral risk factors of HIV in South African drug users. AIDS Behav. 2009;13(2):288-296.

Injection Drug Use Among Street-Involved Youth In A Canadian Setting

Street-involved youth contend with an array of health and social challenges, including elevated rates of blood-borne infections and mortality. In addition, there has been growing concern regarding high-risk drug use among street-involved youth, in particular injection drug use. This study examined the prevalence of injecting and associated risks among street-involved youth in Vancouver, Canada. From September 2005 to November 2007, baseline data were collected as part of a prospective cohort study of street-recruited youth aged 14 to 26. Using multiple logistic regression, youth with and without a history of injection were compared. The sample included 560 youth among whom the median age was 21.9 years; 179 (32%) were female; and 230 (41.1%) reported prior injection drug use. Factors associated with injection drug use in multivariate analyses included age >or= 22 years (adjusted odds ratio [AOR] = 1.18, 95% CI: 1.10-1.28); sex work involvement (AOR = 2.17, 95% CI: 1.35-3.50); non-fatal overdose (AOR = 2.10, 95% CI: 1.38-3.20); and hepatitis C (HCV) infection (AOR = 22.61, 95% CI: 7.78-65.70). These findings highlight a high prevalence of injection drug use among street-involved youth in Vancouver and demonstrate its association with an array of risks and harms, including sex work involvement, overdose, and HCV infection. The data underscore the need for a broad set of policies and interventions to prevent the initiation of injection drug use and address the risks faced by

street-involved youth who are actively injecting. Kerr T, Marshall B, Miller C, Shannon K, Zhang R, Montaner J, Wood E. Injection drug use among street-involved youth in a Canadian setting. BMC Public Health. 2009;9:171-178.

Functional Impairment and Substance Use In Youth Three Years After Detention

This study examines functional impairment across global and specific dimensions among youth 3 years after their detention. Functional impairment was assessed using the Child and Adolescent Functional Assessment Scale (CAFAS) in a large, stratified, random sample of formerly detained youth (N = 1653). More than one-fifth of the individuals in the sample were scored as having marked impairment that required, at minimum, "multiple sources of care" (CAFAS Total Score of > or =100); 7.0% required "intensive intervention" (CAFAS Total Score > or =140). Most of the sample had impairment; only 7.5% had "no noteworthy impairment" (CAFAS Total Score < or =10). Significantly more males were impaired than females. Among males living in the community at follow-up, African Americans and Hispanics were more likely to be impaired than non-Hispanic whites. In comparison to males living in the community, males who were incarcerated at follow-up were significantly more likely to have impaired thinking and impaired functioning at home (if incarcerated, "home" is the correctional facility) but less likely to have substance use problems. Three years after detention, most youth struggle in one or more life domains; more than one in five have marked impairment in functioning. These findings underscore the ongoing costs, to both youth and society, of failing to provide effective rehabilitation to youth after detention. Abram K, Choe J, Washburn J, Romero E, Teplin L. Functional impairment in youth three years after detention. J Adolesc Health. 2009;44(6):528-535.

Modification of the Association Between Serotonin Transporter Genotype and Risk of Posttraumatic Stress Disorder In Adults By County-Level Social Environment

Although both genetic factors and features of the social environment are important predictors of posttraumatic stress disorder (PTSD), there are few data examining gene-social environment interactions in studies of PTSD. The researchers examined whether features of the social environment (county-level crime rate and unemployment) modified the association between the serotonin protein gene (SLC6A4) promoter variant (5-HTTLPR) and risk of current PTSD in a sample of 590 participants from the 2004 Florida Hurricane Study. Interviews conducted in 2005 were used to obtain individual-level risk factor measures and Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, PTSD diagnoses. DNA was extracted from salivary samples. County-level crime and unemployment rates were assessed from Federal Bureau of Investigation and US Census data, respectively. There was a significant interaction between 5-HTTLPR genotype and both crime rate (odds ratio = 2.68, 95% confidence interval: 1.09, 6.57) and unemployment rate (odds ratio = 3.67, 95% confidence interval: 1.42, 9.50) in logistic regression models predicting PTSD risk, after adjustment for individual-level determinants of PTSD. Stratified analyses indicated that the "s" allele of the 5-HTTLPR polymorphism was associated with decreased risk of PTSD in low-risk environments (low crime/unemployment rates) but increased risk of PTSD in high-risk environments. These results suggest that social environment modifies the effect of 5-HTTLPR genotype on PTSD risk. Koenen K, Aiello A, Bakshis E, Amstadter A, Ruggiero K, Acierno R, Kilpatrick D, Gelernter J, Galea S. Modification of the association between serotonin transporter genotype and risk of posttraumatic stress disorder in adults by county-level social environment. Am J Epidemiol. 2009;169(6):704-711.

The Harm Inside: Injection During Incarceration Among Male Injection Drug Users In Tijuana, Mexico

Limited access to sterile syringes and condoms in correctional facilities make these settings high risk environments for HIV transmission. Although incarceration among injection drug users (IDUs) is common, there is limited information regarding specific IDU risk behaviors inside. Researchers examined correlates of incarceration, injection inside and syringe sharing inside among male IDUs recruited in Tijuana, Mexico, using respondent driven sampling (RDS) (n=898). An interviewer administered survey collected data on sociodemographic, behavioral and contextual characteristics. Associations with (a) history of incarceration, (b) injection inside, and (c) syringe sharing inside were identified using univariate and multiple logistic regression models with RDS adjustment. Seventy-six percent of IDUs had been incarcerated, of whom 61% injected inside. Three quarters (75%) of those who injected shared syringes. U.S. deportation [adjusted odds ratio (AOR) =1.61; 95% confidence interval (CI): 1.07, 2.43] and migration (AOR=1.81; 95% CI: 1.12, 2.95) were independently associated with incarceration. Injection inside was independently asso-ciated with recent receptive syringe sharing (AOR=2.46; 95% CI: 1.75, 3.45) and having sex with a man while incarcerated (AOR=3.59; 95% CI: 1.65, 7.83). Sharing syringes inside was indepen-dently associated with having sex with a man while incarcerated (AOR=6.18; 95% CI: 1.78, 21.49). A majority of incarcerated IDUs reported injecting and syringe sharing during incarceration, and these IDUs were more likely to engage in sex with other men. Findings indicate the great need for corrections-based interventions to reduce injection and syringe sharing and risk reduction inter-ventions for male IDUs who have sex with men while incarcerated. Pollini R, Alvelais J, Gallardo M, Vera A, Lozada R, Magis-Rodriquez C, Strathdee S. The harm inside: Injection during incar-ceration among male injection drug users in Tijuana, Mexico. Drug Alc Dep. 2009;103(1-2):52-58.

High Prevalence of Latent Tuberculosis Infection Among Injection Drug Users In Tijuana, Mexico

Researchers studied prevalence and correlates of latent tuberculosis infection (LTBI) among injection drug users (IDUs) in Tijuana, Mexico, where tuberculosis (TB) is endemic. IDUs aged > or =18 years were recruited via respondent-driven sampling (RDS) and underwent standardized interviews, human immunodeficiency virus (HIV) antibody testing and LTBI screening using Quanti-FERON((R))-TB Gold In-Tube, a whole-blood interferon-gamma release assay (IGRA). LTBI prevalence was estimated and correlates were identified using RDS-weighted logistic regression. Of 1020 IDUs, 681 (67%) tested IGRA-positive and 44 (4%) tested HIV-positive. Mean age was 37 years, 88% were male and 98% were Mexican-born. IGRA positivity was associated with recruitment nearest the US border (aOR 1.64, 95%CI 1.09-2.48), increasing years of injection (aOR 1.20/5 years, 95%CI 1.07-1.34), and years lived in Tijuana (aOR 1.10/5 years, 95%CI 1.03-1.18). Speaking some English (aOR 0.38, 95%CI 0.25-0.57) and injecting most often at home in the past 6 months (aOR 0.68, 95%CI 0.45-0.99) were inversely associated with IGRA positivity. Increased LTBI prevalence among IDUs in Tijuana appears to be associated with greater drug involvement. Given the high risk for HIV infection among Tijuana's IDUs, interventions are urgently needed to prevent HIV infection and treat LTBI among IDUs before these epidemics collide. Garfein R, Lozada R, Liu L, Laniado-Laborin R, Rodwell T, Deiss R, Alvelais J, Catanzaro A, Chiles P, Strathdee S. High prevalence of latent tuberculosis infection among injection drug users in Tijuana, Mexico. Int J Tuberc Lung Dis. 2009;13(5):626-632.

Peptic Ulcers and Mental Disorders In Smokers and Alcoholics

Previous studies have documented links between peptic ulcer disease (PUD) and mood and anxiety disorders among adults in the community. Several substance use disorders (e.g., nicotine and alcohol dependence) are highly comorbid with mood/anxiety disorders and have been also linked with PUD. No previous study has examined the potentially explanatory role of substance use disorders in the link between mood and anxiety disorders and PUD. The objective of the study is to examine relationships between a range of mental disorders and PUD among adults in the United States and to examine the potential explanatory role of substance use disorders in these links. Data were drawn from the National Epidemiologic Survey on Alcohol and Related Conditions, a nationally representative sample of US adults 18 years of age and over (N= 43,098). Diagnostic and Statistical Manual for Mental Disorders IV diagnoses of mood, anxiety, and substance use disorders were assessed using the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV, and PUD status was assessed via self-report. Findings show that mood/anxiety disorders were associated with PUD. Specifically, generalized anxiety disorder (GAD) (Odds Ratio (OR) = 3.43) was most strongly associated with PUD, followed by panic disorder (OR = 3.11), dysthymia (OR = 3.59), and bipolar disorder (OR = 2.91). The relationships between most mood/anxiety disorders and PUD were substantially attenuated after adjusting for nicotine and alcohol dependence. Mood/anxiety disorders are associated with increased rates of PUD; nicotine and alcohol dependence seem to play a substantial role in explaining the link with PUD. Goodwin R, Keyes K, Stein M, Talley N. Peptic ulcer and mental disorders among adults in the community: The role of nicotine and alcohol use disorders. Psychosom Med. 2009;71(4):463-468.

Influence of Drinking Quantity on Alcohol Dependence

Recent research suggests that adding a quantity/frequency alcohol consumption measure to the diagnoses of alcohol use disorders may improve construct validity of diagnoses using the Diagnostic and Statistical Manual of Mental and Behavior Disorders (DSM-V). This study explores the epidemiological impact of including weekly at-risk drinking (WAD) in the DSM-IV diagnostic definition of alcohol dependence via three hypothetical reformulations of the current criteria. The sample was the National Epidemiologic Survey on Alcohol and Related Conditions, a nationally representative sample with 43,093 adults aged >18 in the U.S interviewed with the Alcohol Use Disorder and Associated Disabilities Interview Schedule IV. The current (DSM-IV) definition of alcohol dependence was compared with four hypothetical alcohol dependence reformulations that included WAD: (1) WAD added as an eighth criteria; (2) WAD required for a diagnosis; (3) adding abuse and dependence criteria together, and including WAD with a 3 of 12 symptom threshold; (4) adding abuse and dependence criteria together, and including WAD with a 5 of 12 symptom threshold. The inclusion of at-risk drinking as an eighth criterion of alcohol dependence has a minimal impact on the sociodemographic correlates of alcohol dependence but substantially increases the prevalence of dependence (from 3.8% to 5.0%). At-risk drinking as a required criterion or as part of a diagnosis that combines abuse with dependence criteria with a higher threshold (5+ criteria) decreases prevalence and has a larger impact on sociodemographic correlates. Blacks, Hispanics, and women are less likely to be included in diagnostic reformulations that include WAD, whereas individuals with low-income and education are more likely to remain diagnosed. Including WAD as either a requirement of diagnosis or as an additional criterion would have a large impact on the prevalence of alcohol dependence in the general population. The inclusion of a quantity/frequency requirement may eliminate false positives from studies of alcohol disorder etiology and improve phenotype definition for genetic association studies by reducing heterogeneity in the diagnosis, but may also reduce eligibility for treatment services among women and racial/ethnic minorities. Keyes K, Geier T, Grant B, Hasin, D. Influence of a drinking quantity and frequency measure on the prevalence and

demographic correlates of DSM-IV alcohol dependence. Alcohol Clin Exp Res. 2009;33(5):761-771.

Association Between Neurobehavioral Disinhibition and Peer Environment on Illegal Drug Use

Individual and contextual factors jointly participate in the onset and progression of substance abuse; however, the pattern of their relationship in males and females has not been systematically studied. Male and female children and adolescents were compared to determine the relative influence of individual susceptibility (neurobehavioral disinhibition or ND) and social environment (deviancy in peers) on use of illegal drugs. Boys (N = 380) and girls (N = 127) were prospectively tracked from age 10-12 to age 16 to delineate the role of ND and peer deviancy on use of illegal drugs. Girls exhibited lower ND scores than boys in childhood and were less inclined to affiliate with deviant peers. These differences were reduced or disappeared by mid-adolescence. In boys only, peer deviancy in childhood mediated the association between ND and illegal drug use at age 16. In both genders, peer deviancy in mid-adolescence mediated ND and substance abuse at age 16. Individual and contextual risk factors promoting substance abuse are more salient at a younger age in boys compared to girls. These results point to the need for earlier screening and intervention for boys. Kirisci L, Mezzich A, Reynolds M, Tarter R, Aytaclar S. Prospective study of the association between neurobehavioral disinhibition and peer environment on illegal drug use in boys and girls. Am J Drug Alcohol Abuse. 2009;35(3):145-150.

Opportunities To Use Drugs and Stages of Drug Involvement Outside the United States: Evidence From the Republic of Chile

The research team sought to replicate North American research findings regarding the earliest stages of drug involvement by studying youthful drug involvement in the Republic of Chile. In particular, they assessed initial opportunities for licit drug use and transitions leading toward illegal drug use. The researchers surveyed a nationally representative probability sample of middle and high school students in Chile; 30,490 youths completed surveys that assessed age at first drug exposure opportunities and first actual drug use. An estimated 39% of the students had an opportunity to use cannabis, and 70% of these transitioned to actual cannabis use. The probability of cannabis use and the conditional probability of cannabis use were greater for users of alcohol only, tobacco only, and alcohol plus tobacco, as compared to non-users of alcohol and tobacco. Male-female differences in cannabis use were traced back to male-female differences in drug exposure opportunities. The findings suggest that in Chile as in North America, when cannabis use follows alcohol and tobacco use, the mechanism may be understood in two parts: users of alcohol and tobacco are more likely to have opportunities to try cannabis, and once the opportunity occurs, they are more likely to use cannabis. Male-female differences do not seem to be operative within the mechanism that governs transition to use, once the opportunity to use cannabis has occurred. Caris L, Wagner F, R'os-Bedoya C, Anthony J. Opportunities to use drugs and stages of drug involvement outside the United States: Evidence from the Republic of Chile. Drug Alcohol Depend. 2009;102(1-3):30-34.

Lifetime Alcohol Abuse, Dependence, and Binge Drinking

Questions relevant to DSM-V alcohol use disorders (AUD) include whether dimensional measures provide more information than categorical diagnoses, whether to combine abuse and dependence criteria, and whether to add a new diagnostic criterion, binge drinking. Binary and dimensional models of three versions of AUD criteria were investigated: (1) dependence criteria; (2) abuse

and dependence criteria combined; and (3) abuse and dependence criteria combined, with an added binge drinking criterion. In a national sample of lifetime drinkers (N=27,324), the models of AUD criteria were investigated in relation to two well-established risk factors for AUD, family history and early drinking onset. Logistic or Poisson regression modeled the relationships between the validating variables and dependence in categorical, dimensional, and hybrid forms; Wald tests were used to assess differences between the dimensional, categorical, and hybrid models. Alcohol dependence criteria represented a single continuum (family history Wald=9.93, p=0.13; early drinking Wald=7.62, p=0.27) with no support for a categorical or hybrid version of alcohol dependence. Adding four abuse criteria produced similar results for family history (Wald=15.4, p=0.12) although with early drinking, this model showed a trend towards deviating from the data (Wald=16.7, p=0.08). No support was found for any diagnostic threshold at 3, 4, 5, 6, or 7 criteria when abuse and dependence were combined. Adding binge drinking resulted in a significant departure from linearity for family history (Wald=21.8, p=0.03) and early drinking (Wald=23.9, p=0.01). The number of alcohol dependence and abuse criteria met should be explored further as a useful AUD severity indicator or phenotype. Hasin D, Beseler C. Dimensionality of lifetime alcohol abuse, dependence and binge drinking. Drug Alcohol Depend. 2009;101(1-2):53-61.

Linking Adolescent Nicotine Dependence and Common Latent Continuum

Using the theoretical model of nicotine dependence (ND) within the Diagnostic and Statistical Manual of Mental Disorder, 4th Edition (DSM-IV) as a frame of reference, investigators used methods based on item response theory to link alternative instruments assessing adolescent nicotine dependence severity to a common latent continuum. A multi-ethnic cohort of 6th-10th graders selected from the Chicago Public Schools completed 5 household interviews over 2 years. Youth who reported at least some cigarette use in the last 30 days prior to the interviews at waves W3-W5 completed measures of DSM-IV ND, the Modified Fagerstrom Tolerance Questionnaire (mFTQ), and the Nicotine Dependence Syndrome Scale (NDSS), yielding samples of 253, 241, and 296 respondents at W3-W5, respectively. Confirmatory factor analysis supported a primary dimension of ND. Each instrument's items had complementary and stable relationships to ND across multiple waves of assessment. By aligning symptoms along a common latent ND continuum, researchers were able to evaluate the consistency of symptoms from different instruments that target similar content. These methods allowed for an examination of the DSM-IV as a continuous index of ND, the evaluation of the degree of heterogeneity in levels of ND within groups above and below diagnostic thresholds, and the assessment of the utility in using the pattern or particular DSM-IV symptoms that led to each score in further differentiating levels of ND. They also made it possible to examine the concurrent validity of the ND continuum and levels of current of smoking at each wave of assessment. Strong D, Kahler C, Colby S, Griesler P, Kandel D. Linking measures of adolescent nicotine dependence to a common latent continuum. Drug Alcohol Depend. 2009;99(1-3):296-308.

Early-Onset Drug Use and Risk for Drug Dependence Problems

There is substantial evidence that alcohol, tobacco, and cannabis dependence problems surface more quickly when use of these drugs starts before adulthood, but the evidence based on other illicit drugs (e.g., cocaine) is meager. Using existing data from the National Survey on Drug Use and Health (NSDUH), a large-scale population-based study which includes adolescents and adults, researchers examined drug-specific and age-specific variation in profiles of emerging clinical features associated with drug dependence. The risk of experiencing drug dependence problems was found to be robustly greater for

adolescent recent-onset users of cocaine, psychostimulant drugs other than cocaine, analgesics, anxiolytic medicines, inhalants drugs, and cannabis, as compared to adult recent-onset users (odds ratio=1.5-4.3, $p<0.05$). This was not the case for the NSDUH hallucinogens group (e.g., LSD). The findings suggest promoting earlier detection and interventions for drug use, as well as greater parent and peer awareness of drug dependence clinical features that may develop early among young people who have just started using drugs. Chen C, Storr C, Anthony J. Early-onset drug use and risk for drug dependence problems. Addict Behav. 2009;34(3):319-322.

Simultaneous Cannabis and Tobacco Use In Women

Compared to those who reported a lifetime co-occurrence of cannabis and tobacco use, individuals who report simultaneous use of cannabis and tobacco are more likely to also report higher rates of substance-related problems and psycho-pathology. A study of a sample of young women (N=3427) examined (a) co-occurring use, or whether regular cigarette smoking is associated with increased cannabis involvement; (b) simultan-eous use, a special form of co-occurring use where cannabis and cigarettes are typically used on the same occasion (to determine if those who use cannabis and tobacco simultaneously are also more likely to report greater cannabis involvement); and (c) the extent to which latent genetic and environmental factors may contribute to simultaneous use in those with a history of co-occurring cannabis use and regular cigarette smoking. Womenwho reported regular cigarette smoking were 4.5-9.5 times more likely to report co-occurring cannabis use and other stages of cannabis involvement, including DSM-IV cannabis abuse and dependence. In those women who reported co-occurring regular cigarette smoking and lifetime cannabis use (N=1073), simultaneous use of cannabis and tobacco was associated with increased likelihood of negative cannabis-related outcomes. Simultaneous users were 1.6 times more likely to meet criteria for DSM-IV cannabis abuse, even after controlling for early covariates and for prior stages of cannabis involvement. Simultaneous use was not heritable; twin similarity was attributable to shared environmental factors (31%). While this study does not determine causality between simultaneous tobacco-cannabis use and cannabis involvement, results indicate that simultaneous use is potentially a marker for more severe psychosocial consequences associated with cannabis use. Agrawal A, Lynskey M, Madden P, Pergadia M, Bucholz K, Heath A. Simultaneous cannabis and tobacco use and cannabis-related outcomes in young women. Drug Alcohol Depend. 2009;101(1-2):8-12.

Tobacco and Cannabis Co-Occurrence

Qualitative research suggests that a shared route of administration (i.e., inhalation) for common forms of tobacco (i.e., cigarettes) and cannabis (i.e., joints) may contribute to their co-occurring use. Investigators examined data on 43,093 U.S. adults who participated in the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) to examine whether cannabis use and abuse/dependence were associated with smoked (cigarettes, cigars, pipes) versus smokeless (snuff, chewed tobacco) forms of tobacco use, after controlling for socio-demographic, psychiatric, and substance-related covariates. They found that tobacco smoking was associated with a 3.3-4.5 times increased risk for cannabis use and abuse/dependence, respectively. After covariate adjustment for nicotine dependence, tobacco smoking (but not smokeless tobacco) was significantly associated with cannabis use (multinomial odds-ratio (MOR) 1.99) as well as cannabis dependence (MOR 1.55). By contrast, use of smokeless tobacco was not significantly correlated with elevated rates of cannabis use (MOR 0.96) or abuse/ dependence (MOR 1.04). These findings suggest that route of administration may play a role in the observed association between tobacco and cannabis use. This may represent a physiological adapta-tion of the aero-

respiratory system and/or an index of social and cultural influences surrounding the use of smoked vs. smokeless forms of tobacco. Agrawal A, Lynskey M. Tobacco and cannabis co-occurrence: Does route of administration matter? Drug Alcohol Depend. 2009;99(1-3):240-247.

Cigarette-By-Cigarette Satisfaction During Ad Libitum (As Desired) Smoking

Smoking is thought to produce immediate reinforcement, and subjective satisfaction with smoking is thought to influence subsequent smoking. The authors used ecological momentary assessment to assess cigarette-by-cigarette smoking satisfaction in 394 heavy smokers who subsequently attempted to quit. Across 14,882 cigarettes rated, satisfaction averaged 7.06 (0-10 scale), with considerable variation across cigarettes and individuals. Women and African American smokers reported higher satisfaction. More satisfied smokers were more likely to lapse after quitting (Hazard Ratio (HR) =1.1, $p < .03$), whereas less satisfied smokers derived greater benefit from patch treatment to help them achieve abstinence (HR = 1.23, $p<.001$). Cigarettes smoked in positive moods were more satisfying, correcting for mood at the time of rating. The best predictor of subsequent smoking satisfaction was the intensity of craving prior to smoking. Understanding subjective smoking satis-faction provides insight into sources of reinforcement for smoking. Shiffman S, Kirchner T. Cigar-ette-by-cigarette satisfaction during ad libitum smoking. J Abnorm Psych. 2009;118(2):348-359.

Mortality Among Injection Drug Users In Chennai, India (2005-2008)

Injection drug users (IDUs) have estimated mortality rates over 10 times higher than the general population; much of this excess mortality is HIV-associated. Few mortality estimates among IDUs from developing countries, including India, exist. In this study, IDUs (1158) were recruited in Chennai from April 2005 to May 2006; 293 were HIV positive. Information on deaths and causes was obtained through outreach workers and family/network members. Mortality rates and standardized mortality ratios were calculated; multivariate Poisson regression was used to identify predictors of mortality. There were 85 deaths over 1998 person-years (p-y) of follow-up [mortality rate (MR) 4.25 per 100 p-y; 95% confidence interval (CI) = 3.41-5.23]. The overall standardized mortality ratio was 11.1; for HIV-positive IDUs, the standardized mortality ratio was 23.9. Mortality risk among HIV-positive IDUs (MR: 8.88 per 100 p-y) was nearly three times that of negative IDUs (MR: 3.03 per 100 p-y) and increased with declining immune status (CD4 cells > 350: 5.44 per 100 p-y vs. CD4 cells < or = 200: 34.5 per 100 p-y). This association persisted after adjustment for confounders. The leading causes of mortality in both HIV negative and positive IDUs were overdose (n = 22), AIDS (n = 14), tuberculosis (n = 8) and accident/trauma (n = 9). Substantial mortality was observed in this cohort with the highest rates among HIV-positive IDUs with CD4 counts of less than 350 cells/microl. Although non-AIDS deaths outnumbered AIDS-related deaths, the relative contribution of AIDS-associated mortality is likely to increase with advancing HIV disease progression. These data reinforce the need for interventions to reduce the harms associated with drug use and increase HAART access among IDUs in Chennai. Solomon S, Celentano D, Srikrishnan A, Vasudevan C, Anand S, Kumar M, Solomon S, Lucas G, Mehta S. Mortality among injection drug users in Chennai, India (2005-2008). AIDS. 2009;23(8):997-1004.

Predictors of Injection Drug Use Cessation and Relapse in a Prospective Cohort of Young Injection Drug Users In San Francisco, CA (UFO Study)

Studies of injection drug use cessation have largely sampled adults in drug treatment settings. Little is known about injection cessation and relapse among young injection drug users (IDU) in the community. This study included 365 HCV-negative IDU under age 30 years recruited by street outreach and interviewed quarterly for a prospective cohort between January 2000 and February 2008. Participants were followed for 638 person-years and 1996 visits. Survival analysis techniques were used to identify correlates of injection cessation (> or =3 months) and relapse to injection. Sixty-seven percent of subjects were male, the median age was 22 years (interquartile range (IQR) 20-26) and the median years injecting was 3.6 (IQR 1.3-6.5); 28.8% ceased injecting during the follow-up period. Among those that ceased injecting, nearly one-half resumed drug injection on subsequent visits, one-quarter maintained injecting cessation, and one-quarter were lost to follow-up. Participating in a drug treatment program in the last 3 months and injecting less than 30 times per month were associated with injection cessation. Injecting heroin or heroin mixed with other drugs, injecting the residue from previously used drug preparation equipment, drinking alcohol, and using benzodiazepines were negatively associated with cessation. Younger age was associated with relapse to injection. These results suggest that factors associated with stopping injecting involve multiple areas of intervention, including access to drug treatment and behavioral approaches to reduce injection and sustain cessation. The higher incidence of relapse in the younger subjects in this cohort underscores the need for earlier detection and treatment programs targeted to adolescents and transition-age youth. Evans J, Hahn J, Lum P, Stein E, Page K. Predictors of injection drug use cessation and relapse in a prospective cohort of young injection drug users in San Francisco, CA (UFO Study). Drug Alcohol Depend. 2009;101(3):152-157.

Development of Substance Abuse in Adolescents With Bipolar Disorder

Recent work has highlighted important relationships among conduct disorder (CD), substance use disorders (SUD), and bipolar disorder in youth. However, because bipolar disorder and CD are frequently comorbid in the young, the impact of CD in mediating SUD in bipolar disorder youth remains unclear. To help clarify this, a sample of 105 adolescents with DSM-IV bipolar disorder (mean +/- SD age=13.6 +/- 2.50 years) and 98 controls (mean +/- SD age = 13.7 +/- 2.10 years) was comprehensively assessed with a structured psychiatric diagnostic interview for psychopathology and SUD. The study was conducted from January 2000 through December 2004. Among bipolar disorder youth, those with CD were more likely to report cigarette smoking and/or SUD than youth without CD. However, CD preceding SUD or cigarette smoking did not significantly increase the subsequent risk of SUD or cigarette smoking. Adolescents with bipolar disorder and CD were significantly more likely to manifest a combined alcohol plus drug use disorder compared to subjects with bi-polar disorder without CD. While bipolar disorder is a risk factor for SUD and cigarette smoking in a sample of adolescents, comorbidity with preexisting CD does not increase the risk for SUD. Further follow-up of this sample through the full risk of SUD into adulthood is necessary to confirm these findings. Wilens T, Martelon M, Kruesi M, Parcell T, Westerberg D, Schillinger M, Gignac M, Biederman J. Does conduct disorder mediate the development of substance use disorders in adolescents with bipolar disorder? A case-control family study. J Clin Psych. 2009;70(2):259-265.

Quantitative Measurements of Alcoholic Consumption

The purpose of this study was to develop a quantitative measure of alcohol consumption for gene-mapping studies. Using a sample of 3,787 young-adult twin women and an independent sample of 489 men and women from a college

drinking study, researchers developed an alcohol-consumption factor score indexed by (1) maximum typical consumption (log-transformed quantity frequency [LQNTFRQ]), (2) maximum drinks in a 24-hour period (LMAXALC), (3) frequency of drinking five or more drinks per day (FIVE), and (4) frequency of drinking to intoxication (INTOX). The investigators tested (1) for factorial and psychometric equivalence across samples and genders; and (2) for construct validity and its equivalence across samples and genders, using measures of tobacco and cannabis use and family history of alcoholism. They then determined the heritability of the alcohol-consumption factor score using a genetic psychometric model. A single-factor model fit well with factor loadings ranging from .60 to .90. With rare exception, they found support for measurement invariance across the two samples and across genders. Measures of nicotine and cannabis use as well as family history of alcoholism were associated to a similar extent across samples and genders, with the underlying alcohol-consumption factor. Psychometric twin modeling revealed that each of the alcohol-consumption measures (h2=34%-47%) and the underlying factor score (h2=50%) were heritable, with the remainder of the variance attributable to individual-specific environmental factors. The moderately heritable alcohol-consumption factor also accounted for a majority of the genetic variance in LQNTFRQ, LMAXALC, FIVE, and INTOX. The findings suggest that quantitative measures of alcohol consumption with the favorable attributes of measurement invariance, construct validity, and moderate heritability can enhance future gene-mapping efforts, supplementing information afforded by conventional diagnostic measures of alcohol abuse/dependence. Agrawal A, Grant J, Littlefield A, Waldron M, Pergadia M, Lynskey M, Madden P, Todorov A, Trull T, Bucholz K, Todd R, Sher K, Heath A. Developing a quantitative measure of alcohol consumption for genomic studies on prospective cohorts. J Stud Alcohol Drugs. 2009;70(2):157-168.

Multiple Distinct Risk Loci for Nicotine Dependence

Tobacco smoking continues to be a leading cause of preventable death. Recent research has underscored the important role of specific cholinergic nicotinic receptor subunit (CHRN) genes in risk for nicotine dependence and smoking. To detect and characterize the influence of genetic variation on vulnerability to nicotine dependence, 226 single nucleotide polymorphisms (SNPs) covering the complete family of 16 CHRN genes, which encode the nicotinic acetylcholine receptor (nAChR) subunits, were analyzed in a sample of 1,050 nicotine-dependent cases and 879 non-dependent controls of European descent. After correcting for multiple tests across this gene family, significant associations were found for two distinct loci in the CHRNA5-CHRNA3-CHRNB4 gene cluster, one locus in the CHRNB3-CHRNA6 gene cluster, and a fourth, novel locus in the CHRND-CHRNG gene cluster. The two distinct loci in CHRNA5-CHRNA3-CHRNB4 are represented by the non-synonymous SNP rs16969968 in CHRNA5 and by rs578776 in CHRNA3, respectively, and joint analyses show that the associations at these two SNPs are statistically independent. Nominally significant single-SNP association was detected in CHRNA4 and CHRNB1. This is the most comprehensive study of the CHRN genes for involvement with nicotine dependence to date, revealing significant evidence for at least four distinct loci in the nicotinic receptor subunit genes that influence the transition from smoking to nicotine dependence. The findings are discussed with regard to their implications for the development of improved smoking cessation treatments and prevention initiatives. Saccone N, Saccone S, Hinrichs A, Stitzel J, Duan W, Pergadia M, et al., Multiple distinct risk loci for nicotine dependence identified by dense coverage of the complete family of nicotinic receptor subunit (CHRN) genes. Am J Med Genet B Neuropsychiatr Genet. 2009;150B(4):453-466.

Genes Linked To Alcohol Consumption

Previous studies have identified evidence of genetic influence on alcohol use in samples selected to be informative for alcoholism research. However, there are a growing number of genome-wide association studies (GWAS) using samples unselected for alcohol consumption (i.e., selected on other traits and forms of psychopathology), which nevertheless assess consumption as a risk factor. Is it reasonable to expect that genes contributing to variation in alcohol consumption can be identified in such samples? An exploratory approach was taken to determine whether linkage analyses for heaviness of alcohol consumption, using a sample collected for heterogeneous purposes, could replicate previous findings. Quantity and frequency measures of consumption were collected in telephone interviews from community samples. These measures, and genotyping, were available for 5,441 individuals (5,067 quasi-independent sibling pairs). For 1,533 of these individuals, data were collected on two occasions, about 8.2 years apart, providing two datasets that maximize data collected at either a younger or an older age. Analyses were conducted to address the question of whether age and heavier levels of alcohol consumption effects outcome. Linkage results were compared in the younger and older full samples, and with samples in which approximately 10, 20, and 40 of drinkers from the lower end of the distribution of alcohol consumption were dropped. Linkage peaks varied for the age differentia-ted samples and for percentage of light drinkers retained. Larger peaks (LOD scores >2.0) were typically found in regions previously identified in linkage studies and/or containing proposed candidate genes for alcoholism including AGT, CARTPT, OPRD1, PIK3R1, and PDYN. The results suggest that GWAS assessing alcohol consumption as a covariate for other conditions will have some success in identifying genes contributing to consumption-related variation. However, sample characteristics, such as participant age, and trait distribution, may have substantial effects on the strength of the genetic signal. These results can inform forthcoming GWAS where the same restrictions apply. Hansell N, Agrawal A, Whitfield J, Morley K, Gordon S, Lind P, et al., Can we identify genes for alcohol consumption in samples ascertained for heterogeneous purposes? Alcohol Clin Exp Res. 2009;33(4):729-739.

Early Cannabis Use and DSM-IV Nicotine Dependence

Evidence suggests that cannabis users are at increased risk for cigarette smoking. If so, this may be the single most alarming public health challenge posed by cannabis use. Investigators examined whether cannabis use prior to age 17 years is associated with an increased likelihood of DSM-IV nicotine dependence and the extent to which genetic and environmental factors contribute to this association in a population-based cohort of 24-36-year-old Australian male and female twins (N=6257; 286 and 229 discordant pairs). The co-twin-control method, with twin pairs discordant for early cannabis use, was used to examine whether, after controlling for genetic and familial environmental background, there was evidence for an additional influence of early cannabis use on DSM-IV nicotine dependence. Bivariate genetic models were fitted to the full data set to quantify the genetic correlation between early cannabis use and nicotine dependence. The early cannabis-using twin was about twice as likely to report nicotine dependence when compared to their co-twin who had experimented with cigarettes but had never used cannabis. Even when analyses were restricted to cannabis users, earlier age of cannabis use onset conferred greater risk (1.7 times greater) for nicotine dependence than did later onset. This association was governed largely by common genetic liability to early cannabis use and nicotine dependence as demonstrated by genetic correlations of 0.41-0.52. The findings suggest that early-onset cannabis users are at increased risk for nicotine dependence, and that this risk is attributable largely to common genetic vulnerability. There is no evidence for a causal relationship between cannabis use and nicotine dependence. Agrawal A, Lynskey M, Pergadia M, Bucholz K, Heath A, Martin N, Madden P. Early cannabis use and DSM-IV nicotine dependence: A twin study. Addiction.

2008;103(11):1896-1904.

Association Between DSM-IV Nicotine Dependence and Stressful Life Events

Nicotine dependence (ND) is a pervasive public health concern and a leading cause of preventable mortality. Stressful life events (SLEs), which severely disrupt the lives of individuals experiencing such events, have been posited as correlates of persisting ND. While both ND and SLEs have been studied extensively in relation to other variables, there are few instances in which they have been investigated in concert. In this study, researchers used data on 18,013 smokers from the 2001-2002 data set of the National Epidemiological Survey on Alcohol and Related Conditions (NESARC; N= 43,093) to examine whether experiencing a SLE in the past 12 months was associated with meeting criteria for ND in the same past 12 months. Logistic regression analyses were conducted while accounting for a variety of covariates. A majority of the SLEs were associated with past 12 month ND, even after controlling for poverty, psychiatric and substance use disorders, and a prior history of ND (odds-ratios 1.35-2.20). The rates of past 12 month ND were considerably greater in those experiencing more than one SLE. While these data do not allow for making causal interpretations, they suggest an association between SLE and ND. It appears that individuals experiencing SLEs may find it particularly difficult to quit smoking; alternatively, directly or via correlated risks (e.g., living in a high risk neighborhood), smoking may increase the likelihood of exposure to SLEs. Balk E, Lynskey M, Agrawal A. The association between DSM-IV nicotine dependence and stressful life events in the national epidemiologic survey on alcohol and related conditions. Am J Drug Alcohol Abuse. 2009;35(2):85-90.

Distress and Academic Achievement Among Adolescents of Affluence

The main objectives of this study were to prospectively examine the relationship between externalizing (substance use and delinquency) and internalizing (depression and anxiety) dimensions and academic achievement (grades and classroom adjustment), as well as continuity over time in these domains within a sample of wealthy adolescents followed from 10th-12th grades (N = 256). Cluster analyses were used to group participants at 10th grade and then group differences were evaluated on adjustment outcomes over time. Problem behavior clusters revealed differences on academic indices, with the two marijuana using groups-marijuana users and multi-problem youth-exhibiting the worst academic outcomes at all three waves. The two lowest achieving groups reported the highest distress across all externalizing dimensions over time. Stability across the three waves was found for both personal and academic competence as well as the associations between these two domains. Based on youth tracked from sophomore year through the end of high school, these findings indicate strong associations between problem behavior activity and academic underachievement among relatively affluent suburban youth. The findings run counter to others, which indicate that it is cigarette, and not marijuana, use that is a more potent force for academic risk. These results highlight the difficulty of concluding that there is a robust temporal sequence in the complex relationship shared between distress domains and academic achievement. In all likelihood, once the cycle has started, it may be nearly impossible to tease apart which came first. These findings suggest the need for school-based interventions focusing on marijuana use as well as academic problems as related if not bi-directionally influencing one another. Ansary N, Luthar S. Distress and academic achievement among adolescents of affluence: A study of externalizing and internalizing problem behaviors and school performance. Dev Psychopathol. 2009;21(1):319-341.

Vulnerability To Drug-Related Infections and Co-Infections Among Injecting Drug Users In Budapest, Hungary

Drug-related infectious diseases are among the major health consequences of drug use and any existing drug-related infection may predispose injecting drug users (IDUs) to other infections. This study assessed among IDUs in Budapest, Hungary the prevalence of and vulnerability to selected drug-related infections and co-infections. The sample consisted of 186 participants recruited between October 2005 and December 2006. Researchers found 0% HIV, 37% HCV, 24% HAV, and 14% past HBV infection. Infections with Herpes 1 or 2, tuberculosis, Chlamydia, syphilis, and gonorrhea were 79%, 12%, 7%, 4%, and 0%, respectively. Co-infection with HAV/HCV was 12%, HBV/HCV 9%, HAV/HBV 7%, and HAV/HBV/HCV 4%. Those over age 30, the ethnic Roma, and the homeless were more likely to have any hepatitis and a higher number of drug-related infections. Amphetamine injectors were more likely to have a higher number of drug-related infections and those who travelled within Hungary were more likely to have any STI. However, those who worked at least part time and those who were in treatment were less likely to have drug-related infections. These results highlight the need of interventions in Hungary to reach and focus on marginalized (Roma or homeless) IDUs and address not only injecting and sex risk, but also hygienic living and injecting conditions. Furthermore, structural interventions to increase social integration (working or being in treatment) may improve welfare and decrease drug use and infection risk tied to drug use/injection among disadvantaged, marginalized, mostly minority populations. Gyarmathy V, Neaigus A, Ujhelyi E. Vulnerability to drug-related infections and co-infections among injecting drug users in Budapest, Hungary. Eur J Public Health. 2009;19(3):260-265.

Social Influences Upon Injection Initiation Among Street-Involved Youth In Vancouver, Canada: A Qualitative Study

Street-involved youth are a population at risk of adopting injection as a route of drug administration. Preventing the transition to injection drug use among street youth represents a major public health priority. To inform epidemiological research and prevention efforts, researchers conducted a qualitative study on the initiation of injection drug use among street-involved youth in Vancouver, Canada. Qualitative interviews with street youth who inject drugs were used to elicit descriptions of the adoption of injection as a route of administration. Interviewees were recruited from the At-Risk Youth Study (ARYS), a cohort of street-involved youth who use illicit drugs in Vancouver, Canada. Researchers transcribed audio recorded interviews verbatim and then conducted thematic analysis of their content. Of 26 youth aged 16 to 26 who participated in this study, just under half (12) were females. Among the participants, the first injection episode frequently featured another drug user who facilitated the initiation of injecting. Youth narratives indicate that the transition into injecting is influenced by social interactions with drug using peers and evolving perceptions of injecting, and rejecting identification as an injector was important among youth who did not continue to inject. It appears that social conventions discouraging initiating young drug users into injection exist among established injectors, although this ethic is often ignored. The importance of social relationships with other drug users within the adoption of injection drug use highlights the potential of social interventions to prevent injection initiation of injecting in young people. Developing strategies to engage current injectors who are likely to initiate youth into injection could also be important and beneficial to prevention efforts. Small W, Fast D, Krusi A, Wood E, Kerr T. Social influences upon injection initiation among street-involved youth in Vancouver, Canada: A qualitative study. Subst Abuse Treat Prev Policy. 2009;4:1-8.

Homelessness and Unstable Housing Associated With an

Increased Risk of HIV and STI Transmission Among Street-Involved Youth

The role that environmental factors play in driving HIV and STI transmission risk among street-involved youth has not been well examined. The authors examined factors associated with number of sex partners using quasi-Poisson regression and consistent condom use using logistic regression among participants enrolled in the At Risk Youth Study (ARYS). Among 529 multi-ethnic participants ages 16 to 26 years, 253 (47.8%) reported multiple partners while only 127 (24.0%) reported consistent condom use in the past 6 months. Homelessness was inversely associated with consistent condom use (adjusted odds ratio [aOR]=0.47, p=0.008), while unstable housing was positively associated with greater numbers of sex partners (adjusted incidence rate ratio [aIRR]=1.44, p=0.010). These findings highlight the need for interventions and services to modify social and environmental factors that influence risks of unsafe sexual behaviors and HIV/STIs among young street-involved populations. Marshall B, Kerr T, Shoveller J, Patterson T, Buxton J, Wood E. Homelessness and unstable housing associated with an increased risk of HIVand STI transmission among street-involved youth. Health Place. 2009;15(3):753-760.

Structural and Environmental Barriers To Condom Use Negotiation With Clients Among Female Sex Workers: Implications For HIV-Prevention Strategies & Policy

Researchers investigated the relationship between environmental-structural factors and condom-use negotiation with clients among female sex workers. They used baseline data from a 2006 Vancouver, British Columbia, community-based cohort of female sex workers to map the clustering of "hot spots" for being pressured into unprotected sexual intercourse by a client and assess sexual HIV risk. They also used multivariate logistic modeling to estimate the relationship between environmental-structural factors and being pressured by a client into unprotected sexual intercourse. In multivariate analyses, being pressured into having unprotected sexual intercourse was independently associated with having an individual zoning restriction (odds ratio [OR] = 3.39; 95% confidence interval [CI] = 1.00, 9.36), working away from main streets because of policing (OR = 3.01; 95% CI = 1.39, 7.44), borrowing a used crack pipe (OR = 2.51; 95% CI = 1.06, 2.49), client-perpetrated violence (OR = 2.08; 95% CI = 1.06, 4.49), and servicing clients in cars or in public spaces (OR = 2.00; 95% CI = 1.65, 5.73). These findings highlight the growing global concern surrounding the failings of prohibitive sex-work legislation on sex workers' health and safety. Shannon K, Strathdee S, Shoveller J, Rusch M, Kerr T, Tyndall M. Structural and environmental barriers to condom use negotiation with clients among female sex workers: implications for HIV-prevention strategies and policy. Am J Public Health. 2009;99(4):659-665.

Integrative Data Analysis of Multiple Sets

There are both quantitative and methodological techniques that foster the development and maintenance of a cumulative knowledge base within the psychological sciences. Most noteworthy of these techniques is meta-analysis, which allows for the synthesis of summary statistics drawn from multiple studies when the original data are not available. However, when the original data can be obtained from multiple studies, many advantages accrue from the statistical analysis of the pooled data. The authors define integrative data analysis (IDA) as the analysis of multiple data sets that have been pooled into one. Although variants of IDA have been incorporated into other scientific disciplines, the use of these techniques is much less evident in psychology. In this paper, the authors provide an overview of IDA as it may be applied within

the psychological sciences, discuss the relative advantages and disadvantages of IDA, describe analytic strategies for analyzing pooled individual data, and offer recommendations for the use of IDA in practice. Curran P, Hussong A. Integrative data analysis: The simultaneous analysis of multiple data sets. Psychol Methods. 2009;14(2):81-100.

Biculturality and HIV-Risk Behaviors Among Puerto Rican Drug Users In New York City

Biculturality refers to two independent processes of acculturation, one to the host society's culture and another to the culture of origin. This study examined the relationship between biculturality and HIV-related risk behaviors in a sample of injecting and noninjecting Puerto Rican drug users (N = 259), recruited in New York City in 2005-2006. Biculturality was measured by two scales: involvement in (i) American culture (AMBIC) and (ii) Puerto Rican culture Biculturality (PRBIC). The majority (78%) of the participants were males, with a mean age of 42 years. About half were born in Puerto Rico, and the average length of stay in the United States was 26 years. In multiple logistic-regression analysis, AMBIC was significantly related to lower injection risk after controlling for other factors including gender, age, and MMTP enrollment, while PRBIC was a significant predictor of higher sex risk. Involvement in the host culture and the culture of origin differed in their relationship to risk behaviors, indicating that incorporating assessments of biculturality may be useful in assessing and addressing migrants' behaviors, including HIV-risk behaviors. Kang S, Deren S, Mino M, CortŽs D. Biculturality and HIV-risk behaviors among Puerto Rican drug users in New York City. Subst Use Misuse. 2009;44(4):578-592.

Predictors of Sexual Risk Reduction Among Mexican Female Sex Workers Enrolled In A Behavioral Intervention Study

Researchers demonstrated the efficacy of an intervention to increase condom use among female sex workers (FSWs) in Tijuana and Ciudad Juarez, situated on the Mexico-United States border and determined whether increases in condom use were predicted by social cognitive theory and injection drug user status among women randomized to this intervention. HIV-negative FSWs (N=409) aged >or=18 years having unprotected sex with clients within the prior 2 months received a brief individual counseling session integrating motivational interviewing and principles of behavior change (i.e., HIV knowledge, self-efficacy for using condoms, and outcome expectancies). Findings showed that increases in self-efficacy scores were associated with increases in percent condom use (P = 0.008), whereas outcome expectancies were not. FSWs who inject drugs (FSW-IDUs) increased condom use with clients but not to the same extent as other FSWs (P = 0.09). Change in HIV knowledge was positively associated with change in percent condom use among FSW-IDUs (P = 0.03) but not noninjection drug users. These findings indicate that increases in self-efficacy significantly predicted increased condom use among FSWs, consistent with social cognitive theory. Increased HIV knowledge was also important among FSW-IDUs, but their changes in condom use were modest. The findings suggest that enhanced interventions for FSW-IDUs are needed that take into account that substance use during sexual transactions does occur and can compromise safer sex negotiation. Strathdee S, Mausbach B, Lozada R, Staines-Orozco H, Semple S, Abramovitz D, et al., Predictors of sexual risk reduction among mexican female sex workers enrolled in a behavioral intervention study. J Acquir Immune Defic Syndr. 2009;51 Suppl 1:S42-S46.

Women Who Abuse Prescription Opioids: Findings From the Addiction Severity Index-Multimedia Version Connect Prescription

Opioid Database

Evidence suggests gender differences in abuse of prescription opioids. This study aimed to describe characteristics of women who abuse prescription opioids in a treatment-seeking sample and to contrast gender differences among prescription opioid abusers. Data were collected from November 2005 to April 2008 for the Addiction Severity Index Multimedia Version Connect (ASI-MV Connect) database. The data included 29,906 assessments from 220 treatment centers, of which 12.8% (N=3821) reported past month prescription opioid abuse. Women were more likely than men to report use of any prescription opioid (29.8% females vs. 21.1% males, $p<0.001$) and abuse of any prescription opioid (15.4% females vs. 11.1% males, $p<0.001$) in the past month. Women-specific correlates of recent prescription opioid abuse were problem drinking, age <54, inhalant use, residence outside of West US Census region, and history of drug overdose. Men-specific correlates were age <34, currently living with their children, residence in the South and Midwest, hallucinogen use, and recent depression. Women prescription opioid abusers were less likely to report a pain problem although they were more likely to report medical problems than women who abused other drugs. The findings suggest that gender-specific factors should be taken into account in efforts to screen and identify those at highest risk of prescription opioid abuse. Prevention and intervention efforts with a gender-specific approach are warranted. Green T, Grimes Serrano J, Licari A, Budman S, Butler S. Women who abuse prescription opioids: Findings from the addiction severity index-multimedia version connect prescription opioid database. Drug Alcohol Depend. 2009;103(1-2):65-73.

Mental Health Services Use and Symptom Prevalence In A Cohort of Adults on Probation

This study examined the prevalence of mental disorder symptoms among adult probationers and the probability of mental health service use. Data from the 2001 National Household Survey on Drug Abuse were used to obtain information on adults reporting mental disorder symptoms who had been on probation within the past year and those who had not. Twenty-seven percent of probationers (N=311 of 1,168) and 17% of nonprobationers (N=5,830 of 34,230) had mental disorder symptoms. Mental health service use was reported by 23% of both groups. Compared with persons who had not been on probation, probationers were more likely to report psychosis, mania, and posttraumatic stress disorder; both groups were as likely to report depression. The findings suggest that the prevalence of mental disorder symptoms did not differ by probation status. However, the type and distribution of symptoms were significantly different in the two groups. These are important considerations when planning for service connection with mental health providers. Crilly J, Caine E, Lamberti J, Brown T, Friedman B. Mental health services use and symptom prevalence in a cohort of adults on probation. Psychiatr Serv. 2009;60(4):542-544.

Structural and Social Contexts of HIV Risk Among African Americans

HIV continues to be transmitted at unacceptably high rates among African Americans. Most HIV-prevention interventions have focused on behavioral change. To theorize additional approaches to HIV prevention among African Americans, the authors review the literature to describe how sexual networks and drug-injection networks are as important as behavior for HIV transmission. They discuss how higher-order social structures and processes, such as residential racial segregation and racialized policing, may help shape risk networks and behaviors. They then explore three themes in African American

culture (survival, propriety, and struggle) that help to shape risk networks and behaviors. Finally, they conclude with a discussion of how these perspectives might help to reduce HIV transmission among African Americans. Friedman S, Cooper H, Osborne A. Structural and social contexts of HIV risk among African Americans. Am J Public Health. 2009;99(6):1002-1008.

Factors Associated With Event-Level Stimulant Use During Sex In A Sample of Older, Low-Income Men Who Have Sex With Men In Los Angeles

Prior research shows that stimulant use is consistently associated with high-risk sexual behavior in samples of men who have sex with men (MSM), but few studies have explored factors associated with use of crack or methamphetamine during sex during specific sexual events among older, very low-income MSM. This study examined stimulant use during the most recent sexual episodes in a sample of primarily older, very low-income MSM (n=779). Although crack use was more prevalent than methamphetamine use (33% vs. 22%), findings suggest that methamphetamine users may be at greater risk for HIV transmission. HIV prevalence was higher among methamphetamine users (49%) than among crack users (24%). Having unprotected sex (OR 2.77, 95% CI 1.46-5.26), having sex in a public sex venue (OR 3.63, 95% CI 1.52-8.64), having sex with an HIV positive rather than with an HIV negative partner (OR 6.15, 95% CI 2.14-17.62), having exchanged sex for money or drugs (OR 4.16, 95% CI 1.78-9.72), and having a higher number of sexual partners (OR 1.67, 95% CI 1.17-2.38) all were associated with increased odds of methamphetamine use during sex. Fewer high-risk behaviors were associated with increased odds of using crack during sex. Having unprotected sex was associated with increased odds of crack use during sex only when sex partners were perceived to be HIV negative rather than to be HIV positive or of unknown status. These findings on associations between stimulant use during sex and risk behaviors may be important to HIV prevention and drug treatment approaches for urban, older, very poor MSM. Ober A, Shoptaw S, Wang P, Gorbach P, Weiss R. Factors associated with event-level stimulant use during sex in a sample of older, low-income men who have sex with men In Los Angeles. Drug Alc Depend. 2009;102(1-3):123-129.

Cross-Cohort Heterogeneity Encountered While Validating A Model For HIV Disease Progression Among Antiretroviral Initiators

Researchers sought to evaluate a model for predicting time to AIDS or death among HIV-infected persons initiating highly active antiretroviral therapy (HAART). The model was constructed from 1,891 HAART initiators in the Collaborations in HIV Outcomes Research/US (CHORUS) cohort. The model's predictive ability was assessed using internal bootstrap validation techniques and data from 716 HAART initiators at Johns Hopkins HIV Clinical Cohort (JHHCC) in whom HIV disease was, in general, more advanced. The estimated concordance statistic was 0.632 with the bootstrap method and 0.625 in JHHCC. Mean predicted and observed 3-year AIDS-free survival for JHHCC was 0.76 and 0.73 (95% confidence interval [CI], 0.69-0.77), respectively; mean predicted and observed 5-year AIDS-free survival was 0.69 and 0.57 (95% CI, 0.52-0.62), respectively. Sensitivity analyses showed that the discrepancy between predicted and observed AIDS-free survival after 3 years could be due to differences in lost-to-follow-up rates between cohorts. The model was fair at using baseline characteristics to order patients' risk of disease progression, but did not accurately predict AIDS-free survival >3 years after HAART initiation. Different variable definitions, patient characteristics, and loss to follow-up highlight the challenges of using data from one cohort to predict AIDS-free survival in an independent cohort. Shepherd B, Sterling T, Moore R, Raffanti S,

Hulgan T. Cross-cohort heterogeneity encountered while validating a model for HIV disease progression among antiretroviral initiators. J Clin Epidemiol. 2009;62(7):729-737.

Association Between Tobacco Dependence and Quit Attempt Length

This study examined whether Rasch modeling would yield a unidimensional withdrawal sensitivity measure correlating with factors associated with successful smoking cessation. The psychometric Rasch modeling approach was applied to estimate an underlying latent construct (withdrawal sensitivity) in retrospective responses from smokers who reported quitting for 3 or more months at least once. A randomly selected convenience sample of 1644 adult members of an e-mail invitation-only web panel was drawn from consumer databases. The Lifetime Tobacco Use Questionnaire, a self-administered computerized questionnaire was used to assess tobacco use across the life-span, demographics, and ratings of the severity of withdrawal symptoms experienced in respondents' first and most recent quit attempts lasting 3 or more months. Rasch-modeled withdrawal sensitivity was generally unidimensional and was associated with longer periods of smoking cessation. One latent variable accounted for 74% of the variability in symptom scores. Rasch modeling with a single latent factor fitted withdrawal symptoms well, except for increased appetite, for which the fit was marginal. Demographic variables of education, gender, and ethnicity were not related to changes in sensitivity. Correlates of greater withdrawal sensitivity in cessation attempts of at least 3 months included younger age at first quit attempt and indicators of tobacco dependence. The relationship between tobacco dependence symptoms and Rasch-model withdrawal sensitivity demonstrates the utility of modeling to create an individual-specific sensitivity measure as a tool for exploring relationships among sensitivity, dependence, and cessation. Javitz H, Brigham J, Lessov-Schlaggar C, Krasnow R, Swan G. Association of tobacco dependence and quit attempt duration with rasch-modeled withdrawal sensitivity using retrospective measures. Addiction. 2009;104(6):1027-1035.

Patterns of Intermittent Smoking

Non-daily smokers comprise a substantial proportion of US smokers but there has been little study of their patterns of smoking, which are often assumed to reflect "social smoking." Researchers used Ecological Momentary Assessment methods to study smoking patterns in 27 non-daily smoking adults who recorded each cigarette smoked over three weeks by leaving a voice mail message indicating their circumstances at the time of smoking. All told, 689 cigarettes were recorded over 589 person-days of observation. On average, participants smoked on 67% of days, averaging 2.1 (SD=0.91) cigarettes per day on days they smoked; 22% of all cigarettes were smoked in bouts (within an hour of another cigarette). Altogether, 19% of cigarettes were smoked when drinking alcohol and 29% when participants were socializing. Smoking patterns varied widely across participants. A pair of hierarchical cluster analyses distinguished three groups: Those who smoked primarily (81% of cigarettes) in the daytime (Early smokers; n=15, 58% of total sample), those who smoked primarily (75% of cigarettes) at night (Late smokers; n=7, 27%), and a distinct, classic "Social smoking" group (n=4, 15% of total sample), who smoked mostly at night but also primarily when socializing or drinking (86% of their cigarettes), in the evening (71% of their cigarettes), on weekends (65% of their cigarettes), and in bouts (71% of their cigarettes). Overall, results suggest that non-daily smoking patterns are heterogeneous and that non-daily smokers may not be primarily social smokers. Shiffman S, Kirchner T, Ferguson S, Scharf D. Patterns of intermittent smoking: An analysis using ecological momentary assessment. Addict Behav. 2009;34(6-7):514-519.

Secrecy and Risk Among MSM In Tbilisi, Georgia

There is concern that the tremendous economic, social, and political upheavals that the Republic of Georgia has undergone in the years since the fall of the Soviet Union may have created an environment fertile for HIV transmission. Notably absent from official statistics and HIV-related research in Georgia is discussion of men who have sex with men (MSM) and, therefore, little is known about the MSM population or its potential to acquire or transmit HIV. Data were collected from 30 MSM recruited through a testing and counseling center in Tbilisi, the capital of Georgia. Two focus groups with six men each and 18 individual in-depth interviews were conducted between October 2006 and February 2007. The study participants described a Georgian culture that is largely intolerant of sexual contact between men. In describing the various forms of discrimination and violence that they would face should their sexual identities be discovered, the MSM in this sample described a variety of behaviors that they and other Georgian MSM undertake to conceal their sexual behavior. Many of these could put these men and their partners at risk for HIV. Although official HIV rates in Georgia are still low, results from this qualitative study indicate that efforts to educate and to provide unobtrusive and anonymous testing and counseling services to MSM may be critical to the deterrence of an HIV epidemic in the Republic of Georgia. Costenbader E, Otiashvili D, Meyer W, Zule W, Orr A, Kirtadze I. Secrecy and risk among MSM In Tbilisi, Georgia. AIDS Care. 2009;21(5):591-597.

Evaluation of a Patient Referral Contact Tracing Programme For Hepatitis B and C Virus Infection In Drug Injectors

Effective contact tracing for hepatitis B virus (HBV) and hepatitis C virus (HCV) infection could enhance disease control, especially in populations with low HBV vaccination rates and high prevalence of untreated HCV infection. Researchers evaluated a low-cost approach to HBV/HCV contact tracing in injection drug users (IDUs). Index cases (n=26) were IDUs who seroconverted to HBV and/or HCV during a prospective cohort study in Seattle. Interviewers elicited index cases' recent injection partners and administered recall cues and other techniques to boost recall. Index cases received vouchers for free hepatitis testing, which they were to give to locatable partners. Persons redeeming vouchers also received small monetary incentives. Most (26/40) seroconverters participated in the paid contact interviews. Index cases reported many partners (mean=17), and in the aggregate, index cases indicated they could refer more than one third of their elicited partners for testing. Overall, only 17 persons were ultimately referred and just eight of these were confirmed as partners sought for referral. The supplementary elicitation techniques, and especially the recall cues, increased reporting of injection partners substantially. The injection network constructed from reported partnerships was mostly connected and cyclic. Successful contact tracing in IDUs likely requires active involvement by public health staff to locate and notify exposed injection partners. Brewer D, Hagan H. Evaluation of a patient referral contact tracing programme for hepatitis B and C virus infection in drug injectors. Euro Surveill. 2009;14(14):5-9.

Differences In the Drinking Behaviors of Chinese, Filipino, Korean, and Vietnamese College Students

This study examined alcohol drinking behaviors across ethnic subgroups of Asian college students by gender, foreign-born status, and college-related living arrangements. The study sample included 753 male and female undergraduates between the ages of 18 and 27 years who self-identified as Chinese, Filipino, Korean, or Vietnamese and who varied in their foreign-born status. Participants completed a self-administered questionnaire on their

alcohol drinking practices. Analyses found that Korean and Filipino students reported higher levels of alcohol consumption compared with other Asian subgroups. Students living in on-campus dormitories and in off-campus apartments reported higher alcohol consumption than did those living at home. Being born in the United States was a significant predictor of higher levels of alcohol consumption for women but not for men. Results of this study indicate the need for campus alcohol education and prevention programs capable of responding to specific Asian subgroup needs. Lum C, Corliss H, Mays V, Cochran S, Lui C. Differences in the drinking behaviors of Chinese, Filipino, Korean, and Vietnamese college students. J Stud Alcohol Drugs. 2009;70(4):568-574.

Substance-Related Problems and Treatment Among Men Who Have Sex With Men In Comparison To Other Men In Chicago

This study compares a sample of urban men who have sex with men (MSM) with a general population sample of men in the same city on self-reported problems with substance use, substance dependence, and history of substance use treatment. Both samples were randomly selected using multistage probability methods and included 216 MSM and 242 men from the general population sample. All participants completed audio computer-assisted self-interviews, including questions on substance use, problems related to substance use experience-ed in the past 12 months, and substance treatment. Problem use of alcohol, marijuana, and cocaine did not differ between samples. Compared to men in the general population sample, MSM were significantly more likely to experience problems related to the use of sedatives, tranquilizers, or prescription pain relievers. Among MSM, history of substance treatment was associated with a positive HIV test, and treatment usually preceded HIV diagnosis. Findings suggest the need for further research on effective methods for integrating HIV prevention for MSM into substance treatment settings, including physician-administered buprenorphine treatment for opiate addiction. Mackesy-Amiti M, Fendrich M, Johnson T. Substance-related problems and treatment among men who have sex with men in comparison to other men in Chicago. J Subst Abuse Treat. 2009;36(2):227-233.

Causal Inference Methods for Estimating the Effects of Potential Public Health Interventions On Population Disease Burden

Causal inference methods allow estimation of the effects of potential public health interventions on the population burden of disease. Motivated by calls for epidemiologic research to be presented in ways that are more informative for intervention, the researchers present a didactic discussion of the steps required to estimate the population effect of a potential intervention using an imputation-based causal inference method and discuss the assumptions of and limitations to its use. An analysis of neighborhood smoking norms and individual smoking behavior is used as an illustration. The implementation steps include the following: modeling the adjusted exposure and outcome association; imputing the outcome probability for each individual while manipulating the exposure by "setting" it to different values; averaging these probabilities across the population; and bootstrapping confidence intervals. Imputed probabilities represent counterfactual estimates of the population smoking prevalence if neighborhood smoking norms could be manipulated through intervention. The degree to which temporal ordering, randomization, stability, and experimental treatment assignment assumptions are met in the illustrative example is discussed, along with ways that future studies could be designed to better meet the assumptions. With this approach, the potential effects of an intervention targeting neighborhoods, individuals, or other units can be estimated. Ahern J, Hubbard A, Galea S. Estimating the effects of potential public health interventions on population disease burden: a step-by-step illustration of causal inference methods. Am J Epidemiol.

2009;169(9):1140-1147.

The Resource Utilization of Women Who Use Violence In Intimate Relationships

Previous research has found high rates of help seeking among domestic violence victims. However, little is known about the help-seeking patterns of women who use violence (many of whom are also abused). Understanding the resources utilized by women who are violent toward their partners may aid in designing interventions that will help to reduce the women's violence as well as the victimization they may be experiencing. This study examines the resource utilization of 108 women who used violence against a male partner (94% of whom also experienced victimization). Findings revealed that almost all of the women utilized community resources in an attempt to manage the violence in their relationships; victimization was related to resource utilization via self-defense motives, avoidance coping, and posttraumatic stress symptoms; and greater resource utilization was related to lower levels of women's violence against their partners. Findings suggest that community resources may help prevent women's violence. Swan S, Sullivan T. The resource utilization of women who use violence in intimate relationships. J Interpers Violence. 2009;24(6):940-958.

Dimensions of Psychopathy In Relation To Suicidal and Self-Injurious Behavior

Externalizing psychopathology is associated with an increased risk for suicidal behavior. Within the externalizing domain, psychopathy may be an important construct for the understanding of which individuals are at particularly high risk. However, prior studies of psychopathy and suicidal behavior have not distinguished between suicide attempts and nonsuicidal self-injurious behavior (NSIB). The present study used data on 810 civil psychiatric patients from the MacArthur Violence Risk Assessment Project to examine the relationships between scores on the four dimensions of the Psychopathy Checklist: Screening Version (PCL: SV) and suicide attempts and nonsuicidal self-injurious behavior (NSIB). Results indicate that only the antisocial dimension of psychopathy is associated with suicide attempts. With regard to NSIB, an interaction was found such that, among African-Americans, NSIB was more prevalent at higher levels of antisociality. Present findings refine previous results from studies using the two-factor PCL:SV model and have important implications for the assessment of suicide risk. Swogger M, Conner K, Meldrum S, Caine E. Dimensions of psychopathy in relation to suicidal and self-injurious behavior. J Pers Disord. 2009;23(2):201-210.

Director's Report to the National Advisory Council on Drug Abuse - September, 2009

Research Findings - Prevention Research

Intensity of Prevention Training for Practitioners Related to Child Outcomes

This study examined an important but rarely investigated aspect of the dissemination process: the intensity of training provided to practitioners. Counselors in 57 schools were randomly assigned to 1 of 3 conditions: Coping Power-training plus feedback (CP-TF), Coping Power-basic training (CP-BT), or a comparison condition. CP-TF counselors produced reductions in children's externalizing behavior problems and improvements in children's social and academic skills in comparison to results for target children in both the comparison and the CP-BT conditions. Children were screened for participation in the study; children at high risk for aggressive behaviors were invited into the study. In the final sample, 168 children were in the CP-TF school, 183 were in the CP-BT school and 180 were in the comparison condition. Three sets of measures were used to generate data for this study: (1) program implementation, which was assessed through eight variables evaluating concrete aspects of program delivery and counselor engagement in delivering the program; (2) The National Youth Survey (NYS) questionnaire and the Behavior Assessment System for Children were used to assess child delinquency, substance use, and behavioral outcomes; and (3) the Outcome Expectations Questionnaire and the Alabama Parenting Questionnaire were used to assess child and parent mediating processes. Hierarchical Linear Modeling (HLM) was used for the analyses. Results showed that in comparison to children who worked with CP-BT counselors, children who worked with CP-TF counselors had relatively lower levels of teacher-rated and parent-rated externalizing behavior problems, lower rates of child-reported assaultive behaviors, and reductions in their expectations that aggressive behaviors would lead to good outcomes for them. In addition, it was found that training intensity was critical for successful dissemination, although the implementation mechanism underlying this effect remains unclear, as condition effects were not significant for completion of session objectives but were significant for the quality of counselors' engagement with children. Lochman J, Boxmeyer C, Powell N, Qu L, Wells K, Windle M. Dissemination of the coping power program: importance of intensity of counselor training. J Consult Clin Psychol. 2009;77(3):397-409.

Promising Prevention Program to Reduce Tobacco Use Rates among Indian Youth

Project MYTRI (Mobilizing Youth for Tobacco-Related Initiatives in India) is a group-randomized trial designed to assess a multi-component intervention aimed at preventing tobacco use among Indian adolescents. Thirty-two schools in Delhi and Channai, India, were recruited and randomly assigned to an

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intervention or delayed intervention control group. Baseline, intermediate, and outcome data were collected from 2 cohorts of 6th and 8th grade students in 2004; 14,063 students took part in the study and completed a survey in 2004, 2005, or 2006. The two-year intervention consisted of behavioral classroom curricula, school posters, a parental involvement component, and peer-led activism. The main outcome measures were self-reported use of cigarettes, bidis (small hand-rolled, often flavored cigarettes), chewing tobacco and future intentions to smoke or use chewing tobacco. Findings showed that students in the intervention group were significantly less likely than were students in the control group to exhibit increases in cigarette smoking or bidi smoking over the 2-year study period. They were also less likely to intend to smoke or chew tobacco in the future. Perry C, Stigler M, Arora M, Reddy S. Preventing tobacco use among young people in India: Project MYTRI. Am J Public Health. 2009;99(5):899-906.

Brief Family Intervention Improves Maternal Depression Which Mediates Effects on Problem Behaviors in Early Childhood

Maternal depression has been consistently linked to the development of child problem behavior, particularly in early childhood, but few studies have examined whether reductions in maternal depression serve as a mediator in relation to changes associated with a family-based intervention. The current study addressed this issue with a sample of 731 families receiving services from a national food supplement and nutrition program Ð The Women Infants and Children's (WIC) program. Families were recruited from 3 WIC sites in Urban, Suburban and Semi-Urban/Rural communities. Families with toddlers between ages 2 and 3 were screened and then randomized to a brief family intervention, the Family Check-Up, which included linked interventions that were tailored and adapted to the families needs. Follow-up intervention services were provided at age 3 and follow-up of child outcomes occurred at ages 3 and 4. Between ages 2 and 4, families received an average of 2.8 to 3 intervention sessions. Latent growth models revealed intervention effects for early externalizing and internalizing problems from 2 to 4, and reductions in maternal depression from ages 2 to 3. In addition, reductions in maternal depression mediated improvements in both child externalizing and internalizing problem behavior after accounting for the potential mediating effects of improvements in positive parenting. The results are discussed with respect to targeting maternal depression in future intervention studies aimed at improving early child problem behavior. In summary, this study of a brief, family-based prevention intervention, tailored to family needs, demonstrated benefits on maternal mental health, which mediated intervention effects on child behavior problems. Shaw D, Connell A, Dishion T, Wilson M, Gardner F. Improvements in maternal depression as a mediator of intervention effects on early childhood problem behavior. Dev Psychopathol. 2009;21(2):417-439.

Child's Genetic Risk for Negative Affect and Poor Self-Control Moderates the Impact of a Parenting Intervention on Parental Depressive Symptoms

A previous report in the Journal of Family Psychology described the results of a randomized prevention trial contrasting families who participated in the Strong African American Families Program (SAAF, a preventive intervention for rural African American parents and their 11-year-olds) with control families. The current report examines a novel contextual variable, child's genetic risk status for negative affect and poor self-control, as a moderator of treatment effects on caregiver's depression. Genetic data were obtained from youth saliva samples (n=109). The primary study hypothesis of differential program impact on caregiver depression as a function of youth genetic risk was confirmed. Among caregivers with initially elevated scores on the Center for Epidemiological Studies-Depression scale, an indicator of depressive

symptomology, SAAF participation was associated with greater impact on depressive symptoms among those whose children were at genetic risk. This finding suggests that effect size estimates based on full samples may underestimate the impact of prevention programs on at-risk subgroups, such as parents with depressive symptoms. Beach S, Brody G, Kogan S, Philibert R, Chen Y, Lei M. Change in caregiver depression in response to parent training: genetic moderation of intervention effects. J Fam Psychol. 2009;23(1):112-117.

Multidimensional Treatment Foster Care Program for Preschoolers Effects Electrophysio-logical Measures

The current study was designed to assess the impact of a family-based preventive intervention for preschool-aged, maltreated children in foster care by using behavioral measures (i.e., accuracy and reaction times) and electrophysiological measures (i.e., event-related potentials). These measures were recorded during a computerized flanker task designed to assess cognitive control and response monitoring. The sample was recruited from a larger randomized efficacy trial of Multidimensional Treatment Foster Care for Preschoolers (MTFC-P) which included foster children assigned to the intervention condition (n = 10), foster children assigned to a services-as-usual comparison condition (n = 13), and low-income, non-maltreated community children (n = 11). Overall the sample included 46 children (age range=4.87Ð6.99 years, M=5.94 years; 25 males and 21 females). Children's behavioral and electrophysiological performance on the task was generally consistent with previous research with adults and older children. There were no group differences on the behavioral measures of cognitive control or response monitoring. Notably, however, group differences were observed on the electrophysiological measures of response monitoring. Specifically, the foster children who received services as usual were significantly less responsive to performance feedback about errors than the foster children who received the intervention and the non-maltreated children. This methodology provides an important new approach for assessing the effects of psychosocial preventive interventions for foster care children at both the behavioral and the physiological levels of analysis. Bruce J, McDermott J, Fisher P, Fox N. Using behavioral and electrophysiological measures to assess the effects of a preventive intervention: a preliminary study with preschool-aged foster children. Prev Sci. 2009;10(2):129-140.

Involved-Supportive Parenting Moderates Impact of Genetic Vulnerability on Substance Use

The authors used a longitudinal, prospective design to investigate a moderation effect of parenting style in the association between a genetic vulnerability factor, a variable nucleotide repeat polymorphism in the promoter region of 5HTT (5-HTTLPR), and increases in youths' substance use. The primary study hypothesis predicted that involved-supportive parenting would attenuate the link between the 5-HTTLPR polymorphism and longitudinal increases in substance use. African American youths residing in rural Georgia (N = 253, mean age = 11.5 years) provided 4 waves of data on their substance use and the mothers of the youths provided data on their parenting practices. Genetic data were obtained from youths via saliva samples. Latent growth curve modeling indicated that 5-HTTLPR status (presence of 1 or 2 copies of the s allele) was linked with increases in substance use over time; however, this association was greatly reduced when youths received high levels of involved-supportive parenting. This study demonstrates that parenting processes have the potential to ameliorate genetic risk. Brody G, Beach S, Philibert R, Chen Y, Lei M, Murry V, Brown A. Parenting moderates a genetic vulnerability factor in longitudinal increases in youths' substance use. J Consult Clin Psychol. 2009;77(1):1-11.

Neural Correlates of Emotional Reactivity in Sensation Seeking

High sensation seeking has been linked to increased risk for drug abuse and other negative behavioral outcomes. This study explored the neurobiological basis of this personality trait using functional magnetic resonance imaging (FMRI). High sensation seekers (HSSs) and low sensation seekers (LSSs) viewed high- and low-arousal pictures. Participants were healthy adults, ages 18 through 25, whose scores on the Brief Sensation-Seeking Scale placed them in the top (HSSs; n=20; 10 males, 10 females) and bottom (LSSs; n=20; 10 males, 10 females) quartiles of population-based norms. Exclusion criteria included the presence of metal in or on the body, pregnancy, a prior neurological or psychiatric diagnosis, learning disability, a history of substance abuse or smoking, current use of central nervous system medications, left-handedness, and poor vision that could not be corrected. Comparison of the groups revealed that HSSs showed stronger FMRI responses to high-arousal stimuli in brain regions associated with arousal and reinforcement (right insula, posterior medial orbit frontal cortex), whereas LSSs showed greater activation and earlier onset of FMRI responses to high-arousal stimuli in regions involved in emotional regulation (anterior medial orbit frontal cortex, anterior cingulate). Furthermore, FMRI response in anterior medial orbit frontal cortex and anterior cingulate was negatively correlated with urgency. Finally, LSSs showed greater sensitivity to the valence of the stimuli than did HSSs. These distinct neurobiological profiles suggest that HSSs exhibit neural responses consistent with an overactive approach system, whereas LSSs exhibit responses consistent with a stronger inhibitory system. Joseph JE, Liu X, Jiang Y, Lynam D, Kelly TH. Neural correlates of emotional reactivity in sensation seeking. Psychol Sci. 2009;20(2):215-223.

Cigarette Smoking Following Rape

Although prior research has identified increases in cigarette smoking following trauma exposure, no studies have examined smoking following rape. The present study identified and characterized longitudinal trajectories (< 3 months, 3-6 months, and >6 months post assault) of smoking following a rape (N=152) in a sample of 268 female sexual assault victims participating in a forensic medical exam. Of participants endorsing smoking post rape, two trajectories were identified, with the majority of participants (74.6%) evidencing smoking with a slight decrease over time and remaining participants showing heavy smoking with a slight increase over time (25.4%). Heavy smokers consumed more than twice as many cigarettes as moderate smokers at 3-month post-rape, evidencing increased smoking over time. Additionally, having sustained an injury during rape increased the likelihood of being in the heavy smoking group. The association between injury and smoking may be related to attempts at pain management, or due to restricted activity levels. Early identification and efforts at reducing smoking with these subsets of rape victims are warranted. Ananda AB, Resnick HS, Nugent NR, Acierno R, Rheingold AA, Minhinnett R, Kilpatrick DG. Longitudinal trajectories of cigarette smoking following rape. J Trauma Stress. 2009;22(2):113-121.

Sexual Risk-Taking among African American College Men

This study investigated covariates related to risky sexual behaviors among young African American men enrolled at historically Black colleges and universities (HBCUs). Analyses were based on data gathered from 1837 male freshmen enrolled at 34 HBCUs who participated in the 2001 HBCU Substance Use Survey. The covariates of risky sexual behavior assessed included condom nonuse, engaging in sexual activity with multiple partners, and history of a sexually transmitted disease. Young Black men who had sex with men were

more likely to engage in risky sexual behaviors than were young men who had sex with women. Two additional factors, early onset of sexual activity and consumption of alcohol or drugs before sexual activity, were independently associated with modestly higher odds of sexual risk behaviors. Results suggest that services designed to prevent sexually transmitted diseases should be provided to all male college students and that prevention should address drug and alcohol use before sexual activity. Browne D, Clubb P, Wang Y, Wagner F. Drug use and high-risk sexual behaviors among African American men who have sex with men and men who have sex with women. Am J Public Health. 2009;99(6):1062-1066.

Stakeholder Perceptions of Prevention Modalities in Tijuana, Mexico

Injection drug use is a growing public health crisis along the U.S.-Mexican border and rising rates of blood-borne infections highlight the pressing need for harm reduction interventions. In-depth qualitative interviews were conducted with 40 stakeholders (i.e., pharmacists, legal professionals, health officials, religious officials, drug treatment providers, and law enforcement personnel) to explore the acceptability and feasibility of interventions to reduce drug-related harm in Tijuana, Mexico. Interviews were taped, transcribed verbatim, and translated. Content analysis indicated varying levels of support regarding the acceptance and feasibility of needle exchange programs (NEPs), syringe vending machines, and safer injection facilities (SIFs), structural barriers and suggestions for implementation. NEPs were deemed the most acceptable (75%); however, only half believed these could be feasibly implemented, citing barriers involving religion, police, and lack of political will, public awareness, and funding. Results from this study may assist policy strategists in implementing social-structural interventions that will help create enabling environments that facilitate the scale-up and implementation of harm reduction in Tijuana. Philbin MM, Mantsios A, Lozada R, Case P, Pollini RA, Alvelais J, Latkin C, Magis-Rodriguez C, Strathdee SA. Exploring stakeholder perceptions of acceptability and feasibility of needle exchange programmes, syringe vending machines and safer injection facilities in Tijuana, Mexico. Int J Drug Policy. 2009;20(4):329-335.

School-Based Tobacco Prevention Program in India Has Impact on Psychosocial Risk Factors for Intentions To Use Tobacco

The current study used mediation analysis to investigate whether Project MYTRI (Mobilizing Youth for Tobacco-Related Initiatives in India) altered the psychosocial risk factors as intended by the intervention, and whether the changes in psychosocial risk factors were responsible for altering students' tobacco use intentions. Multi-level mediation models were estimated using student data from baseline and 1-year follow-up surveys. Results indicated that the psychosocial risk factors Knowledge of Health Effects, Normative Beliefs, and Reasons to Use Tobacco were significant mediators between the intervention activities and students' tobacco use intentions. These findings are consistent with the broad goal of the first year curriculumÑto fortify students' knowledge and beliefs about tobacco useÑtoward the aim of reducing intentions to use tobacco. Bate SL, Stigler MH, Thompson MS, Arora M, Perry CL, Reddy KS. Psychosocial mediators of a school-based tobacco prevention program in india: results from the first year of Project MYRTI. Prev Sci. 2009;10:116-128.

Moderators of Outcome of a Brief Intervention for High Risk Toddlers and their Families

This study investigated moderators of change in an empirically supported

family-centered intervention (the Family Check-Up) for problem behavior in early childhood. Participants were 731 2- to 3-year-olds (49% girls; 28% African American, 50% European American, 13% biracial) from low-income families and had been screened for risk of family stress and early-onset problem behavior. They were randomized to the Family Check-Up intervention or to a no-intervention control group. Latent growth models examined sociodemographic and parent psychological risk factors as potential moderators of change in problem behavior between ages 2, 3, and 4. Results revealed 2 moderators of intervention effectiveness. Caregivers with the lowest educational levels were more responsive to the family-centered intervention, and 2-parent families were more responsive to the intervention. Other risk factors showed no predictive effects. Overall, findings suggest that this brief family-centered intervention can be effective in reaching the most distressed and most disadvantaged families, compared to those who are more advantaged. However, results suggest that more attention may be needed to address the intervention needs of single parent families in reducing problem behavior in early childhood. Gardner F, Connell A, Trentacosta C, Shaw D, Dishion T, Wilson M. Moderators of outcome in a brief family-centered intervention for preventing early problem behavior. J Consult Clin Psychol. 2009;77(3):543-553.

Preventing Multiple Negative Adolescent Outcomes Following Divorce

This paper presents experimental tests of the Oregon delinquency model applied within a randomized design of an at-risk sample of divorced, single mothers and their elementary school-aged sons. In the theoretical model, ineffective parenting practices and deviant peer association serve as the primary mechanisms for growth in adolescent delinquent behavior and early arrests. Participants included 238 mothers and sons who were initially recruited after the divorce, and when the child was in first, second or third grade. Multiple-method assessments of mothers and sons included delinquency as measured by teacher reports and official arrest records, parenting skills measured by observations of parent-child interactions, and deviant peer association as reported by focal boys. The intervention consisted of 14 sessions of parent group meetings held weekly. The intervention focused on five parenting practices: skill encouragement, limit setting, monitoring, problem solving, and positive involvement. To meet the needs of divorced families, the intervention included content to address issues related to divorce, including emotion regulation, managing inter-parental conflict, and addressing children's divorce related concerns. Intention-to-treat analyses were conducted using Latent Growth Models. Analyses of the 9-year follow-up data indicated that the Oregon model of parent management training significantly reduced teacher-reported delinquency and police arrests for focal boys. As hypothesized, the experiments demonstrated that improving parenting practices and reducing contacts with deviant peers served as mediating mechanisms for reducing rates of adolescent delinquency. As predicted, there was also a significant delay in the timing of police arrests for youth in the experimental as compared to the control group. Forgatch M, Patterson G, Degarmo D, Beldavs Z. Testing the Oregon Delinquency Model with 9-Year follow-up of the Oregon Divorce Study. Dev. Psychopathol. 2009;21(2):637-660.

Predictors of Response to Parent Management Training

This study examined whether attendance and quality of participation in parent management training predicted treatment response. Data were from 445 parents enrolled in the intervention condition of the Fast Track study (55% minority; 62% single; almost all of low socioeconomic status) who had 1st-grade children with severe conduct problems (445 children; 72% boys; 45% European American, 53% African American, and 2% Asian American, Latino, or

American Indian). Children were about 6 years old (M = 6.47 years, SD = 0.48) when the intervention began. Quality of participation in weekly parent groups was based on group leader ratings. Parent outcomes were based on interviewer ratings, behavioral observations, parent reports, and teacher ratings. Results of hierarchical linear models suggested that few family characteristics predicted attendance and that attendance was not related to changes in parenting over the year. However, several family characteristics predicted quality of participation in parent management training, and this in turn predicted changes in parenting Ð parental perceptions, warmth, physical punishment, and school involvement. Nix R, Bierman K, McMahon R, McMahon RT. How attendance and quality of participation affect treatment response to parent management training. J Consult Clin Psychol. 2009;77(3):429-438.

Delaying First Time Cigarette Use among Urban Youth

Two first-grade, universal preventive interventions were investigated to determine the influence of depressed mood, the interventions, and their interaction on delaying first time cigarette use through age 19. Both interventions were designed to improve student behavior and learning. One intervention focused on improving teacher behavior management and instructional skills (Classroom-Centered, CC); the other focused on the family-school partnership (FSP). Self-reports of smoking behavior and depressed mood were collected on an annual basis from grade 6 through age 19. The present analyses were restricted to the 563 youth who had never smoked by grade 6, or 83% of the original sample of first grade participants. Discrete-time survival analysis was used to examine the effects of depressed mood and the interventions on first tobacco cigarette smoked. Analyses revealed that depressed mood was associated with reduced time to the first cigarette smoked (adjusted hazard ratio, aHR: 1.4; 95% CI: 1.1-1.9), whereas the CC intervention prolonged the time before first cigarette smoked (aHR: 0.8; 95% CI: 0.7-0.9). No significant variation in the effect of depressed mood on first cigarette used was found by gender or grade, nor was the effect of the CC intervention moderated by depressed mood. FSP did not play a significant role in delaying participants first time smoking in middle or late adolescence. Authors proposed that strategies to prevent tobacco cigarette smoking should include both a focus on early success in elementary school as well as on depressed mood in adolescence. Wang Y, Browne D, Petras H, Stuart E, Wagner F, Lambert S, Kellam S, Ialongo N. Depressed mood and the effect of two universal first grade preventive interventions on survival to the first tobacco cigarette smoked among urban youth. Drug Alc Depend. 2009;100(3):194-203.

Adolescent Belief that Using Inhalants May Increase Social Acceptance and Gain Parental Attention

With an eye toward future prevention efforts, this study explored perceptions of inhalant utility among young adolescents in the United States. The study makes use of data gathered via nine focus groups conducted in Tucson, Arizona in 2004. A focus group approach was selected as the method of data collection in order to generate new insights and hypotheses regarding the nature of inhalant use among middle school students. Of the nine focus groups conducted, one consisted of only males and one of exclusively females (of the same grade). The remaining seven groups consisted of males and females of the same grade. Participants ranged from 11 to 16 years of age (M = 13.2). The race/ethnicity composition of the groups was as follows: American Indian/Alaska Native n=3 (6.4%); Black/African-American n=4 (8.5%); Hispanic or Latino/Latina n=15 (31.9%); White or Caucasian (non-Hispanic) n=19 (40.4%); Other n=6 (13.7%). Thirteen participants (27.7%) indicated some degree of past inhalant use. Three main themes emerged concerning the perceived utility of inhalant use: (1) inhalant use as a means of mental escape,

(2) inhalant use as a social tool, and (3) inhalant use as a parental relations tool (as a means to deal with lack of parental attention). Additionally, participants discussed an interaction hypothesis regarding inhalant use and popularity. Surprisingly, participants less frequently spoke of situations in which they were pressured to use inhalants, compared to situations in which young adolescents, believing that inhalants will increase social acceptance. This study represents the first step toward understanding the outcomes young adolescents associate with inhalant use. Siegel J, Alvaro E, Patel N, Crano W. "You would probably want to do it. Cause that's what made them popular": Exploring perceptions of inhalant utility among young adolescent nonusers and occasional users. Subst Use Misuse. 2009;44(5):597-615.

Parental Knowledge about Children's Whereabouts and Parental Warmth Inversely Relate to Youth Marijuana Use

Despite research indicating that effective parenting plays an important protective role in adolescent risk behaviors, few studies have applied theory to examine this link with marijuana use. In the current study, secondary analysis were obtained from the restricted version of the National Survey of Parents and Youth, which was conducted to evaluate the National Youth Anti-Drug Media Campaign (N = 2,141 adolescents aged 12-18, 51.1% male). As posited by the Theory of Planned Behavior (TPB), this study hypothesized that parental knowledge (of adolescent activities and whereabouts) and parental warmth are antecedents of adolescents' marijuana beliefs-attitudes, subjective norms, and perceived behavioral control. These three types of beliefs were hypothesized to predict marijuana intention, which in turn was hypothesized to predict marijuana consumption. Results of confirmatory factor analysis corroborated the psychometric properties of the two-factor parenting structure as well as the five-factor structure of the TPB. Further, the proposed integrative predictive framework, estimated with a latent structural equation model, was largely supported. Parental knowledge of adolescent activities and whereabouts inversely predicted pro-marijuana attitudes, subjective norms, and perceived behavioral control; parental warmth inversely predicted pro-marijuana attitudes and subjective norms. Marijuana intention, but not perceived behavioral control, predicted marijuana use 1 year later. In households with high parental knowledge, parental warmth also was perceived to be high ($r = .54$, $p < .001$). Owing to the analysis of nationally representative data, results are generalizable to the United States population of adolescents 12-18 years of age. Lac A, Alvaro E, Crano W, Siegel J. Pathways from parental knowledge and warmth to adolescent marijuana use: An extension to the theory of planned behavior. Prev Sci. 2009;10(1):22-32.

Predicting Substance Use and Sexual Behavior in Subgroups of Hispanic Adolescents

Hispanic adolescents are a rapidly growing population and are highly vulnerable to substance abuse and HIV infection. Many interventions implemented thus far have been "one size fits all" models that deliver the same dosage and sequence of modules to all participants. To more effectively prevent substance use and HIV in Hispanic adolescents, different risk profiles and subgroups should be considered. This used intrapersonal risks (e.g., attitudes toward risk taking), and eco-develop-mental risks (e.g., negative parenting), to identify Hispanic adolescent subgroups and to compare substance use rates and sexual behavior by risk subgroup. The study participants were 254 Hispanic adolescents enrolled in a substance abuse and HIV prevention study. The results indicate that a larger proportion with high eco-developmental risk (irrespective of the intrapersonal risk for sub-stance use) report lifetime and past 90-day cigarette and illicit drug use. In contrast, a larger propor-tion with high intrapersonal risk for unsafe sex (irrespective of eco-developmental risk) report early sex initiation and sexually transmitted disease incidence. Prado G, Schwartz S,

Maldonado-Molina M, Huang S, Pantin H, Lopez B, Szapocznik J. Eco-developmental x intrapersonal risk: substance use and sexual behavior in Hispanic adolescents. Health Educ Behav. 2009;36(1):45-61.

Predictors of Functional Resilience in Children of Individuals in Methadone Treatment

This study describes the adversities experienced by a sample of children of opiate-dependent parents, examines criteria for young adulthood functional resilience, and tests parent, child, and school predictors of resilience. The Focus on Families (FOF) project was a randomized trial of a family-focused intervention with opiate-dependent individuals in methadone treatment and their children. Analyses were conducted on data from the children in treatment and control families during the original study (1991-1995) and a long-term follow-up interview (2005-2006). Although all participants had an opiate-dependent parent, 70% experienced two or more additional types of childhood adversity and 20% experienced four or more types. A total of 24% met the following three criteria for functional resilience at the time of their young-adult interview: (1) working or being enrolled in school, (2) no history of substance abuse or dependence, and (3) no adult criminal charges in the prior 5 years. The FOF intervention did not significantly predict functional resilience. Girls were approximately four times more likely to exhibit resilience than boys. Experiencing a wider range of adversities in addition to having an opiate-dependent parent did not reduce the likelihood of functional resilience. Of the five child, family, and school predictors tested, only lower externalizing or internalizing problems in childhood were significantly associated with the likelihood of functional resilience (odds ratio=.30, p=.04) as a young adult. These findings suggest that early intervention with families with opiate-dependent parents to prevent and reduce internal-izeing and externalizing problems in their children holds the most promise of supporting resilient adaptation in early adulthood. Skinner M, Haggerty K, Fleming C, Catalano R. Predicting function-al resilience among young-adult children of opiate-dependent parents. J Adol. Health. 2009;44(3): 283-290.

Black-White Similarities in Parental Influences on Teen Smoking

The health risks associated with smoking disproportionately burden Blacks, and Black adults are more likely to smoke than are White adults. Most adult smokers have their first smoking experience as teenagers; however, rates of smoking initiation during adolescence remain lower among Black compared with White youth. The level and impact of family and peer risk and protective factors on adolescent smoking across both groups were modeled prospectively from 8th to 10th grade in a sample of 331 (Black n = 162, White n = 168) families using data from self-administered computer-assisted questionnaires. Predictors included parent smoking, guidelines against substance use, monitoring, consistent discipline, attachment to parents, and association with deviant peers. Mean-level differences indicated greater risk for Black teens in some cases and higher protection in others. Multiple-group structural equation modeling indicated no race differences. Several factors affected both groups: (a) parenting factors reduced association with deviant peers, (b) association with deviant peers increased the risk of smoking in the 10th grade, and (c) teens were more likely to smoke if their parents smoked. The authors propose that reduced smoking among Black teens compared with White teens may be due to the protection provided by clear parental guidelines about substance use and clearly stated consequences for failure to observe those guidelines. Skinner M, Haggerty K, Catalano R. Parental and peer influences on teen smoking: are white and black families different? Nicotine Tob Res. 2009;11(5):558-563.

Social Context and Identity are Related to Problem Behavior in

High-Risk Hispanic Adolescents

The present study was designed to examine the extent to which (a) family and school functioning and (b) personal and ethnic identity are associated with conduct problems, drug use, and sexual risk taking in a sample of 227 high-risk Hispanic adolescents. Adolescents participated in the study with their primary parents, who were mostly mothers. Adolescents completed measures of family and school functioning, personal and ethnic identity, conduct problems, and drug use. Parents completed measures of family functioning and adolescent conduct problems. Results indicated that school functioning and personal identity confusion were related to alcohol use, illicit drug use, and sexual risk taking indirectly through adolescent reports of conduct problems. Adolescent reports of family functioning were related to alcohol use, illicit drug use, and sexual risk taking through school functioning and conduct problems. Results are discussed in terms of the problem behavior syndrome and in terms of the finding of relative independence of contextual and identity variables vis-ˆ-vis conduct problems, substance use, and sexual risk taking. Schwartz SJ, Mason CA, Pantin H, Wang W, Brown CH, Campo A, Szapocznik J. Relationships of social context and identity to problem behavior among high-risk Hispanic adolescents. Youth Soc. 2009;40(4):541-570.

Evidence of Memory Deficits and Hippocampal Dysfunction in HIV+ Women

Neurocognitive studies of HIV typically target executive functions dependent on frontostriatal circuitry. The integrity of medial temporal systems has received considerably less attention despite high hippocampal viral load. Studies also predominately involve HIV+ men, though HIV+ women may be at increased risk for cognitive dysfunction due to the high prevalence of psychosocial/mental health problems and lower educational attainment. This preliminary investigation of episodic memory and its neural correlates in HIV-infected and at-risk uninfected women was conducted with 54 HIV+ and 12 HIV- women (mean age = 43 years; 86% African American) recruited from the Chicago site of the Women's Interagency HIV Study. Participants completed standardized tests of verbal and visual episodic memory, working memory, and executive function. A subset of 11 women also underwent functional MRI during a delayed verbal episodic memory task. HIV serostatus predicted significantly lower immediate and delayed verbal episodic memory, working memory, and visual memory. Preliminary neuroimaging findings revealed group differences in bilateral hippocampal function, with HIV+ women showing decreased activation during encoding and increased activation during delayed recognition. These alterations correlated with worse episodic verbal memory. These results suggest that verbal episodic memory deficits are evident in HIV+ women and may be associated with hippocampal dysfunction at both encoding and retrieval. Maki P, Cohen M, Weber K, Little D, Fornelli D, Rubin L, Perschler P, Gould F, Martin E. Impairments in memory and hippocampal function in HIV-positive vs. HIV-negative women: A preliminary study. Neurology. 2009;72(19):1661-1668.

Disinhibited Social Behavior among Internationally Adopted Children

Post-institutionalized children frequently demonstrate persistent socioemotional difficulties. For example, some post-institutionalized children display an unusual lack of social reserve with unfamiliar adults. This behavior, which has been referred to as indiscriminate friendliness, disinhibited attachment behavior, and disinhibited social behavior, was examined by comparing children internationally adopted from institutional care to children internationally adopted from foster care and children raised by their biological families.

Etiological factors and behavioral correlates were also investigated. The study sample included 120 6- to 7-year-old children. The children were equally distributed across the institutional care, foster care, and non-adopted groups. The adopted children had been internationally adopted into the United States after receiving institutional care or foster care for the majority of their lives. The children in the institutional care group had spent at least 70% of their lives in institutional care and no more than 6 months in family-based care prior to adoption, and the children in the foster care group had spent at least 70% of their lives in foster care and no more than 2 months in institutional care prior to adoption. The adopted children were required to have been adopted prior to the age of 36 months to ensure adequate time in their adoptive homes. The children in the non-adopted group were raised by their biological families in the United States. The groups did not differ in terms of age, and there were 30 girls and 10 boys in each group. Analyses showed that both groups of adopted children displayed more disinhibited social behavior than the non-adopted children. Of the etiological factors examined, only the length of time in institutional care was related to disinhibited social behavior. Disinhibited social behavior was not significantly correlated with general cognitive ability, attachment-related behaviors, or basic emotion abilities. However, this behavior was negatively associated with inhibitory control abilities even after controlling for the length of time in institutional care. These results suggest that disinhibited social behavior might reflect underlying deficits in inhibitory control. Bruce J, Tarullo A, Gunnar M. Disinhibited social behavior among internationally adopted children. Dev Psychopathol. 2009;21(1):157-171.

Development and Validation of a Questionnaire for Determining Marijuana Use Motives

Relatively little research has evaluated motives for using marijuana based on users' self-reported reasons. This article details the construction and psychometric validation of a new marijuana motives questionnaire. Participants included 346 marijuana-using college students who completed online assessments regarding their motives for, frequency of, and problems associated with their marijuana use. Exploratory and confirmatory factor analysis supported a 12-factor scale, including the following: (1) Enjoyment, (2) Conformity, (3) Coping, (4) Experimentation, (5) Boredom, (6) Alcohol, (7) Celebration, (8) Altered Perception, (9) Social Anxiety, (10) Relative Low Risk, (11) Sleep/Rest, and (12) Availability. Regression results indicated enjoyment, boredom, altered perception, relative low-risk, and sleep/rest were each uniquely associated with greater frequency of use. Experimentation and availability motives were associated with less use. After accounting for use, coping and sleep/rest were associated with significantly more consequences whereas enjoyment was associated with fewer consequences. Additional results comparing the scale to an existing marijuana motives measure indicated comparatively good convergent validity. Lee C, Neighbors C, Hendershot C, Grossbard J. Development and preliminary validation of a comprehensive marijuana motives questionnaire. J Stud Alcohol Drugs. 2009;70(2):279-287.

Efficiency and Quality of Mixed-mode Surveys to Assess Sexual Activity and Drug Use

This study examines whether it is possible to take advantage of the time and cost efficiencies of a Web mode of survey administration while minimizing coverage and non-response error by offering in-person interviews for participants who lack Internet access or are reluctant to use the Web mode. Furthermore the investigators examine whether responses to questions concerning sexual activity and drug use differ by mode of survey administration. This project is nested in the long-term follow up of a prevention study, and participants in the study (n=386) were on average 18 years old at the time of the survey. Participants in the study were randomly assigned to two

conditions of mixed-mode approaches to data collection. One condition started with a Web survey and followed with an in-person interview for non-completers after a specified period of time while the other condition began with an in-person interview and followed with a Web survey for non-completers. The two conditions are compared with regard to cost, time, and error. Overall completion rates are compared for the two conditions. The Web-first condition resulted in cost savings although the overall completion rates for the 2 conditions were similar. On average, in-person-first condition participants completed surveys earlier in the field period than Web-first condition participants. Based on intent-to-treat analyses, little evidence was found of condition effects on response bias, with respect to rates or levels of reported behavior. McMorris B, Petrie R, Catalano R, Fleming C, Haggerty K, Abbott R. Use of web and in-person survey modes to gather data from young adults on sex and drug use: an evaluation of cost, time, and survey error based on a randomized mixed-mode design. Eval Rev. 2009;33(2):138-158.

Pilot Prevention Program for Homeless Women in the Transition to Adulthood

Among young women who are impoverished and homeless, the transition to adulthood (ages 18-25) is associated with alcohol and drug use, risky sexual activity, and increased risk of being victimized by intimate partner violence. "The Power of YOU," a program using motivational interviewing, was designed to address these problems. This program was piloted with 31 homeless women (ages 18-25) in 7 focus groups. Women completed questionnaires assessing background characteristics and satisfaction at the end of each group. Each group was followed by a feedback session that was audio-recorded and transcribed. Women expressed satisfaction and provided consistently positive feedback on the intervention, reporting that it was 'helpful to know how to put a condom on' and that they appreciated the attention paid to safety planning. Results from this pilot suggest this program may hold promise in helping homeless young women in the transition to adulthood and that the approach of motivational interviewing appeared appropriate for this population. Wenzel SL, D'Amico EJ, Barnes D, Gilbert ML. A pilot of a tripartite prevention program for homeless young women in the transition to adulthood. Women's Health Issues. 2009;19(3):193-201.

Director's Report to the National Advisory Council on Drug Abuse - September, 2009

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

Intermittent Marijuana Use is Associated with Improved Retention in Naltrexone Treatment for Opiate-Dependence

Naltrexone is a theoretically promising alternative to agonist substitution treatment for opioid dependence, but its effectiveness has been severely limited by poor adherence. This study examined, in an independent sample, a previously observed association between moderate cannabis use and improved retention in naltrexone treatment. Opioid dependent patients (N = 63), admitted for inpatient detoxification and induction onto oral naltrexone, and randomized into a six-month trial of intensive behavioral therapy (Behavioral Naltrexone Therapy) versus a control behavioral therapy (Compliance Enhancement), were classified into three levels of cannabis use during treatment based on biweekly urine toxicology: abstinent (0% cannabis positive urine samples); intermittent use (1% to 79% cannabis positive samples); and consistent use (80% or greater cannabis positive samples). Intermittent cannabis users showed superior retention in naltrexone treatment (median days retained = 133), compared to abstinent (median = 35) or consistent users (median = 35). Intermittent cannabis use was also associated with greater adherence to naltrexone pill-taking. Treatment interacted with cannabis use level, such that intensive behavioral therapy appeared to moderate the adverse prognosis in the consistent cannabis use group. Experimental studies are needed to directly test the hypothesis that cannabinoid agonists exert a beneficial pharmacological effect on naltrexone maintenance and to understand the mechanism. Raby WN, Carpenter KM, Rothenberg J, Brooks AC, Jiang H, Sullivan M, Bisaga A, Comer S, Nunes EV. Intermittent marijuana use is associated with improved retention in naltrexone treatment for opiate-dependence. Am J Addict. 2009 Jul-Aug;18(4):301-308.

Extended Treatment of Older Cigarette Smokers

Dr. Sharon Hall and colleagues at the University of California San Francisco conducted the present study to determine the efficacy of extended cognitive behavioral and pharmacological interventions in older smokers (greater than 49 years of age) and to determine if gender differences in efficacy existed. Participants who smoked at least 10 cigarettes per day received a 12-week treatment that included group counseling, nicotine replacement therapy (NRT) and bupropion. After initial treatment, participants were randomized to one of four conditions, independent of smoking status. The four conditions were: 1) Standard Treatment (ST; no further treatment; 2) Extended NRT (E-NRT; 40 weeks of nicotine gum availability); 3) Extended Cognitive Behavioral Therapy (E-CBT; 11 cognitive behavioral sessions over a 40-week period); or 4) E-CBT plus E-NRT (E-Combined: 11 cognitive behavioral sessions plus 40 weeks

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nicotine gum availability). Participants were assessed at weeks 24, 52, 64, and 104 for smoking abstinence. The E-CBT condition produced high abstinence rates that were maintained throughout the two year study period and was significantly more effective than E-NRT and ST across that period. The authors concluded that extended cognitive behavioral treatments can produce high and stable cigarette abstinence rates for both men and women. NRT does not add to the efficacy of extended CBT, and may hamper its' efficacy. Further research is needed to determine if these results can be replicated in a sample with a greater range of ages, and improved upon with the addition of medications other than NRT. Hall SM, Humfleet GL, Munoz RF, Reus VI, Robbins JA, Prochaska JJ. Extended treatment of older cigarette smokers. Addiction. 2009 Jun;104(6):1043-1052.

Contingency Management and Motivational Enhancement for College Student Smokers

Dr. Tevyaw and colleagues at Brown University conducted this study to examine the efficacy of Motivational Enhancement Therapy (MET) and Contingency Management (CM) for college student smokers. In a 2 x 2 experimental design, 110 nontreatment-seeking daily smokers were randomly assigned to three weeks of CM vs. noncontingent reinforcement (NR) and to three individual sessions of MET vs. a relaxation control. Carbon monoxide (CO) samples were collected twice daily for three weeks. Participants earned $5 for providing each sample and those randomized to CM earned escalating monetary rewards based on CO reductions (week 1) and smoking abstinence (weeks 2-3). The participants assigned to the CM condition had significantly lower CO levels than those assigned to NR. Those in the CM and MET groups reported greater interest in quitting smoking post-treatment, but rates of abstinence at follow-up were very low (4% at 6-month follow-up) and did not differ by group. The authors suggest that the short-term efficacy of CM is supported for college students. However future research should explore enhancements to CM, including a longer intervention period and the recruitment of smokers who are motivated to quit. Tevyaw T, Colby SM, Tidey JW, Kahler CW, Rohsenow DJ, Barnett NP, Gwaltney CJ, Monti PM. Contingency management and motivational enhancement: A randomized clinical trial for college student smokers. Nicotine & Tobacco Research. 2009, Jan;11(6): 739-749.

Mediators of the Relationship Between NRT and Smoking Abstinence Among People Living with HIV/AIDS

Researchers at Brown University conducted this study to determine if psychosocial variables, such as self-efficacy and decisional balance, mediated the relationship between nicotine replacement therapy (NRT) and long-term abstinence. Multivariate analyses identified self-efficacy to refuse cigarettes and decisional balance (beliefs about smoking) as predictors of 6-month abstinence and therefore potential mediators of the NRT treatment effect found in this sample. Findings of this study provide evidence that improving self-efficacy to resist smoking temptations may be a psychological mechanism that results from the success experiences boosted by NRT treatments. Racial/ethnic differences were found among participants. Hispanic Americans were almost three times as likely to be abstinent compared with European American participants, which was due in part to larger gains in self-efficacy from baseline to 6-month follow-up. African Americans' self-efficacy to quit was of comparable magnitude to Hispanics. However, those improvements did not translate into improved abstinence rates. In sum, this study found the efficacy of NRT compliance on 6-month quit rates to be mediated by positive changes in self-efficacy to resist temptations to smoke and, to a lesser extent, changes in beliefs about the pros and cons of quitting smoking. This was the case for all ethnic-racial groups, with the exception of African Americans in which

Planned Meetings

Publications

Staff Highlights

Grantee Honors

increased self-efficacy did not translate to abstinence. Specific psychosocial factors should be addressed with greater awareness of how cultural and social contextual factors impact treatment response. Stanton CA, Lloyd-Richardson EE, Papandonatos GD, de Dios MA, Niaura R. Mediators of the relationship between nicotine replacement therapy and smoking abstinence among people living with HIV/AIDS. AIDS Education and Prevention. 2009;21:Supplement A: 65-80.

Depressive Symptoms Predict Smoking Status among Pregnant Women

This study conducted by researchers at the University of Vermont compared smokers and spontaneous quitters on psychological functioning. Data were obtained from 127 women enrolled in a trial to test smoking cessation and relapse prevention interventions during pregnancy and postpartum. Smokers and spontaneous quitters differed on sociodemographic and smoking characteristics. In terms of psychological functioning, smokers reported significantly more depression/anxiety symptoms and withdrawn behavior than spontaneous quitters. Higher depression scores were associated with increased odds of continued smoking, even after controlling for sociodemographic and smoking variables in multivariate analyses. These results suggest that depressive symptoms may be an independent contributor to the problem of continued smoking during pregnancy, which may have implications for smoking-cessation interventions among pregnant women. Linares Scott TJ, Heil SH, Higgins ST, Badger GJ, Bernstein IM. Depressive symptoms predict smoking status among pregnant women. Addictive Behaviors. 2009;34:705-708.

Short-Term Weight Gain by Menstrual Phase Following Smoking Cessation in Women

Dr. Sharon Allen and colleagues at the University of Minnesota conducted this trial to examine short-term weight gain by menstrual phase following a quit attempt. The aim of the study was to assess whether greater weight gain, due to smoking abstinence, occurs during luteal verses follicular phase. Women were randomized to quit smoking during the follicular or luteal phase of their cycle and followed for four weeks. The results showed that participants who quit smoking experienced significantly more weight gain than those who quit for less than 24 hours. However, if smoking abstinence is achieved, the menstrual phase in which a woman quits does not play a role in short-term weight gain. Allen SS, Allen AM, Mooney M, Bade T. Short-term weight gain by menstrual phase following smoking cessation in women. Eating Behaviors. 2009; 10:52-55.

Stigma, Disclosure, and Depressive Symptoms Among Informal Caregivers of People Living with HIV/AIDS

Informal care receipt is associated with better HIV treatment outcomes among patients vulnerable to treatment failure. Yet, informal caregiving can be highly stressful, leading to distress and cessation of caregiving. Research on factors contributing to informal caregivers' psychological distress may advance our understanding of how to improve caregivers' well-being and sustained HIV caregiving for a vulnerable population. The authors examined relationships among caregiver stigma, disclosure, and depressive symptoms in a cross-sectional sample of 207 informal caregivers of people living with HIV/AIDS (PLWHAs) in Baltimore, Maryland. Caregivers were primarily African American, low-income, urban adults participating in the Action, Resources, and Knowledge (ARK) study, which recruited urban PLWHAs and their main supporters. Results indicated that among caregivers, HIV caregiving-related

stigma was associated with more depressive symptoms, while disclosure of caregiving status was associated with fewer symptoms. The authors also explored the buffering effect of disclosure in the relationship between stigma and depressive symptoms. Results indicated that among those who reported greater stigma, there was a significant decrease in depressive symptoms as the number of disclosures increased. In contrast, participants who indicated lower stigma had consistently fewer depressive symptoms regardless of number of disclosures. These results suggest the need for interventions to address high levels of depressive symptoms among informal HIV caregivers, particularly those who report greater caregiving stigma and less disclosure of their caregiver status. In addition, future research should examine these relationships further using longitudinal data from informal caregivers and their care recipients. Mitchell MM, Knowlton A. Stigma, disclosure, and depressive symptoms among informal caregivers of people living with HIV/AIDS. AIDS Patient Care STDS. 2009 July. [E-pub ahead of print].

Developing an Integrated Treatment for Substance Use and Depression using CognitiveÐBehavioral Therapy

Providing a unified treatment approach to meet the substance abuse and mental health needs of clients is the preferred model for addressing co-occurring disorders. The authors developed a group-based cognitive-behavioral (CBT) integrated treatment for depression and substance use disorders (SUD) that could be delivered by counselors in SUD treatment settings and evaluated its feasibility and acceptability. The authors conducted an in-depth case study examining one implementation of the treatment using 15 focus groups with clients and semistructured interviews with counselors and administrators. Using CBT as a treatment approach to integrate the treatment was widely accepted by clients, counselors, and administrators. Clients stated the treatment was applicable to multiple aspects of their lives and allowed them to recognize their clinical improvements over time. Counselors and administrators discussed challenges for long-term feasibility. Key decisions used to develop the treatment and recommendations for implement-ting integrated care in SUD settings are discussed. Osilla KC, Hepner KA, Munoz RF, Woo SW, Watkins K. Developing an integrated treatment for substance use and depression using cognitiveÐbehavioral therapy. Journal of Substance Abuse Treatment. 2009 June [E-pub ahead of print].

A Randomized Controlled Trial of a Money Management-Based Substance Use Intervention

Money management has been implemented, often in bundled interventions, as a strategy to counteract spending of public support checks and other funds on drugs and alcohol. The authors conducted a randomized controlled trial of a voluntary money management program as an adjunctive treatment for patients in treatment for mental illness, substance use disorders, or both. In the advisor-teller money manager (ATM) intervention, a money manager stores patients' checkbooks and automated bank cards, trains patients to manage their own funds, and links spending to activities related to their treatment goals. Eighty-five veterans with recent use of alcohol or cocaine were randomly assigned to 36 weeks of the ATM intervention or a control intervention (completion of a simple financial workbook). With ATM, 75% of veterans gave their checkbook to their money manager to hold, and participants attended significantly more therapy sessions than those assigned to the control therapy (mean of 20.6 versus 8.1 sessions). Although participants assigned to ATM did not show significantly greater improvement over time on the primary outcomes (self-reported abstinence from alcohol and cocaine and negative urine tests for cocaine metabolite), they reduced their Addiction Severity Index drug and alcohol use composite scale scores more rapidly than the control group. High rates of abstinence in both groups created a ceiling effect, limiting the power to

detect improved abstinence rates. In this relatively small trial, ATM, a money management intervention, showed promise in engaging patients, improving their money management, and improving some substance abuse outcomes. Rosen MI, Carroll KM, Stefanovics E, Rosenheck RA. A randomized controlled trial of a money management-based substance use intervention. Psychiatric Services. 2009 Apr;60(4): 498-504.

Depression Among Methamphetamine Users: Association with Outcomes from the Methamphetamine Treatment Project at 3-Year Follow-Up

Although depression is highly comorbid with substance use disorders, little is known about the clinical course and outcomes of methamphetamine (MA) users with depressive symptoms and syndromes. In this study of MA-dependent individuals entering psychosocial treatment, the authors predicted that (1) depressive symptoms would decline during treatment, an effect that would vary as a function of MA use and (2) depression diagnoses post-treatment would be associated with poorer outcomes. Participants (N = 526) were assessed for depression, substance use, and psychosocial outcomes at baseline, treatment discharge, and 3-year follow-up. Depressive symptoms declined significantly during treatment, an effect that was greatest among those who abstained from MA. Major depression at follow-up was associated with poorer MA use outcomes and impairment across multiple domains of functioning. The findings highlight the relationship of depressive symptoms and diagnoses to treatment outcomes, and suggest a need for further studies of depression in populations using MA. Glasner-Edwards S, Marinelli-Casey P, Hillhouse M, Ang A, Mooney LJ, Rawson R, Methamphetamine Treatment Project Corporate Authors. Depression among methamphetamine users: Association with outcomes from the methamphetamine treatment project at 3-year follow-up. Journal of Nervous and Mental Dis. 2009 Apr;197(4):225-231.

The Need for Smoking Cessation Among HIV-Positive Smokers

Most HIV-positive persons in the U.S. smoke cigarettes. Despite substantial clinical advances in HIV care in the era of highly active antiretroviral therapy (HAART), HIV-positive persons are at high risk of tobacco-related disease and death. HIV-positive persons have complex social, economic, psychiatric, and medical needs that may impact smoking behavior and response to smoking cessation interventions, but there is a dearth of research on smoking cessation interventions tailored to HIV-positive persons. HIV care providers should treat tobacco use with the array of evidence-based smoking cessation treatments available, updating their clinical practice as new data emerge. This article reviews the literature on the health consequences of tobacco use in HIV-positive persons, the treatment of tobacco dependence, and the research to date on smoking cessation interventions in HIV-positive persons, and it presents recommendations for future research and intervention. Nahvi, S, Cooperman, NA. Review: The need for smoking cessation among HIV-positive smokers. AIDS Education and Prevention. 2009 Jun;21(3 Suppl):14-27.

Self-Management of Injection-Related Wounds Among Injecting Drug Users Injection-related wounds are an important complication of injection drug use

This study describes behaviors related to self-management of injection-related wounds and identifies factors associated with behaviors that may increase the potential for harm. The authors conducted interviews with 101 injecting drug users in Washington, DC. A total of 82 (81.2%) injecting drug users reported ever having an injection-related wound, and of these 93.9% reported self-management of their wounds. The most commonly reported behaviors were

cleaning and applying ointment to wounds; however, several participants engaged in behaviors determined to be more potentially harmful, including acquiring antibiotics without prescriptions and manipulating their wounds. In multivariate analysis, injecting drug users who had ever injected amphetamines were more likely to engage in potentially harmful self-management behaviors (adjusted odds ratio = 4.38; 95% confidence interval = 1.15-16.64). Self-management of injection-related wounds is common and certain behaviors may increase the potential for harm. Further research is needed to best focus efforts to improve wound care for injecting drug users. Roose RJ, Hayashi AS, Cunningham CO. Self-management of injection related wounds among injecting drug users. J Addict Dis. 2009;28(1):74-80.

Successful Treatment of Chronic Hepatitis C with Pegylated Interferon in Combination with Ribavirin in a Methadone Maintenance Treatment Program

Injection drug users constitute 60% of the more than 4 million people in the United States with hepatitis C virus (HCV), including many methadone maintenance patients. Few data exist describing clinical outcomes for patients receiving HCV treatment on-site in methadone maintenance settings. In this retrospective study, the authors describe clinical outcomes for 73 patients receiving HCV treatment on-site in a methadone maintenance treatment program. Fifty-five percent of patients achieved end-of-treatment response, and 45% achieved sustained viral response. These treatment response rates are nearly equivalent to previously published HCV treatment response rates, despite high prevalence of ongoing drug use (49%), psychiatric comorbidity (67%), and HIV coinfection (32%). These data show that on-site HCV treatment with pegylated interferon and ribavirin is effective in methadone-maintained patients, many of whom are active drug users, psychiatrically ill, or HIV coinfected, and that methadone maintenance treatment programs represent an opportunity to safely treat chronic hepatitis C. Litwin AH, Harris Jr. KA, Nahvi S, Zamor PJ, Soloway IJ, Tenore PL, Kaswan D, Gourevitch, MN, Arnsten JH. Successful treatment of chronic hepatitis C with pegylated interferon in combination with ribavirin in a methadone maintenance treatment program. Journal of Substance Abuse Treatment 2009 Jul;37(1):32-40.

A Treatment for Substance Abusing Pregnant Women

The authors describe the adaptation of a manualized behavioral treatment for substance using pregnant women that includes components of motivational interviewing and cognitive therapy. In a pilot study conducted in 2006-2007, five non-behavioral health clinicians were trained to provide the treatment to 14 women. Therapy was administered concurrent with routine prenatal care at inner-city maternal health clinics in New Haven and Bridgeport, Connecticut, small urban cities in the USA. Substance use was monitored by self report, and urine and breath tests. Treatment fidelity was assessed using the Yale Adherence and Competence System. Behavioral treatment delivery in this setting is feasible and is being evaluated in a randomized, controlled, clinical trial. Yonkers KA, Howell HB, Allen AE, Ball SA, Pantalon MV, Rounsaville BJ. A treatment for substance abusing pregnant women. Archives of Women's Mental Health. 2009 Aug;12(4):221-227.

Beck Depression Inventory for Depression Screening in Substance-Abusing Adolescents

Co-occurring major depressive disorder (MDD) in adolescents with substance use disorders (SUD) has been linked to poor treatment outcomes. Use of validated depression screens in adolescent SUD populations may improve the detection of depression. In this secondary analysis of data, the authors

evaluated the diagnostic efficiency of the Beck Depression Inventory (BDI) in detecting MDD, as assessed by psychiatrists administering the Diagnostic Interview for Children and Adolescents, and its factor structure, internal consistency, and discriminant validity in a clinical sample of treatment-seeking adolescents with SUD (n = 145). Results indicate that BDI scores of 12 and higher had the optimal sensitivity (73%), whereas BDI scores of 17 and higher, the most optimal specificity (75%). Five factors accounted for approximately 56% of the variance. Overall, internal consistency was high, and the BDI adequately discriminated MDD from non-MDD cases. Results support the use of BDI as a screen for MDD with moderate to high psychometric properties in an adolescent SUD sample. Subramaniam G, Harrell P, Huntley E, Tracy M. Beck Depression Inventory for depression screening in substance-abusing adolescents. J Subst Abuse Treat. 2009 Jul;37(1):25-31.

Troubled Parents, Motivated Adolescents: Predicting Motivation to Change Substance Use among Runaways

Runaway adolescents engage in high rates of substance use and report significant family and individual problems. However, in general, adolescents report low motivation to change their substance use. Because a higher level of motivation for changing substance use is associated with greater substance abuse treatment success, identifying variables associated with motivation for change can be useful for enhancing treatment success. In this study, predictors of motivation for changing substance use were examined among 140 shelter-recruited adolescents and their parents/primary caretakers. Several findings were noteworthy. A perceived negative family environment increased parents' and adolescents' depressive symptoms, which increased adolescents' motivation to change. Also, greater severity of adolescent substance use predicted higher motivation to change. Consideration of the family environment and parent problems when addressing motivation for changing substance use among these adolescents might be important foci for motivational interventions and future research. Slesnick N, Bartle-Haring S, Erdem G, Budde H, Letcher A, Bantchevska D, Patton R. Troubled parents, motivated adolescents: Predicting motivation to change substance use among runaways. Addict Behav. 2009 Aug;34(8):675-684.

Culturally Informed and Flexible Family-Based Treatment for Adolescents: A Tailored and Integrative Treatment for Hispanic Youth

The increasing utilization of evidence-based treatments has highlighted the need for treatment development efforts that can craft interventions that are effective with Hispanic substance abusing youth and their families. The list of evidence-based treatments is extremely limited in its inclusion of interventions that are explicitly responsive to the unique characteristics and treatment needs of young Hispanics and that have been rigorously tested with this population. Some treatments that have been tested with Hispanics do not articulate the manner in which cultural characteristics and therapy processes interact. Other treatments have emphasized the important role of culture but have not been tested rigorously. A focus on how treatment processes interact with patient characteristics is particularly relevant in the Hispanic population because of the considerable heterogeneity beneath the Hispanic umbrella. The authors describe a new program of clinical research that focuses on articulating how the varied profiles with regard to immigration stressors, acculturation processes, values clashes, sense of belonging to the community, discrimination, and knowledge about issues important to adolescent health can be more effectively addressed by a culturally informed treatment. Santisteban DA, Mena MP. Culturally informed and flexible family-based treatment for adolescents: A tailored and integrative treatment for Hispanic youth. Family Process. 2009 Jun;48(2):253-268.

Methamphetamine Users Explain Continuing Drug Use and Relapse

A variety of theories exist about why drug abusers relapse including avoiding withdrawal or pain, positive reinforcement or "pleasure seeking", craving, habits, and impulsivity. Researchers at Baylor College of Medicine surveyed methamphetamine users about why they continued to use following a period of cessation. In general pleasure seeking was the dominant reason for resuming methamphetamine use followed by impulsivity and habits. Craving and avoidance of pain were the least frequent reasons for relapse. This is significant because it suggests that new treatments should target habits, impulsivity and especially alternative sources of pleasure. Newton TF, De La Garza R II, Kalechstein AD, Tziortzis D, Jacobsen CA. Theories of addiction: Methamphetamine users' explanations for continuing drug use and relapse. Am J Addict 2009 Jul-Aug;18(4):294-300.

Congruence of BOLD Response across Intertemporal Choice Conditions: Fictive and Real Money Gains and Losses

Delay (or temporal) discounting refers to the devaluation of an outcome as a function of the time to the delivery of that outcome. Delay discounting has been proposed to underlie impulsive decision making, with increased levels of discounting observed in drug-dependent cohorts. Intertemporal choice is predicated on the valuation of commodities with respect to delay until their receipt. Subjective value of a future outcome decreases, or is discounted, as a function of that delay. Although behavioral studies suggest no difference between the devaluation of real and fictive outcomes, no neuroimaging studies have investigated potential differences in the underlying deliberative process. Dr. Bickel and colleagues at the University of Arkansas for Medical Sciences compared behavioral and neural correlates of intertemporal valuation of real and hypothetical monetary gains as well as hypothetical losses, which have been posited to involve different mechanisms. Behavioral and neuroimaging sessions were conducted in which participants made intertemporal choice decisions in a gains condition using both real and hypothetical $100 money and in a loss condition using a fictive $100 money. Within-subject comparison of behavioral data revealed no significant difference between levels of discounting across the three conditions. Random-effects analysis of functional magnetic resonance imaging (fMRI) data of each of the three discounting conditions independently revealed significant signal change in limbic (anterior ingulate, striatum, posterior cingulate) and executive functioning areas (lateral prefrontal cortex). These data support a concordance between real and hypothetical conditions from delay-discounting studies and further suggest a congruence of the fMRI blood oxygen level-dependent signal across brain regions associated with the deliberative process of different forms of intertemporal choice. Bickel WK, Pitcock JA, Yi R, Angtuaco EJ. Congruence of BOLD response across intertemporal choice conditions: Fictive and real money gains and losses. J Neurosci. 2009 Jul 8;29(27):8839-8846.

Temporal Horizon: Modulation by Smoking Status and Gender

Recently, delay discounting has been argued to be conceptually consistent with the notion of temporal horizon. Cigarette smokers discount past and future rewards symmetrically and more than controls: is discounting a measure of impulsivity? Temporal horizon refers to the temporal distance over which behavioral events or objects can influence behavior. This study examined the results on two putative measures of temporal horizon, future time perspective (FTP) and delay discounting, collected over three separate studies (n=227), to determine the influence of smoking and gender on temporal horizon. By

comparing the results on these temporal horizon measures they addressed an underserved population: women who smoke. One of the measures of FTP indicates that smoking women have a shorter temporal horizon than their nonsmoking counterparts. Additionally, the story completion measures of FTP are positively correlated with delay discounting. In contrast, results of delay discounting measures showed no difference between smoking women and nonsmoking women, while results of delay discounting measures indicated smoking men have a shorter temporal horizon than non-smoking men. Additionally, the results of the FTP story completion measure indicated that lower third income earners had a shortened temporal horizon compared to upper third income earners. A possible explanation for these results is explored, and the implications of the modulation of temporal horizon by gender and smoking are discussed. Jones BA, Landes RD, Yi R, Bickel WK. Temporal horizon: Modulation by smoking status and gender. Drug Alc Depend. 2009 May [E-pub ahead of print].

Latent Structure of Facets of Alcohol Reinforcement from a Behavioral Economic Demand Curve

Behavioral economic demand curves are quantitative representations of the relationship between consumption of a drug and its cost. Demand curves provide a multidimensional assessment of reinforcement, but the relationships among the various indices of reinforcement have been largely unstudied. The objective of the study was to use exploratory factor analysis to examine the underlying factor structure of the facets of alcohol reinforcement generated from an alcohol demand curve. Participants were 267 weekly drinkers who underwent a single group assessment session. Alcohol demand curves were generated via an alcohol purchase task, which assessed consumption at 14 levels of prices from $0 to $9. The results revealed a clear two-factor solution, which were interpreted as "Persistence," reflecting sensitivity to escalating price, and "Amplitude," reflecting the amount consumed and spent. These findings suggest that alcohol reinforcement as measured via a demand curve is binary in nature, with separate dimensions of price-sensitivity and volumetric consumption. If supported, these findings may contribute theoretically and experimentally to a reinforcement-based approach to alcohol use and misuse. Mackillop J, Murphy JG, Tidey JW, Kahler CW, Ray LA, Bickel WK. Latent structure of facets of alcohol reinforcement from a behavioral economic demand curve. Psychopharmacology. 2009 Mar14;203(1):33-40.

Cost Analysis of Clinic and Office-Based Treatment of Opioid Dependence: Results with Methadone and Buprenorphine in Clinically Stable Patients

The cost of providing and receiving treatment for opioid dependence can determine its adoption. To compare the cost of clinic-based methadone (MC), office-based methadone (MO), and office-based buprenorphine (BO) an analysis of treatment and patient costs over 6 months of maintenance in patients who had previously been stabilized for at least 1 year was performed. Dr. Schottenfeld and colleagues from Yale University did statistical comparisons using ANOVA and chi-square tests and performed a sensitivity analysis varying cost estimates and intensity of clinical contact. The cost of providing 1 month of treatment per patient was $147 (MC), $220 (MO) and $336 (BO). Mean monthly medication cost was $93 (MC), $86 (MO) and $257 (BO). The cost to patients was $92 (MC), $63 (MO) and $38 (BO). Sensitivity analyses, varying cost estimates and clinical contact, result in total monthly costs of $117 to $183 (MC), $149 to $279 (MO), $292 to $499 (BO). Monthly patient costs were $84 to $133 (MC), $55 to $105 (MO) and $34 to $65 (BO). The authors conclude that providing clinic-based methadone is least expensive. The price of buprenorphine accounts for a major portion of the difference in costs. For patients, office-based treatment may be less expensive. Jones ES, Moore BA,

Sindelar JL, O'Connor PG, Schottenfeld RS, Fiellin DA. Cost analysis of clinic and office-based treatment of opioid dependence: Results with methadone and buprenorphine in clinically stable patients. Drug Alcohol Depend. 2009 Jan 1;99(1-3):132-140.

Relations among Psychopathology, Substance Use, and Physical Pain Experiences in Methadone-Maintained Patients

Dr. Schottenfeld and colleagues from Yale University conducted this study to examine differences in psychiatric distress and substance use (licit and illicit) in methadone maintenance treatment (MMT) patients with a variety of pain experiences. Parametric and nonparametric statistical tests were performed on data obtained from 150 patients currently enrolled in MMT. Results suggested that, in comparison to MMT patients reporting no pain in the previous week, those with chronic severe pain (CSP; i.e., pain lasting at least 6 months with moderate to severe pain intensity or significant pain interference) exhibited significantly higher levels of depression, anxiety, somatization, overall psychiatric distress, and personality disorder criteria but reported comparable rates of substance use. A third group, i.e., non-CSP MMT patients reporting some pain in the past week, differed significantly from the other 2 pain groups on somatization and global psychiatric distress but reported comparable rates of substance use. Pain-related differences in psychiatric problems exist in MMT patients and may have implications for program planning and outreach efforts. Barry DT, Beitel M, Garnet B, Joshi D, Rosenblum A, Schottenfeld RS. Relations among psychopathology, substance use, and physical pain experiences in methadone-maintained patients. J Clin Psychiatry. 2009; Jul 14. [E-pub ahead of print].

Caffeine Withdrawal, Acute Effects, Tolerance, and Absence of Net Beneficial Effects of Chronic Administration: Cerebral Blood Flow Velocity, Quantitative EEG, and Subjective Effects

Although the subjective effects of caffeine abstinence, acute and chronic administration, and tolerance are well described, the corresponding neurophysiological effects are not. In the current study, caffeine withdrawal, acute caffeine effects, caffeine tolerance, and net beneficial effects of chronic caffeine administration were investigated using cerebral blood flow velocity, quantitative electroencephalography (EEG), and subjective effects. Specifically, sixteen regular caffeine users participated in this double-blind, within-subject study during which they received acute caffeine and placebo challenges (1) while maintained on 400 mg caffeine daily for > 14 days and (2) while maintained on placebo for > 14 days. Blood flow velocity was determined for the middle (MCA) and anterior (ACA) cerebral arteries using pulsed transcranial Doppler sonography. EEG was recorded from 16 scalp sites. Subjective effects were assessed with questionnaires. Acute caffeine abstinence (evaluated 24 h after placebo substitution) increased mean, systolic, and diastolic velocity in the MCA and ACA and decreased pulsatility index in the MCA. Acute caffeine abstinence increased EEG theta and decreased beta 2 power. Acute caffeine abstinence also increased measures of Tired, Fatigue, Sluggish, and Weary and decreased ratings of Energetic, Friendly, Lively, and Vigor. Acute caffeine effects were demonstrated across a wide range of measures, including cerebral blood flow, EEG, and subjective effects. Tolerance and "complete" tolerance were observed on subjective but not physiological measures. Chronic caffeine effects were demonstrated only on the measure of EEG beta 2 power. Acute caffeine abstinence and administration produced changes in cerebral blood flow velocity, EEG, and subjective effects. Tolerance to subjective but not physiological measures was demonstrated. There was almost no evidence for net effects of chronic caffeine administration on these measures. Overall, these findings provide the most rigorous demonstration to date of physiological effects of caffeine withdrawal. Sigmon SC, Herning RI, Better W, Cadet JL,

Griffiths RR. Caffeine withdrawal, acute effects, tolerance, and absence of net beneficial effects of chronic administration: Cerebral blood flow velocity, quantitative EEG, and subjective effects. Psychopharm. 2009 Jul;204(4):573-585.

Increased Drinking in a Trial of Treatments for Marijuana Dependence: Substance Substitution?

Dr. Kadden and others at the University of Connecticut examined the extent to which participants in a study of treatments for marijuana dependence may have increased their use of alcohol when they reduced or ceased marijuana use. Specifically, participants were randomly assigned to one of four psychosocial treatments and followed at 3-month intervals for 1 year. The authors found that of the 207 participants with data at post-treatment and at least one other follow-up, 73% reported an increase of at least 10% in drinking days over their level at intake, and 65% reported an increase of at least 10% in drinks per drinking day. Drinking increases were not related to treatment condition or to change in marijuana use, but were related to baseline drinking. For example, those with less baseline drinking tended to increase their drinking during treatment and those with more baseline drinking reported less drinking during treatment. Thereafter, drinking levels remained fairly stable throughout the follow-up year. The results suggest that use of alcohol and marijuana are independent of one another. Kadden RM, Litt MD, Kabela-Cormier E, Petry NM. Increased drinking in a trial of treatments for marijuana dependence: Substance substitution? Drug Alcohol Depend. 2009; Jul 14. [E-pub ahead of print].

Director's Report to the National Advisory Council on Drug Abuse - September, 2009

Research Findings - Research on Pharmacotherapies for Drug Abuse

Dual Dopamine/Serotonin Releasers: Potential Treatment Agents for Stimulant Addiction

The evidence supporting the utility of dual releaser during cocaine and alcohol withdrawal was summarized. Data demonstrating the "antistimulant" role of 5-HT-sub(2C) receptors were presented and the mechanisms of potential adverse effects discussed. PAL-287, a novel DA/5-HT releaser, suppressed cocaine self-administration without reinforcing properties by itself. This report demonstrated that DA/5-HT releasers could be useful adjunct therapy for cocaine and alcohol addictions and potential medication for obesity, attention-deficit disorder, and depression. Rothman RB, Blough BE, Baumann MH. Dual dopamine/serotonin releasers: potential treatment agents for stimulant addiction. Exp Clin Psychopharmacol. 2008; Dec;16(6):458-474.

(1R, 3S)-(-)-trans-PAT: A Novel Full-efficacy Serotonin 5-HT2C Receptor Agonist with 5-HT2A and 5-HT2B Receptor Inverse Agonist/antagonist Activity

This paper reports 5-HT2 receptor affinity and function of (1R,3S)-(-)-trans-PAT, a small molecule that produces anorexia and weight-loss after peripheral administration to mice. It is a stereoselective agonist at 5-HT2C receptor and an inverse agonist and competitive antagonist at 5-HT2A/2B (Ki=37, 410, 1200 nM, respectively and EC50/IC50=20, 490 and 1,000 nM, respectively). In addition to being a tool for studying 5-HT(2) receptor structure and function, (-)-trans-PAT is a novel medication compound for treating obesity and neuropsychiatric disorders. Booth RG, Fang L, Huang Y, Wilczynski A, Sivendran S. (1R, 3S)-(-)-trans-PAT: a novel full-efficacy serotonin 5-HT2C receptor agonist with 5-HT2A and 5-HT2B receptor inverse agonist/antagonist activity. Eur J Pharmacol. 2009; Aug 1;615(1-3):1-9.

Effects of the Monoamine Uptake Inhibitors RTI-112 and RTI-113 on Cocaine- and Food-Maintained Responding in Rhesus Monkeys

The present study compared the effects of a non-selective monoamine uptake inhibitor (RTI-112) and a dopamine-selective uptake inhibitor (RTI-113) on cocaine- and food-maintained responding in rhesus monkeys. Both produced dose-dependent, sustained and nearly complete elimination of cocaine self-administration. The potency to cocaine was similar to that to food. These findings do not support the hypothesis that pharmacological selectivity to block dopamine uptake is associated with behavioral selectivity to decrease cocaine- vs. food-maintained responding in rhesus monkeys. Negus SS, Mello NK,

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Kimmel HL, Howell LL, Carroll FI. Effects of the monoamine uptake inhibitors RTI-112 and RTI-113 on cocaine- and food-maintained responding in rhesus monkeys. Pharmacol Biochem Behav. 2009; Jan;91(3):333-338.

Attenuation of Methamphetamine-induced Effects Through the Antagonism of Sigma (Sigma) Receptors: Evidence from In Vivo and In Vitro Studies

In the present study, AC927, a sigma receptor antagonist, had preferential affinity for sigma receptors compared to 29 other receptors, transporters and ion channels. Pretreatment of mice with AC927 significantly attenuated METH-induced locomotor stimulation, striatal dopamine depletions, striatal dopamine transporter reductions, and hyperthermia. Co-incubation with AC927 in cells mitigated METH-induced cytotoxicity. Matsumoto RR, Shaikh J, Wilson LL, Vedam S, Coop A. Attenuation of methamphetamine-induced effects through the antagonism of sigma (sigma) receptors: Evidence from in vivo and in vitro studies. Eur Neuropsychopharmacol. 2008; Dec;18(12):871-881.

Thermostable Variants of Cocaine Esterase for Long-time Protection Against Cocaine Toxicity

A major obstacle to the clinical application of cocaine esterase (CocE) against cocaine toxicity is the thermoinstability of native CocE with a half-life of only a few minutes at physiological temperature (37 degrees C). An integrated computational-experimental effort has yielded a CocE variant with a approximately 30-fold increase in plasma half-life both in vitro and in vivo. The novel design strategy can be applicable to progein mutants in general in improving their thermostability. Gao D, Narasimhan DL, Macdonald J, Brim R, Ko MC, Landry DW, Woods JH, Sunahara RK, Zhan CG. Thermostable variants of cocaine esterase for long-time protection against cocaine toxicity. Mol Pharmacol. 2009; Feb;75(2):318-323.

The Acute Behavioral Effects of Methamphetamine, d-amphetamine, and Methylphenidate Overlap Extensively in Humans

Methamphetamine abuse is a significant public health concern. Although widely studied in laboratory animals, little is known about the abuse-related behavioral effects of methamphetamine relative to other abused stimulants in controlled laboratory settings in humans. The aim of this study was to examine the discriminative stimulus, subject-rated, performance, and cardiovascular effects of methamphetamine in humans. In the present study, subjects first learned to discriminate 10 mg of oral methamphetamine from placebo. After acquiring the discrimination, a range of oral doses of methamphetamine, d-amphetamine, methylphenidate, and triazolam were tested. Methamphetamine functioned as a discriminative stimulus and produced prototypical stimulant-like subject-rated effects. d-Amphetamine and methylphenidate produced dose-related increases in methamphetamine-appropriate responding, whereas triazolam did not. d-Amphetamine and methylphenidate produced stimulant-like behavioral effects, whereas triazolam produced sedative-like effects. Methamphetamine, but no other drug, increased heart rate, systolic pressure, and diastolic pressure significantly above placebo levels. Performance in the Digit-Symbol Substitution Test was not affected by any of the drugs tested. Overall, these results demonstrate that the acute behavioral effects of methamphetamine, d-amphetamine, and methylphenidate overlap extensively in humans, which is concordant with findings from preclinical studies. Future studies should assess whether the similarity in the behavioral effects of methamphetamine and related stimulants can be extended to other behavioral assays, such as measures of reinforcement, in humans. Sevak RJ, Stoops WW,

Planned Meetings

Publications

Staff Highlights

Grantee Honors

Hays LR, Rush CR, Discriminative stimulus and subject-rated effects of methamphetamine, d-amphetamine, methylphenidate and triazolamin methamphetamine-trained humans. J Pharmacol Exp Ther. 2009; Mar;328(3):1007-1018.

Evaluation of Subjective Effects of Aripiprazole and Methamphetamine in Methamphetamine -dependent Volunteers

This study investigated the safety and potential efficacy of aripiprazole in 16 methamphetamine-dependent patients as a treatment for methamphetamine addiction. The study was a double-blind in-patient clinical pharmacology study to assess potential interactions between intravenous methamphetamine (15 mg and 30 mg) and oral aripiprazole (15 mg). Following baseline methamphetamine dosing, subjects received 2 weeks treatment with aripiprazole (n=8) or placebo (n=8). Participants then completed cue exposure sessions using neutral and methamphet-amine-related cues, and methamphetamine dosing was then repeated. Aripiprazole treatment had no effect on cue-induced methamphetamine craving or on daily baseline craving assessed over the course of medication treatment, although treatment was associated with increased craving independent of methamphetamine dosing. Aripiprazole treatment did not alter the pharmaco-kinetics of methamphetamine, and reduced increase in systolic blood pressure following methamphetamine dosing. The findings indicate that aripiprazole treatment appears safe in volunteers with methamphetamine dependence, although it increases some of the rewarding and stimulatory effects produced by methamphetamine, indicating that 15 mg aripiprazole is unlikely to be efficacious for the treatment of methamphetamine dependence. Newton TF, Reid MS, De La Garza R, Mahoney JJ, Abad A, Condos R, et al., Evaluation of Subjective Effects of Aripiprazole and Methamphetamine in Methamphetamine-dependent volunteers. Int. J. Neuropsychopharm. 2008;11:1037-1045.

Methamphetamine Self-Administration by Humans Subjected to Abrupt Shift and Sleep Schedule Changes

Methamphetamine attenuates disruptions that occur after changes in work shifts. The reinforcing effects of the drug during shift work have yet to be characterized. This study examined methamphetamine-related mood, performance, and reinforcing effects during simulated shift work. In this 19-day study, ten volunteers were given an opportunity to self-administer 10 mg oral methamphetamine or receive a $1 voucher before and after an 8-hour work period for four consecutive days under two shift conditions. Night-shift work disrupted psycho-motor task performance and some ratings of mood, especially on the first night. Participants chose to take methamphetamine significantly more often on the first night-shift night compared with the first day-shift day. Participants selected markedly more methamphetamine doses before the work period than after it. The data showed that methamphetamine self-administration occurred more often before work than after work, suggesting that the use of methamphetamine by shift workers may be one strategy employed to meet behavioral demands, especially under conditions engendering poor performance, fatigue, and/or sleep disruptons. Kirkpatrick MG, Haney M, Vosburg SK, Comer SD, Foltin RW, Hart CL. Methamphetamine self-administration by humans subjects to abrupt shift and sleep schedule changes. Psychopharmacology. 2009;203:771-780.

Unrestricted Access to Methamphetamine or Cocaine in the Past is Associated with Increased Current Use

Laboratory animals allowed to self-administer stimulants for extended periods of time escalate drug intake compared to animals that self-administer under

temporally limited conditions. This phenomenon has not been systematically investigated in humans. Investigators interviewed 106 (77 male, 29 female) methamphetamine (Meth) and 96 (81 male, 15 female) cocaine (Coc) users to determine if they had experienced discrete period(s) of unrestricted access to unlimited quantities of Meth or Coc in the past. Fifty-eight Meth users and 53 Coc users reported having a discrete period of unrestricted access in the past, but not in the present. Meth-using participants with a prior history of unrestricted access reported significantly more current Meth use, compared to Meth users with no prior history of unrestricted access. Specifically, these participants reported more days used in the past 30 d, more days of use per week, greater use per day and greater total use per week ($p<0.05$ for each). Coc-using participants with a prior history of unrestricted access also reported significantly more current Coc use, compared to Coc users with no prior history of unrestricted access. This was true across all measures of current use for these participants, including more days used in the past 30 days, more days of use per week, greater use per day, and higher total use per week ($p<0.02$ for each). Taken together, these results suggest that a history of unrestricted access to stimulants is associated with long-lasting increases in stimulant use. Culbertson C, De La Garza R, Costello M, Newton TF, Unrestricted access to methamphetamine or cocaine in the past is associated with increased current use. Int J Neuropsychopharmacol. 2009;Jun;12(5):677-685.

Atomoxetine Treatment for Cocaine Abuse and Adult Attention-Deficit Hyperactivity Disorder (ADHD): A Preliminary Open Trial

The purpose of this 12-week open trial was to evaluate the potential utility of atomoxetine for the treatment of attention deficit hyperactivity disorder (ADHD) in cocaine-dependent treatment seekers. The sample consisted of 20 participants with all participants meeting DSM-IV-TR criteria for ADHD and cocaine dependence (CD). Using several measures to assess ADHD, there was a significant reduction in ADHD symptoms. There was no significant decrease in cocaine use throughout the trial. Taken together, although cocaine-dependent individuals showed some reduction in ADHD symptoms while receiving atomoxetine, the high drop-out rate and lack of impact on cocaine use may limit its utility in ADHD adults who are currently abusing cocaine. Levin FR, Mariani JJ, Secora A, Brooks D, Cheng WY, Bisaga A, Nunes E, Aharonovich E, Raby W, Hennessy G. J. Dual Diagn. 2009 Jan 1;5(1):41-56.

Repeated Dosing with Oral Cocaine in Humans: Assessment of Direct Effects, Withdrawal, and Pharmacokinetics

Cocaine withdrawal symptoms are thought to play a role in relapse; studies characterizing the symptomatology have yielded mixed findings. This study sought to examine the pharmacodynamic/pharmacokinetic profile of repeated high dose exposure to oral cocaine and characterize acute and protracted withdrawal in cocaine abusers. This study employed a repeated-dosing, single-blind design in which subjects (n = 9), resided for 40 days on a closed ward. They were maintained for two 4-day cocaine exposure periods (Days 1-4 & Days 9-12, cocaine 175 mg, p.o.; 5 hourly doses; 875 mg/day) separated by a 4-day matched placebo exposure period (Days 5-8). After these 12 days, an additional period of 28 days of placebo maintenance followed (Days 13-40). Test sessions were conducted during each phase; measures of mood, drug effects, sleep, pharmacokinetics, and prolactin were collected throughout the study. The dosing regimen produced cocaine plasma concentrations (Cmax of 680 ng/mL) two to threefold higher than typically seen in acute dose studies. Prototypic psychostimulant effects, including subjective ratings of euphoric effects (liking, high, good effects) and significant cardiopressor effects, were sustained during the active dosing periods, corresponding to the rise and fall of plasma cocaine. Withdrawal-like symptoms (i.e., disruptions of sleep, increased ratings of anxiety, irritability, crashing) were observed within 24-hr after

cessation of dosing. Cocaine reduced prolactin acutely, but no sustained alterations were observed for this measure or for other signs or symptoms during the 28-day abstinence period. These findings indicate that exposure to controlled high doses of cocaine produces modest symptoms consistent with cocaine withdrawal within hours of cessation of dosing but provide no evidence of symptoms persisting beyond 24 hours. Walsh SL, Stoops WW, Moody DE, Lin SW, Bigelow GE, Repeated dosing with oral cocaine in humans: Assessment of direct effects, withdrawal, and pharmacokinetics. Exp Clin Psychopharmacol. 2009; Aug;17(4):205-216.

Association Analysis Between Polymorphisms in the Conserved Dopamine Neurotrophic Factor (CDNF) Gene and Cocaine Dependence

Cocaine-induced neuroplasticity changes in the mesocorticolimbic dopamine systems are thought to be involved in the pathophysiology of cocaine dependence. Since neurotrophic factors have been observed to prevent/reverse and mimic cocaine-induced neurobiological changes in the brain, related genes are plausible candidates for susceptibility to cocaine dependence. The novel conserved dopamine neurotrophic factor protein (CDNF) promotes the survival, growth, and function of dopamine-specific neurons and is expressed in brain regions that undergo cocaine-induced neuroplasticity. In this study, the investigators hypothesized that polymorphisms in the CDNF gene (CDNF/ARMETL1) contribute to increased risk for cocaine dependence. Cocaine dependent individuals (n=351) and unaffected controls (n=257) of African descent were genotyped for four single nucleotide polymorphisms (SNPs) in the CDNF gene (rs11259365, rs7094179, rs7900873, rs2278871). No significant differences were observed in allele, genotype, or haplotype frequencies between cases and controls for any of the tested SNPs. This study suggests that there is no association between variants in the CDNF gene and cocaine dependence. However, additional studies using larger sample sizes, comprehensive SNP coverage, and clinically homogenous populations are necessary before confidently excluding CDNF as a significant genetic risk factor for cocaine dependence. Lohoff FW, Bloch PJ, Ferraro TN, Berrettini WH, Pettinati HM, Dackins CA, O'Brien CP, Kampman KM, Oslin DW. Association analysis between polymorphisms in the conserved dopamine neurotropic factor (CDNF) gene and cocaine dependence. Neuroscience Letters. 2009; 453:199-203.

Comparisons of Subjective, Pharmacokinetic, and Physiological Effects of Marijuana Smoked as Joints and Blunts

Recent increases in marijuana smoking among the young adult population have been accompanied by the popularization of smoking marijuana as blunts instead of as joints. Blunts consist of marijuana wrapped in tobacco leaves, whereas joints consist of marijuana wrapped in cigarette paper. To date, the effects of marijuana smoked as joints and blunts have not been systematically compared. This within-subject, randomized, double-blind, placebo-controlled study sought to directly compare the subjective, physiological, and pharmacokinetic effects of marijuana smoked by these two methods. Marijuana blunt smokers (12 women and 12 men) were recruited and participated in a 6-session outpatient study. Participants were blindfolded and smoked three puffs from either a blunt or a joint containing marijuana with varying Delta(9)-tetrahydrocannabinol (THC) concentrations (0.0, 1.8, and 3.6%). Subjective, physiological (heart rate, blood pressure, and carbon monoxide levels) and pharmacokinetic effects (plasma THC concentration) were monitored before and at specified time points for 3h after smoking. Joints produced greater increases in plasma THC and subjective ratings of marijuana intoxication, strength, and quality compared to blunts, and these effects were more pronounced in women compared to men. However, blunts produced equiva-lent

increases in heart rate and higher carbon monoxide levels than joints, despite producing lower levels of plasma THC. These findings demonstrate that smoking marijuana in a tobacco leaf may increase the risks of marijuana use by enhancing carbon monoxide exposure and increasing heart rate compared to joints. Cooper ZD, Haney M. Comparison of subjective, pharmacokinetic, and physiological effects of marijuana smoked as joints and blunts. Drug and Alc Dep. 2009;103:107-113.

Actions of Delta-9-tetrahydrocannabinol (THC) in Cannabis: Relation to Use, Abuse, Dependence

Cannabis use disorders have been identified as a relevant clinical issue. A subset of cannabis smokers seeks treatment for their cannabis use, yet few succeed in maintaining long-term abstinence. The rewarding and positive reinforcing effects of the primary psychoactive component of smoked cannabis, THC, are mediated by the cannabinoid CB1 receptor; the CB1 receptor has also been shown to mediate cannabis dependence and withdrawal. This paper reviews findings implicating the CB1 receptor in the behavioral effects of exogenous cannabinoids with a focus on cannabinoid dependence and reinforcement, and discusses the prevalence of cannabis use and dependence, cannabinoids and reward, reinforcing effects of cannabinoids, cannabinoid dependence and withdrawal, and the opioidergic contribution to cannabinoid effects. The conclusions are that across species, cannabinoids produce positive affective, rewarding, and reinforcing effects. Upon repeated drug administration, cannabinoid dependence develops marked by a withdrawal syndrome that is induced by either a cannabinoid antagonist or abstinence. The positive effects likely promote use, whereas both the positive and negative effects (dependence and withdrawal) of repeated use contribute to the difficulty that a subset of cannabis users have achieving and maintaining abstinence. Across species, the behavioral effects of cannabis, THC, and synthetic cannabinoids are clearly mediated by the endogenous cannabinoid systems. Cooper ZD, Haney M. Actions of delta-9-tetrahydro-cannabinol in cannabis: relation to use, abuse, dependence. Int. Rev. Psychiatry. 2009; April 1: 21(2):104-112.

The Effect of Olanzapine Pretreatment on Acute Cocaine Toxicity in Mice

Acute cocaine poisoning causes neuroexcitation and can be fatal. The toxic effects of cocaine can be attenuated by antagonists of serotonin, muscarinic cholinergic, and dopamine receptors. Olanzapine, an atypical antipsychotic medication, is an antagonist of these receptors. The objective of this study is to evaluate the efficacy of olanzapine pretreatment for attenuation of acute cocaine toxicity using a mouse model. Eighty male CF-1 mice were randomly assigned to olanzapine (1 mg/kg) or placebo pretreatment. Fifteen minutes later, all animals received 103 mg/kg intraperitoneal cocaine. Overall mortality was 11% for olanzapine-treated animals and 45% for placebo. Olanzapine also appeared to alter the characteristics of seizures due to cocaine. In this model of acute cocaine toxicity, olanza-pine pretreatment attenuated acute cocaine toxicity. Olanzapine should be evaluated further as a po-tential treatment for acute cocaine poisoning. Heard KJ, Cleveland NR, Krier S. The effect of olan-zapine pretreatment on acute cocaine toxicity in mice. Clin Tox (Phila). 2009 Jul;47(6):542-544.

Cue-Induced Dopamine Release Predicts Cocaine Preference: Positron Emission Tomography Studies in Freely Moving Rodents

Positron emission tomography studies in drug-addicted patients have shown that exposure to drug-related cues increases striatal dopamine, which displaces

binding of the D(2) ligand, [(11)C]-raclopride. However, it is not known if animals will also show cue-induced displacement of [(11)C]-raclopride binding. In this study, the authors use [(11)C]-raclopride imaging in awake rodents to capture cue-induced changes in dopamine release associated with the conditioned place preference model of drug craving. Ten animals were conditioned to receive cocaine in a contextually distinct environment from where they received saline. Following conditioning, each animal was tested for preference and then received two separate [(11)C]-raclopride scans. For each scan, animals were confined to the cocaine and/or the saline-paired environment for the first 25 min of uptake, after which they were anesthetized and scanned. [(11)C]-raclopride uptake in the saline-paired environment served as a within-animal control for uptake in the cocaine-paired environment. Cocaine produced a significant place preference ($p = 0.004$) and exposure to the cocaine-paired environment decreased [(11)C]-raclopride binding relative to the saline-paired environment in both the dorsal (20%; $p < 0.002$) and ventral striatum (22%; $p < 0.05$). The change in [(11)C]-raclopride binding correlated with preference in the ventral striatum ($R(2) = -0.87$; $p = 0.003$). In this region, animals who showed little or no preference exhibited little or no change in [(11)C]-raclopride binding in the cocaine-paired environment. This noninvasive procedure of monitoring neurochemical events in freely moving, behaving animals advances preclinical molecular imaging by interrogating the degree to which animal models reflect the human condition on multiple dimensions, both biological and behavioral. Schiffer WK, Liebling CN, Reiszel C, Hooker JM, Brodie JD, Dewey SL. Cue-induced dopamine release predicts cocaine preference: positron emission tomography studies in freely moving rodents. J Neurosci. 2009 May 13;29(19):6176-6185.

Pharmacotherapy for Cannabis Dependence - How Close Are We?

Cannabis is the most widely used illicit drug in the world. Treatment admissions for cannabis use disorders have risen considerably in recent years, and the identification of medications that can be used to improve treatment outcomes among this population is a priority for researchers and clinicians. To date, several medications have been investigated for indications of clinically desirable effects among cannabis users (e.g. reduced withdrawal, attenuation of subjective or reinforcing effects, reduced relapse). Medications studied have included those: (i) known to be effective in the treatment of other drug use disorders; (ii) known to alleviate symptoms of cannabis withdrawal (e.g. dysphoric mood, irritability); or (iii) that directly affect endogenous cannabinoid receptor function. Results from controlled laboratory studies and small open-label clinical studies indicate that buspirone, dronabinol, fluoxetine, lithium and lofexidine may have therapeutic benefit for those seeking treatment for cannabis-related problems. However, controlled clinical trials have not been conducted and are needed to both confirm the potential clinical efficacy of these medications and to validate the laboratory models being used to study candidate medications. Although the recent increase in research towards the development of pharmacotherapy for cannabis use disorders has yielded promising leads, well controlled clinical trials are needed to support broad clinical use of these medications to treat cannabis use disorders. Vandrey R, Haney M. CNS Drugs. 2009;23(7):543-553.

Methadone and Buprenorphine Prescribing and Referral Practices in US Prison Systems: Results from a Nationwide Survey

More than 50% of incarcerated individuals have a history of substance use, and over 200,000 individuals with heroin addiction pass through American correctional facilities annually. Opiate replacement therapy (ORT) with methadone or buprenorphine is an effective treatment for opiate dependence and can reduce drug-related disease and recidivism for inmates. Provision of ORT is nevertheless a frequently neglected intervention in the correctional

setting. This paper reports a survey of the 50 state Departments of Corrections; Washington, District of Columbia (DC); and Federal Department of Corrections' medical directors or their equivalents about their facilities' ORT prescribing policies and referral programs for inmates leaving prison. The investigators received responses from 51 of 52 prison systems nationwide. Twenty-eight prison systems (55%) offer methadone to inmates in some situations. Methadone use varies widely across states: over 50% of correctional facilities that offer methadone do so exclusively for pregnant women or for chronic pain management. Seven states' prison systems (14%) offer buprenorphine to some inmates. The most common reason cited for not offering ORT was that facilities "prefer drug-free detoxification over providing methadone or buprenorphine." Twenty-three states' prison systems (45%) provide referrals for some inmates to methadone maintenance programs after release, which increased from 8% in 2003; 15 states' prison systems (29%) provide some referrals to community buprenorphine providers. The conclusion is, that despite demonstrated social, medical, and economic benefits of providing ORT to inmates during incarceration and linkage to ORT upon release, many prison systems nationwide still do not offer pharmacological treatment for opiate addiction or referrals for ORT upon release. Nunn A, Zaller N, Dickman S, Trimbur C, Nijhawan A, Rich JD. Drug and Alcohol Dep. 2009; [E-pub ahead of print].

Attitudes Toward Methadone Among Out-of-Treatment Minority Injection Drug Users: Implications for Health Disparities

Injection drug use (IDU) continues to be a significant public health issue in the U.S. and internationally, and there is evidence to suggest that the burden of injection drug use and associated morbidity and mortality falls disproportionately on minority communities. IDU is responsible for a significant portion of new and existing HIV/AIDS cases in many parts of the world. In the U.S., the prevalence of HIV and hepatitis C virus is higher among populations of African-American and Latino injection drug users (IDUs) than among white IDUs. Methadone maintenance therapy (MMT) has been demonstrated to effectively reduce opiate use, HIV risk behaviors and transmission, general mortality and criminal behavior, but opiate-dependent minorities are less likely to access MMT than whites. A better understanding of the obstacles minority IDUs face accessing treatment is needed to engage racial and ethnic disparities in IDU as well as drug-related morbidity and mortality. This study explores knowledge, attitudes and beliefs about methadone among 53 out-of-treatment Latino and African-American IDUs in Providence, RI. The findings suggest that negative perceptions of methadone persist among racial and ethnic minority IDUs in Providence, including beliefs that methadone is detrimental to health and that people should attempt to discontinue methadone treatment. Additional potential obstacles to entering methadone therapy include cost and the difficulty of regularly attending a methadone clinic as well as the belief that an individual on MMT is not abstinent from drugs. The investigators recommend that substance use researchers and treatment professionals should engage minority communities, particularly Latino communities, in order to better understand the treatment needs of a diverse population, develop culturally appropriate MMT programs, and raise awareness of the benefits of MMT. Zaller ND, Bazazi AR, Velazquez L, Rich JD. Attitudes toward methadone among out-of-treatment minority injection drug users: implications for health disparities. Int J Environ Res Public Health. 2009; 6:787-797.

Patients Maintained on Methadone or Buprenorphine During Pregnancy Can Have Adequate Pain Control Postpartum

Empirical evidence is needed to guide adequate postpartum pain relief of methadone and buprenorphine stabilized patients. To that end, the objective of this study was to first determine the adequacy of pain control using non-opioid

and opioid medication in participants stabilized on buprenorphine or methadone before a vaginal delivery. Secondly the study attempted to compare the amount of non-opioid and opioid medication needed for adequate pain control for buprenorphine- and methadone-maintained patients during the immediate postpartum period. Pain control adequacy and amount of non-opioid and opioid medication needed in buprenorphine- and methadone-maintained patients, over the first five days postpartum, were examined. Pain ratings and number of opioid medication doses decreased over time in both medication groups. While the buprenorphine and methadone groups began with similar mean daily ibuprofen (IB) doses, the buprenorphine group decreased its IB use, while the methadone group increased its IB use. Patients treated daily with either buprenorphine or methadone can have adequate pain control postpartum with opioid medication and IB. Pain control is dependent on the opioid-agonist medication in use at delivery, and must be individualized. Jones HE, O'Grady K, Dahne J, Johnson R, Lemoine L, Milio L, Ordean A, Selby P. Management of acute postpartum pain in patients maintained on methadone or buprenorphine during pregnancy. Am J Drug Alcohol Abuse. 2009; 35(3):151-156.

Variable Buprenorphine Excretion During Pregnancy May Indicate Metabolic Changes Requiring Dose Adjustment During Later Stages of Gestation

Buprenorphine (BUP) is under investigation as a medication therapy for opioid-dependent pregnant women. This study investigated BUP and metabolite disposition in urine from women maintained on BUP during the second and third trimesters of pregnancy and postpartum. Investigators measured BUP, norbuprenorphine (NBUP), buprenorphine glucuronide (BUP-Gluc), and NBUP-Gluc concentrations in 515 urine specimens collected thrice weekly from 9 women during pregnancy and postpartum. They examined ratios of metabolites across trimesters and postpartum to identify possible changes in metabolism during pregnancy. NBUP-Gluc was the primary metabolite identified in urine and exceeded BUP-Gluc concentrations in 99% of specimens. Whereas BUP-Gluc was identified in more specimens than NBUP, NBUP exceeded BUP-Gluc concentrations in 77.9% of specimens that contained both analytes. Among all participants, the mean BUP-Gluc:NBUP-Gluc ratio was significantly higher in the second trimester compared to the third trimester, and there were significant intrasubject differences between trimesters in 71% of participants. In 3 women, the percent daily dose excreted was higher during pregnancy than postpregnancy, consistent with other data indicating increased renal elimination of drugs during pregnancy. These data are the first to evaluate urinary disposition of BUP and metabolites in a cohort of pregnant women. Variable BUP excretion during pregnancy may indicate metabolic changes requiring dose adjustment during later stages of gestation. Kacinko SL, Jones HE, Johnson RE, Choo RE, Concheiro-Guisan M, Huestis MA. Urinary excretion of buprenorphine, norbuprenorphine, buprenorphine-glucuronide and norbuprenorphine-glucuronide in pregnant women receiving buprenorphine maintenance treatment. Clin Chem. 2009; Jun;55(6):1177-1187.

Passive Immunization with a Nicotine-Specific Monoclonal Antibody Decreases Brain Nicotine Levels But Does Not Precipitate Withdrawal in Nicotine-Dependent Rats

Vaccination against nicotine is under investigation as a treatment for tobacco dependence. Passive immunization with nicotine-specific antibodies represents a complementary strategy to vaccination. A potential adverse effect of passive immunization in nicotine-dependent individuals is that it may lead to a rapid reduction in brain nicotine levels and trigger withdrawal. The goal of this study was to determine if passive immunization with the nicotine-specific monoclonal antibody Nic311 precipitated withdrawal in nicotine-dependent rats as measured by increases in brain reward thresholds and somatic signs. Another

cohort of rats was used to measure brain nicotine levels after Nic311 administration. Nic311 30, 80 or 240 mg/kg reduced brain nicotine concentrations by 45, 83 or 92% compared to controls. None of these Nic311 doses precipitated withdrawal measured at intervals up to 72 h following antibody administration. Administration of the nicotinic antagonist mecamylamine precipitated a robust nicotine withdrawal syndrome. Therefore, a substantial, but not complete, acute reduction in brain nicotine levels following passive immunization was not sufficient to precipitate nicotine withdrawal in nicotine-dependent rats. The Nic311 doses used have been shown to attenuate the behavioral effects of nicotine, suggesting that the use of passive immunization to treat nicotine addiction is not likely to precipitate withdrawal. Roiko SA, Harris AC, LeSage MG, Keyler DE, Pentel PR. Passive immunization with a nicotine-specific monoclonal antibody decreases brain nicotine levels but does not precipitate withdrawal in nicotine-dependent rats. Pharmacol Biochem Behav 2009 August;93(2):105-111.

Effect of Rapamycin on Cue-induced Drug Craving in Abstinent Heroin Addicts

The mammalian target of rapamycin is an evolutionarily conserved serine-threonine kinase (mTOR), which controls protein synthesis and catabolism in response to environmental cues. This randomized double-blind clinical trial enrolled 60 abstinent heroin addicts and randomly assigned them to three groups: placebo, 2.5 mg and 5 mg rapamycin. The participants were given the cue-reactivity paradigm with 5 min exposures to neutral and drug-related imagery while craving, anxiety, blood pressure and heart rate pre- and post-exposure were assessed. The investigators found that drug-related cues increased both craving and anxiety of abstinent heroin addicts, and had no effect on blood pressure and heart rate. A single high-dose of rapamycin significantly reduced the craving, but not anxiety induced by drug-related cues. These findings suggested that rapamycin merits outpatient clinical trials as a potential pharmacotherapy for relapse prevention from drug-related cue induced craving. Shi J, Jun W, Zhao LY et al. Effect of rapamycin on cue-induced drug craving in abstinent heroin addicts. Eur J Pharmacol 2009 August 1;615(1-3):108-112.

Do Stimulants Protect Against Psychiatric Disorders in Youth with ADHD? A 10-Year Follow-Up Study

Little is known about the effect of stimulant treatment in youth with attention-deficit/hyperactivity disorder (ADHD) on the subsequent development of comorbid psychiatric disorders. The investigators tested the association between stimulant treatment and the subsequent development of psychiatric comorbidity in a longitudinal sample of patients with ADHD. They conducted a case-control, 10-year prospective follow-up study into young-adult years of youth with ADHD. At baseline, the investigators assessed consecutively referred white male children with (n = 140) and without (n = 120) ADHD, aged 6 to 18 years. At the 10-year follow-up, 112 (80%) and 105 (88%) of the children in the ADHD and control groups, respectively, were reassessed (mean age: 22 years). The association between stimulant treatment in childhood and adolescence and subsequent comorbid disorders and grade retention by using proportional hazards survival models was examined. Of the 112 participants with ADHD, 82 (73%) were previously treated with stimulants. Participants with ADHD who were treated with stimulants were significantly less likely to subsequently develop depressive and anxiety disorders and disruptive behavior and less likely to repeat a grade compared with participants with ADHD who were not treated. The results suggest evidence that stimulant treatment decreases the risk for subsequent comorbid psychiatric disorders and academic failure in youth with ADHD. Biederman J, Monuteaux MC, Spencer T, Wilens TE, Faraone SV. Do stimulants protect against psychiatric disorders in youth with

ADHD? A 10-year follow-up study. Pediatrics 2009 July;124(1):71-78.

Intermittent Marijuana Use is Associated with Improved Retention in Naltrexone Treatment for Opiate-Dependence

Naltrexone is a theoretically promising alternative to agonist substitution treatment for opioid dependence, but its effectiveness has been severely limited by poor adherence. This study examined, in an independent sample, a previously observed association between moderate cannabis use and improved retention in naltrexone treatment. Opioid dependent patients (N = 63), admitted for inpatient detoxification and induction onto oral naltrexone, and randomized into a six-month trial of intensive behavioral therapy (Behavioral Naltrexone Therapy) versus a control behavioral therapy (Compliance Enhancement), were classified into three levels of cannabis use during treatment based on biweekly urine toxicology: abstinent (0% cannabis positive urine samples); intermittent use (1% to 79% cannabis positive samples); and consistent use (80% or greater cannabis positive samples). Intermittent cannabis users showed superior retention in naltrexone treatment (median days retained = 133; mean=112.8, SE=17.5), compared to abstinent (median=35; mean=47.3, SE=9.2) or consistent users (median=35; mean=68.3, SE=14.1) (log rank=12.2, df=2, p=.002). The effect remained significant in a Cox model after adjustment for baseline level of heroin use and during treatment level of cocaine use. Intermittent cannabis use was also associated with greater adherence to naltrexone pill-taking. Treatment interacted with cannabis use level, such that intensive behavioral therapy appeared to moderate the adverse prognosis in the consistent cannabis use group. The association between moderate cannabis use and improved retention on naltrexone treatment was replicated. Experimental studies are needed to directly test the hypothesis that cannabinoid agonists exert a beneficial pharmacological effect on naltrexone maintenance and to understand the mechanism. Raby WN, Carpenter KM, Rothenberg J et al. Intermittent marijuana use is associated with improved retention in naltrexone treatment for opiate-dependence. Am J Addict 2009 July;18(4):301-308.

Nicotine Withdrawal and Craving in Adolescents: Effects of Sex and Hormonal Contraceptive Use

While sex differences in the nicotine withdrawal (NW) symptoms and craving (NC) have been extensively described in adult cigarette smokers, few studies have investigated these phenomena in adolescents. The investigators evaluated the effect of gender and hormonal contraception (HC) on NW and NC during the first 14 days of cessation in adolescent smokers using data from a randomized, placebo-controlled, double-blind trial of the transdermal nicotine replacement therapy for smoking cessation. Analyses showed similar levels of NW severity in males and females, regardless of HC use. However, significantly higher NC was observed in females compared to males, (2.22+/-0.12 vs. 1.65+/-1.14; p=0.003). Further, females not using HC reported the highest level of NC (2.38+/-0.16) followed by females using HC (2.08+/-0.25) and males (1.71+/-0.16; p=0.007). The current findings suggest that adolescent females experience similar NW severity to males, but have stronger NC. Further, the use of hormonal contraceptives may impact the severity of craving. Addressing these different symptoms in adolescents may be useful in increasing smoking cessation rates in this special population of smokers. Dickmann PJ, Mooney ME, Allen SS, Hanson K, Hatsukami DK. Nicotine withdrawal and craving in adolescents: effects of sex and hormonal contraceptive use. Addict Behav 2009 June;34(6-7):620-623.

The Effect of Cannabis Compared with Alcohol on Driving

The prevalence of both alcohol and cannabis use and the high morbidity associated with motor vehicle crashes has lead to a plethora of research on the link between the two. Drunk drivers are involved in 25% of motor vehicle fatalities, and many accidents involve drivers who test positive for cannabis. Cannabis and alcohol acutely impair several driving-related skills in a dose-related fashion, but the effects of cannabis vary more between individuals than they do with alcohol because of tolerance, differences in smoking technique, and different absorptions of Delta(9)-tetrahydrocannabinol (THC), the active ingredient in marijuana. Detrimental effects of cannabis use vary in a dose-related fashion, and are more pronounced with highly automatic driving functions than with more complex tasks that require conscious control, whereas alcohol produces an opposite pattern of impairment. Because of both this and an increased awareness that they are impaired, marijuana smokers tend to compensate effectively while driving by utilizing a variety of behavioral strategies. Combining marijuana with alcohol eliminates the ability to use such strategies effectively, however, and results in impairment even at doses which would be insignificant were they of either drug alone. Epidemiological studies have been inconclusive regarding whether cannabis use causes an increased risk of accidents; in contrast, unanimity exists that alcohol use increases crash risk. Furthermore, the risk from driving under the influence of both alcohol and cannabis is greater than the risk of driving under the influence of either alone. Future research should focus on resolving contradictions posed by previous studies, and patients who smoke cannabis should be counseled to wait several hours before driving, and avoid combining the two drugs. Sewell RA, Poling J, Sofuoglu M. The effect of cannabis compared with alcohol on driving. Am J Addict 2009 May;18(3):185-193.

Neurotransmission-Related Genetic Polymorphisms, Negative Affectivity Traits, and Gender Predict Tobacco Abstinence Symptoms Across 44 Days With and Without Nicotine Patch

Genetic and personality trait moderators of tobacco abstinence-symptom trajectories were assessed in a highly controlled study. Based on evidence suggesting their importance in stress reactivity and smoking, moderators studied were serotonin transporter gene (5-HTTLPR) and dopamine D2 receptor gene (DRD2) polymorphisms and personality traits related to negative affect (NA). Smokers were randomly assigned to quit smoking with nicotine or placebo patches. Financial incentives resulted in 80% verified abstinence across the 44-day study. Individuals with 1 or 2 short alleles of 5-HTTLPR (S carriers) experienced larger increases in NA symptoms than did those without a short allele. Nicotine replacement therapy (NRT) alleviated anxiety only in S carriers. NRT reduced NA to a greater extent in DRD2 A1 carriers than in A2A2 individuals during the 1st 2 weeks of treatment (when on the 21-mg patch); however, A1 carriers experienced a renewal of NA symptoms when switched to the 7-mg patch and when off the patch, while A2A2 individuals continued to benefit from NRT. The results suggest that the effects of genotype and treatment may vary across different durations of abstinence, treatment doses, and genotypes. Gilbert DG, Zuo Y, Rabinovich NE, Riise H, Needham R, Huggenvik JI. Neurotransmission-related genetic polymorphisms, negative affectivity traits, and gender predict tobacco abstinence symptoms across 44 days with and without nicotine patch. J Abnorm Psychol 2009 May;118(2):322-334.

Multi-Center Trial of Baclofen for Abstinence Initiation in Severe Cocaine-Dependent Individuals

Baclofen is a GABA(B) receptor agonist that in preclinical and early pilot clinical trials has shown promise for the treatment of cocaine dependence. The purpose of this multi-site, double-blind study, was to compare the safety and efficacy of baclofen (60 mg/day) vs placebo in an 8-week treatment of

individuals with severe cocaine dependence. The primary outcome measure was subjects' self-reported cocaine use substantiated by urine benzoylecgonine (BE). Analysis of the data did not show a significant difference between the groups treated with baclofen and placebo. The current results do not support a role for 60 mg baclofen in treating cocaine dependence in the population studied. The contrast of this result to earlier, preclinical and human pilot data with baclofen may reflect the trial's focus on severe cocaine-dependent users, and/or the need for a higher baclofen dose. Baclofen's potential as a relapse prevention agent was not tested by the current design, but may be a useful target for future studies. Kahn R, Biswas K, Childress AR, Shoptaw S, Fudala PJ, Gorgon L, Montoya I, Collins J, McSherry F, Li SH, Chiang N, Alathari H, Watson D, Liberto J, Beresford T, Stock C, Wallace C, Gruber V, Elkashef A. Drug Alcohol Depend. 2009 Jul 1;103(1-2):59-64. E-pub 2009 May 2.

Director's Report to the National Advisory Council on Drug Abuse - September, 2009

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

HIV/AIDS:

Medication Assisted Treatment in the Treatment of Drug Abuse and Dependence in HIV/AIDS Infected Drug Users

Drug use and HIV/AIDS are global public health issues. The World Health Organization (WHO) estimates that up to 30% of HIV infections are related to drug use and associated behaviors. The intersection, of the twin epidemics of HIV and drug/alcohol use, results in difficult medical management issues for the health care providers and researchers who work in the expanding global HIV prevention and treatment fields. Access to care and treatment, medication adherence to multiple therapeutic regimens, and concomitant drug - drug interactions of prescribed treatments are difficult barriers for drug users to overcome without directed interventions. Injection drug users are frequently disenfranchised from medical care and suffer sigma and discrimination creating additional barriers to care and treatment for their drug abuse and dependence as well as HIV infection. In an increasing number of studies, medication assisted treatment of drug abuse and dependence has been shown to be an important HIV prevention intervention. Controlling the global transmission of HIV will require further investment in evidence-based interventions and programs to enhance access to care and treatment of individuals who abuse illicit drugs and alcohol. In this review, the authors present the cumulative evidence of the importance of medication assisted treatment in the prevention, care, and treatment of HIV infected individuals who also abuse drugs and alcohol. Kresina T, Bruce D, McCance-Katz E. Curr HIV Res. 2009; Jul7(4):354-364.

Tubular Cell HIV-1 gp120 Expression Induces Caspase 8 Activation and Apoptosis

Renal biopsy data indicate that tubular epithelial cells serve as a reservoir for HIV-1 infection. The authorss studied the effect of HIV-1 gp120 envelope gene expression on tubular cell apoptosis. HIV-1 gp120 was expressed in a lentiviral vector pHR-CMV-IRES2-EGFP-ΔB. This plasmid construct was used to produce pseudotyped virus using VSV-G envelope to enhance the tropism for efficient viral transduction. Human proximal tubular (HK-2) cells were transduced and assayed for cellular injury by trypan blue exclusion, Hoechst and PI staining, TUNEL, and cell cycle staging. HIV-1 gp120-transduced HK-2 cells showed cellular injury in a time-dependent manner. Gp120-transduced cells showed 2.5-fold greater apoptosis when compared with vector-transduced cells. Cell cycle analysis did not reveal any alteration between gp120-transduced cells and vector-transduced cells. Gp120-transduced cells showed higher expression

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of both Fas and FasL, whereas pretreatment with anti-FasL antibody partially inhibited gp120-induced tubular cell apoptosis. Similarly, pretreatment with caspase-8 inhibitor attenuated gp120-induced HK2 cell apoptosis. Moreover, gp120-transduced cells showed activation of caspase 8. These results suggest that HIV-1 gp120 expression induces tubular cell apoptosis through the extrinsic pathway by enhancing Fas and FasL expression and activation of caspase-8. Vashistha H, Husain M, Kumar D, Singhal P. Ren Fail. 2009;1(4):303-312.

AZT 5'-triphosphate Nanoformulation Suppresses Human Immunodeficiency Virus Type 1 Replication in Peripheral Blood Mononuclear Cells

Inefficient cellular phosphorylation of nucleoside and nucleotide analog reverse transcriptase inhibitors (NRTIs) to their active nucleoside 5'-triphosphate (NTPs) form is one of the limitations for human immunodeficiency virus (HIV) therapy. Reported herein is direct binding of 3'-azido-3'-deoxythymidine-5'-triphosphate (AZTTP) onto magnetic nanoparticles (Fe3O4; magnetite) due to ionic interaction. This magnetic nanoparticle bound AZTTP (MP-AZTTP) completely retained its biological activity as assessed by suppression of HIV-1 replication in peripheral blood mononuclear cells. The developed MP-AZTTP nanoformulation can be used for targeting active NRTIs to the brain by application of an external magnetic force and thereby eliminate the brain HIV reservoir and help to treat NeuroAIDS. Saiyed Z, Gandhi N, Nair M. J Neurovirol. 2009; Jul 2:1-5.

Drug Use and Weight Loss in HIV-infected Hispanic Men

Weight loss is an independent risk factor for mortality in HIV but the role of drug use in HIV-related weight loss is not well described. This study was conducted to determine the role of drug use in HIV-related weight loss. Men (n=304), all of whom were Hispanic, were recruited into one of three groups: HIV-infected drug users; HIV-non-infected drug users; and HIV-infected non-drug users. Body mass index (BMI) was measured at successive visits. The groups were re-categorized based on self-reported drug use at the current visit into: (1) users of cocaine alone; (2) users of cocaine and opiates; (3) users of opiates alone; (4) former drug users; and (5) those who denied ever using drugs (all HIV-infected). The effect on BMI of the duration of use of the specific drug types was evaluated using repeated-measures analyses. Longer duration of exclusive opiate use or mixed cocaine and opiate use did not affect BMI in the men, regardless of HIV status. Exclusive cocaine use was associated with a decline in BMI among HIV-infected men (-0.070 kg/m2 per month duration of use; SE=0.033; p=0.037) but not among HIV-uninfected men (0.024 kg/m2 per month; SE=0.023; p=0.29). Adjustment for marijuana, cigarette and alcohol use in all men, or for CD4 count, viral load or HIV medication use in the HIV-infected men, did not alter the conclusions. In conclusion, the use of opiates or combined opiates and cocaine does not increase the risk of weight loss in the presence or absence of HIV infection. Exclusive cocaine use may exacerbate weight loss in HIV-infection. Forrester JE, Tucker KL, Skinner S, Terrin N. AIDS Care. 2009; August; 20(7):868- 875.

Nutrition Issues in Chronic Drug Users Living With HIV Infection

Human immunodeficiency virus (HIV) infection and chronic drug abuse both compromise nutritional status. For individuals with both disorders, the combined effects on wasting, the nutritional consequence that is most closely linked to mortality, appear to be synergistic. Substance abuse clinicians can improve and extend patients' lives by recommending healthy diets; observing and assessing for food insecurity, nutritional deficits, signs of weight loss and

wasting, body composition changes, and metabolic abnormalities; and providing referrals to food programs and nutritionists. More studies are needed on the nutritional consequences of using specific illicit drugs, the impact on health of specific micronutrient and metabolic deficiencies seen in people with HIV, and the causes and clinical implications of body fat changes associated with HIV. Hendricks K, Gorbach S. Add Sci & Clin Prac. 2009;Apr 5(1):16-23.

Latently-infected CD4+ T cells are Enriched for HIV-1 Tat Variants with Impaired Transactivation Activity

The ability of HIV to establish latent infection in CD4+ lymphocytes represents a major barrier to the eradication of HIV. It is not clear what mechanisms favor latent over productive infection, but prior studies have suggested a role for the viral transcription factor Tat or its RNA target, TAR. Using samples from five individuals who were started on ART within 6 months of infection and achieved a viral load < 50 (suppressed), one- and two-exon tat RNA from HIV propagated ex vivo from baseline plasma and from co-cultures of CD4+ T cells obtained at baseline and suppressed time points were isolated. Compared to virus from the baseline plasma (mostly from productively-infected CD4+ T cells), virus from the baseline and suppressed co-cultures (mostly from latently-infected cells) had more Tat variants with impaired transactivation activity. These findings suggest that impaired activity in the Tat-TAR axis may contribute to the establishment of latent infection in CD4+ T cells. Yukl S, Pillai S, Li P, Chang K, Pasutti W, Ahlgren C, Havlir D, Strain M, GŸnthard H, Richman D, Rice A, Daar E, Little S and Wong J. Virology. 2009;387:98-108.

Diagnosis of Acute HIV Infection in Connecticut

Acute HIV infection (AHI) is the earliest stage of HIV disease, when plasma HIV viremia, but not HIV antibodies, can be detected. Acute HIV infection often presents as a nonspecific viral syndrome. However, its diagnosis, which enables linkage to early medical care and limits further HIV transmission, is seldom made. The study describes the experience of Yale's Center for Interdisciplinary Research on AIDS with AHI diagnosis in Connecticut, as a participating center in the National Institute of Mental Health Multisite AHI Study. The team sought to identify AHI cases by clinical referrals and by screening for AHI at two substance abuse care facilities and an STD clinic. One case by referral and one through screening of 590 persons were identified. Screening for AHI is feasible and probably cost effective. Primary care providers should include AHI in the differential diagnosis when patients present with a nonspecific viral syndrome. Dubrow R, Sikkema KJ, Mayer KH, Bruce RD, Julian P, Rodriguez I, Beckwith C, Roome A, Dunne D, Boeving A, Kidder TJ, Jenkins H, Dobson M, Becker J, Merson MH. Conn Med. 2009; Jun-Jul;73(6):325-331.

Pregnancy Among HIV-infected Refugees in Rhode Island

In 1999, immigration laws lifted previous barriers, allowing more HIV-infected refugees entrance to the US. Many of these refugees are women of reproductive age. At this center in Providence, RI, a significant number of HIV-infected refugees have become pregnant since resettling in the US. The pregnancies seen among these predominantly West African HIV-infected refugees are described. A retrospective chart review was conducted on all HIV-infected female refugees who established care from 2000-2006. During this period 28 HIV-infected female refugees entered from Liberia. Of these, 79% (22) women entered during 2000- 2006, with 20 pregnancies among 14 women between the median time from resettlement in the US to first pregnancy of 16 (<1-69) months. The median age at time of first pregnancy was 29 years (19-39). At time of pregnancy, the median CD4 count was 506

cells/mL and median plasma viral load (PVL) was 3.36 log10 copies/ml. There were nine deliveries, one current pregnancy and one loss to follow-up. Other pregnancy outcomes included five terminations and three spontaneous abortions. All women received antiretroviral therapy during their pregnancy. At the time of delivery the median PVL was <1.88 log. There was one HIV transmission from mother to child. Two women became pregnant while on efavirenz, which was subsequently discontinued. One of the women delivered a normal term infant; the other relocated and transferred her care. Among this cohort of HIV-infected refugees, there is a high rate of pregnancy, highlighting the need for timely initiation of medical care including comprehensive preconception counseling, upon resettlement in the US. Blood E, Beckwith C, Bazerman L, Cu-Uvin S, Mitty J. AIDS Care. 2009; Feb;21(2):207-211.

HIV Infection in Refugees: A Case-Control Analysis of Refugees in Rhode Island

The number of HIV-infected refugees entering the USA is increasing. There is little data describing the HIV-infected refugee population and the challenges encountered when caring for them. A retrospective case-control analysis of HIV-infected refugees in order to characterize their co-morbidities, baseline HIV characteristics, and longitudinal care compared to HIV-infected non-refugees was conducted. A retrospective chart review was performed of HIV-infected refugees and non-refugees who were matched for gender, age, and time of establishment of initial HIV care. The refugee population studied was largely from West Africa. Refugees were more likely than non-refugees to have heterosexual risk for HIV infection, latent tuberculosis infection, and active hepatitis B. Refugees were less likely than non-refugees to have a history of substance use, start antiretrovirals, and be enrolled in a clinical study. The baseline CD4 counts and HIV plasma viral loads were similar between the two groups. Clinicians caring for West African HIV-infected refugees should be knowledgeable about likely co-morbidities and the impact of cultural differences on HIV care. Further studies are needed to develop culturally competent HIV treatment, education, and prevention programs for refugees who are beginning a new life in the USA. Beckwith CG, DeLong AK, Desjardins SF, Gillani F, Bazerman L, Mitty JA, Ross H, Cu-Uvin S. Int J Infect Dis. 2009; Mar;13(2):186-192.

Lessons Learned from a Training Collaboration Between An Ivy League Institution and a Historically Black University

The Miriam Hospital, Brown Medical School, and Jackson State University developed a joint training program for predoctoral, Black psychology students under the auspices of a training grant funded by the National Institutes of Health. The development and success of this collaboration between two institutions with federally funded training programs for HIV/AIDS research are rooted in the individual commitment of key investigators who shared a common goal that transcended institutional allegiances and a program official at the National Institute on Drug Abuse. The students in the program at Jackson State University had unlimited access to the clinical research resources and mentoring expertise at Brown Medical School. This innovative program began in 2001 and addresses the need for Black leaders in clinical research and academia who will focus on HIV and other infections that disproportionately affect the Black community. This collaboration has served as a bridge between an Ivy League institution and a historically Black university for training in clinical research to develop successful minority academicians. Flanigan TP, Payne N, Simmons E, Hyde J, Sly K, Zlotnick C. Am J Public Health. 2009; Apr;99 Suppl 1:S57-60.

Low-Abundance HIV Drug-Resistant Viral Variants in Treatment-

Experienced Persons Correlate with Historical Antiretroviral Use

It is largely unknown how frequently low-abundance HIV drug-resistant variants at levels under limit of detection of conventional genotyping are present in antiretroviral-experienced persons experiencing virologic failure. Further, the clinical implications of low-abundance drug-resistant variants at time of virologic failure are unknown. Plasma samples from 22 antiretroviral-experienced subjects collected at time of virologic failure were obtained from a specimen bank. The prevalence and profile of drug-resistant mutations were determined using Sanger sequencing and ultra-deep pyrosequencing. Genotypes were interpreted using Stanford HIV database algorithm. Antiretroviral treatment histories were obtained by chart review and correlated with drug-resistant mutations. Low-abundance drug-resistant mutations were detected in all 22 subjects by deep sequencing and only in 3 subjects by Sanger sequencing. In total they accounted for 90 of 247 mutations (36%) detected by deep sequencing; the majority of these (95%) were not detected by standard genotyping. A mean of 4 additional mutations per subject were detected by deep sequencing. The additional low abundance drug-resistant mutations increased a subject's genotypic resistance to one or more antiretrovirals in 17 of 22 subjects. When correlated with subjects' antiretroviral treatment histories, the additional low-abundance drug resistant mutations correlated with the failing antiretroviral drugs in 21% of subjects and correlated with historical antiretroviral use in 79% of subjects. Low-abundance HIV drug-resistant mutations in antiretroviral-experienced subjects at time of virologic failure can increase a subject's overall burden of resistance, yet commonly go unrecognized by conventional genotyping. The majority of unrecognized resistant mutations correlate with historical antiretroviral use. Ultra-deep sequencing can provide important historical resistance information for clinicians when planning subsequent antiretroviral regimens for highly treatment-experienced patients, particularly when their prior treatment histories and longitudinal genotypes are not available. Le T, Chiarella J, Simen BB, Hanczaruk B, Egholm M, Landry ML, Dieckhaus K, Rosen MI, Kozal MJ. Low-abundance HIV drug-resistant viral variants in treatment-experienced persons correlate with historical antiretroviral use. PLoS One. 2009 Jun 29;4(6):e6079.

HIV/HCV:

Assessment of Liver Fibrosis by Transient Elastography in Persons with Hepatitis C Virus

Infection or HIV-Hepatitis C Virus Coinfection Transient elastography is a novel, noninvasive method for staging liver fibrosis. Eelastography with histologic methods among hepatitis C virus (HCV)-infected and human immunodeficiency virus (HIV)-HCV-coinfected participants in an urban, predominantly black study population were compared. Participants recruited from the AIDS Linked to the Intravenous Experience and the Johns Hopkins HIV Clinical Cohort studies underwent elastography to determine liver stiffness measurements. Liver biopsy specimens were staged F0-F4 in accordance with the Metavir score. Diagnostic accuracy and determination of liver stiffness cutoff values, compared with histologic methods, were determined by receiver operating characteristic analysis. Logistic regression methods identified parameters associated with discordant classification status. Of 192 participants, 139 (72%) were coinfected with HIV and HCV, 121 (63%) had insignificant fibrosis, and 48 (25%) had cirrhosis. Overall, the area-under-the-curve receiver operating characteristic was 0.87 for detection of both significant fibrosis (95% confidence interval, 0.82-0.92) and cirrhosis (95% confidence interval, 0.81-0.93). With use of cutoff values of _9.3 kPa for fibrosis and _12.3 kPa for cirrhosis, 79%-83% of participants were correctly classified by liver stiffness measurement (compared with histologic methods); accuracy appeared to be

higher among HIV-uninfected participants than among HIV-infected participants. Most discordance occurred when liver stiffness measurements indicated liver disease and histologic examination did not (in 16% of participants); the patients with these discordant results were more likely to have attributes that increased the odds of significant fibrosis, such as elevated serum fibrosis markers or HIV-related immunosuppression, compared with persons in whom low fibrosis was predicted by both examination of a biopsy specimen and elastography. For most HCV-infected persons, fibrosis stage predicted by elastography is similar to that predicted by examination of a biopsy specimen. Elastography-based measurement of liver stiffness holds promise to expand liver disease screening and monitoring, particularly among injection drug users. Kirk G, Astemborski J, Mehta S, Spoler C, Fisher C, Allen D, et al., Clin Infect Dis. 2009; Apr 1;48(7):963-972.

Acute Hepatitis C Virus Infection in an HIV Clinic and in Community Settings

Recent European, Australian, and US reports of clusters of sexually transmitted acute HCV infection among HIV-infected men who have sex with men (MSM) have led to a call for regular screening of at-risk individuals. Acute HCV among HIV-infected persons is underrecognized and alanine aminotransferase (ALT) elevations often attributed to hepatotoxicity due to highly active antiretroviral therapy, leading to unwarranted treatment interruptions. In Rhode Island, at Brown University, the authors are prospectively studying a low-cost screening strategy to identify acute HCV with routine blood tests in an HIV clinic. Fifty-nine HIV-infected, HCV antibody-negative individuals receiving primary HIV care at a Ryan White-funded clinic who were ³18 years of age, with drug and/or sexual HCV risk behavior within the prior 6 months, were prospectively enrolled. At quarterly routine clinic visits, ALT levels are measured and a Behavioral Risk Questionnaire completed. ALT rise prompts HCV RNA testing: For normal baseline, if ALT becomes abnormal (>45 IU/ml) or increases by ³20 IU/ml; and for elevated baseline, if ALT increases by 50%. Risk reduction counseling, testing for sexually transmitted infections, and drug treatment are provided. Acute HCV is classified as either a baseline incident infection (anti-HCV negative but HCV RNA positive with an elevated ALT and subsequent HCV antibody seroconversion) or a prospective incident infection (baseline HCV antibody and RNA negative, but with newly detectable HCV RNA after a rise in ALT followed by HCV antibody seroconversion). Individuals with acute HCV are interviewed about risk behaviors leading to acquisition, followed to determine treatment candidacy, educated about potential benefits of early therapy, and provided with on-site evaluation and HCV treatment. The study is ongoing. At baseline, 1 incident acute HCV infection was identified. Traumatic sexual and drug practices that may transmit HCV were prevalent, although more than half of participants rated their risk for acute HCV as low. A smaller number of HIV-infected individuals who were identified clinically were also followed. Risk factors include sexual transmission for 1 (MSM with genotype 1 who achieved sustained virologic response with 6 months of HCV therapy) and drug injection for 3 (1 spontaneously resolved infection; 2 declined therapy and developed chronic HCV). Screening for acute HCV at one of Rhode Island's gay bathhouses, the largest MSM sex club in New England, with >15,000 members is also being explored. Development of this study has led to routine availability of HCV antibody testing at the bathhouse with facilitated referral into care for HCV antibody-positive individuals. HIV/HCV coinfected individuals may have the most to lose with later diagnosis and the most to gain from earlier therapy and preventive intervention. Thus, although many questions remain regarding biology, precise modes of transmission, and predictors of acute HCV, the authors endorse a more aggressive approach to acute HCV surveillance and diagnosis among HIV-infected individuals as per the European AIDS Clinical Society's recent Coinfection Guidelines. Recommendations include serologic testing for HCV on initial physician visit and then annually thereafter, plus HCV

RNA for patients with risk factors (eg, injection drug use, mucosal traumatic sex) who have an unexplained increase in transaminases and negative HCV antibody. Taylor L, Mayer K. Correspondence 2411. 2009; May 3 Available online.

HCV / HBV, Liver Disease:

Role of Molecular Mimicry of Hepatitis C Virus Protein with Platelet GPIIIa in Hepatitis C-Related

Immunologic Thrombocytopenia Patients with HIV-1 immune-related thrombocytopenia (HIV-1-ITP) have a unique Ab against platelet GPIIIa49-66 capable of inducing oxidative platelet fragmentation in the absence of complement. HIV-1-seropositive drug abusers are more prone to develop immune thrombocytopenia than non-drug abusers and have a higher coinfection with hepatitis C virus (HCV) than non-drug abusers (90% vs 30%). Molecular mimicry was sought by screening a phage peptide library with anti-GPIIIa49-66 antibody as bait for peptides sharing homology sequences with HCV. Several phage peptide clones had 70% homology with HCV protein. Sera from dually infected thrombocytopenic patients with HCV and HIV-ITP reacted strongly with 4 nonconserved peptides from HCV core envelope 1. Reactivity correlated inversely with platelet count ($r2 = 0.7$, $P < .01$). Ab raised against peptide PHC09 in GPIIIa-/- mice induced thrombocytopenia in wild-type mice. Affinity-purified IgG against PHC09 induced oxidative platelet fragmentation in vitro. Drug abusers dually infected with HCV and HIV-1 had a greater incidence and severity of thrombocytopenia as well as titer of anti-GPIIIa49-66/PHC09 Ab. NZB/W F1 mice injected with recombinant core envelope 1 developed Ab versus PHC09 and significantly decreased their platelet count ($P < .001$). Thus, HCV core envelope 1 can induce thrombocytopenia by molecular mimicry with GPIIIa49-66. Zhang W, Nardi M, Borkowsky W, Li Z, and Karpatkin S. Blood. 2009; April 23; 113(17): 4086-4093.

Adherence to Medication for Chronic Hepatitis C - Building on the Model of Human Immunodeficiency Virus Antiretroviral Adherence Research

Treatment of hepatitis C virus (HCV) infection with pegylated interferon/ribavirin achieves sustained virological response in up to 56% of HCV mono-infected patients and 40% of HCV/human immunodeficiency virus (HIV)-co-infected patients. The relationship of patient adherence to outcome warrants study. The aim of this study was to review comprehensively research on patient-missed doses to HCV treatment and discuss applicable research from adherence to HIV antiretroviral therapy. Publications were identified by PubMed searches using the keywords: adherence, compliance, hepatitis C virus, interferon and ribavirin. The term 'non-adherence' differs in how it is used in the HCV from the HIV literature. In HCV, 'non-adherence' refers primarily to dose reductions by the clinician and early treatment discontinuation. In contrast, in HIV, 'non-adherence' refers primarily to patient-missed doses. Few data have been published on the rates of missed dose adherence to pegylated interferon/ribavirin and its relationship to virological response. As HCV treatment becomes more complex with new classes of agents, adherence will be increasingly important to treatment success as resistance mutations may develop with suboptimal dosing of HCV enzyme inhibitors. HIV adherence research can be applied to that on HCV to establish accurate methods to assess adherence, investigate determinants of non-adherence and develop strategies to optimize adherence. Weiss JJ, Brau N, Stivala A, Swan T, Fishbein T. Aliment Pharmacol Ther. 2009; Jul 30(1):14-27.

Student Volunteers Screen Drug Users for Viral Hepatitis

The Viral Hepatitis Integration Project (VHIP) provides injection drug users with viral hepatitis vaccination, screening and treatment referral services. These services are co-located with a streetside, mobile syringe exchange in a neighborhood in which illicit drug use is highly prevalent. Year 1 and 2 students from the Albert Einstein Medical School volunteer to perform phlebotomy, vaccinate and counsel syringe exchange clients about viral hepatitis. The VHIP was developed to meet the needs of both students and syringe exchange clients. Substance abuse disorders are common among patients, yet few medical students have exposure to drug users prior to their clinical rotations. Little time is devoted to formal teaching about these complex disorders in medical school. Medical students attend the VHIP in pairs; each pair includes one experienced and one novice volunteer. Students are accompanied by the VHIP program coordinator and a health care provider (doctor or Physician Assistant) with expertise in addiction medicine. The medical providers deliver ongoing supervision and support of the students, both on-site and in quarterly meetings. Additionally, medical providers model professional and compassionate behavior in caring for active drug users. To date, 36 medical students have participated in the VHIP. Students have provided vaccinations, viral hepatitis screening, and health counseling to over 200 syringe exchange clients. A self-administered, open-ended survey of student volunteers revealed that they valued learning about the lives of drug users, practicing skills in vaccination and phlebotomy, and having the chance to work with underserved patients. All the students found the experience enjoyable, and many expressed a wish to have more opportunities to volunteer in similar settings. Stein MR, Soloway I, Litwin AH. Student volunteers screen drug users for viral hepatitis. Student Medical Education. 2009 May;43:481-482.

In Vitro Characterization of a miR-122-Sensitive Double-helical Switch Element in the 5' Region of Hepatitis C Virus RNA

It has been proposed that the hepatitis C virus (HCV) internal ribosome entry site (IRES) resides within a locked conformation, owing to annealing of its immediate flanking sequences. In this study, structure probing using Escherichia coli dsRNA-specific RNase III and other classical tools showed that this region switches to an open conformation triggered by the liver-specific microRNA, miR-122. This structural transition, observed in vitro, may be the mechanistic basis for the involvement of downstream IRES structural domain VI in translation, as well as providing a role of liver-specific miR-122 in HCV infection. In addition, the induced RNA switching at the 5' untranslated region could ultimately represent a new mechanism of action of micro-RNAs. D'az-Toledano R, Ariza-Mateos A, Birk A, Mart'nez-Garc'a, B and G—mez J. Nucleic Acids Res. 2009; Jul 3 available on line.

More Rare Birds, and the Occasional Swan

The Urban Health Study recruited semiannual cross-sections of persons who injected illicit drugs from the streets and other natural settings in inner-city neighborhoods in the San Francisco Bay area. Of nearly 14,000 persons enrolled from 1986 through 2002, nearly 5000 participated more than once (mean, 4.5 visits), comprising a passive, embedded cohort. Participants were interviewed, tested for HIV antibody, and given harm reduction counseling and referrals to needed services. Data from the interviews, blood samples, and add-on studies were used to study health and illness among persons who inject illicit drugs and evaluate interventions. Findings from this cohort have been published in >100 articles, describing basic biological, clinical, immunologic, and epidemiologic investigations; social and behavioral studies; and research on health services, health policy, and legal policy. From 1998 through 2002, 4018 study participants received hepatitis B and C serologic testing, of whom 3548 (88%) tested positive for antibodies to the hepatitis C virus (HCV). Of

those testing negative, 84 returned for a subsequent visit, and 24 tested positive for HCV antibody, representing prospectively identified seroconversions. Retrospective testing of stored serum identified an additional 43 seroconversions from 1986 through 1998. Ongoing analyses are examining HCV prevalence, incidence, and risk factors, and genetic factors associated with resistance to viral infection and persistence. The Swan Project began recruiting injection drug users (IDUs) aged 18-35 on the Lower East Side of Manhattan in 2005; >500 IDUs have been interviewed and tested for HIV and HCV antibody, and 150 who have tested HCV antibody negative have enrolled in a prospective cohort. Cohort members undergo biweekly risk behavior interviews and HCV RNA testing to detect new HCV infections as soon as possible after they are acquired, along with counseling and referrals to needed services. Biweekly interviewing and testing has proved feasible, reveals more risk behavior than quarterly or semiannual interviewing, and identifies the timing of risk behavior and infections more precisely, providing increased power to detect associations between specific injection practices and contexts and HCV acquisition. Identifying these risk factors is urgent because HCV still spreads rapidly among IDUs, even where access to sterile syringes has dramatically reduced transmission. The incidence of new infections in Swan participants during follow-up fell 3-fold from 2005 to 2007, whereas the incidence during the period immediately preceding enrollment, calculated using data on window period infections, did not fall, suggesting that the reduction might have resulted from our intervention. The authors are prospectively studying the clinical features, immunology, and virology of acute infection, and comparing those who clear infection, those who develop chronic infection, and those who remain uninfected. They have found HCV-specific cellular responses in nearly 50% of seronegative, HCV RNA-negative persons in this cohort. This study provides the rare opportunity to analyze blood specimens collected before infection and then from the same person weekly during acute infection. Participants who do not clear infection within 90 days are offered antiviral treatment through a unique, multidisciplinary program. To date, the authors have identified 21 prospectively observed infections, 18 persons in the seronegative window period on enrollment, 3 recent seroconverters, and 12 possible reinfections. Edlin B, Shu M, Winkelstein E, Des Jarlais D, Busch M, Rehermann B, O'Brien T, Talal A, Tobler L, Zeremski M and Beeder A. Gastroenterology. 2009; June 136(7):2412-2414.

Methylation Regulates Hepatitis B Viral Protein Expression

Hepatitis B virus (HBV)DNA has been shown to contain CpGislands that are methylated in human tissue, which suggests a role for methylation in regulating viral protein production. However, data are lacking about whether methylation regulates viral gene expression. To investigate the hypothesis that methylation of viral DNA regulates viral gene expression, unmethylated, partially methylated, and fully methylated viral DNA was transfected into HepG2 cells. In addition, a new assay was designed that specifically identifies methylated covalently closed circular DNA (cccDNA) in human liver tissue. Transfection of methylated HBV DNA led to reduced HBV mRNA levels in HepG2 cells, decreased surface and core protein expression in these cells, and decreased secretion of HBV viral proteins into the cell supernatant. These data provide direct evidence that CpG islands regulate gene transcription of HBV. Furthermore, methylated cccDNA was found in tumor and nonneoplastic human liver tissues. Finally, an in vitro equivalent of cccDNA showed decreased viral protein production in HepG2 cells after DNA methylation. Taken together, these data demonstrate that methylation of viral CpG islands can regulate viral protein production. Vivekanandan P, Thomas D, and Torbenson M . J Infect Dis. 2009; May 1;199(9):1286-1291.

Predictors of Injection Drug Use Cessation and Relapse in a Prospective Cohort of Young Injection Drug Users in San

Francisco, CA (UFO Study)

Studies of injection drug use (IDU) cessation have largely sampled adults in drug treatment settings. Little is known about injection cessation and relapse among young IDU in the community. A total of 365 HCV-negative IDU under age 30 years were recruited by street outreach and interviewed quarterly for a prospective cohort between 1/2000 and 2/2008. Participants were followed for a total of 638 person-years and 1996 visits. Survival analysis techniques to identify correlates of injection cessation (> or =3 months) and relapse to injection were used. 67% of subjects were male, median age was 22 years and median years injecting was 3.6, 28.8% ceased injecting during the follow-up period. Among those that ceased injecting, nearly one-half resumed drug injection on subsequent visits, one-quarter maintained injecting cessation, and one-quarter were lost to follow-up. Participating in a drug treatment program in the last 3 months and injecting less than 30 times per month were associated with injection cessation. Injecting heroin or heroin mixed with other drugs, injecting the residue from previously used drug preparation equipment, drinking alcohol, and using benzodiazepines were negatively associated with cessation. Younger age was associated with relapse to injection. These results suggest that factors associated with stopping injecting involve multiple areas of intervention, including access to drug treatment and behavioral approaches to reduce injection and sustain cessation. The higher incidence of relapse in the younger subjects in this cohort underscores the need for earlier detection and treatment programs targeted to adolescents and transition-age youth. In conclusion, young IDU remain at high risk of blood-borne infections and other negative health outcomes. Understanding of longitudinal patterns of injection drug use cessation and relapse and their determinants is critical for guiding public health interventions to reduce morbidity and mortality. Evans JL, Hahn JA, Lum PJ, Stein ES, Page K. Drug Alc Dep 2009;101(3): 152-157.

Risk Behaviors after Hepatitis C Virus Seroconversion in Young Injection Drug Users in San Francisco

The rationale for screening populations at risk for hepatitis C virus infection (HCV) includes the possibility of altering risk behaviors that impact disease progression and transmission. This study prospectively examined young injection drug users (IDU) to determine if behaviors changed after they were made aware of HCV seroconversion. The effects of HCV seroconversion coupled with post-test counseling on risk behaviors (alcohol use, non-injection and injection drug use, lending and sharing injecting equipment, and having sex without a condom) and depression symptoms were estimated using conditional logistic regression, fitting odds-ratios for immediately after disclosure and 6 and 12 months later, and adjusting for secular effects. 112 participants met inclusion criteria, i.e. they were documented HCV seronegative at study onset and subsequently seroconverted during the follow-up period, with infection confirmed by HCV RNA testing. HCV seroconversion was independently associated with a decreased likelihood of consuming alcohol (OR=0.52; 95% CI: 0.27-1.00, p=0.05) and using non-injection drugs (OR=0.40; 95% CI: 0.20-0.81, p=0.01) immediately after disclosure, however, results were not sustained over time. There were significant (p<0.05) declines in the use of alcohol, injection and non-injection drugs, and sharing equipment associated with time that were independent from the effect of seroconversion. Making young IDU aware of their HCV seroconversion may have a modest effect on alcohol and non-injection drug use that is not sustained over time. Tsui JI, Vittinghoff E, Hahn JA, Evans JL, Davidson PJ, Drug Alc Depend. 2009; Jul 30.

Non-AIDS:

Impact of South American Heroin on the US Heroin Market 1993-2004

The past two decades have seen an increase in heroin-related morbidity and mortality in the United States. Trends in US heroin retail price and purity, including the effect of entry of Colombian-sourced heroin on the US heroin market were reported. The average standardized price ($/mg-pure) and purity (% by weight) of heroin from 1993 to 2004 was obtained from US Drug Enforcement Agency retail purchase data for 20 metropolitan statistical areas. Univariate statistics, robust Ordinary Least Squares regression and mixed fixed and random effect growth curve models were used to predict the price and purity data in each metropolitan statistical area over time. Over the 12 study years, heroin price decreased 62%. The median percentage of all heroin samples that are of South American origin increased an absolute 7% per year. Multivariate models suggest percent South American heroin is a significant predictor of lower heroin price and higher purity adjusting for time and demographics. These analyses reveal trends to historically low-cost heroin in many US cities. These changes correspond to the entrance into and rapid domination of the US heroin market by Colombian-sourced heroin. The implications of these changes are discussed. Ciccaronea D, Unickb G, Kraus A. International Journal of Drug Police. 2009; Sept 20(5):392-401.

Depression and Anxiety in Adolescent Females: The Impact of Sleep Preference and Body Mass Index

To examine the differences in depressive symptoms and anxiety between (a) normal weight and overweight, and (b) morning type and evening type (sleep chronotype) adolescent girls. The interaction of sleep chronotype and weight and depressive symptoms and anxiety were also examined. The design consisted of a cross-sectional study of 264 adolescent females (mean age = 14.9 ± 2.2, range 11-17 years). Sleep chronotype, depressive symptoms, and anxiety were obtained by self-report questionnaire. The mean of three measurements of height and weight was used to calculate the body mass index (BMI). BMI was plotted on the CDC BMI-for-age growth charts to obtain percentile ranking. Participants were categorized into two groups according to BMI percentile: normal weight (<85th percentile) and overweight (³85th percentile). Compared with normal-weight females, overweight females were more likely to be non-Caucasian, lower socioeconomic status, have more advanced pubic hair and breast stages, and earlier age at menarche. No differences were observed with respect to sleep chronotype, depressive symptoms, and trait anxiety between normal weight and overweight females. Evening chronotype was associated with more depressive symptoms (B = -.65, $p < .01$) and higher trait anxiety (B = -.22, $p < .05$). Evening chronotype was associated with more depressive symptoms in both normal-weight and overweight females. However, the association was stronger in overweight females. Individually, sleep and weight impact physical and mental health during adolescence. The combination of evening chronotype and overweight appears to have the strongest association on the emotional health of adolescent females. Further investigations are needed to provide potential biological mechanisms for this relationship. Negriff S, Dorn L, Susman E, Huand B. J Adolesc Health. 2009; Jun 44(6):554-560.

Thrombin Induces Tumor Cell Cycle Activation and Spontaneous Growth by Down-regulation of p27Kip1, in Association with the Up-regulation of Skp2 and MiR-222

The effect of thrombin on tumor cell cycle activation and spontaneous growth was examined in synchronized serumstarved tumor cell lines and a model of spontaneous prostate cancer develop-ment in TRAMP mice. BrdUrd incorporation and propidium iodide staining of prostate LNCaP cells arrested in G0 and treated with thrombin or serum revealed a 48- and 29-fold increase in

S phase cells, respectively, at 8 hours. Similar results were obtained with TRAMP cells and a glioblastoma cell line, T98G. Cell cycle kinases and inhibitors in synchronized tumor cells revealed high levels of p27Kip1 and low levels of Skp2 and cyclins D1 and A. Addition of thrombin, TFLLRN, or serum down-regulated p27Kip1 with concomitant induction of Skp2, Cyclin D1, and Cyclin A with similar kinetics. LNCaP p27Kip1-transfected cells or Skp2 knockdown cells were refractory to thrombin-induced cell cycle activation. MicroRNA 222, an inhibitor of p27Kip1, was robustly up-regulated by thrombin. The in vitro observations were tested in vivo with transgenic TRAMP mice. Repetitive thrombin injection enhanced prostate tumor volume 6- to 8-fold ($P < 0.04$). Repetitive hirudin, a specific potent antithrombin, decreased tumor volume 13- to 24-fold ($P < 0.04$). Thus, thrombin stimulates tumor cell growth in vivo by down-regulation of p27Kip1. Hu L, Ibrahim S, Liu C, Skaar K, Pagano M, Karpatkin S. Cancer Res. 2009; Apr 15;69(8):3374-3381.

C-Terminal ADAMTS-18 Fragment Induces Oxidative Platelet Fragmentation, Dissolves Platelet Aggregates, and Protects Against Carotid Artery Occlusion and Cerebral Stroke

Anti-platelet integrin GPIIIa49-66 antibody (Ab) induces complement-independent platelet oxidative fragmentation and death by generation of platelet peroxide following NADPH oxidase activation. A C-terminal 385-amino acid fragment of ADAMTS-18 (a disintegrin metalloproteinase with thrombospondin motifs produced in endothelial cells) induces oxidative platelet fragmentation in an identical kinetic fashion as anti-GPIIIa49-66 Ab. Endothelial cell ADAMTS-18 secretion is enhanced by thrombin and activated by thrombin cleavage to fragment platelets. Platelet aggregates produced ex vivo with ADP or collagen and fibrinogen are destroyed by the C-terminal ADAMTS-18 fragment. Anti-ADAMTS-18 Ab shortens the tail vein bleeding time. The C-terminal fragment protects against FeCl3-induced carotid artery thrombosis as well as cerebral infarction in a postischemic stroke model. Thus, a new mechanism is proposed for platelet thrombus clearance, via platelet oxidative fragmentation induced by thrombin cleavage of ADAMTS-18. Li Z, Nardi M, Li YS, Zhang W, Pan R, Dang S, et al., Blood. 2009; Jun 11;113(24):6046-6047.

Lack of Reduction in Buprenorphine Injection After Introduction of Co-Formulated Buprenorphine/Naloxone to the Malaysian Market

Diversion of buprenorphine (BPN) has been described in settings where it is legally prescribed and has resulted in increasing concern. To address this concern, co-formulation of buprenorphine/naloxone (BPN/NLX) replaced buprenor-phine alone in Malaysia in December 2006. To assess the significance of BPN/NLX introduction, 41 BPN/NLX injectors in Kuala Lumpur, Malaysia were recruited using a modified snowball recruitment technique. In January 2007, all subjects had previously injected BPN alone. During the transition from injecting BPN alone to co-formulated BPN/NLX, the mean daily BPN injection dose increased from 1.88 mg (range 1.0-4.0 mg) to 2.49 mg/day ($p < .001$). Overall, 18 (44%) subjects increased their daily amount of injection while 22 (54%) had no change in dose; only one subject reduced the amount of injection. Development of opioid withdrawal symptoms was the primary outcome, however the only symptom that was significantly associated with BPN/NLX dosage was the report of "stomach pains" ($p = .01$). In logistic regression analysis, the development of opioid withdrawal symptoms was associated with increased benzodiazepine injection and increased syringe sharing. These data suggests that the introduction of BPN/NLX did not reduce injection related risk behaviors such as syringe sharing and was associated with increased benzodiazepine use. Evidence-based approaches to treat BPN

injection are urgently needed. Bruce D, Govindasamy S, Sylla L, Kamarulzaman A, Altice F. The American Journal of Drug and Alcohol Abuse. 2009; March;35(2):68-72.

Contemporary Clinical Opioid Use: Opportunities and Challenges

Opiate analgesics have been used by humans for thousands of years and are the longest continuously used class of medications. The recent increased interest in opiates (drugs derived from opium) and opioids (more generally, any natural or synthetic drug that binds to an opioid receptor) has evolved largely from 5 directions: (1) advances in the design of new opioid receptor agonist and antagonist drugs; (2) expansion and innovation in methods of drug delivery; (3) increased public awareness of pain management options and the appropriateness of aggressively treating pain (eg, declaration of pain as the "fifth vital sign" and pain relief as a fundamental human right); (4) growing recognition of the serious consequences of opioid misuse, misadventure, and addiction; and (5) medicolegal aspects of practitioners' prescribing practices and legal prosecution for "overprescribing." These and related issues are addressed in 4 articles and 1 additional editorial in the current issue of Mayo Clinic Proceedings. Specifically, Passik discusses long-term prescription opioid therapy; Argoff and Silvershein address the use of long- vs short-acting opioids for treating chronic noncancer pain; Smith reviews opioid metabolism; and Berge et al discuss chemical dependency in physicians, with a focus on opioids. In their editorial, Oreskovich and Caldeiro discuss whether select groups of health care professionals, such as anesthesiologists, have unacceptably poor outcomes after initial opioid addiction and whether this should dictate policies of rehabilitation and possible return to clinical practice. Lanier WL, Kharasch ED. Mayo Clin Proc. 2009; Jul 84(7):572-575.

Serum IL-6 Levels are Associated with Significant Coronary Stenosis in Cardiovascularly Asymptomatic Inner-city Black Adults in the US

The objective of this study was to explore whether increased levels of inflammatory cytokines are associated with the risk of clinically silent coronary artery disease. Three-hundred-fifty-six black adults aged 25-54 residing in inner city of Baltimore, Maryland, United States were included in this study. Sociodemographics were assessed as were lipid profiles, IL-6, tumor necrosis factor-alpha (TNF-alpha), soluble intercellular adhesion molecule-1 (sICAM-1), and high-sensitivity C-reactive protein (hs-CRP) levels. Computed tomography (CT) coronary angiography was performed. Coronary calcification was identified in 22.5 % participants and 14 % had significant (³50 %) coronary stenosis. Multiple logistic regression analyses suggested that IL-6 levels were independently associated with the presence of coronary calcification and significant coronary stenosis, while TNF-alpha, sICAM-1 and hs-CRP levels were not. This study underscores a critical role for IL-6 in atherosclerosis and suggests that IL-6 may be a marker for significant coronary stenosis in cardiovascularly asymptomatic individuals. Lai S, Fishman E, Lai H, Pannu H, Detrick B. Inflamm Res. 2009;58:15-21.

Director's Report to the National Advisory Council on Drug Abuse - September, 2009

Research Findings - Services Research

Accessing Antiretroviral Therapy Following Release from Prison

Interruption of antiretroviral therapy (ART) during the first weeks after release from prison may increase risk for adverse clinical outcomes, transmission of human immunodeficiency virus (HIV), and drug-resistant HIV reservoirs in the community. The extent to which HIV-infected inmates experience ART interruption following release from prison is unknown. To determine the proportion of inmates who filled an ART prescription within 60 days after release from prison and to examine predictors of this outcome. This paper reports on a retrospective cohort study of all 2115 HIV-infected inmates released from the Texas Department of Criminal Justice prison system between January 2004 and December 2007 and who were receiving ART before release. Measured against the proportion of inmates who filled an ART prescription within 10, 30, and 60 days of release from prison. Among the entire study cohort (N = 2115), an initial prescription for ART was filled by 115 (5.4%) inmates within 10 days of release (95% confidence interval [CI], 4.5%-6.5%), by 375 (17.7%) within 30 days (95% CI, 16.2%-19.4%), and by 634 (30.0%) within 60 days (95% CI, 28.1%-32.0%). In a multivariate analysis of predictors (including sex, age, race/ethnicity, viral load, duration of ART, year of discharge, duration of incarceration, parole, and AIDS Drug Assistance Program application assistance), Hispanic and African American inmates were less likely to fill a prescription within 10 days (adjusted estimated risk ratio [RR], 0.4 [95% CI, 0.2-0.8] and 0.4 [95% CI, 0.3-0.7], respectively) and 30 days (adjusted estimated RR, 0.7 [95% CI, 0.5-0.9] and 0.7 [95% CI, 0.5-0.9]). Inmates with an undetectable viral load were more likely to fill a prescription within 10 days (adjusted estimated RR, 1.8 [95% CI, 1.2-2.7]), 30 days (1.5 [95% CI, 1.2-1.8]), and 60 days (1.3 [95% CI, 1.1-1.5]). Inmates released on parole were more likely to fill a prescription within 30 days (adjusted estimated RR, 1.3 [95% CI, 1.1-1.6]) and 60 days (1.5 [95% CI, 1.4-1.7]). Inmates who received assistance completing a Texas AIDS Drug Assistance Program application were more likely to fill a prescription within 10 days (adjusted estimated RR, 3.1 [95% CI, 2.0-4.9]), 30 days (1.8 [95% CI, 1.4-2.2]), and 60 days (1.3 [95% CI, 1.1-1.4]). This study shows that only a small percentage of Texas prison inmates receiving ART while incarcerated filled an initial ART prescription within 60 days of their release. Baillargeon J, Giordano T, Rich J, Wu Z, Wells K, Pollock B, Paar D. Accessing antiretroviral therapy following release from prison. JAMA. 2009;301(8):848-857.

Prevalence of Past Year Assault Among Inner-city Emergency Department Patients

This is one of the first studies to determine the rates of past year non-partner violent assault, both victimization and aggression, and assess variables

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associated with non-partner violent assault, particularly with regard to substance use. A cross-sectional computerized standardized survey study (n=10,744) was conducted to assess non-partner violent assault, physical and mental health, and substance use among patients presenting to an inner-city ED during 2 years. Patients (aged 19 to 60 years) with normal vital signs in an urban emergency department (ED) from 9 am to 11 pm were eligible; pregnant patients and those with a chief complaint of psychiatric evaluation were excluded. 10,744 patients were enrolled (80% response rate); 14% of the sample reported any past year non-partner violent assault (9% perpetration; 11% victimization). The authors conducted regression analyses, and found that participants with any past year non-partner violent assault (victimization or aggression) were more likely than their counterparts to be men (2.2), to be single (1.5), to be unemployed (1.1), to present to the ED for injury (1.9), and to report poor physical health (1.3) or poor mental health (1.9). They were less likely to be black (0.8), or older (0.95). Alcohol use (1.7), marijuana use (2.4), cocaine use (3.1), prescription drug use (1.4), and past treatment (1.7) were associated with experiencing past year non-partner violent assault. This study found a high percentage (14%) of patients seeking care in this inner-city ED experience violence with a non-partner. Substance use-specifically cocaine-was the strongest predictor of any non-partner violent assault. Cunningham R, Murray R, Walton M, Chermack S, Wojnar M, Wozniak P, Booth B, Blow F. Prevalence of past year assault among inner-city emergency department patients. Ann Emerg Med. 2009;53(6):814-823.e15.

Results From Two Randomized Clinical Trials Evaluating the Impact of Quarterly Recovery Management Checkups With Adult Chronic Substance Users

Post-discharge monitoring and early reintervention have become standard practice when managing numerous chronic conditions. These two experiments tested the effectiveness of recovery management checkup (RMC) protocols for adult chronic substance users. RMC included quarterly monitoring; motivational interviewing to provide personalized feedback and to resolve ambivalence about substance use; treatment linkage, engagement and retention protocols to increase the amount of treatment received. Recruited from sequential addiction treatment admissions, participants in the two experiments were, on average, 36 versus 38 years of age, mainly female (59% versus 46%), African American (85% versus 80%) and met past-year criteria for dependence (87% versus 76%). Participants in both experiments were assigned randomly to the RMC or control condition and interviewed quarterly for 2 years. The Global Appraisal of Individual Needs (GAIN) was the main assessment instrument. RMC participant outcomes were better than control participants in both experiments. Effect sizes were larger in the second experiment in terms of reducing days to readmission (Cohen's d = 0.41 versus d = 0.22), successive quarters in the community using substances (d = -0.32 versus -0.19), past-month symptoms of abuse/dependence (d = -0.23 versus -0.02) and increasing the days of abstinence over 2 years (d = +0.29 versus 0.04). RMC, which provided ongoing monitoring and linkage, is feasible to conduct and is effective for adults with chronic substance dependence. Scott C, Dennis M. Results from two randomized clinical trials evaluating the impact of quarterly recovery management checkups with adult chronic substance users. Addiction. 2009;104(6):959-971.

Gender and Comorbidity Among Individuals With Opioid Use Disorders in the NESARC Study

This study examines gender differences in the association of lifetime mental and substance use disorders among individuals with opioid use disorders in the United States. The sample (N=578) is from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), which is a representative

household survey. Bivariate analyses and logistic regression modeling were conducted. About 70% of the sample had a lifetime non-substance use Axis I disorder; women were about twice as likely as men to have either a mood or anxiety disorder. About half of the sample had a personality disorder, with women more likely to have paranoid disorder and men more likely to have antisocial personality disorder. Individuals with a lifetime mental disorder were about three times more likely than others to be dependent on other substances, independent of gender. The study demonstrated an inverse relationship between lifetime mental and other substance use disorders, with women having significantly higher odds for several of the mental disorders and men having greater odds of other substance use disorders. Grella C, Karno M, Warda U, Niv N, Moore A. Gender and comorbidity among individuals with opioid use disorders in the NESARC study. Addict Behav. 2009;34(6-7):498-504.

HAART Receipt and Viral Suppression Among HIV-Infected Patients With Co-Occurring Mental Illness and Illicit Drug Use

Mental illness (MI) and illicit drug use (DU) frequently co-occur. The study sought to determine the individual and combined effects of MI and DU on highly active antiretroviral therapy (HAART) receipt and HIV-RNA suppression among individuals engaged in HIV care. Using 2004 data from the HIV Research Network (HIVRN), researchers performed a cross-sectional study of HIV-infected patients followed at seven primary care sites. Outcomes of interest were HAART receipt and virological suppression, defined as an HIV-RNA <400 copies/ml. Independent variables of interest were: (1) MI/DU; (2) DU only; (3) MI only; and (4) Neither. Chi-square analysis was used for comparison of categorical variables, and logistic regression to adjust for age, race, sex frequency of outpatient visits, years in clinical care, CD4 nadir, and study site. During 2004, 10,284 individuals in the HIVRN were either on HAART or HAART eligible defined as a CD4 cell count < or =350. Nearly half had neither MI nor DU (41%), 22% MI only, 15% DU only, and 22% both MI and DU. In multivariate analysis, co-occurring MI/DU was associated with the lowest odds of HAART receipt (Adjusted Odds Ratio: 0.63 (95% CI: (0.55-0.72]), followed by those with DU only (0.75(0.63-0.87)), compared to those with neither. Among those on HAART, concurrent MI/DU (0.66 (0.58-0.75)), DU only (0.77 (0.67-0.88)), were also associated with a decreased odds of HIV-RNA suppression compared to those with neither. MI only was not associated with a statistically significant decrease in HAART receipt (0.93(0.81-1.07)) or viral suppression (0.93 (0.82-1.05)) compared to those with neither. Post-estimation testing revealed a significant difference between those with MI/DU and DU only, and MI/DU and MI only. Co-occurring MI and DU is associated with lower HAART receipt and viral suppression compared to individuals with either MI or DU or neither. Integrating HIV, substance abuse, and mental health care may improve outcomes in this population. Chander G, Himelhoch S, Fleishman J, Hellinger J, Gaist P, Moore R, Gebo K. HAART receipt and viral suppression among HIV-infected patients with co-occurring mental illness and illicit drug use. AIDS Care. 2009;21(5):655-663.

A Practical Clinical Trial of Coordinated Care Management to Treat Substance Use Disorders Among Public Assistance Beneficiaries

This study tested whether coordinated care management (CCM), a continuity of care intervention for substance use disorders (SUD), improved rates of abstinence when compared with usual welfare management for substance-using single adults and adults with dependent children applying for public assistance. The study was designed as a practical clinical trial and was implemented in partnership with a large city welfare agency. Participants were 421 welfare applicants identified via SUD screening and assigned via an unbiased computerized allocation program to a site that provided either CCM (n

= 232) or usual care (UC; n = 189). Outcomes were assessed for 1 year post-baseline with self-reports and biological measures of substance use. As hypothesized, for participants not enrolled in methadone maintenance programs (n = 313), CCM clients received significantly more services than did UC clients. Nonmethadone CCM also showed significantly higher abstinence rates (odds ratio = 1.75; 95% confidence interval = 1.12, 2.76; d = 0.31) that emerged early in treatment and were sustained throughout follow-up. In contrast, no treatment services or outcome effects were found for methadone maintenance clients (n = 108). Findings suggest that CCM is promising as a wraparound to SUD treatment for welfare recipients. Morgenstern J, Hogue A, Dauber S, Dasaro C, McKay J. A practical clinical trial of coordinated care management to treat substance use disorders among public assistance beneficiaries. J Consult Clin Psychol. 2009;77 (2):257-269.

Race and Ethnic Differences in the Prevalence of Gambling Disorders: Results From a National Sample

Prior research suggests that racial minority groups in the United States are more vulnerable to develop a gambling disorder than whites. However, no national survey on gambling disorders exists that has focused on ethnic differences. Analyses of this study were based on the National Epidemiologic Survey on Alcohol and Related Conditions, a large (N=43,093) nationally representative survey of the adult (> or =18 years of age) population residing in households during 2001-2002 period. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision diagnoses of pathological gambling, mood, anxiety, drug use, and personality disorders were based on the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version. The authors found that the prevalence rates of disordered gambling among blacks (2.2%) and Native/Asian Americans (2.3%) were higher than that of whites (1.2%). Demographic characteristics and psychiatric comorbidity differed among Hispanic, black, and white disordered gamblers. However, all racial and ethnic groups evidenced similarities with respect to symptom patterns, time course, and treatment seeking for pathological gambling. The prevalence of disordered gambling, but not its onset or course of symptoms, varies by racial and ethnic group. These varying prevalence rates may reflect, at least in part, cultural differences in gambling and its acceptability and accessibility. These data may inform the need for targeted prevention strategies for high-risk racial and ethnic groups. Alegria A, Petry N, Hasin D, Liu S, Grant B, Blanco C. Disordered gambling among racial and ethnic groups in the us: results from the National Epidemiologic Survey on Alcohol and Related Conditions. CNS Spectr. 2009;14(3):132-142.

CO Exposure and Subjective Nicotine / Tobacco Effects in Waterpipe Tobacco Smokers

Waterpipe tobacco smoking is increasing in popularity though the toxicant exposure and effects associated with this tobacco use method are not well understood. In this study, 61 waterpipe tobacco smokers (56 males; mean age ± SD , 30.9 ± 9.5 years; mean number of weekly waterpipe smoking episodes, 7.8 ± 5.7; mean duration of waterpipe smoking 8.5 ± 6.1 years) abstained from smoking for at least 24 hr and then smoked tobacco from a waterpipe ad libitum in a laboratory. Before and after smoking, expired-air carbon monoxide (CO) and subjective effects were assessed; puff topography was measured during smoking. It was found that each mean waterpipe use episode duration was 33.1 ± 13.1 min. Expired-air CO increased significantly from a mean of 4.0 ± 1.7 before to 35.5 ± 32.7 after smoking. On average, participants took 169 ± 100 puffs, with a mean puff volume of 511 ± 333 ml. Urge to smoke, restlessness, craving, and other tobacco abstinence symptoms were reduced significantly after smoking, while ratings of dizzy, lightheaded, and other direct effects of nicotine increased. In this study expired-air CO and puff topography

data indicate that, relative to a single cigarette, a single waterpipe tobacco smoking episode is associated with greater smoke exposure. Abstinent waterpipe tobacco smokers report symptoms similar to those reported by abstinent cigarette smokers, and these symptoms are reduced by subsequent waterpipe tobacco smoking. Taken together, these data are consistent with the hypothesis that waterpipe tobacco smoking is likely associated with the risk of tobacco/nicotine dependence. Maziak W, Rastam S, Ibrahim I, Ward, KD, Shihadeh A, Eissenberg T. CO exposure, puff topography, and subjective effects in waterpipe tobacco smokers. Nicotine Tob Res. 2009;1:1-6.

Are Differences in Guidelines for the Treatment of Nicotine Dependence and Dependence on Other Drugs Justified?

Despite the many similarities between nicotine dependence and other drug dependences, national guidelines for their treatment differ in several respects. The recent national guideline for the treatment of nicotine dependence has (i) less emphasis on detailed assessment; (ii) less emphasis on treatment of psychiatric comorbidity; (iii) less acceptance of reduction of use as an initial treatment goal; (iv) greater emphasis on pharmacological interventions; and (v) less emphasis on psychosocial treatment than national guidelines for non-nicotine dependences. These treatment differences may occur because (i) nicotine does not cause behavioral intoxication; (ii) psychiatric comorbidity is less problematic with nicotine dependence; (iii) psychosocial problems are less severe with nicotine dependence; and (iv) available pharmacotherapies for nicotine dependence are safer, more numerous and more easily available. However, it is unclear to the authors whether these treatment differences are, in fact, justifiable because of the scarcity of empirical tests. Several possible empirical tests are suggested to answer this question. Hughes JR, Weiss RD. Are differences in guidelines for the treatment of nicotine dependence and non-nicotine dependence justified? Addiction. 2009;1-7 [E-pub ahead of print].

Treatment Fidelity and Retention are Associated with Adolescent Addiction Treatment Outcomes

The purpose of this study was to examine the extent to which exposure to Adolescent Community Reinforcement Approach (A-CRA) intervention procedures mediated the relationship between treatment retention and outcomes. The underlying theory of A-CRA is that rearranging environmental contingencies so that non-using behavior is more rewarding than drug using behavior will prevent or reduce alcohol and other drug (AOD) use. Data from 399 adolescents, who participated in one of four randomly controlled trials of the Adolescent Community Reinforcement Approach (A-CRA) intervention, were used. Exposure to A-CRA was a key measure of treatment fidelity, a count of the 15 procedures and case-management activities which are outlined in the A-CRA and case-management manuals and are scored dichotomously as either completed or not completed. As anticipated, zero-order correlations indicated that retention in treatment was a significant predictor of AOD use ($r = -0.18$, $p < .001$). However, the association between retention and AOD use was reduced to non-significance ($p = .39$) when exposure to A-CRA procedures was included in the structural equation model. The results of this study suggest that exposure to treatment procedures may be a mediator in the treatment process, providing support for "specific ingredients" of treatment impacting treatment outcome. The current findings are useful, as little research to date has identified significant mediators of the relationship between retention and treatment outcomes or identified target thresholds of treatment exposure. Garner B, Godley S, Funk R, Dennis M, Smith J, Godley M. Exposure to adolescent community reinforcement approach treatment procedures as a mediator of the relationship between adolescent substance abuse treatment retention and outcome. J Subst Abuse Treat. 2009;36(3):252-264.

Drug Use and Sexually Transmitted Diseases Among Female and Male Arrested Youths

Knowledge of the rates and correlates of sexually transmitted diseases (STD) among incarcerated juvenile offenders has been limited to mostly male samples. Data were collected on 442 female and 506 male youths processed at a centralized juvenile justice intake facility. FemaleÐmale, multi-group latent class analyses identified two subgroups, of youths, High Risk and Lower Risk, described by a latent construct of risk based on drug test results, STD test results, and a classifica-tion for the seriousness of arrest charge. The results found a similar classification distinguished High Risk and Lower Risk male and female youths. High Risk youth had higher rates of positive STD results, of positive urinalysis for marijuana and cocaine, and of being charged with a serious offense. In addition, 66% of the girls and 57% of the boys in this sample who tested positive for an STD were released back into the community after arrest. Overall, the findings raise serious public health and social welfare concerns, for both the youths and the community. Dembo R, Belenko S, Childs K, Wareham J. Drug use and sexually transmitted diseases among female and male arrested youths. J Behav Med. 2009;32:129-141.

Violent Offenses Associated with Co-Occurring Substance Use and Mental Health Problems: Evidence from CJ-DATS

The present study examines the relationship between substance use, mental health problems, and violence in a sample of offenders released from prison and referred to substance abuse treatment programs. Data from 34 sites (n = 1,349) in a federally funded coopera-tive, the Criminal Justice Drug Abuse Treatment Studies (CJ-DATS), were analyzed. Among parolees referred to substance abuse treatment, self-reports for the six-month period before the arrest resulting in their incarceration revealed frequent problems with both substance use and mental health. For most offenders with substance use problems, the quantity of alcohol consumed and the frequency of drug use were associated with a greater probability of self-reported violence. Mental health problems were not indicative of increases in violent behavior, with the exception of antisocial personality problems, which were associated with violence. The paper emphasizes the importance of providing substance abuse treatment in relation to violent behavior among offenders with mental health problems being discharged to the community. Sacks S, Cleland C, Melnick G, Flynn P, Knight K, Friedmann P, Prendergast M, Coen C. Violent offenses associated with co-occurring substance use and mental health problems: Evidence from CJ-DATS. Behav Sci Law. 2009;27(1):51-69.

Suicide Ideation, Attempts, Prevalent Among Adolescents in Substance Abuse Treatment

Data from CSAT/SAMHSA's Adolescent Treatment Models program were analyzed to determine the rates of suicide ideation and attempts among adolescents entering 11 treatment programs across the country. 948 clients, including 110 in long-term residential, 468 in short-term residential, and 370 in outpatient treatment, were followed for one year post-intake with interim assessments and were assessed with the Global Appraisal of Individual Needs (GAIN). Results indicate that 30% of the youth reported ideating in at least one interview, and 12% reported a suicide attempt. Multivariate regression results reveal that those with a conduct disorder (OR=1.09, CI 1.03-1.15), depression (OR=1.22, CI 1.10-1.36) had higher odds of ideating, while Black adolescents had lower odds (OR=0.24, CI 0.08-0.73). Attempts were more likely among those who had ideated (OR=8.55, CI 3.62-20.17) or who had a conduct disorder (OR=1.23 CI 1.10-1.38). The results suggest that efforts to prevent suicide among adolescents in substance abuse treatment, particularly those

with conduct disorders, may be appropriate. Ramchand R, Griffin B, Harris K, McCaffrey D, Morral A. A prospective investigation of suicide ideation, attempts, and use of mental health service among adolescents in substance abuse treatment. Psychol Addict Behav. 2008;22(4):524-532.

Young Adults Seek Treatment for Smoking Cessation Less Often Than Older Adults

Young adult smokers (18-24 year olds) do not seek treatment for smoking cessation as often as older smokers. Two commonly hypothesized reasons for this are that younger smokers are not aware of treatments or cannot afford them. The State of Vermont provides free smoking cessation treatment, and most young smokers are aware of this; thus, the PI and study team tested whether young adult smokers from Vermont would still underutilize treatment via a secondary analysis of the popula-tion-based 2005 VT Adult Tobacco Survey. (n=2000). It was found in this study with small sample size and limited racial variability, that young adult smokers from Vermont were less likely to have used medication (24% vs. 58%; relative risk=0.42) or psychosocial (28% vs. 53%; relative risk =0.54) treatment than middle-aged smokers (25-44 year olds). This study indicates that reasons other than awareness and cost cause young adult smokers to not seek treatment. Hughes JR, Cohen B, Callas PW. Treatment seeking for smoking cessation among young adults. J Subst Abuse Treat. 2009:1-3.

Non-structured Treatment Interruptions Among Injection Drug Users in Baltimore, MD

This study characterized patterns of highly active antiretroviral therapy (HAART) use and predictors of non-structured treatment interruptions (NTIs) among injection drug users (IDUs) in Baltimore, MD. Three hundred thirty-five IDUs who initiated HAART from 1996 to 2006 were studied. NTIs were defined as any subsequent 6-month interval where HAART was not reported. Predictors of the first NTI and subsequent restart of HAART were examined using Cox regression. Two hundred sixty (78%) reported > or =1 NTI. Of 215 with > or =1 follow-up visit after the NTI, 44 (20%) never restarted HAART, 62 (29%) restarted and remained on HAART, and 109 (51%) reported multiple NTIs. NTIs were less likely among those who initiated HAART in later calendar years and had a recent outpatient visit and more likely among women, persons with detectable HIV RNA at the prior visit, and those who reported injecting daily. Among those with NTIs, interruptions occurred earlier in persons who were younger, who did not have a prior AIDS diagnosis, and who were actively injecting; NTIs lasted longer in persons who had higher HIV RNA levels, in persons who were incarcerated, and in persons drinking alcohol. A recent outpatient visit and not actively injecting were associated with restarting HAART. NTIs were common in this population and occurred most frequently in the setting of active drug use and disruption of health care. Effective linkages between primary care for HIV and substance abuse treatment may improve HAART outcomes in this population. Kavasery R, Galai N, Astemborski J, Lucas G, Celentano D, Kirk G, Mehta S. Nonstructured treatment interruptions among injection drug users in Baltimore, MD. J Acquir Immune Defic Syndr. 2009;50(4):360-366.

Outcome Trajectories in Drug Court Do All Participants Have Serious Drug Problems?

Graduation rates in drug courts average 50% to 70%, but it is unclear what proportion of graduates responded to the drug court services and what proportion might not have had serious drug problems on entry. This study cluster analyzes urine drug screen results during the first 14 weeks of

treatment on 284 participants from three misdemeanor drug courts. A four-cluster solution (R squared > .75) produced distinct subgroups characterized by (a) consistently drug-negative urine specimens (34% of the sample), (b) consistently drug-positive specimens (21%), (c) consistently missed urine specimens (26%), and (d) urine specimens that began as drug positive but became progressively drug negative over time (19%). These data suggest that approximately one third of the participants might not have had serious drug problems on entry. Approximately one fifth appeared to respond to drug court services, and nearly one half continued to exhibit problems after 14 weeks. Implications for adaptive programming in drug courts are discussed. DeMatteo D, Marlowe DB, Festinger DS, Arabia PL. Outcome trajectories in drug court: do all participants have serious drug problems? Criminal Justice and Behavior. 2009;36:354-368.

Factors Influencing Consent to HIV Testing Among Wives of Heavy Drinkers in India

This study examined the influence of socio cultural factors, perception of risk and exposure to violence on consent to HIV testing among at risk women in an urban slum in India. Married women (n=100) chosen via a multistage probability sampling in a section of Bangalore, India, between 18 and 44 years, sexually active and considered to be at risk because of their husband's hazardous drinking were recruited for the study. Factors influencing refusal of and consent to HIV testing were documented. Data collected on 100 participants indicated that over half the sample (58%) refused consent for HIV testing. There were no significant differences between the groups who consented and those who refused on perception of risk and exposure to violence. Reasons women refused testing include the following: spouse/family would not allow it (40%), believed that they were not at risk or would test negative (29%) and underwent HIV testing during an earlier pregnancy (21%). Among those who consented for HIV testing, 79% did so because the testing site was easily accessible, 67% consented because testing was free and because the importance of HIV testing was understood. The findings highlight the role of social, logistic and awareness related factors in utilizing voluntary counseling and testing services by women in this slum community. Generalization of the findings is a limitation, however few studies documents factors important to promote HIV testing in, particularly among at risk monogamous women. Furthermore, this study indicates better consent rates among women in developing countries are ultimately achievable by improving logistics, increasing awareness and involving significant others. Satyanarayana V, Chandra P, Vaddiparti K, Benegal V, Cottler L. Factors influencing consent to HIV testing among wives of heavy drinkers in an urban slum in India. AIDS Care. 2009;21(5):615-621.

Factors Mediating and Moderating the Relationship Between Gender and Utilization of Health Care Among Puerto Rican Drug Users in New York

This study examined factors that mediate and moderate the relationship between gender and utilization of mental health and medical services in the past year among Puerto Rican drug users (308 females; 892 males) recruited in New York City. Experience of sexual or physical abuse, injection drug use, relationship variables (e.g., having a sexual partner who is an injection drug user), and serious or chronic mental/medical conditions were used as potential mediators and moderators. Both sexual and physical abuse mediated gender effects on use of mental health services. Having chronic medical problems mediated the relationship between gender and utilization of medical and mental health services. Significant interaction effects of gender by depression, physical abuse, and HIV sero-status on utilization of medical services were found. Health (particularly mental health) care was under-utilized by both

women and men, despite high rates of depression and chronic medical conditions. The finding of under-use of medical services by HIV-positive drug users (particularly by HIV-positive women) indicates a need for further efforts to engage all HIV-positive persons in care. The findings also indicate an on-going need for mental and other health services for drug users who have been victims of abuse. Kang S, Deren S. Factors mediating and moderating the relationship between gender and utilization of health care among Puerto Rican drug users in New York. Drug Alcohol Depend. 2009;102(1-3):138-143.

Relationship Between Stress, Substance Use and Sexual Risk Behaviors Among Primary Care Patients in Cape Town, South Africa

Authors assessed the relationship between stress, substance use and sexual risk behaviors in a primary care population in Cape Town, South Africa. A random sample of participants (and over-sampled 18-24-year-olds) from 14 of the 49 clinics in Cape Town's public health sector using stratified random sampling (n = 2,618), was selected. PI and study team evaluated current hazardous drug and alcohol use and three domains of stressors (Personal Threats, Lacking Basic Needs, and Interpersonal Problems). It was found that several personal threat stressors and an interpersonal problem stressor were related to sexual risk behaviors. With stressors included in the model, hazardous alcohol use, but not hazardous drug use, was related to higher rates of sexual risk behaviors. These findings suggest a positive screening for hazardous alcohol use should alert providers about possible sexual risk behaviors and vice versa. Additionally, it can be seen from this study that it is important to address a broad scope of social problems and incorporate stress and substance use in HIV prevention campaigns. Avalos LA, Mertens JR, Ward CL, Flisher AJ, Bresick GF, Weisner CM. Stress, substance use and sexual risk behaviors among primary care patients in Cape Town, South Africa. AIDS Behav. 2009:0-1.

Management Practices in Substance Abuse Treatment Programs

Efforts to understand how to improve the delivery of substance abuse treatment have led to a recent call for studies on the "business of addiction treatment." This study adapts an innovative survey tool to collect baseline management practice data from 147 addiction treatment programs enrolled in the Network for the Improvement of Addiction Treatment 200 project (NIATx). Measures of "good" management practice were strongly associated with days to treatment admission. Management practice scores were weakly associated with revenues per employee but were not correlated with operating margins. Better management practices were more prevalent among programs with a higher number of competitors in their catchment area. McConnell KJ, Hoffman KA, Quanbeck A, McCarty D. Management practices in substance abuse treatment programs. J Subst Abuse Treat. 2009:79-89.

Psychotic Symptoms, Disorders and Outcomes Among US Latinos

In US regional studies, Latinos frequently endorse psychotic symptoms associated with impairment and mental health service use, yet do not meet criteria for psychotic disorder. Using a nationally representative Latino sample (N = 2554), the authors examined the prevalence of psychotic symptoms, their relationship to psychotic disorder, their correlates, and their relationship to mental health outcomes. In this sample, 9.5% (SE = 0.7) endorsed 1 or more lifetime psychotic symptoms, yet 93% of endorsers did not meet Structured Clinical Interview for DSM-IV criteria for psychotic disorders. Endorsement was associated with physical and emotional distress, particularly lifetime anxiety and current substance use disorder. Acculturation to US society and reliance on

spiritual/religious help were also associated with psychotic symptom endorsement. These symptoms have substantial clinical significance, being independently associated with suicidal ideation, mental health-related disability, and outpatient mental health service utilization. Endorsed psychotic symptoms in Latinos may constitute a clinically significant marker of general psychiatric vulnerability rather than a sign of psychotic disorder. Lewis-Fern‡ndez R, Horvitz-Lennon M, Blanco C, Guarnaccia P, Cao Z, Alegr'a M. Significance of endorsement of psychotic symptoms by US Latinos. J Nerv Ment Dis. 2009;197(5):337-347.

The Attitudes of Females in Drug Court Toward Additional Safeguards in Research Studies

This article examines the attitudes of 97 women from the St. Louis City Drug Court who previously participated in an HIV prevention study. Data from the previous study indicated that the women met multiple criteria for vulnerability in research. Federal regulations require that such participants be provided with "additional safeguards." The survey explored the following questions: (1) What are participants' attitudes toward commonly proposed additional safeguards for vulnerable participants in research, and (2) Are attitudes toward safeguards related to participants' previous compliance with an HIV prevention protocol? The researchers found preferences regarding safeguards in research were not significantly related to participants' compliance in the previous study. However, most participants wanted researchers to take extra measures not only to provide consent information, but to ensure that they are not high on drugs, that they understand relevant information, and that they retain consent information at each visit. Most participants wanted researchers themselves, and not a third party, to assume this responsibility. DuBois JM, O'Leary CC, Cottler LB. The attitudes of females in drug court toward additional. Prev Sci. 2009;10:0-1.

Director's Report to the National Advisory Council on Drug Abuse - September, 2009

Research Findings - CTN-Related Research

Correspondence of Motivational Enhancement Treatment Integrity Ratings Among Therapists, Supervisors, and Observers

This study examined the correspondence of treatment integrity ratings (adherence and competence) among community program therapists, supervisors, and observers for therapists who used motivational enhancement therapy (MET) within a National Institute on Drug Abuse Clinical Trials Network protocol. The results suggested there was reasonable agreement between the three groups of raters about the presence or absence of several fundamental MET strategies. Moreover, relative to observers, therapists and supervisors were more positive in their evaluations of the therapists' MET adherence and competence. These findings underscore the need for objective monitoring of therapists' performance when using empirically supported treatments and for adequately training therapists and supervisors to evaluate their treatment implementation in community programs. These findings are also consistent with observations that different perspectives on the therapeutic process are not interchangeable. Martino S, Ball S, Nich C, Frankforter TL, Carroll KM. Psychother Res. 2009 Mar;19(2):181-193.

Quality Assurance of Research Protocols Conducted in the Community: The National Institute on Drug Abuse Clinical Trials Network Experience

Quality assurance (QA) of clinical trials is essential to protect the welfare of trial participants and the integrity of the data collected. This article describes the experience of the National Institute on Drug Abuse's (NIDA) National Drug Abuse Treatment Clinical Trials Network (CTN) in devising and implementing a three-tiered QA model for rigorous multi-site randomized clinical trials implemented in community-based substance abuse treatment programs. The CTN QA model combined local and national resources and was developed to address the unique needs of clinical trial sites with limited research experience. Between January 2001 and September 2005, the CTN implemented 21 protocols, of which 18 were randomized clinical trials, one was a quality improvement study and two were surveys. Approximately 160 community-based treatment programs participated in the 19 studies, with a total of 6,560 participants randomized across the sites. During this time, 1,937 QA site visits were reported across the three tiers of monitoring. Examples are presented to highlight training, protocol violation monitoring, site visit frequency and intensity and cost considerations. Cost of monitoring depended on the location of the sites and the salaries of the staff involved. One limitation with this study was that QA data from the entire network were not easily available for review as much of the data were not electronically accessible. The authors reviewed and discussed a representative sample of internal data from the studies and

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participating sites. The lessons learned from the CTN's experience included the need for balancing thoroughness with efficiency, monitoring early, assessing research staff abilities in order to judge the need for proactive, focused attention, providing targeted training sessions, and developing flexible tools. Rosa C, Campbell A, Kleppinger C, Sampson R, Tyson C, Mamay-Gentilin S. Clin Trials. 2009 Apr;6(2):151-161.

Brief Strategic Family Therapy for Adolescent Drug Abusers: A Multi-Site Effectiveness Study

This design paper describes the following aspects of the study: specific aims, research design and study organization, assessment of primary and secondary outcomes, study treatments, data analysis plan, and data monitoring and safety reporting. Within the National Institute on Drug Abuse's (NIDA's) Clinical Trials Network, BSFT (Brief Strategic Family Therapy) is being compared to treatment as usual (TAU) in a multisite, prospective randomized clinical trial for drug using adolescents and their families in outpatient settings. The effectiveness of BSFT is being compared to TAU in reducing adolescent drug use, conduct problems, and sexually risky behaviors as well as in improving family functioning and adolescent prosocial behaviors. Robbins MS, Szapocznik J, Horigian VE, Feaster DJ, Puccinelli M, Jacobs P, Burlew K, Werstlein R, Bachrach K, Brigham G. Contemp Clin Trials. 2009 May;30(3):269-278. E-pub 2009 Jan 17.

An Item Response Theory Modeling of Alcohol and Marijuana Dependences: A National Drug Abuse Treatment Clinical Trials Network Study

The aim of this study was to examine psychometric properties of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), diagnostics criteria for alcohol and marijuana dependences among 462 alcohol users and 311 marijuana users enrolled in two multisite trials of the National Drug Abuse Treatment Clinical Trials Network. Diagnostic questions were assessed by the DSM-IV checklist. Data were analyzed by the item response theory and the multiple indicators-multiple causes method procedures. Criterion symptoms of alcohol and marijuana dependences exhibited a high level of internal consistency. All individual symptoms showed good discrimination in distinguishing alcohol or marijuana users between high and low severity levels of the continuum. In both groups, "withdrawal" appeared to measure the most severe symptom of the dependence continuum. There was little evidence of measurement nonequivalence in assessing symptoms of dependence by gender, age, race/ethnicity, and educational level. These findings highlight the clinical utility of the DSM-IV checklist in assessing alcohol- and marijuana dependence syndromes among treatment-seeking substance users. Wu LT, Pan JJ, Blazer DG, Tai B, Stitzer ML, Brooner RK, Woody GE, Patkar AA, Blaine JD. J Stud Alcohol Drugs. 2009 May;70(3): 414-425.

The Impact of Trauma-Focused Group Therapy upon HIV Sexual Risk Behaviors in the NIDA Clinical Trials Network "Women and Trauma" Multi-Site Study

Women in drug treatment struggle with co-occurring problems, including trauma and post-traumatic stress disorder (PTSD), which can heighten HIV risk. This study examines the impact of two group therapy interventions on reduction of unprotected sexual occasions (USO) among women with substance use disorders (SUD) and PTSD. Participants were 346 women recruited from and receiving treat-ment at six community-based drug treatment programs participating in NIDA's Clinical Trials Network. Participants were randomized to

receive 12-sessions of either seeking safety (SS), a cognitive behavioral intervention for women with PTSD and SUD, or women's health education (WHE), an attention control psychoeducational group. Participants receiving SS who were at higher sexual risk (i.e., at least 12 USO per month) significantly reduced the number of USO over 12-month follow up compared to WHE. High risk women with co-occurring PTSD and addiction may benefit from treatment addressing coping skills and trauma to reduce HIV risk. Hien DA, Campbell AN, Killeen T, Hu MC, Hansen C, Jiang H, et al., AIDS Behav. 2009 May 19.[E-pub ahead of print].

Heterogeneity of Stimulant Dependence: A National Drug Abuse Treatment Clinical Trials Network Study

The authors investigated the presence of DSM-IV subtyping for dependence on cocaine and amphetamines (with versus without physical dependence) among outpatient stimulant users enrolled in a multisite study of the Clinical Trials Network (CTN). Three mutually exclusive groups were identified: primary cocaine users (n = 287), primary amphetamine users (n = 99), and dual users (cocaine and amphetamines; n = 29). Distinct subtypes were examined with latent class and logistic regression procedures. Cocaine users were distinct from amphetamine users in age and race/ethnicity. There were four distinct classes of primary cocaine users: non-dependence (15%), compulsive use (14%), tolerance and compulsive use (15%), and physiological dependence (tolerance, withdrawal, and compulsive use; 56%). Three distinct classes of primary amphetamine users were identified: non-dependence (11%), intermediate physiological dependence (31%), and physiological dependence (58%). Regardless of stimulants used, most female users were in the most severe or the physiological dependence group. These results lend support for subtyping dependence in the emerging DSM-V. Wu LT, Blazer DG, Patkar AA, Stitzer ML, Wakim PG, Brooner RK. Am J Addict. 2009 May-Jun;18(3):206-218.

Facilitating Outpatient Treatment Entry Following Detoxification for Injection Drug Use: A Multisite Test of Three Interventions

A multisite, randomized trial within the National Drug Abuse Treatment Clinical Trials Network (CTN) was conducted to test 3 interventions to enhance treatment initiation following detoxification: (a) a single session, therapeutic alliance intervention (TA) added to usual treatment; (b) a 2-session, counseling and education, HIV/HCV risk reduction intervention (C&E), added to usual treatment; and (c) treatment as usual (TAU) only. Injection drug users (n=632) enrolled in residential detoxification at 8 community treatment programs were randomized to 1 of the 3 study conditions. TA participants reported entering outpatient treatment sooner and in greater numbers than TAU participants. Reported treatment entry for C&E fell between TA and TAU with no significant differences between C&E and the other conditions. There were no differences among the interventions in retention, as measured by weeks of outpatient treatment for all participants who reported treatment entry. Alliance building interventions appear to be effective in facilitating transfer from detoxification to outpatient treatment, but additional treatment engagement interventions may be necessary to improve retention. Campbell BK, Fuller BE, Lee ES, Tillotson C, Woelfel T, Jenkins L, Robinson J, Booth RE, McCarty D. Psychol Addict Behav. 2009 Jun;23(2):260-270.

Disparities in Health Services for HIV/AIDS, Hepatitis C Virus, and Sexually Transmitted Infections: Role of Substance Abuse Treatment Programs

The prominence of healthcare disparities in public health discussions has

spurred interest in the identification of those disparities, studying their causes, and pursuing possible remedies. Women and minority populations experience disparities in health and healthcare related to many factors including access to services. These disparities extend to issues around addiction and addiction-related infections. The findings of this report suggest that there appear to be some alignment between services offered and these health and healthcare disparities. In a cross-sectional, descriptive design, treatment program administrators across the United States within the National Drug Abuse Treatment Clinical Trials Network (protocol CTN-0012) provided information on program characteristics, the availability of infection-related services (4 medical services and 3 nonmedical services for HIV, hepatitis C virus, and sexually transmitted infections), and barriers to providing infection-related services. Of 319 programs surveyed, 269 participated. Of these, 80% provided addiction services for special populations. Programs providing addiction services designed for at least one special population were more likely to provide infection-related health services, especially HIV-related education (94% vs. 85%) and patient counseling (76% vs. 60%) and were more likely to include outpatient addiction services (86% vs. 57%) and outreach and support services (92% vs. 70%). Primary barriers to providing infection-related services included government funding, private health insurance, and patient acceptance. But despite those barriers, programs with addiction services designed for women and nonwhite ethnic/racial populations provide infection-related health services more often than programs without these specially designed addiction services. The findings of this study strongly suggest that the tailoring of substance abuse treatment is an important public health strategy in addressing both the control of these infections and perhaps in reducing some of the disparities associated with them. Brown LS Jr, Kritz SA, Muhammad A, Bini EJ, Goldsmith RJ, Robinson J, Alderson D, Hasin DS, Rotrosen J. J Addict Med. 2009;3(2):95-102.

Evaluating Motivational Enhancement Therapy Adherence and Competence Among Spanish-Speaking Therapists

Despite the fact that the number of Hispanic individuals in need of treatment for substance use problems is increasing internationally, no studies have investigated the extent to which therapists can provide empirically supported treatments to Spanish-speaking clients with adequate fidelity. Twenty-three bilingual Hispanic therapists from five community outpatient treatment programs in the United States were randomly assigned to deliver either three sessions of motivational enhancement therapy (MET) or an equivalent number of drug counseling-as-usual (CAU) sessions in Spanish to 405 Spanish-speaking clients randomly assigned to these conditions. Independent ratings of 325 sessions indicated the adherence/competence rating system had good to excellent interrater reliability and indicated strong support for an a priori defined fundamental MET skill factor. Support for an advanced MET skill factor was relatively weaker. The rating scale indicated significant differences in therapists' MET adherence and competence across conditions. These findings indicate that the rating system has promise for assessing the performance of therapists who deliver MET in Spanish and suggest that bilingual Spanish-speaking therapists from the community can be trained to implement MET with adequate fidelity and skill using an intensive multisite training and supervision model. Santa Ana EJ, Carroll KM, A–ez L, Paris M Jr, Ball SA, Nich C, Frankforter TL, Suarez-Morales L, Szapocznik J, Martino S. Drug Alc Depend. 2009 Jul 1;103(1-2):44-51. E-pub 2009 Apr 24.

The Construct and Measurement Equivalence of Cocaine and Opioid Dependences: A National Drug Abuse Treatment Clinical Trials Network (CTN) Study

Although DSM-IV criteria are widely used in making diagnoses of substance use

disorders, gaps exist regarding diagnosis classification, use of dependence criteria, and effects of measurement bias on diagnosis assessment. Researchers examined the construct and measurement equivalence of diagnostic criteria for cocaine and opioid dependences, including whether each criterion maps onto the dependence construct, how well each criterion performs, how much information each contributes to a diagnosis, and whether symptom-endorsing is equivalent between demographic groups. Item response theory (IRT) and multiple indicators-multiple causes (MIMIC) modeling were performed on a sample of stimulant-using methadone maintenance patients enrolled in a multisite study of the National Drug Abuse Treatment Clinical Trials Network (CTN) (N=383). Participants were recruited from six community-based methadone maintenance treatment programs associated with the CTN and major U.S. providers. Cocaine and opioid dependences were assessed by DSM-IV Checklist. IRT modeling showed that symptoms of cocaine and opioid dependences, respectively, were arrayed along a continuum of severity. All symptoms had moderate to high discrimination in distinguishing drug users between severity levels. "Withdrawal" identified the most severe symptom of the cocaine dependence continuum. MIMIC modeling revealed some support for measurement equivalence. Study results suggest that self-reported symptoms of cocaine and opioid dependences and their underlying constructs can be measured appropriately among treatment-seeking polysubstance users. Wu LT, Pan JJ, Blazer DG, Tai B, Brooner RK, Stitzer ML, Patkar AA, Blaine JD. Drug Alcohol Depend. 2009 Aug 1;103(3):114-123. E-pub 2009 May 6.

Multisite Randomized Trial of Behavioral Interventions for Women with Co-occurring PTSD and Substance Use Disorders

The authors compared the effectiveness of the Seeking Safety group, cognitive-behavioral treatment for substance use disorder and posttraumatic stress disorder (PTSD), to an active comparison health education group (Women's Health Education [WHE]) within the National Institute on Drug Abuse's Clinical Trials Network. The authors randomized 353 women to receive 12 sessions of Seeking Safety (M = 6.2 sessions) or WHE (M = 6.0 sessions) with follow-up assessment 1 week and 3, 6, and 12 months posttreatment. Primary outcomes were the Clinician Administered PTSD Scale (CAPS), the PTSD Symptom Scale-Self Report (PSS-SR), and a substance use inventory (self-reported abstinence and percentage of days of use over 7 days). Intention-to-treat analysis showed large, clinically significant reductions in CAPS and PSS-SR symptoms (d = 1.94 and 1.12, respectively) but no reliable difference between conditions. Substance use outcomes were not significantly different over time between the two treatments and at follow-up showed no significant change from baseline. Study results do not favor Seeking Safety over WHE as an adjunct to substance use disorder treatment for women with PTSD and reflect considerable opportunity to improve clinical outcomes in community-based treatments for these co-occurring conditions. Hien DA, Wells EA, Jiang H, Suarez-Morales L, Campbell AN, Cohen LR, Miele GM, Killeen T, Brigham GS, Zhang Y, Hansen C, Hodgkins C, Hatch-Maillette M, Brown C, Kulaga A, Kristman-Valente A, Chu M, Sage R, Robinson JA, Liu D, Nunes EV. J Consult Clin Psychol. 2009 Aug;77(4):607-619.

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Research Findings - International Research

Effects of Modafinil on Dopamine Transporter Systems

Dr. Raka Jain of the All India Institute of Medical Sciences and a recipient of a NIDA INVEST Fellowship (1996Ð1997) and DISCA award (2006) joined Dr. Michael H. Baumann, IRP, and other colleagues to uncover key findings about modafinil, a drug that has been used off-label to treat cocaine dependence. In a recent study, the researchers examined modafinil's interaction with various receptors and transporters and compared the drug's effects to those of the indirect dopamine agonists GBR12909 and (+)-methamphetamine (METH). Results provide evidence for the involvement of dopamine transporters in the behavioral stimulant effects of modafinil. The finding that modafinil pretreatment reduced behavioral and neurochemical effects of METH support the drug's potential use as an adjunct for treating METH addiction. Zolkowska D, Jain R, Rothman RB, Partilla JS, Roth BL, Setola V, Prisinzano TE, Baumann MH. Evidence for the involvement of dopamine transporters in behavioral stimulant effects of modafinil. Journal of Pharmacology and Experimental Therapeutics. 2009 May;329(2):738-746. Epub 2009 Feb 5.

Publications by Former NIDA Hubert H. Humphrey Fellows

HHH Fellow: Arthur Guerra de Andrade, Brazil, 1991-1992
A high smoking prevalence has been registered among alcoholics. It has been pointed out that alcoholic smokers may have a more severe course and greater severity of alcoholism. This study aims at comparing smoking and non-smoking alcoholics in terms of treatment outcomes and verifying the efficacy of topiramate and naltrexone to decrease the use of cigarettes among alcoholic smokers. The investigation was a double-blind, placebo-controlled, 12-week study carried out at the University of S‹o Paulo, Brazil. The sample comprised 155 male alcohol-dependent outpatients (52 non-smokers and 103 smokers), 18-60 years of age, with an International Classification of Diseases (ICD-10) diagnosis of alcohol dependence. After a 1-week detoxification period, the patients randomly received placebo, naltrexone (50mg/day) or topiramate (up to 300mg/day). Only the alcoholic smokers who adhered to the treatment were evaluated with reference to the smoking reduction. Cox regression analysis revealed that the smoking status among alcoholics increased the odds of relapse into drinking by 65%, independently of the medications prescribed, using the intention-to-treat method. Topiramate showed effectiveness to reduce the number of cigarettes smoked when compared to placebo among adherent patients (mean difference=7.91, $p<0.01$). There were no significant differences between the naltrexone group and the placebo group. The results of this study confirm that the treatment is more challenging for smoking alcoholics than for non-smoking ones and support the efficacy of topiramate in the smoking reduction among male alcoholic smokers who adhered to the

treatment. Baltieri DA, Dar— FR, Ribeiro PL, Andrade AG. Effects of topiramate or naltrexone on tobacco use among male alcohol-dependent outpatients. Drug Alcohol Depend. 2009 Jul 10. [E-pub ahead of print].

HHH Fellow: Tomas Zabransky, Czech Republic, 2003-2004

The aims of this study were to report the results of a comprehensive literature search of studies of mortality among people who use amphetamines. Three electronic databases were searched (EMBASE, Medline and PsycINFO) and "grey" literature was located. Shortlists of papers were circulated to experts to ascertain whether any important papers had been missed. Papers were hand-searched to retrieve any additional relevant articles. Studies meeting inclusion criteria were prospective cohort studies examining mortality risk among dependent and problematic amphetamine users. Crude mortality rates (CMR/100PY) and standardised mortality ratios (SMRs) were the primary outcome measures considered. Data on overall mortality, and rates for specific causes of death, were of interest. 2,187 articles and 9 grey literature sources were obtained. After thorough review, 72 articles were identified as reporting on amphetamine-related mortality, 7 provided data from cohort studies of users. An additional study of Swedish military conscripts was identified by the authors during correspondence with other researchers. The geographic spread of cohorts was restricted to high income countries with the exception of one Thai study; reporting of standard parameters in mortality studies was often sparse. The estimated CMRs ranged from 0 in Australia to 2.95 (1.46-4.59) in Thailand. The Czech cohort reported the only SMR: 6.22 overall, males: 5.87, females: 7.84. Given the widespread use of amphetamines, the known non-fatal adverse effects of use and the mortality rates reported here, cohort studies investigating the morbidity and mortality associated with such drug use should be a research priority. Singleton J, Degenhardt L, Hall W, Zabransky T. Mortality among amphetamine users: A systematic review of cohort studies. Drug Alcohol Depend. 2009 Jul 22. [E-pub ahead of print].

HHH Fellow: Olga Toussova, Russia, 2001-2002

The epidemic of HIV in St. Petersburg, which is currently concentrated among injection drug users (IDUs), may be penetrating into the general population. Non-IDUs who have IDU sex partners (SP) could be potential bridges in an expanding epidemic. To investigate potential bridges, the authors accrued a convenience sample of 288 non-IDUs whose HIV diagnosis was attributed to sexual transmission and determined the proportion that had IDUs among their SP. Having IDU SP ever (lifetime) and IDU SP in the last year were the key variables for the analysis of potential bridges in this study. The interaction of gender and age was found to be a significant predictor of having lifetime IDU SP ($p = 0.006$, chi (2) test) and IDU SP in the last year ($p = 0.05$, chi (2) test): females aged 26 and younger were more likely to have both lifetime IDU SP and IDU SP in the last year. Among the group of young females, 46% reported ever having an IDU SP. Out of young women reporting ever having an IDU SP, 85% also reported at least one lifetime non-IDU SP. Among the females aged 26 or younger, a lower level of education (odds ratio [OR] = 2.7, confidence interval [CI] = 1.1-6.7), being born in St. Petersburg (OR = 2.9, CI = 1.2-7.2), and alcohol use in the last 30 days (OR = 3.5, CI = 1.3-9.6) were significant correlates for ever having had an IDU SP. Urgent efforts are necessary to expand HIV prevention to target the potential bridging population to prevent further transmission. Toussova O, Shcherbakova I, Volkova G, Niccolai L, Heimer R, Kozlov A. Potential bridges of heterosexual HIV transmission from drug users to the general population in St. Petersburg, Russia: is it easy to be a young female? J Urban Health. 2009 Jul;86 Suppl 1:121-130.

HHH Fellow: Olga Toussova, Russia, 2001-2002

The HIV epidemic that began in Russia in the mid-1990s has been concentrated mostly among drug users (DUs). Recent evidence of increasing HIV cases among non-DUs attributed to sexual behavior raises potential

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concern about a more generalized epidemic. The purpose of this analysis is to examine the potential for HIV transmission from DUs to their non-DU sex partners. Analyses are conducted using data collected during 2005-2008 in St. Petersburg, Russia. A total of 631 DUs were recruited into the sample with an HIV prevalence of 45%. A majority (84%) of DUs reported being sexually active in the past 6 months, and the DU status of their sex partners was reported as follows: 54% DU, 40% non-DU, and 6% unknown DU status. In 41% of partnerships with an HIV-negative or unknown status partner not known to be DU (potential bridging partnerships), the last reported intercourse was unprotected. Female DUs with potential bridging partnerships were more likely than male DUs to be younger and report homelessness and to have multiple or new sex partners. Many non-DU sex partners of DUs enrolled in the study reported new sex partners in the past 6 months (66%), unprotected intercourse at last sex (60%), and multiple sex partners in the past 6 months (48%). HIV prevalence in this group was 15% (eight out of 53). The high prevalence of HIV among DUs, their sexual contact with non-DUs, and the high-risk sexual behaviors of this potential bridging population together indicate the real potential for an increasingly generalized epidemic. The degree to which there will be further transmission from non-DU sex partners of DUs who exhibit high levels of sex risk behaviors to other non-DU sex partners deserves further study. Niccolai LM, Shcherbakova IS, Toussova OV, Kozlov AP, Heimer R. The potential for bridging of HIV transmission in the Russian Federation: sex risk behaviors and HIV prevalence among drug users (DUs) and their non-DU sex partners. J Urban Health. 2009 Jul;86 Suppl 1:131-143.

HHH Fellow: Flavio Pechansky, Brazil, 1993-1994

Brazil lacks information about driving under the influence of alcohol (DUI) originated from representative samples obtained from the general population. 333 subjects with a valid driver's license and drinking in the last 12 months were drawn from a multistaged sample of 2,346 adults from the first Brazilian Household Survey of Patterns of Alcohol Use. A multivariate analysis was conducted to understand the associations between risk factors and driving after drinking three or more drinks. The overall DUI prevalence reported in the sample was 34.7% - 42.5% among males and 9.2% among females. Being male (OR = 6.0, 95% CI 2.9-12.6), having a previous DUI accident (OR = 7.9, 95% CI 2.5-24.9), binging in the last year (OR = 2.2, 95% CI 1.03-4.5) and having an unfavorable opinion towards policies (OR = 2.9, 95% CI 1.4-6.2) remained associated with heavy drinking and driving after model adjustments. This was the first study evaluating driving under the influence of alcohol in a representative sample of the Brazilian population. The prevalence of DUI found is alarming, and possibly underestimated in the sample. Results demonstrate the need for more studies on this association and show directions towards preventive strategies for the specific high-risk group of male drivers with previous problems with alcohol and unfavorable opinions about prevention policies. Pechansky F, De Boni R, Diemen LV, Bumaguin D, Pinsky I, Zaleski M, Caetano R, Laranjeira R. Highly reported prevalence of drinking and driving in Brazil: data from the first representative household study. Rev Bras Psiquiatr. 2009 Jun;31(2):125-130.

HHH Fellow: Berna Ulu&gcaron;, Turkey 1995-1996

Recent neuroimaging studies support functional and structural alterations in the dorsolateral prefrontal cortex (DLPFC), particularly on the left side in patients with major depressive disorders (MDD). The aim of the present study was to examine the biochemical characteristics of left DLPFC as measured on proton ((1)H) magnetic resonance spectroscopy (MRS) in patients with drug-na•ve first-episode MDD and a healthy control group. A second aim was to assess the effect of antidepressant treatment on the metabolites of DLPFC. Short-echo single-voxel (1)H-MRS was done for the left DLPFC in 17 female drug-free MDD patients (mean age +/- SD, 30.9 +/- 6.9 years) and 13 matched control subjects (mean age +/- SD, 29.1 +/- 6.2 years) and was repeated at 8 weeks following antidepressant treatment. Comparison of

baseline values indicated that there were no significant differences in any of the metabolite ratios (N-acetyl aspartate/creatine [NAA/Cr], myoinositol [Ino]/Cr, and choline [Cho]/Cr) between patients and controls. Significant differences were detected between pre- and post-treatment Ino/Cr ratios (0.67 +/- 0.13, 0.58 +/- 0.22, P = 0.032, respectively), although there was no difference in NAA/Cr and Cho/Cr ratios. Although no significant metabolic alterations exist in female patients with drug-na•ve first-episode MDD as evaluated on (1)H-MRS, an increase in Ino/Cr was observed following 8-week antidepressant treatment. These findings give rise to the possibility that non-neuronal cells, particularly glial cells that are probably damaged, play a role in the action of antidepressant treatment. Kaymak SU, Demir B, O&gcaron;uz KK, SentŸrk S, Ulu&gcaron; B. Antidepressant effect detected on proton magnetic resonance spectroscopy in drug-na•ve female patients with first-episode major depression. Psychiatry and Clinical Neurosciences 2009 Jun;63(3):350-356.

Director's Report to the National Advisory Council on Drug Abuse - September, 2009

Research Findings - Intramural Research

Cellular Neurobiology Research Branch

Proteomics Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Interactions Between Calmodulin, Adenosine A2A and Dopamine D2 Receptors

The Ca2+-binding protein calmodulin (CaM) has been shown to bind directly to cytoplasmic domains of some G protein-coupled receptors (GPCRs), including the dopamine D2 receptor. CaM binds to the N-terminal portion of the long third intracellular loop of the D2 receptor, within an Arg-rich epitope that is also involved in the binding to Gi/o proteins and to the adenosine A2A receptor, with the formation of A2A-D2 receptor heteromers. In the present work, by using proteomics and Bioluminescence Resonance Energy Transfer (BRET) techniques, IRP scientists provide evidence for the binding of CaM to the A2A receptor. By using BRET and sequential resonance energy transfer (SRET) techniques, evidence was obtained for CaM-A2A-D2 receptor oligomerization. BRET competition experiments indicated that, in the A2A-D2 receptor heteromer, CaM binds preferentially to a proximal C-terminus epitope of the A2A receptor. Furthermore, Ca2+ was found to induce conformational changes in the CaM-A2A-D2 receptor oligomer and to selectively modulate A2A and D2 receptor-mediated MAPK signaling in the A2A-D2 receptor heteromer. These results may have implications for basal ganglia disorders since A2A-D2 receptor heteromers are being considered as a target for anti-parkinsonian agents.
Navarro G, Aymerich MS, Marcellino D, Cortes A, Casado V, Mallol J, Canela EI, Agnati LF, Woods AS, Fuxe K, Lluis C, Lanciego JL, Ferre S, Franco R. Interactions between calmodulin, adenosine A2A and dopamine D2 receptors. J Biol Chem. 2009 Jul 24. [E-pub ahead of print].

Neuroimaging Research Branch

Association of Nicotine Addiction and Nicotine's Actions with Separate Cingulate Cortex Functional Circuits

Understanding the mechanisms underlying nicotine addiction to develop more effective treatment is a public health priority. Research consistently shows that nicotine transiently improves multiple cognitive functions. However, using nicotine replacement to treat nicotine addiction yields generally inconsistent results. Although this dichotomy is well known, the reasons are unclear. Imaging studies showed that nicotine challenges almost always involves the cingulate cortex, suggesting that this locus may be a key region associated with nicotine addiction and its treatment. IRP researchers thus sought to identify cingulate functional circuits that are associated with the severity of nicotine addiction and study how nicotine affects them by means of region-

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specific resting-state functional magnetic resonance imaging. Clearly separated pathways that correlated with nicotine addiction vs. nicotine's action were found. The severity of nicotine addiction was associated with the strength of dorsal anterior cingulate cortex (dACC)Ðstriatal circuits, which were not modified by nicotine patch administration. In contrast, short-term nicotine administration enhanced cingulate-neocortical functional connectivity patterns, which may play a role in nicotine's cognition-enhancing properties. These data suggest that resting-state dACC-striatum functional connectivity may serve as a circuit-level biomarker for nicotine addiction, and that the development of new therapeutic agents aiming to enhance the dACC-striatum functional pathways may be effective for nicotine addiction treatment. Hong Le, Gu H, Yang Y, Ross TJ, Salmeron BJ, Buchholz B, Thaker GK, Stein EA. Association of nicotine addiction and nicotine's actions with separate cingulate cortex functional circuits. Arch Gen Psych. 2009;66:431-441.

Baseline Expression of a4b2* Nicotinic Acetylcholine Receptors Predicts Motivation to Self-Administer Nicotine

Marked interindividual differences in vulnerability to nicotine dependence exist, but factors underlying such differences are not well understood. The midbrain α4B2* subtype of nicotinic acetylcholine receptors (nAChRs) has been implicated in mediation of the reinforcing effects of nicotine responsible for dependence. However, no study has been performed evaluating the impact of interindividual differences in midbrain nAChR levels on motivation to self-administer nicotine. As such, baseline levels of α4B2* nAChRs were measured using 2-[18F]fluoro-A-85380 (2-FA) and positron emission tomography (PET) in five squirrel monkeys. Motivation to self-administer nicotine (number of lever presses) was subsequently measured using a progressive-ratio (PR) schedule of reinforcement. Greater motivation to self-administer nicotine was associated with lower levels of midbrain nAChRs. These results suggest that level of expression of nAChRs is a contributing factor in the development of nicotine dependence. Similarly, it has been previously shown that low levels of dopamine D2 receptors (DRD2) are associated with a higher preference for psychostimulant use in humans and nonhuman primates. Together, results from these PET studies of dopaminergic and nicotinic cholinergic transmission suggest that an inverse relationship between the availability of receptors that mediate reinforcement and the motivation to take drugs exists across different neuro-transmitter systems. Le Foll B, Chefer SI, Kimes AS, Shumway D, Stein EA, Mukhin AG, Goldberg SR. Baseline expression of a4b2* nicotinic acetylcholine receptors predicts motivation to self-administer nicotine. Biological Psychiatry. 2009;65:714-716.

Early Life Stress Induces Long-term Morphological Changes in Primate Brain

Traumatic experiences in early childhood are associated with increased risk of developing stress-related disorders, which are linked to structural brain abnormalities. However, it is unclear whether these volumetric brain changes are present before disease onset or reflect the consequences of disease progression. As such, IRP scientists sought to identify structural abnormalities in the nonhuman primate brain that may predict increased risk of stress-related neuropsychiatric disorders in human beings. Rhesus monkeys were divided into 2 groups at birth: a group raised with their mothers and other juvenile and adult animals (mother reared) and a group raised with 3 age-matched monkeys only (peer reared) for the first 6 months of life. Anatomical brain images were acquired in juvenile male and female rhesus monkeys using magnetic resonance imaging. Volumetric measures of the anterior cingulate cortex, medial prefrontal cortex, hippocampus, corpus callosum, and cerebellar vermis were compared between mother-reared (n = 15) and peer-reared animals (n = 13). Compared with mother-reared monkeys, the authors found an enlarged vermis, dorsomedial prefrontal cortex, and dorsal anterior cingulate cortex in peer-reared monkeys without any apparent differences in the corpus callosum and hippocampus. These changes may be a structural

Planned Meetings

Publications

Staff Highlights

Grantee Honors

phenotype for increased risk of stress-related neuropsychiatric disorders in human beings. Spinelli S, Chefer SI, Suomi SJ, Higley D, Barr CS, Stein EA. Early life stress induces long-term morphological changes in primate brain. Arch Gen Psych. 2009;66:658-665.

Patients with Schizophrenia Have A Reduced Neural Response to Both Unpredictable and Predictable Primary Reinforcers

One prevalent theory of learning states that dopamine neurons signal mismatches between expected and actual outcomes, called temporal difference errors (TDEs). Evidence indicates that dopamine system dysfunction is involved in negative symptoms of schizophrenia (SZ), including avolition and anhedonia. As such, IRP investigators predicted that brain responses to TDEs in dopamine midbrain nuclei and target areas would be abnormal in SZ. A total of 18 clinically stable patients with chronic SZ and 18 controls participated in an fMRI study, which used a passive conditioning task. In the task, the delivery of a small amount of juice followed a light stimulus by exactly 6 s on approximately 75% of 78 total trials, and was further delayed by 4Ð7 s on the remaining trials. The delayed juice delivery was designed to elicit the two types of TDE signals, associated with the recognition that a reward was omitted at the expected time, and delivered at an unexpected time. Main effects of TDE valence and group differences in the positiveÐnegative TDE contrast (unexpected juice deliveriesÐjuice omissions) were assessed through whole-brain and regions of interest (ROI) analyses. Main effects of TDE valence were observed for the entire sample in the midbrain, left putamen, left cerebellum, and primary gustatory cortex, bilaterally. Whole-brain analyses revealed group differences in the positiveÐnegative TDE contrast in the right putamen and left precentral gyrus, whereas ROI analyses revealed additional group differences in the midbrain, insula, and parietal operculum, on the right, the putamen and cerebellum, on the left, and the frontal operculum, bilaterally. Further, these group differences were generally driven by attenuated responses in patients to positive TDEs (unexpected juice deliveries), whereas responses to negative TDEs (unexpected juice omissions) were largely intact. Patients also showed reductions in responses to juice deliveries on standard trials, and more blunted reinforcer responses in the left putamen corresponded to higher ratings of avolition. These results provide evidence that SZ patients show abnormal brain responses associated with the processing of a primary reinforcer, which may be a source of motivational deficits. Waltz JA, Schweitzer JB, Gold JM, Kurup PK, Ross TJ, Salmeron BJ, Rose EJ, McClure SM, Stein EA. Patients with Schizophrenia have a reduced neural response to both unpredictable and predictable primary reinforcers. Neuropsychopharmacology. 2009;34:1567-1577.

Mapping Functional Connectivity Based On Synchronized CMRO2 Fluctuations During the Resting State

Synchronized low-frequency fluctuations in the resting state functional MRI (fMRI) signal have been suggested to be associated with functional connectivity in brain networks. However, the underlying mechanism of this connectivity is still poorly understood. Synchronized fluctuations could either originate from hemodynamic oscillations or represent true neuronal signaling. To better interpret the resting signal, in the current work, IRP researchers examined spontaneous fluctuations at the level of cerebral metabolic rate of oxygenation (CMRO2), an index reflecting regional oxygen consumption and metabolism, and thus less sensitive to vascular dynamics. The CMRO2 signal was obtained based on a biophysical model with data acquired from simultaneous blood oxygenation level dependent (BOLD) and perfusion signals. CMRO2-based functional connectivity maps were generated in three brain networks: visual, default-mode, and hippocampus. Experiments were performed on twelve healthy participants during 'resting state' and as a comparison, with a visual task. CMRO2 signals in each of the above mentioned brain networks showed significant correlations. Functional connectivity maps from the CMRO2 signal are, in general, similar to those from BOLD and perfusion. In addition, the

authors demonstrated that the three parameters (M, α and B) in the biophysical model for calculating CMRO2 have negligible effects on the determination of the CMRO2-based connectivity strength. This study provides evidence that the spontaneous fluctuations in fMRI at rest likely originate from dynamic changes of cerebral metabolism reflecting neuronal activity. Wu CW, Gu H, Lu H, Stein EA, Chen J-H, Yang Y. Mapping functional connectivity based on synchronized CMRO2 fluctuations during the resting state. NeuroImage. 2009;45:694-701.

A Single High Dose of Methamphetamine Increases Cocaine Self Administration by Depletion of Striatal Dopamine in Rats

Psychostimulant addicts often take high doses of drugs, and high doses of psychostimulants such as methamphetamine (METH) are neurotoxic to striatal dopamine (DA) terminals. Yet, the effects of high doses of METH on drug-seeking and drug-taking behavior have not been examined. In the present study, IRP scientists found that single high doses of METH in rats (10Ð20 mg/kg) dose-dependently increased cocaine self-administration under fixed-ratio 2 (FR2) reinforcement conditions, while higher doses (40 mg/kgx1 or 10 mg/kg/2 hx4) caused high mortality among rats maintained on daily cocaine self-administration. The increased cocaine self-administration appeared to be a compensatory response to reduced cocaine reward after METH, because the same doses of METH caused a dose-dependent reduction both in "break-point" levels for cocaine self-administration under progressive-ratio reinforcement and in nucleus accumbens DA response to acute cocaine. Further, METH (10Ð20 mg/kg) produced large DA release (4000%Ð6000% over baseline), followed by a significant reduction in striatal DA and 3,4-dihydroxyphenylacetic acid (DOPAC) contents, but without significant changes in striatal DA transporter levels. These findings suggest that the present high doses of METH caused striatal DA depletion or hypofunction without severe damage in DA terminals, which may contribute to the increased cocaine-taking behavior observed in the present study. Provided that the present doses of METH may mimic METH overdose incidents in humans, the present findings suggest that METH-induced DA depletion or neurotoxicity may lead to an increase in subsequent drug-taking and drug-seeking behavior. Xi Z-X, Kleitz H, Deng X, Ladenheim B, Peng X-Q, Li X, Gardner EL, Stein EA, Cadet JL A single high dose of methamphetamine increases cocaine self administration by depletion of striatal dopamine in rats. Neuroscience. 2009;161:392-402.

Clinical Psychopharmacology Section, Chemical Biology Research Branch

The Impact of Early Environmental Rearing Condition on the Discriminative Stimulus Effects and Fos Expression Induced by Cocaine in Adult Male and Female Rats

A number of environmental manipulations, including maternal separation (MS), have been shown to alter behavioral responses to drugs of abuse. This study assessed if MS affected the stimulus and Fos-inducing effects of cocaine. In experiment 1, male and female Sprague-Dawley rats were exposed to brief maternal separations (BMS), long maternal separations (LMS), or animal facility rearing (AFR) and then trained as adults to discriminate cocaine (10 mg/kg, intraperitoneally) from saline. Following training, generalization tests to novel doses of cocaine and other dopaminergic compounds were performed. Assessments of variations in training dose pretreatment times were also made. In experiment 2, male and female rats exposed to MS conditions were administered cocaine or saline for 14 days, and Fos expression in the mesolimbic system was measured. In males, BMS retarded the acquisition of the cocaine discrimination. Generalization to novel doses of cocaine did not differ among rearing conditions, but the training dose cue lasted longer in LMS. Distinct generalization and ED(50) profiles were found between male rearing conditions for all dopamine compounds. While BMS females had higher cocaine

ED(50) estimates, no other differences were found in females. LMS males and females, as well as AFR females, had significant increases in Fos expression after cocaine in a region-specific manner. No differences were found with other rearing groups. Early environmental variables altered the stimulus effects (in a sex-dependent manner) as well as the neuronal responsiveness to cocaine, which may be mediated by the dopamine system. Kohut SJ, Roma PG, Davis CM, Zernig G, Saria A, Dominguez JM, Rice KC, Riley AL. The impact of early environmental rearing condition on the discriminative stimulus effects and Fos expression induced by cocaine in adult male and female rats. Psychopharmacology (Berl). 2009 Apr;203(2): 383-397. E-pub 2008 Oct 25.

D2-like Agonist-Induced PE and Yawning are Differentially Mediated by the D3 (Induction) and D2 Receptors (Inhibition)

Dopamine D2-like agonists induce penile erection (PE) and yawning in a variety of species, effects that have recently been suggested to be specifically mediated by the D4 and D3 receptors, respectively. The current studies were aimed at characterizing a series of D2, D3, and D4 agonists with respect to their capacity to induce PE and yawning in the rat, as well as the pro-erectile effects of apomorphine in wild-type and D4 receptor (R) knock-out (KO) mice. All D3 agonists induced dose-dependent increases in PE and yawning over a similar range of doses, whereas significant increases in PE or yawning were not observed with any of the D4 agonists. Likewise, D2, D3, and D4 antagonists were assessed for their capacity to alter apomorphine- and pramipexole-induced PE and yawning. The D3 antagonist, PG01037, inhibited the induction of PE and yawning, whereas the D2 antagonist, L-741,626, reversed the inhibition of PE and yawning observed at higher doses. The D4 antagonist, L-745,870, did not alter apomorphine- or pramipexole-induced PE or yawning. A role for the D3 receptor was further supported as apomorphine was equipotent at inducing PE in wild-type and D4R KO mice, effects that were inhibited by the D3 antagonist, PG01037, in both wild-type and D4R KO mice. Together, these studies provide strong support that D2-like agonist-induced PE and yawning are differentially mediated by the D3 (induction) and D2 receptors (inhibition). These studies fail to support a role for the D4 receptor in the regulation of PE or yawning by D2-like agonists. Collins GT, Truccone A, Haji-Abdi F, Newman AH, Grundt P, Rice K, Husbands SM, Greedy BM, Enguehard-Gueiffier C, Gueiffier A, Chen J, Wang S, Katz JL, Grandy DK, Sunahara RK, Woods JH. Proerectile effects of dopamine D2-like agonists are mediated by the D3 receptor in rats and mice. J Pharm Exp Ther. 2009 Apr;329(1):210-217. E-pub 2009 Jan 9.

The Sigma-Receptor Antagonist BD-1063 Decreases Ethanol Intake and Reinforcement in Animal Models of Excessive Drinking

Sigma-Receptors (SigRs) have been implicated in behavioral and appetitive effects of psychostimulants and may also modulate the motivating properties of ethanol. This study tested the hypothesis that SigRs modulate ethanol reinforcement and contribute to excessive ethanol intake. The effects of subcutaneous treatment with the potent, selective Sig-1R antagonist BD-1063 on operant ethanol self-administration were studied in two models of excessive drinking-Sardinian alcohol-preferring (sP) rats and acutely withdrawn ethanol-dependent Wistar rats-and compared to ethanol self administration in nondependent Wistar controls. To assess the specificity of action, the effects of BD-1063 on self-administration of an equally reinforcing saccharin solution were determined in Wistar and sP rats. Gene expression of Sig-1R in reward-related brain areas implicated in ethanol reinforcement was compared between ethanol-na•ve sP and Wistar rats and withdrawn ethanol-dependent Wistar rats. BD-1063 dose dependently reduced ethanol self-administration in sP rats (3.3-11 mg/kg) and withdrawn, dependent Wistar rats (4-11 mg/kg) at doses that did not modify mean ethanol self-administration in nondependent Wistar controls. BD-1063 did not reduce concurrent water self-administration and did not comparably suppress saccharin self administration, suggesting selectivity of action. BD-1063 also reduced the breakpoints of sP rats to work for ethanol

under a progressive-ratio reinforcement schedule. Ethanol naive sP rats and 24-h withdrawn, dependent Wistar rats showed reduced Sig-1R mRNA expression in the nucleus accumbens. The results suggest that SigR systems may contribute to innate or ethanol-induced increases in susceptibility to self-administer high ethanol levels, identifying a potential neuroadaptive mechanism contributing to excessive drinking and a therapeutic target for alcohol abuse and dependence. Sabino V, Cottone P, Zhao Y, Iyer MR, Steardo L Jr., Steardo L, Rice KC, Conti B, Koob GF, Zorrilla EP. The sigma-receptor antagonist BD-1063 decreases ethanol intake and reinforcement in animal models of excessive drinking. Neuropsychopharmacology. 2009 May;34(6):1482-1493. E-pub 2008 Oct 22.

Discriminative Stimulus Effects of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane in Rhesus Monkeys: Antagonism and Apparent pA2 Analyses

Discriminative stimulus effects of the serotonin (5-HT) receptor agonist 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) have been studied in rats and, more recently, in rhesus monkeys. This study examined DOM, 2,5-dimethoxy-4-(n)-propylthiophenethylamine (2C-T-7), and dipropyltryptamine hydrochloride (DPT) alone and in combination with three antagonists, MDL100907 [(+/-)2,3-dimethoxyphenyl-1-[2-(4-piperidine)-methanol]], ketanserin [3-[2-[4-(4-fluorobenzoyl) piperidin-1-yl]ethyl]-1H-quinazoline-2,4-dione], and ritanserin [6-[2-[4-[bis(4-fluorophenyl) methylidene]piperidin-1-yl]ethyl]-7-methyl-[1,3]thiazolo[2,3-b]pyrimidin-5-one], to identify the 5-HT receptor subtype(s) that mediates the discriminative stimulus effects of these 5-HT receptor agonists. Four adult rhesus monkeys discriminated between 0.32 mg/kg s.c. DOM and vehicle while responding under a fixed ratio 5 schedule of stimulus shock termination. DOM, 2C-T-7, and DPT dose-dependently increased responding on the DOM-associated lever. MDL100907 (0.001-0.01 mg/kg), ketanserin (0.01-0.1 mg/kg), and ritanserin (0.01-0.1 mg/kg) each shifted the dose-response curves of DOM, 2C-T-7, and DPT rightward in a parallel manner. Schild analysis of each drug combination was consistent with a simple, competitive, and reversible interaction. Similar apparent affinity (pA(2)) values were obtained for MDL100907 in combination with DOM (8.61), 2C-T-7 (8.58), or DPT (8.50), for ketanserin with DOM (7.67), 2C-T-7 (7.75), or DPT (7.71), and for ritanserin with DOM (7.65), 2C-T-7 (7.75), or DPT (7.65). Potency of antagonists in this study was correlated with binding affinity at 5-HT(2A) receptors and not at 5-HT(2C) or alpha(1) adrenergic receptors. This study used Schild analysis to examine receptor mechanisms mediating the discriminative stimulus effects of hallucinogenic drugs acting at 5-HT receptors; results provide quantitative evidence for the predominant, if not exclusive, role of 5-HT(2A) receptors in the discriminative stimulus effects of DOM, 2C-T-7, and DPT in rhesus monkeys. Li JX, Rice KC, France CP. Discriminative stimulus effects of 1- (2,5-dimethoxy-4-methylphenyl)-2-aminopropane in rhesus monkeys: antagonism and apparent pA2 analyses. J Pharmacol Exp Ther. 2009 Mar;328(3):976-981. E-pub 2008 Dec 19.

Blockade of the Serotonin 5-HT2A Receptor Suppresses Cue-Evoked Reinstatement of Cocaine-Seeking Behavior in a Rat Self-Administration Model

The serotonin 5-HT2A receptor (5-HT-sub(2A)R) may play a role in reinstatement of drug-seeking. This study investigated the ability of a selective 5-HT-sub(2A)R antagonist to suppress reinstatement evoked by exposure to cues conditioned to cocaine self administration. Cocaine self-administration (0.75 mg/kg/0.1 mL/6 s infusion; FR 4) was trained in na•ve, free-fed rats to allow interpretation of results independent from changes related to food deprivation stress. Pretreatment with the selective 5-HTsub(2A)R antagonist M100907 (volinanserin) failed to reduce rates of operant responding for cocaine infusions. On the other hand, M100907 (0.001-0.8 mg/kg ip) significantly suppressed the cue-induced reinstatement of cocaine-seeking behavior following extinction; effective M100907 doses did not alter operant

responding for cues previously associated with sucrose self-administration. Importantly, a greater magnitude of active lever presses on the initial extinction session (high extinction responders) predicted the maximal susceptibility to M100907-induced suppression of cue-evoked reinstatement. The findings indicate that blockade of the 5-HT-sub(2A)R attenuates the incentive-motivational effects of cocaine-paired cues, particularly in high extinction responders, and suggests that M100907 may afford a therapeutic advance in suppression of cue-evoked craving and/or relapse. Nic Dhonnchadha BA, Fox RG, Stutz SJ, Rice KC, Cunningham KA. Blockade of the serotonin 5-HT2A receptor suppresses cue-evoked reinstatement of cocaine-seeking behavior in a rat self-administration model. Behav Neurosci. 2009 Apr;123(2):382-396.

Protracted Withdrawal from Alcohol and Drugs of Abuse Impairs Long term Potentiation of Intrinsic Excitability in the Juxtacapsular Bed Nucleus of the Stria Terminalis

The juxta-capsular bed nucleus of the stria terminalis (jcBNST) is activated in response to basolateral amygdala (BLA) inputs through the stria terminalis and projects back to the anterior BLA and to the central nucleus of the amygdala. Here IRP scientists show a form of long term potentiation of the intrinsic excitability (LTP-IE) of jcBNST neurons in response to high-frequency stimulation of the stria terminalis. This LTP-IE, which was characterized by a decrease in the firing threshold and increased temporal fidelity of firing, was impaired during protracted withdrawal from self-administration of alcohol, cocaine, and heroin. Such impairment was graded and was more pronounced in rats that self administered amounts of the drugs sufficient to maintain dependence. Dysregulation of the corticotropin-releasing factor (CRF) system has been implicated in manifestation of protracted withdrawal from dependent drug use. Administration of the selective corticotropin-releasing factor receptor 1 (CRF(1)) antagonist R121919 [2,5-dimethyl-3-(6-dimethyl-4-methylpyridin-3-yl)-7-dipropylamino-pyrazolo[1,5-a]pyrimidine)], but not of the CRF(2) antagonist astressin(2)-B, normalized jcBNST LTP-IE in animals with a history of alcohol dependence; repeated, but not acute, administration of CRF itself produced a decreased jcBNST LTP-IE. Thus, changes in the intrinsic properties of jcBNST neurons mediated by chronic activation of the CRF system may contribute to the persistent emotional dysregulation associated with protracted withdrawal. Francesconi W, Berton F, Repunte-Canonigo V, Hagihara K, Thurbon, D, LeKic D, Specio SE, Greenwell TN, Chen SA, Rice KC, Richardson HN, O'Dell LE, Zorrilla EP, Morales M, Koob GF, SannaPP. Protracted withdrawal from alcohol and drugs of abuse impairs long term potentiation of intrinsic excitability in the juxtacapsular bed nucleus of the stria terminalis. J Neurosci. 2009 Apr 29;29(17):5389-5401.

Location, Structure, and Dynamics of the Synthetic Cannabinoid Ligand CP-55,940 in Lipid Bilayers

The widely used hydrophobic cannabinoid ligand CP-55,940 partitions with high efficiency into biomembranes. IRP researchers studied the location, orientation, and dynamics of CP-55,940 in POPC bilayers by solid-state NMR. Chemical-shift perturbation of POPC protons from the aromatic ring-current effect, as well as 1H NMR cross-relaxation rates, locate the hydroxyphenyl ring of the ligand near the lipid glycerol, carbonyls, and upper acyl-chain methylenes. Order parameters of the hydroxyphenyl ring determined by the 1H-13C DIPSHIFT experiment indicate that the bond between the hydroxyphenyl and hydroxyl-cyclohexyl rings is oriented perpendicular to the bilayer normal. 2H NMR order parameters of the nonyl tail are very low, indicating that the hydrophobic chain maintains a high level of conformational flexibility in the membrane. Lateral diffusion rates of CP-55,940 and POPC were measured by 1H magic-angle spinning NMR with pulsed magnetic field gradients. The rate of CP-55,940 diffusion is comparable to the rate of lipid diffusion. The magnitude of cross-relaxation and diffusion rates suggests that associations between CP-55,940 and lipids are with lifetimes of a fraction of a microsecond. With its flexible

hydrophobic tail, CP-55,940 may efficiently approach the binding site of the cannabinoid receptor from the lipid-water interface by lateral diffusion. Kimura T, Cheng K, Rice KC, Gawrisch K. Location, structure, and dynamics of the synthetic cannabinoid ligand CP-55,940 in lipid bilayers. Biophys J. 2009 Jun 17;96(12): 4916-4924.

Probes for Narcotic Receptor Mediated Phenomena

Enantiomers of N-substituted benzofuro [2,3-c]pyridin-6-ols have been synthesized, and the subnanomolar affinity and potent agonist activity of the known racemic N-phenethyl substituted benzofuro[2,3-c]pyridin-6-ol can now be ascribed to the 4aS,9aR enantiomer. The energy-minimized structures suggest that the active enantiomer bears a greater three-dimensional resemblance to morphine than to an ostensibly structurally similar oxide-bridged phenylmorphan. Structural features of the conformers of Nsubstituted benzofuro[2,3-c]pyridin-6-ols were compared to provide the rationale for their binding affinity. Zhang Y, Lee YS, Rothman RB, Dersch CM, Deschamps JR, Jacobson AE, Rice KC. Probes for Narcotic Receptor Mediated Phenomena. 39. (1) Enantiomeric NSubstituted Benzofuro[2,3-c]pyridin-6-ols: Synthesis and Topological Relationship to Oxide-Bridged Phenylmorphans (2). J. Med Chem. 2009 Jul 24. [E-pub ahead of print].

Serotonergic Hyperinnervation and Effective Serotonin Blockade in an FGF Receptor Developmental Model of Psychosis

The role of fibroblast growth factor receptors (FGFR) in normal brain development has been well-documented in transgenic and knock-out mouse models. Changes in FGF and its receptors have also been observed in schizophrenia and related developmental disorders. The current study examines a transgenic th(tk-)/th(tk-) mouse model with FGF receptor signaling disruption targeted to dopamine (DA) neurons, resulting in neurodevelopmental, anatomical, and biochemical alterations similar to those observed in human schizophrenia. IRP researchers show in th(tk-)/th(tk-) mice that hypoplastic development of DA systems induces serotonergic hyperinnervation of midbrain DA nuclei, demonstrating the co-developmental relationship between DA and 5-HT systems. Behaviorally, th(tk-)/th(tk-) mice displayed impaired sensory gaiting and reduced social interactions correctable by atypical antipsychotics (AAPD) and a specific 5-HT2A antagonist, M100907. The adult onset of neurochemical and behavioral deficits was consistent with the postpubertal time course of psychotic symptoms in schizophrenia and related disorders. The spectrum of abnormalities observed in th(tk-)/th(tk-) mice and the ability of AAPD to correct the behavioral deficits consistent with human psychosis suggests that midbrain 5-HT2A-controlling systems are important loci of therapeutic action. These results may provide further insight into the complex multineurotransmitter etiology of neurodevelopmental diseases such autism, bipolar disorder, Asperger's Syndrome and schizophrenia. Klejbor I, Kucinski A, Wersinger SR, Corso T, Spodnik JH, Dziewiatkowski J, Morys J, Hesse RA, Rice KC, Miletich R, Stachowiak EK, Stachowiak MK. Serotonergic hyperinnervation and effective serotonin blockade in an FGF receptor developmental model of psychosis. Schizophr Res. 2009 Jun 29. [E-pub ahead of print].

Differential Involvement of the Norepinephrine, Serotonin and Dopamine Reuptake

Transporter Proteins in Cocaine-Induced Taste Aversion Despite the impact of cocaine's aversive effects on its abuse potential, the neurochemical basis of these aversive effects remains poorly understood. By blocking the reuptake of the monoamine neurotransmitters dopamine (DA), norepinephrine (NE) and serotonin (5-HT) into the presynaptic terminal, cocaine acts as a potent indirect agonist of each of these systems. The following studies attempted to assess the extent of monoaminergic mediation of cocaine's aversive effects using conditioned taste aversion (CTA) learning [Garcia J, Kimeldorf DJ, Koelling RA. Conditioned aversion to saccharin resulting from exposure to gamma radiation.

Science 1955;122:157-158.]. Specifically, Experiment 1 assessed the ability of selective monoamine transporter inhibitors, e.g., DAT (vanoxerine), NET (nisoxetine) and SERT (fluoxetine), to induce taste aversions (relative to cocaine). Only the NET inhibitor approximated the aversive strength of cocaine. Experiment 2 compared the effects of pretreatment of each of these transport inhibitors on the development of a cocaine-induced CTA. Pretreatment with nisoxetine and fluoxetine both attenuated cocaine-induced aversions in a manner comparable to that produced by cocaine itself. The DAT inhibitor was without effect. Combined, the results of these investigations indicate little or no involvement of dopaminergic systems in cocaine's aversive effects while NE appears to contribute most substantially, with a possible modulatory involvement by serotonin. Jones JD, Hall FS, Uhl GR, Rice K, Riley AL. Differential Involvement of the Norepinephrine, Serotonin and Dopamine Reuptake Transporter Proteins in Cocaine-Induced Taste Aversion. Pharm Biochem Behav. 2009 Jul;93(1):75-81. E-pub 2009 Apr 17.

Opiate-Agonist Induced Taste Aversion Learning in the Fischer 344 and Lewis Inbred Rat Strains: Evidence for Differential Mu Opioid Receptor Activation

The Fischer 344 (F344) and Lewis (LEW) inbred rat strains react differently to morphine in a number of behavioral and physiological preparations, including the acquisition of aversions induced by this compound. The present experiment tested the ability of various compounds with relative selectivity at kappa, delta and mu receptor subtypes to assess the relative roles of these subtypes in mediating the differential aversive effects of morphine in the two strains. In the assessment of the role of the kappa receptor in morphine-induced aversions, animals in both strains were given access to saccharin followed by varying doses of the kappa agonist (-)-U50,488H (0.0, 0.28, 0.90 and 1.60 mg/kg). Although (-)-U50,488H induced aversions in both strains, no strain differences emerged. A separate subset of subjects was trained with the selective delta opioid agonist, SNC80 (0.0, 5.6, 10.0 and 18.0 mg/kg), and again although SNC80 induced aversions, there were no strain differences. Finally, a third subset of subjects was trained with heroin (0.0, 3.2, 5.6 and 10.0 mg/kg), a compound with activity at all three opiate receptor subtypes. Although heroin induced aversions in both strains, the aversions were significantly greater in the F344 strain, suggesting that differential activation of the mu opioid receptor likely mediates the reported strain differences in morphine-induced aversion learning. These data were discussed in terms of strain differences in opioid system functioning and the implications of such differences for other morphine-induced behavioral effects reported in F344 and LEW rats. Davis CM, Rice KC, Riley AL. Opiate-agonist induced taste aversion learning in the Fischer 344 and Lewis inbred rat strains: Evidence for differential mu opioid receptor activation. Pharmacol Biochem Behav. 2009 Jun 7. [E-pub ahead of print].

Nicotine Psychopharmacology Section, Clinical Pharmacology and Therapeutics Branch

Reliability and Validity of a Short Form of the Marijuana Craving Questionnaire

The Marijuana Craving Questionnaire (MCQ) is a valid and reliable, 47-item self-report instrument that assesses marijuana craving along four dimensions: compulsivity, emotionality, expectancy, and purposefulness. For use in research and clinical settings, IRP investigators constructed a 12-item version of the MCQ by selecting three items from each of the four factors that exhibited the greatest within-factor internal consistency (Cronbach's alpha coefficient). Adult marijuana users (n = 490), who had made at least one serious attempt to quit marijuana use but were not seeking treatment, completed the MCQ-Short Form (MCQ-SF) in a single session. Confirmatory factor analysis of the MCQ-SF indicated good fit with the 4-factor MCQ model, and the coefficient of congruence indicated moderate similarity in factor patterns and loadings

between the MCQ and MCQ-SF. Homogeneity (unidimensionality and internal consistency) of MCQ-SF factors was also consistent with reliability values obtained in the initial validation of the MCQ. Findings of psychometric fidelity indicate that the MCQ-SF is a reliable and valid measure of the same multidimensional aspects of marijuana craving as the MCQ in marijuana users not seeking treatment. Heishman SJ, Evans RJ, Singleton EG, Levin KH, Copersino ML, Gorelick DA. Reliability and validity of a short form of the Marijuana Craving Questionnaire. Drug Alcohol Depend. 2009;102:35-40.

Psychobiology Section, Medications Discovery Research Branch

Assessment of Reinforcing Effects of Benztropine Analogs and their Effects on Cocaine Self-Administration in Rats: Comparisons with Monoamine Uptake Inhibitors

Benztropine (BZT) analogs inhibit dopamine uptake but are less effective than cocaine in producing behavioral effects predicting abuse liability. IRP scientists compared reinforcing effects of intravenous BZT analogs with those of standard monoamine uptake inhibitors and the effects of their oral pretreatment on cocaine self-administration. Rats self-administered cocaine [0.032-1.0 mg/kg/injection (inj)] with maximal rates maintained by 0.32 mg/kg/inj cocaine or methylphenidate, when substituted for cocaine. The N-methyl BZT analog, AHN 1-055 was also self administered, although only at a single dose and to less of an extent than cocaine. Neither the N-allyl (AHN 2-005) nor N-butyl (JHW 007) BZT analogs were self administered. Similarly, neither nisoxetine nor citalopram were self administered. Presession treatment with methylphenidate shifted the cocaine self-administration dose-effect curve leftward, i.e. potentiated cocaine. Effects of nisoxetine and citalopram pretreatments were not significant. An intermediate dose of AHN 1-055 (32 mg/kg, p.o.) increased self administration of low cocaine doses and decreased self administration of higher cocaine doses. A higher dose of AHN 1-055 completely eliminated cocaine self administration. Both AHN 2-005 and JHW 007 dose-dependently (10-32 mg/kg) decreased cocaine self-administration, shifting its dose-effect curve down. Decreases in cocaine self administration responding occurred at doses of BZT analogs that did not affect responding maintained by food reinforcement. These findings further support the low abuse liability of BZT analogs and their potential development as medications for cocaine abuse. Hiranita T, Soto PL, Newman AH, Katz JL. Assessment of reinforcing effects of benztropine analogs and their effects on cocaine self-administration in rats: Comparisons with monoamine uptake inhibitors. Journal of Pharmacology and Experimental Therapeutics. 2009 May; 329(2):677-686.

Medicinal Chemistry Section, Medications Discovery Research Branch

High Affinity and Enantioselective D3 Receptor Antagonists

In the present report, the D3 receptor pharmacophore is modified in the 2,3-diCl- and 2-OCH3-phenyl piperazine class of compounds with the goal to improve D3 receptor affinity and selectivity. This extension of structure-activity relationships (SAR) has resulted in the identification of the first enantioselective D3 antagonists (R- and S-PG 648) to be reported, wherein enantioselectivity is more pronounced at D3 than at D2, and that a binding region on the second extracellular loop (E2) may play a role in both enantioselectivity and D3 receptor selectivity. Moreover, IRP scientists have discovered some of the most D3-selective compounds reported to date that show high affinity (Ki =1 nM) for D3 and ~400-fold selectivity over the D2 receptor subtype. Several of these analogues showed exquisite selectivity for D3 receptors over >60 other receptors further underscoring their value as in vivo research tools. These lead compounds also have appropriate physical characteristics for in vivo exploration and therefore will be useful in determining how intrinsic activity at D3 receptors tested in vitro is related to

behaviors in animal models of addiction and other neuropsychiatric disorders. Newman AH, Grundt P, Cyriac GC, Deschamps JR, Taylor M, Kumar R, Ho D, Luedtke RR. N-(4-(4-(2,3-Dichloro- or 2-methoxyphenyl) piperazin-1-yl)-butyl)-heterobiarylcarboxamides with functionalized linking chains as high affinity and enantioselective D3 receptor antagonists. J Med Chem. 2009;52:2559-2570.

Novel mGluR5 Antagonists

The metabotropic glutamate receptor subtype 5 (mGluR5) has been implicated in anxiety, depression, pain, mental retardation and addiction. The potent and selective noncompetitive mGluR5 antagonist 2-methyl-6-(phenylethynyl)pyridine (MPEP) has been a critically important tool used to further elucidate the role of mGluR5 in these CNS disorders. In an effort to provide novel and structurally diverse selective mGluR5 antagonists, IRP investigators previously described a set of analogues with moderate activity wherein the alkyne bond was replaced with an amide group. In the present report, extended series of both amide and alkyne-based ligands were synthesized. MGluR5 binding and functional data were obtained that identified 1) several novel alkynes with higher affinity than MPEP at mGluR5 but 2) most structural variations to the amide template were not well tolerated, although a few potent amides were discovered. Several of these novel analogues show drug-like physical properties (e.g. cLogP range= 2-5) that support their use for in vivo investigation into the role of mGluR5 in CNS disorders. Kulkarni SS, Zou M-F, Cao J, Deschamps JR, Rodriguez A, Conn PJ, Newman AH. Structure Activity Relationships Comparing N-(6-methylpyridin-yl)-substituted Aryl Amides to 2-Methyl-6-(substituted-arylethynyl) pyridines or 2-Methyl-4-(substituted-aryl ethynyl)thiazoles as Novel mGluR5 antagonists. J Med Chem. 2009;52:3563-3575.

Visualization of Dopamine Transporter Trafficking in Live Neurons by Use of Fluorescent Cocaine Analogues

The dopamine transporter (DAT) mediates reuptake of dopamine from the synaptic cleft and is a target for widely abused psychostimulants such as cocaine and amphetamine. Nonetheless, still little is known about the cellular distribution and trafficking of natively expressed DAT. Here IRP researchers use novel fluorescently tagged cocaine analogues to visualize DAT and DAT trafficking in cultured live midbrain dopaminergic neurons. The fluorescent tags were extended from the tropane N- position of 2B-carbomethoxy-3B-(3,4-dichlorophenyl)tropane using an ethylamino-linker. The rhodamine, Oregon Green or Cy3 labeled ligands had high binding affinity for DAT and enabled specific labeling of DAT in live neurons and visualization by confocal imaging. In the dopaminergic neurons, DAT was uniformly distributed in the plasma membrane of the soma, the neuronal extensions and varicosities along these extensions. FRAP (fluorescence recovery after photobleaching) experiments demonstrated bidirectional movement of DAT in the extensions and indicated that DAT is highly mobile both in the extensions and in the varicosities (immobile fraction <~30%). DAT was constitutively internalized into vesicular structures likely representing intracellular transporter pools. The internalization was blocked by lentiviral-mediated expression of dominant-negative dynamin and internalized DAT displayed partial co-localization with the early endosomal marker EGFP-Rab5 and with the transferring receptor. DAT internalization and function was not affected by activation of protein kinase C (PKC) with phorbol-12-myristate-13-acetate (PMA) or by inhibition with staurosporine or GF109203X. These data are in contrast to findings for DAT in transfected heterologous cells and challenge the paradigm that trafficking and cellular distribution of endogenous DAT is subject to regulation by PKC. Eriksen J, Rasmussen SGF, Vaegter CB, Cha JH, Zou M-F, Newman AH, Gether U. Visualization of dopamine transporter trafficking in live neurons by use of fluorescent cocaine analogues. J Neurosci. 2009;29(21):6794-6808.

Director's Report to the National Advisory Council on Drug Abuse - September, 2009

Program Activities

New NIDA PAs and RFAs

On June 25, 2009, NIDA issued a Program Announcement (PA) entitled **Cutting-Edge Basic Research Awards (CEBRA) (R21) (PAR-09-222)**. The CEBRA is designed to foster highly innovative or conceptually creative research related to drug abuse and addiction and how to prevent and treat them. It supports research that is high-risk and potentially high-impact that is underrepresented or not included in NIDA's current portfolio. The proposed research should: (1) test a highly novel and significant hypothesis for which there is scant precedent or preliminary data and which, if confirmed, would have a substantial impact on current thinking; and/or (2) develop or adapt innovative techniques or methods for addiction research, or that have promising applicability to drug abuse research. This FOA will use the NIH Exploratory/Developmental (R21) grant mechanism with modifications.

On July 22, 2009, NIDA issued a PA entitled **HIV/AIDS, Drug Use, and Vulnerable Populations in the US (R21) (PA-09-237)**. This Funding Opportunity Announcement (FOA) encourages Research Project Grant (R01) applications to identify the role(s) that drug abuse plays in fueling the HIV/AIDS epidemic in vulnerable groups (racial/ethnic minorities, men who have sex with men, youth) in the United States and to develop effective interventions to prevent new infections and to improve the health and well-being of those living with HIV/AIDS. It is essential to understand the factors (biological, behavioral, psychosocial, environmental, institutional, etc.) responsible for the profoundly disproportionate burden of HIV/AIDS among vulnerable groups. This FOA will support studies to: 1) understand the contribution of drug abuse (both injection and non-injection) to the acquisition and/or transmission of HIV; 2) study disease progression and disease outcomes; 3) develop and/or improve prevention and treatment interventions; 4) address organizational, structural, and/or community level factors including social, drug-using, and sexual networks.

On July 23, 2009, NIDA issued a PA entitled **Behavioral Science Track Award for Rapid Transition (B/START) (R03) (PAR-09-239)**. This FOA will use the NIH Small Research Grant (R03) award mechanism and seeks to facilitate the entry of beginning investigators into the field of behavioral science research related to drug abuse. To be appropriate for a B/START award, research must be primarily focused on behavioral processes and research questions. The R03 grant mechanism supports different types of projects including pilot and feasibility studies; secondary analysis of existing data; small, self-contained research projects; development of research methodology; and development of new research technology. The R03 is intended to support small research projects that can be carried out in a short period of time with limited resources.

On May 28, 2009, NIDA issued an RFA entitled **Integrating Translational Neuroscience and Adolescent Drug Abuse Treatment (R21) (RFA-DA-10-003)**. The goal of this FOA is to discover innovative approaches to drug abuse treatment for adolescents integrating innovations in neuroscience. This FOA encourages exploratory/developmental grant applications to develop collaborations integrating developmental neuroscience and adolescent drug abuse treatment. The primary goal of this announcement is to facilitate translational research that ultimately integrates findings from research on brain development, cognition and neuroscience into the development of innovative and effective, developmentally sensitive drug abuse treatments for adolescents. The grants awarded under this program will allow investigative teams exploratory and planning resources to develop

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translational research proposals for subsequent R01 grant application. This may include preliminary studies, scientific workshops, specialized training in research methodologies and other collaborative activities to foster multidisciplinary and/or multi-site translational research approaches to adolescent drug abuse treatment. Opening Date for this RFA: August 1, 2009; Letters of Intent Receipt Date: August 1, 2009; Application Due Date: September 1, 2009.

On May 29, 2009, NIDA issued an RFA entitled **International Research Collaborations on HIV/AIDS and Drug Use (R01) (RFA-DA-10-008)**. This FOA solicits RO1 grant applications from applicant organizations that propose to conduct collaborative regionally focused international research on drug use and HIV/AIDS. This program fosters research related to biomedical and clinical science, epidemiology, prevention, and treatment of HIV/AIDS associated with drug use. The FOA seeks to foster international research collaborations with a regional geographic focus that take advantage of populations, resources, talent, or environmental/contextual conditions outside the U.S. that offer special opportunities to advance scientific knowledge. Opening Date for this RFA: October 18, 2009; Letters of Intent Receipt Date: October 18, 2009; Application Due Date: November 18, 2009.

On June 1, 2009, NIDA issued an RFA entitled **The National Drug Abuse Treatment Clinical Trials Network (U10) (RFA-DA-10-009)**. This FOA announces a competition for new cooperative agreement applications and cooperative agreement renewal applications from established clinical investigators to participate in the National Drug Abuse Treatment Clinical Trials Network (CTN). As a nation-wide partnership for translational research among addiction treatment providers, researchers, and NIDA staff, the CTN's mission is to test and validate effective and efficient treatments that can be adopted by addiction treatment providers through-out the Nation, using science as the vehicle. The CTN provides an enterprise in which community-based addiction service providers, other health practitioners working with patients that have addiction problems, addiction treatment researchers, and NIDA cooperatively develop, validate, refine, and deliver new treatment options for patients in community-level clinical practice. Letters of Intent Receipt Date: October 2, 2009;Application Receipt Date: November 2, 2009.

PAs/RFAs Issued with Other NIH Components/Agencies

On May 15, 2009, NIDA, in collaboration with a number of other NIH components issued a PA entitled **NIH Clinical Trial Planning Grant Program (R34) (PA-09-186)**. This FOA invites applications under the NIH Clinical Trial Planning Grant Program, the purpose of which is to provide support for the development of a Phase III clinical trial. This includes the establishment of the research team, the development of tools for data management and oversight of the research, the definition of recruitment strategies, and the finalization of the protocol and other essential elements of the study included in a manual of operations/procedures. The Clinical Trial Planning Grant is not designed for the collection of preliminary data or the conduct of pilot studies to support the rationale for a clinical trial.

On June 12, 2009, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral MD/PhD and Other Dual Doctoral Degree Fellows (F30) (PA-09-207)**. The purpose of the Ruth L. Kirschstein National Research Service Awards (Kirschstein-NRSA) is to provide support to individuals for combined MD/PhD and other dual doctoral degree training (e.g. DO/PhD, DDS/PhD, AuD/PhD). The participating Institutes award this Kirschstein-NRSA individual fellowship (F30) to qualified applicants with the potential to become productive, independent, highly trained physician-scientists and other clinician-scientists, including patient-oriented researchers in their scientific mission areas. This funding opportunity supports individual predoctoral F30 fellowships with the expectation that these training opportunities will increase the number of future investigators with both clinical knowledge and skills in basic, translational or clinical research.

On June 12, 2009, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral Fellows (F31) (PA-09-208)**. The purpose of this individual predoctoral research training fellowship is to provide support for promising doctoral candidates who will be performing dissertation research and training in scientific health-related fields relevant to the missions of the participating NIH Institutes and Centers (ICs) during the tenure of the award.

On June 11, 2009, NIDA, in collaboration with numerous other NIH components,

Planned Meetings

Publications

Staff Highlights

Grantee Honors

issued a PA entitled **Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral Fellowships (F31) to Promote Diversity in Health-Related Research (PA-09-209)**. The purpose of this individual predoctoral research training fellowship is to improve the diversity of the health-related research workforce by supporting the training of predoctoral students from groups that have been shown to be underrepresented. Such candidates include individuals from underrepresented racial and ethnic groups, individuals with disabilities, and individuals from disadvantaged backgrounds. Detailed eligibility criteria are described in the full announcement.

On June 12, 2009, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Ruth L. Kirschstein National Research Service Awards (NRSA) for Individual Postdoctoral Fellows (F32) (PA-09-210)**. The purpose of this individual postdoctoral research training fellowship is to provide support to promising Fellowship Applicants with the potential to become productive, independent investigators in scientific health-related research fields relevant to the missions of participating NIH Institutes and Centers.

On June 12, 2009, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Ruth L. Kirschstein National Research Service Awards (NRSA) for Individual Senior Fellows (F33) (PA-09-211)**. The National Institutes of Health (NIH) awards individual senior level research training fellowships to experienced scientists who wish to make major changes in the direction of their research careers or who wish to broaden their scientific background by acquiring new research capabilities as independent investigators in research fields relevant to the missions of participating NIH Institutes and Centers.

On July 22, 2009 NIDA, in collaboration with the National Institute of Nursing Research (NINR), issued a PA entitled **HIV/AIDS, Drug Use, and Vulnerable Populations in the US (R01) (PA-09-236)**. This FOA encourages Research Project Grant (R01) applications to identify the role(s) that drug abuse plays in fueling the HIV/AIDS epidemic in vulnerable groups (racial/ethnic minorities, men who have sex with men, youth) in the United States and to develop effective interventions to prevent new infections and to improve the health and well-being of those living with HIV/AIDS. It is essential to understand the factors (biological, behavioral, psychosocial, environmental, institutional, etc.) responsible for the profoundly disproportionate burden of HIV/AIDS among vulnerable groups. This FOA will support studies to: 1) understand the contribution of drug abuse (both injection and non-injection) to the acquisition and/or transmission of HIV; 2) study disease progression and disease outcomes; 3) develop and/or improve prevention and treatment interventions; 4) address organizational, structural, and/or community level factors including social, drug-using, and sexual networks.

On August 5, 2009, NIDA, in collaboration with numerous other NIH Institutes, issued a PA entitled **Innovations in Biomedical Computational Science and Technology (R01) (PAR-09-218)**. The NIH is interested in promoting research and developments in biomedical informatics and computational biology that will support rapid progress in areas of scientific opportunity in biomedical research. As defined here, biomedical informatics and computational biology includes database design, graphical interfaces, querying approaches, data retrieval, data visualization and manipulation, data integration through the development of integrated analytical tools, and tools for electronic collaboration, as well as computational and mathematical research including the development of structural, functional, integrative, and analytical computational models and simulations.

On August 5, 2009, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Innovations in Biomedical Computational Science and Technology Initiative (SBIR [R43/R44]) (PAR-09-220)**. This FOA solicits Small Business Innovation Research (SBIR) grant applications from small business concerns (SBCs) that propose innovative research in biomedical informatics and computational biology to promote the progress of biomedical research. There exists an expanding need to speed the progress of biomedical research through the power of computing to manage and analyze data and to model biological processes. The NIH is interested in promoting research and developments in biomedical computational science and technology that will support rapid progress in areas of scientific opportunity in biomedical research. As defined here biomedical computing or biomedical information science and technology includes database design, graphical interfaces, querying approaches, data retrieval, data visualization and manipulation, data integration through the development of integrated analytical tools, and tools for electronic collaboration, as well as computational research including the development of

structural, functional, integrative, and analytical computational models and simulations.

On August 5, 2009, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Innovations in Biomedical Computational Science and Technology Initiative (STTR [R41/R42]) (PAR-09-221)**. This FOA solicits Small Business Technology Transfer (STTR) grant applications from small business concerns (SBCs) that propose innovative research in biomedical informatics and computational biology to promote the progress of biomedical research. There exists an expanding need to speed the progress of biomedical research through the power of computing to manage and analyze data and to model biological processes. The NIH is interested in promoting research and developments in biomedical computational science and technology that will support rapid progress in areas of scientific opportunity in biomedical research. As defined here biomedical computing or biomedical information science and technology includes database design, graphical interfaces, querying approaches, data retrieval, data visualization and manipulation, data integration through the development of integrated analytical tools, and tools for electronic collaboration, as well as computational research including the development of structural, functional, integrative, and analytical computational models and simulations.

On August 13, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Optimization of Small Molecule Probes for the Nervous System (R21) (PAR-09-251)**. This FOA encourages research grant applications from institutions/organizations that propose to develop new small molecule probes for investigating biological function in the nervous system via the application of advanced medicinal chemistry and the biological testing of compounds. Eligible investigators will have identified probe candidates via screening of small molecule collections, using in vitro assays of biological activity developed to interrogate these collections, and be able to show that the structural features of these small molecules are related to their biological activity. Proposals should nominate small molecule probe candidates from distinct structural series for the further, iterative design and testing of analogues in structure-activity relationship studies, using in vitro assays of biological function adapted to the medium throughput screening requirements of this work. These studies should have the goal of developing a small molecule probe possessing the attributes (eg: affinity, selectivity, activity) required for its use in future pharmacological studies proposed by the investigator.

On August 17, 2009, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Exploratory Innovations in Biomedical Computational Science and Technology (R21) (PAR-09-219)**. The NIH is interested in promoting research and developments in biomedical informatics and computational biology that will support rapid progress in areas of scientific opportunity in biomedical research. As defined here, biomedical informatics and computational biology includes database design, graphical interfaces, querying approaches, data retrieval, data visualization and manipulation, data integration through the development of integrated analytical tools, and tools for electronic collaboration, as well as computational and mathematical research including the development of structural, functional, integrative, and analytical computational models and simulations. This FOA will utilize the R21 grant mechanism. This FOA is intended to support exploratory biomedical informatics and computational biology researchÑapplications should be innovative, with high risk/high impact in new areas that are lacking preliminary data or development.

On June 2, 2009, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Recovery Act Limited Competition: Biomedical Research, Development, and Growth to Spur the Acceleration of New Technologies (BRDG-SPAN) Pilot Program (RC3) (RFA-OD-09-008)**. This FOA, supported by funds provided to the NIH under the American Recovery & Reinvestment Act of 2009, Public Law 111-5, solicits grant applications for a new initiative called Biomedical Research, Development, and Growth to Spur the Acceleration of New Technologies (BRDG-SPAN) Pilot Program (RC3). The purpose of this pilot program is to address the funding gap between promising research and development (R&D) and transitioning to the market by contributing to the critical funding needed by applicants to pursue the next appropriate milestone(s) toward ultimate commercial-ization; i.e., to carry out later stage research activities necessary to that end. This program aims to accelerate the transition of research innovations and technologies toward the development of products or services that will improve human health, help advance the mission of NIH and its Institutes and Centers (ICs), and create significant value and economic stimulus. Opening Date: August 1, 2009; Letters of Intent Due Date:

August 3, 2009; Application Due Date: September 1, 2009.

On June 2, 2009, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Recovery Act Limited Competition: Small Business Catalyst Awards for Accelerating Innovative Research (R43) (RFA-OD-09-009)**. This NIH FOA, supported by funds provided to the NIH under the American Recovery & Reinvestment Act of 2009 ("Recovery Act" or "ARRA"), Public Law 111-5, invites grant applications from small business concerns that propose to accelerate innovation through high risk, high reward research and development (R&D) that has commercial potential and is relevant to the mission of the NIH. The Small Business Catalyst Award is further expected to support entrepreneurs of exceptional creativity, drawn from scientific and technological environments beyond NIH, who propose pioneering and possibly transformative approaches to addressing major biomedical or behavioral challenges with the potential for downstream commercial development. Opening Date: August 1, 2009; Letters of Intent Due Date: August 3, 2009; Application Due Date: September 1, 2009.

On July 15, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **The Human Connectome Project (U54) (RFA-MH-10-020)**. This FOA is issued as an initiative of the NIH Blueprint for Neuroscience Research. The Neuroscience Blueprint is a collaborative framework through which 16 NIH Institutes, Centers and Offices jointly support neuroscience-related research, with the aim of accelerating discoveries and reducing the burden of nervous system disorders. The overall purpose of this five year Human Connectome Project (HCP) is to develop and share knowledge about the structural and functional connectivity of the human brain. This purpose will be pursued through the following specific efforts: Existing, but cutting-edge, non-invasive imaging technologies will be optimized and combined to acquire structural and functional in vivo data about axonal projections and neural connections from brains of hundreds of healthy adults. Demographic data and data regarding sensory, motor, cognitive, emotional, and social function will also be collected for each subject, as will DNA samples and blood (to establish cell lines). Models to better understand and use these data will be developed. Connectivity patterns will be linked to existing architectonic data. Data and models will be made available to the research community immediately via a user-friendly system to include tools to query, organize, visualize and analyze data. Outreach activities will be conducted to engage and educate the research community about the imaging tools, data, models, and informatics tools. Letters of Intent Receipt Date: October 24, 2009; Application Receipt Date: November 24, 2009.

On July 17, 2009, NIDA, in collaboration with a number of other NIH components, issued an RFA entitled **Building Interdisciplinary Research Careers in Women's Health (K12) (RFA-OD-09-006)**. The NIH Office of Research on Women's Health (ORWH) and its cosponsors invite institutional career development award applications for Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Career Development Programs, hereafter termed "Programs." Programs will support mentored research career development of junior faculty members, known as BIRCWH Scholars, who have recently completed clinical training or postdoctoral fellowships, and who will be engaged in interdisciplinary basic, translational, behavioral, clinical, and/or health services research relevant to women's health or sex/gender factors. Letters of Intent Receipt Date: September 23, 2009; Application Receipt Date: October 22, 2009.

On July 29, 2009, NIDA, in collaboration with NIAAA, NCI, and the Department of Veterans Affairs, issued an RFA entitled **Substance Use and Abuse among U.S. Military Personnel, Veterans and their Families (R01) (RFA-DA-10-001)**. This FOA is issued to enhance and accelerate research on the epidemiology/ etiology, identification, and prevention and treatment of alcohol, tobacco, and other drug use and abuse (including illicit and prescription drugs) and associated mental health problems among active-duty or recently separated (e.g., Iraq and Afghanistan) military troops and their families. VA has specific interest in supporting research directed towards advancing prevention and treatment of mental health and comorbid substance use/abuse problems in veterans of Iraq and Afghanistan deployments (including National Guard and Reservists) and their families. Opening Date: November 22, 2009; Application Due Date: December 22, 2009.

On July 29, 2009, NIDA, in collaboration with NIAAA, and NCI, issued an RFA entitled **Substance Use and Abuse among U.S. Military Personnel, Veterans and their Families (R21) (RFA-DA-10-002)**. This FOA is issued for exploratory and pilot feasibility studies designed to enhance and accelerate research on the epidemiology/ etiology, identification, and prevention and treatment of alcohol, tobacco, and other

drug use and abuse (including illicit and prescription drugs) and associated mental health problems among active-duty or recently separated (e.g., Iraq and Afghanistan) military troops and their families. This FOA will utilize the R21 grant mechanism and runs in parallel with a FOA of identical scientific scope, DA-10-001 that solicits applications under the R01 mechanism. Opening Date: November 22, 2009; Letters of Intent Receipt Date: November 23, 2009; Application Due Date: December 22, 2009.

Other Program Activities

Clinical Trials Network (CTN) Update

RFP: Proposals in response to the RFP N01DA-9-2217, Data and Statistics Center for the NIDA Clinical Trials Network, were reviewed in May, 2009, with an award planned around mid-September.

Protocols: A total of 43 protocols have been initiated since 2001, including multi-site clinical trials (29), multi-site surveys (3), studies in special populations (5), and secondary analyses of data across various trials (6). Twenty-three trials have completed data lock; one is in the follow-up, data-lock phase; three are currently enrolling and five are in development. In addition, 18 ancillary studies have been supported by CTN and non-CTN funds. Seven protocols are in the development phase. Over 11,000 participants have enrolled in studies.

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

- **Protocol CTN 0001**, Buprenorphine/Naloxone versus Clonidine for Inpatient Opiate Detoxification
- **Protocol CTN 0002**, Buprenorphine/Naloxone versus Clonidine for Outpatient Opiate Detoxification
- **Protocol CTN 0005**, MI (Motivational Interviewing) To Improve Treatment Engagement and Outcome in Subjects Seeking Treatment for Substance Abuse
- **Protocol CTN 0006**, Motivational Incentives for Enhanced Drug Abuse Recovery: Drug Free Clinics
- **Protocol CTN 0007**, Motivational Incentives for Enhanced Drug Abuse Recovery: Methadone Clinics

Primary outcome papers are published or in press for:

- **Protocol CTN 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 Heroin Addicted 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 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 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.

- **Protocol CTN 0029**, A Pilot Study of Osmotic-Release Methylphenidate (OROS MPH) in Initiating and Maintaining Abstinence in Smokers with ADHD.

In addition, the following protocols have submitted primary paper:

- **Protocol CTN 0017**, HIV and HCV Intervention in Drug Treatment Settings

The following protocols have locked the data:

- **Protocol CTN 0014**, Brief Strategic Family Therapy for Adolescent Drug Abusers (BSFT)
- **Protocol CTN 0028**, Randomized Controlled Trial of Osmotic-Release Methylphenidate (OROS MPH) for Attention Deficit Hyperactivity Disorder (ADHD) in Adolescents with Substance Use Disorders (SUD).

The following protocols has ended new enrollment, and are in the follow-up or data-lock phase:

- **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 9 sites, and has randomized 653 participants into phase 1 and 360 participants into phase 2.
- **CTN 0030A1**, Collection of Economic Data for the Prescription Opioid Addiction Treatment Study. This ancillary study was conducted in collaboration with NIDA DESPR and it is in the data analysis phase.
- **CTN 0030A2**, Effects of Chronic Opioids is conducted in collaboration with NIDA DCNBR to obtain anatomical MR scans in subjects with a history of opioid use to evaluate neural changes that may occur with such use and compare with age/gender healthy controls. This study is in the data analysis phase.
- **CTN 0030A3**, POATS Long-Term Follow Up Study (LTFU) is being implemented at all POATS sites to examine long-term outcomes for individuals who participated in CTN-0030 with opioid analgesic (OA) dependence.
- **Protocol CTN 0032**, HIV Rapid Testing and Counseling in Drug Abuse Treatment Programs in the U.S. This study seeks to evaluate the most effective strategy to ensure that persons in drug treatment programs are tested for HIV and receive their HIV test results. The protocol has completed the enrollment phase and the one-month follow-up for the primary goal. Twelve hundred and eighty one patients in 12 CTN drug abuse community centers were enrolled in 5 months with a 97.5% retention rate at one-month follow-up.
- **CTN 0032A1**, Economic Analysis of HIV Rapid Testing in Drug Abuse Treatment Programs. This is an ancillary study is an assessment of the cost-effectiveness of on-site HIV testing in drug abuse treatment settings vs. referral for off-site testing. The PI is Dr. Bruce Schackman. The project is conducted in collaboration with NIDA's DESPR.

The following protocols are currently enrolling:

- **Protocol CTN 0027**, Starting Treatment with Agonist Replacement Therapies (START) is a randomized, open-label, multi-center study that was developed in collaboration with the Division of Pharmacotherapies & Medical Consequences of Drug Abuse (DPMCDA). Enrollment began in April 2006. As of February 28, 2009, 1,040 participants had been randomized.

- **CTN 0027A1**, START Pharmacogenetics: Exploratory Genetic Studies In Starting Treatment With Agonist Replacement Therapies.
- **CTN-0027A2**, Retention of Suboxone Patients in START: Perspectives of Providers and Patients. The overall purposes of the supplemental study are to identify and assess barriers for retaining Suboxone patients. This

ancillary study is 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. As of August 3, 2009, two of the three Wave 1 sites have completed recruitment and the third Wave 1 site is approaching its final recruitment target. The seven Wave 2 sites continue to actively recruit.
- **CTN 0031A1**, An Evaluation of Neurocognitive Function, Oxidative Damage, and Their Association with Treatment Outcomes in Methamphetamine and Cocaine Abusers. Potential participants are being recruited at six sites.
- **CTN 0031A2**, The Role of Alcohol Consumption in Classifications of Alcohol Use Disorders: A Clinical Study. It investigates the utility of adding a frequency measure of alcohol consumption (i.e., the first three items of the Alcohol Use Disorders Identification Test [AUDIT-C]), to the DSM-IV diagnostic criteria for alcohol use disorders. This study is funded by an MOU between NIDA and NIAAA. Data will be collected for this study throughout the life of the main STAGE-12 study.
- **Protocol CTN 0033-Ot**, Methamphetamine Use among American Indians. The first area of research emphasis in the National Institute on Drug Abuse's Strategic Plan on Reducing Health Disparities (2004 Revision) is the epidemiology of drug abuse, health consequences and infectious diseases among minority populations. The study is a collaboration among four Nodes: Pacific NW, Southwest, Oregon/Hawaii, and Ohio Valley.
- **Protocol CTN 0035-Ot**, Access to HIV and Hepatitis Screening and Care among Ethnic Minority Drug Users In and Out of Drug Treatment. This study is in collaboration with the NIH National Center for Minority Health and Health Disparities and is being conducted in the California/Arizona Node.
- **Protocol CTN 0036-Ot**, Epidemiology and Ethnographic Survey of "Cheese" Heroin Use among Hispanics in Dallas County. This study is in collaboration with the NIH National Center for Minority Health and Health Disparities and is being conducted in the Texas Node.

The following protocols are in the development phase:

- **Protocol CTN 0034-Ot**, Developing Research Capacity and Culturally Appropriate Research Methods: Community-based Participatory Research Manual for Collaborative Research in Drug Abuse for American Indians and Alaska Natives. This study is in collaboration with the NIH National Center for Minority Health and Health Disparities and will be conducted in the Pacific Northwest Node.
- **Protocol CTN 0037**, Exercise as a Treatment for Substance Use Disorders. This clinical trial will test the effectiveness of the addition of exercise in improving drug abuse treatment outcomes.
- **Protocol CTN-0038-Ot**, Barriers to Substance Abuse Treatment among Asian Americans and Pacific Islanders. The objective of this study is to gain a better understanding of the factors that may influence the under-utilization of substance abuse treatment services by Asian Americans and Pacific Islanders (AAPIs) and the readiness of substance abuse treatment programs serving AAPIs to participate in clinical trials and adopt evidence based practices. This study is a collaboration with NIH NCMHD.
- **Protocol CTN 0044**, Web-delivery of Evidence-Based, Psychosocial Treatment for Substance Use Disorders. The purpose of this study is to evaluate the effectiveness of adding an interactive, web-based version of the Community Reinforcement Approach (CRA) intervention plus abstinence incentives as an adjunct to community-based, outpatient substance abuse treatment.
- **Protocol CTN 0045-Ot**,Rates of HIV Testing and Barriers to Testing in African Americans Receiving Substance Abuse Treatment. This is an observational study seeking to: (1) Compare the proportion of African American and non-African Americans receiving treatment at substance abuse treatment clinics that have been tested for HIV within the past 12

months; (2) Observe relationships between rates of African Americans who have not been tested and a) the types of testing offered at substance abuse treatment clinics and b) the types of outreach strategies used to engage persons in HIV testing; and (3) assess African American clients' self-reported barriers to accessing HIV testing, in relation to other ethnicities.

- **Protocol CTN-0046**, Smoking-Cessation and Stimulant Treatment (S-CAST): Evaluation of the Impact of Concurrent Outpatient Smoking-Cessation and Stimulant Treatment on Stimulant-Dependence Outcomes. The primary objective of this study is to evaluate the impact of substance abuse treatment as usual plus smoking cessation treatment (TAU+SCT), relative to substance abuse treatment as usual (TAU), on drug abuse outcomes.
- **Protocol CTN-0047**, Screening, Motivational Assessment, Referral and Treatment in Emergency Departments (SMART-ED). The study objective is to evaluate the implementation of and outcomes associated with a screening and brief intervention (SBI) process to identify individuals with substance use, abuse, or dependence seen in emergency departments (EDs) and to provide interventions and/or referral to treatment consistent with the severity of their substance use disorder.
- **Protocol CTN-0048**, Screening, Motivational Assessment, Referral and Treatment in Dental Clinics. This concept is currently being developed into a protocol, in collaboration with the NIDCR and their clinical networks.

In addition to the primary CTN trials, there are currently five secondary analyses using data across several of the completed trials:

1. Gender Differences in the Prevalence and Predictors of HIV Risk Behaviors, PI: Audrey Brooks (CA/AZ Node);
2. Pattern of alcohol use and alcohol-related diagnoses among drug abusing/dependent participants, PIs: Dennis Donovan and Bryan Hartzler (Pacific Northwest Node);
3. The relationships between demographic characteristics of patients and therapists, measures of therapeutic process and therapeutic alliance, and outcomes, PIs: Alyssa Forcehimes (Southwest Node) and Kathleen Burlew (Ohio Valley Node);
4. The Efficacy of Motivational Enhancement Therapy for African Americans, PI: Kathleen Burlew (Ohio Valley Node);
5. Substance Abuse Treatment Outcomes in Racial/Ethnic Minority Populations, PI: Carmen Masson (California-Arizona Node).

There are also about 40 funded studies supported by independent grants that use CTN studies as a platform.

Summer Research with NIDA

The Special Populations Office coordinated the 13th annual Summer Research with NIDA program. Sixty-eight high school and college students engaged in drug abuse research with various NIDA grantees for 8-10 weeks over the summer. Participants received certificates of completion and were invited to submit their photo and brief statements about their research experience to the NIDA Notes editor for inclusion in an upcoming issue.

NIDA's New and Competing Continuation Grants Awarded Since May 2009

Agrawal, Arpana -- Washington University
Characterizing the 3-Year Course of Cannabis Involvement in NESARC

Ahijevych, Karen L. -- Ohio State University
Bitter Taste Phenotype as a Risk Factor of Oral Nicotine Replacement Non-adherence

Akbarali, Hamid I. -- Virginia Commonwealth University
Morphine-Induced Tolerance in the Ileum and Colon

Al'absi, Mustafa N. -- University of Minnesota (Duluth)
Khat Research Program: Neurobehavioral Impact of Long-Term Use

Aldrich, Jane V. -- University of Kansas (Lawrence)
Affinity Labels for Opioid Receptors

Amara, Susan G. -- University of Pittsburgh at Pittsburgh
Molecular Studies of Catecholamine Transporters

Ambrose, Bridget Kathleen -- Johns Hopkins University
Tobacco Smoking and Cessation Seeking Behavior in the ALIVE Study

Ames, Susan L. -- Claremont Graduate University
Functional Imaging of Implicit Marijuana Associations during IAT Performance

Andrews, Judy A. -- Oregon Research Institute
Childhood and Adolescent Predictors of Substance Abuse in Emerging Adulthood

Aron, Adam Robert -- University of California (San Diego)
Fronto-Basal-Ganglia Circuits for Selective Stopping and Braking

Arria, Amelia M. -- University of Maryland (College Park Campus)
Drug Abuse Trajectories in the Transition to Adulthood: Risk Factors and Outcomes

Aston-Jones, Gary S. -- Medical University of South Carolina
Gene Transfer into Selected Brain Neurons In Vivo

Avison, Malcolm J. -- Vanderbilt University
High Resolution MRI Mapping of CNS Plasticity

Baker, David A. -- Marquette University
Targeting System XC- for the Treatment of Addiction

Barcelo, Helene -- Arizona State University (Tempe Campus)
Application of Discrete Homotopy Theory to the Study of Children's Social Network

Bardo, Michael T. -- University of Kentucky
Novelty, Dopamine and Response to Amphetamine

Barker, Eric L. -- Purdue University (West Lafayette)
Lipidomic Profile of Endocannabinoids from Neuronal Cells

Barres, Ben A. -- Stanford University
The Role of Glia in the Formation of Functional Synapses

Barth, Alison L. -- Carnegie-Mellon University
Experience Dependent Plasticity in a fosGFP Mouse

Bassell, Gary J. -- Emory University
Identification of Localized MiRNAS for Neuronal Development and Plasticity

Bazemore-Walker, Carthene R. -- Brown University
Proteomic Characterization of the Sigma-1 Receptor and Its Signaling Complex

Beauvais, Frederick -- Colorado State University (Fort Collins)
Drug Use among Young Indians: Epidemiology and Prediction

Becker, Jill B. -- University of Michigan at Ann Arbor
Gender Differences in Drug Abuse

Becker, Jill B. -- University of Michigan at Ann Arbor
Drug Abuse: Sex Differences in Developmental and Environmental Influences

Belenko, Steven -- Temple University
The Pennsylvania Research Center at Temple University

Berg, Kelly -- University of Texas Health Science Center (San Antonio)
Delta-Kappa Opioid Receptor Interactions: Ligand-Dependent Effects

Berman, Phillip -- University of California (Santa Cruz)
HIV Variation in Injection Drug Users: Mapping Broadly Neutralizing Antibodies

Berns, Gregory S. -- Emory University
Neurobiology of Uncertainty

Berns, Gregory S. -- Emory University

Neurobiological Circuits of Gain and Loss during Risky Decision Making

Berrettini, Wade H. -- University of Pennsylvania
Genetics of Nicotine Dependence

Berridge, Kent C. -- University of Michigan at Ann Arbor
Cue-Triggered Reward Seeking

Berwid, Olga G. -- Queens College
Impact of Stimulant Treatment on Neural Reward Circuitry Functioning in ADHD

Beveridge, Thomas J.R. -- Wake Forest University (Health Sciences)
Effect of Cocaine Self-Administration on Metabotropic Glutamate Systems

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

Bhagwagar, Zubin -- Yale University
A Pet Study of 5-HT1B Receptor Binding as a Novel Biomarker for Cocaine Dependency

Bibb, James A. -- University of Texas S.W. Medical Center (Dallas)
The Role of Cdk5 in Addiction

Bierut, Laura J. -- Washington University
Genetics Study of Nicotine Dependence in African Americans

Bisaga, Adam Mariusz -- Columbia University Health Sciences
Dronabinol Naltrexone Treatment for Opioid Dependence

Blanco, Carlos -- New York State Psychiatric Institute
Substance Use Comorbidity Care: Evidence-Based Stepped Strategies for Depression

Blough, Bruce E. -- Research Triangle Institute
Development of Potential Treatment Medications for Drug Abuse

Blow, Frederic C. -- University of Michigan at Ann Arbor
Optimizing SBIRT for Drug-Using Patients in an Inner-City Emergency Department

Bock, Beth C. -- Miriam Hospital
Examining a Text Message Intervention for Smoking Cessation

Boeri, Miriam W. -- Kennesaw State University
Older Drug Users: A Life Course Study of Turning Points in Drug Use and Injection

Bohn, Laura M. -- Scripps Research Institute
Agonist-Directed MOR Desensitization in Opioid Analgesic Tolerance

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

Booth, Robert E. -- University of Colorado (Denver)
Understanding the Role of Power in Drug Use and HIV Risk Behaviors among...

Boyd, Carol J. -- University of Michigan at Ann Arbor
A Prospective Study of the Nonmedical Use of Prescription Medications by Adolescence

Bradesi, Sylvie S. -- Brentwood Biomedical Research Institute
Spinal Glia Activation in Chronic Stress-Induced Visceral Hyperalgesia

Branch, Marc N. -- University of Florida
Behavioral Determinants of Cocaine Tolerance

Braver, Todd -- Washington University
Negative Reinforcement Effects on Neural Mechanisms of Cognitive Control

Brecht, Mary-Lynn -- University of California (Los Angeles)
Methamphetamine Abuse: Long-Term Trajectories, Correlates, Treatment Effects

Brown, David R. -- University of Minnesota (Twin Cities)
Mucosal Defense Mechanisms in Substance Abuse

Brown, Joshua W. -- Indiana University (Bloomington)
Neural Mechanisms of Risky Behavior Avoidance

Brown, Richard A. -- Butler Hospital (Providence, RI)

Distress Tolerance Treatment for Smoking Cessation

Bruce, Jacqueline -- Oregon Social Learning Center, Inc.
Risk for Substance Use in Foster Adolescents: An fMRI Study of Inhibitory Control

Bruijnzeel, Adriaan W. -- University of Florida
Nicotine Dependence and Central Adiposity Signaling

Buch, Shilpa J. -- University of Kansas Medical Center
PLGA/Antisense IL-10: Gene Therapy for Cocaine Abusers with HAD

Burstein, Sumner H. -- University of Massachusetts Medical School (Worcester)
The Elmiric Acids: Biologically Active Anandamide Analogs

Carise, Deni -- Treatment Research Institute, Inc. (TRI)
Toolkits: Will Implementing An Evidence-Based Curriculum Improve Group Counseling?

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

Carrasco, Gonzalo Andres -- University of Kansas (Lawrence)
Neuroendocrine Supersensitivity of 5-HT2A Receptors

Carroll, Frank I. -- Research Triangle Institute
Design and Development of Pharmacotherapies for Treating Stimulant Abuse

Case, Patricia L. -- Fenway Community Health Center
Feasibility of Pharmacy-Based HIV Interventions among IDUS: 2 New England Cities

Castillo, Pablo E. -- Yeshiva University
Presynaptic Forms of Long-Term Plasticity in the CNS

Chang, Sulie Lin -- Seton Hall University
Mechanisms of Nicotine's Behavioral Effects on the HIV-1 Transgenic Rat

Chen, Dong Feng -- Schepens Eye Research Institute
Glial Modulation of Cortical Development and Drug of Abuse-Induced Brain Damage

Chen, Hao -- University of Tennessee Health Science Center
Insular Cortex and Reinstatement of Nicotine Seeking Behavior

Chen, Kevin W. -- University of Maryland (Baltimore)
Treatment of Cocaine Addiction with Integrative Meditation

Chen, Rong -- University of Michigan at Ann Arbor
PKC-Beta Regulation of the Dopamine Transporter Trafficking

Cherner, Mariana -- University of California (San Diego)
COMT Genotype and Risky Decision Making in HIV and Methamphetamine Dependence

Childress, Anna Rose -- University of Pennsylvania
Extinction of Limbic Activation to "Unseen" Cocaine Cues

Cinciripini, Paul Michael -- University of Texas (M.D. Anderson Cancer Center)
Effectiveness of Varenicline vs. Varenicline plus Bupropion for Smoking Cessation

Cinciripini, Paul Michael -- University of Texas (M.D. Anderson Cancer Center)
Error Sensitivity as a Predictor of Nicotine withdrawal and Smoking Cessation

Clarke, Jennifer Grace -- Memorial Hospital of Rhode Island
Sustaining Tobacco Abstinence after Incarceration

Cochran, Bryan Neil -- University of Montana
Predicting the Development of Opioid Abuse or Dependence

Coffman, Donna Lynn -- Pennsylvania State University (University Park)
Causal Inference for Mediation Models in Substance Abuse Prevention Research

Collins, David -- Pacific Institute for Research and Evaluation
Mobilizing the Community to Reduce Teen Prescription Drug Abuse

Connett, Deborah Finfgeld -- University of Missouri (Columbia)
Optimal Treatment: Recovery Frameworks for Women with Substance Abuse Problems

Cooper, Hannah L. -- Emory University
Public Housing Relocations: Impact on Healthcare Access, Drug Use and Sexual Health

Cooper, Hannah L. -- Emory University
Exploring HIV Risk in Drug-Using Black Women with an Incarcerated Partner

Cosgrove, Kelly P. -- Yale University
Dopaminergic and Endocannabinoid Interactions in Nicotine Dependence

Cravatt, Benjamin F. -- Scripps Research Institute
Endocannabinoid Metabolic Enzymes: Structure, Function, In Vivo Inhibition

Crystal, Ronald G. -- Weill Medical College of Cornell University
Adenovirus-Based Nanoparticle Vaccines

Cubbins, Lisa Ann -- Battelle Centers/Public Health Research and Evaluation
Immigration Effects on Substance Abuse, Mental Health and Treatment Gaps

Cunningham, Rebecca M. -- University of Michigan at Ann Arbor
Substance Use among Violently Injured Youth in an Urban ER: Services and Outcome

Dafny, Nachum -- University of Texas Health Science Center (Houston)
How and Where Methylphenidate Exerts Effect in Adolescent and Adult Brains

Dallery, Jesse -- National Development and Research Institute
Technological Innovations in a Behavioral Treatment for Cigarette Smoking

Davies, Huw M. -- Emory University
Design of New Treatment Agents for Drug Abuse

De Biasi, Mariella -- Baylor College of Medicine
Stress, Anxiety, and Nicotine Withdrawal

De La Garza, Richard -- Baylor College of Medicine
Rivastigmine and Huperzine A as Potential Treatments for Cocaine Addiction

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

Des Jarlais, Don C. -- Beth Israel Medical Center (New York)
Risk Factors for HIV/AIDS in Drug Users

Desai, Rajeev I. -- Mc Lean Hospital (Belmont, MA)
Nicotinic Modulation of Methamphetamine's Behavioral and Neurochemical Effects

Deutch, Ariel Y. -- Vanderbilt University
The Role of Claustrum in Substance Abuse and Cognition

Deutsch, Dale G. -- State University New York (Stony Brook)
Endocannabinoid Inactivation: Plasma Membrane Uptake and Cellular Trafficking

Deutsch, Dale G. -- State University New York (Stony Brook)
The Biosynthesis of Anandamide

Deutsch, Dale G. -- State University New York (Stony Brook)
Endocannabinoid Intracellular Transporters

Dierker, Lisa C. -- Wesleyan University
Individual Differences in Smoking Exposure and Nicotine Dependence Sensitivity

Dileone, Ralph J. -- Yale University
Development of Neuronal Tracers to Study Leptin Modulation of Dopamine Circuits

Dillon, Glenn H. -- University of North Texas Health Science Center
Mechanisms of Carisoprodol Abuse

Dimmitt Champion, Jane -- University of Texas Health Science Center (San Antonio)
Translation of Interventions for Rural Mexican-American Adolescent Women

Dodge, Kenneth A. -- Duke University
Development and Prevention of Substance Abuse Problems

Doherty, Irene A. -- University of North Carolina (Chapel Hill)
The Nexus of Drugs, Sex Networks, HIV and Syphilis in Young African American MSM

Dominguez, Juan M. -- University of Texas (Austin)
A Role for the Medial Preoptic Area in Regulating Gender-Sensitive Differences...

Dorn, Lorah D. -- Children's Hospital Medical Center (Cincinnati)
Metabolic Consequences of Substance Use in Adolescent Girls

Dow-Edwards, Diana L. -- SUNY Downstate Medical Center
Binge Cocaine during Pregnancy in the Rat

Draine, Jeffrey N. -- University of Pennsylvania
Education and Empowerment Intervention for HIV Prevention In and Out of Jail

Drobes, David J. -- H. Lee Moffitt Cancer Center and Research Institute
Influence of Smoking Abstinence and Age on ERP Indices of Attentional Control

D'souza, Deepak Cyril -- Yale University
Imaging Nicotinic Acetylcholine Receptors in Schizophrenia

Dunlap, Laura J. -- Research Triangle Institute
Evaluation of a Web-Based Instrument for Service-Level Cost Estimation in Drug Abuse

Eby, Lillian T. -- University of Georgia (UGA)
Understanding the Adoption and Implementation of Tobacco-Free Regulation in..

Eisch, Amelia J. -- University of Texas S.W. Medical Center (Dallas)
Opiates and Adult Neurogenesis

El-Hage, Nazira -- Virginia Commonwealth University
Oxidative Damage and Proteasome Activity: Role of Opioid in HIV-HCV Infection

Elmer, Gregory I. -- University of Maryland (Baltimore)
Pattern Array: In Vivo Mining for Novel Psychoactive Drug Discovery

Engstrom, Malitta V. -- University of Chicago
Family Therapy Development for Incarcerated Mothers with Substance Use Disorders

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

Evans, David E. -- H. Lee Moffitt Cancer Center and Research Institute
Automatic Attention to Smoking Cues: Neural Correlates

Evans, David E. -- H. Lee Moffitt Cancer Center and Research Institute
Genetic Moderation of Attentional Deficits Resulting from Nicotine Withdrawal

Everall, Ian Paul -- University of California (San Diego)
COMT Genotype and Executive Function in HIV Infection and Methamphetamine Use

Fals-Stewart, William S. -- University of Rochester
Cognitive Rehabilitation for Substance Abusing Adolescents

Fatemi, S. Hossein -- University of Minnesota (Twin Cities)
Varenicline and Smoking Cessation in Schizophrenia

Feinberg, Mark Ethan -- Pennsylvania State University (University Park)
Pilot Study of Sibling Prevention Program

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

Flagel, Shelly Beth -- University of Michigan at Ann Arbor
Individual Differences in Incentive Salience Attribution: Relevance to Addiction

Flanagan, Constance A. -- Pennsylvania State University (University Park)
Friends Helping Friends: Socially Responsible ATOD Prevention

Flower, E. Keith -- California Pacific Medical Center Research Institute
A Pilot Trial of Naltrexone for Methamphetamine Addiction - Role of the A118G SNP

Floyd, Leah -- Johns Hopkins University
Race and HIV-Risk: Contextual and Neurocognitive Influences on Sex Partnerships

Foley, Kristie L. -- Davidson College
Implementation and Dissemination of Tobacco Cessation Strategies in Free Clinics

Franklin, Teresa R. -- University of Pennsylvana
Dopaminergic Variants Involved in Smoking Behavior: A Perfusion fMRI Study

Friedman, Samuel R. -- National Development and Research Institutes
Community Vulnerability and Responses to Drug-User-Related HIV/AIDS

Friedmann, Peter D. -- Rhode Island Hospital (Providence, RI)
Continuum of Care for Drug-Involved Offenders

Froeliger, Brett -- Duke University
Neuropharmacology of Emotion-Cognition Interaction in Nicotine Dependence

Galli, Aurelio Antonio -- Vanderbilt University
Molecular Mechanisms of Stimulant Abuse

Garofalo, Robert -- Children's Memorial Hospital (Chicago)
Syndemic Development and HIV Risk among Vulnerable Young Men

Gentry, W Brooks -- University of Arkansas Medical Sciences (Little Rock)
Monoamine Antagonist Therapies for Methamphetamine Abuse

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

Geppert, Cynthia Ann Martha -- Biomedical Research Institute of New Mexico
A Survey Study of Informed Consent Processes in Addiction Treatment

Girdler, Susan S. -- University of North Carolina (Chapel Hill)
Stress Responses, Psychosocial Stress and Pain Perception in African Americans

Glass, Michael J. -- Weill Medical College of Cornell University
Glutamate Receptors and Opioid Dependence: Molecules, Circuits and Behavior

Glass, Michael J. -- Weill Medical College of Cornell University
Amygdala AMPA GLuR2 Deletion and Opioid Dependence

Gold, Jeffrey Ira -- Children's Hospital (Los Angeles)
Virtual Reality Analgesia: Using fMRI to Explore the Central Mechanisms of..

Golub, Sarit A. -- Hunter College
Neurocognitive Deficits, Substance Use, and HIV Risk Behavior

Gonzalez-Haddad, Gerardo -- University of Massachusetts Medical School (Worcester)
Memantine-Enhanced Buprenorphine Treatment for Opioid-Dependent Young Adults

Goodwin, Amy K. -- Johns Hopkins University
Hallucinogen Self-Administration in Baboons

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

Gray, Kevin M. -- Medical University of South Carolina
A Controlled Trial of N-Acetylcysteine (NAC) in Cannabis Dependent Adolescents

Green, Alan I. -- Dartmouth College
Cannabis and Schizophrenia: Self-Medication and Agonist Treatment?

Green, Kerry M. -- University of Maryland (College Park Campus)
Substance Use and Psychological Problems among African Americans into Midlife

Greenwald, Mark K. -- Wayne State University
Human Laboratory Model of Cocaine Treatment: Behavioral Economic Analysis

Grigson, Patricia Sue -- Pennsylvania State University (Hershey Medical Center)
Drugs of Abuse, Reward Comparison, and the Thalamus

Grucza, Richard A. -- Washington University
Early Substance Use and Addiction: Genes, Environment, and Epidemiology

Gu, Howard H. -- Ohio State University
Mechanism of Drug Addiction

Gu, Howard H. -- Ohio State University
Cocaine Degrading Enzymes from Pest Insects of Coca Plants

Guydish, Joseph R. -- University of California (San Francisco)
Impact of Core Implementation Components on Adoption

Halkitis, Perry N. -- New York University
Syndemic Production among Emergent Adult Men

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

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

Hansen, William B. -- Tanglewood Research, Inc.
The Impact of Adaptation on Successful Implementation

Hao, Shuanglin -- University of Michigan at Ann Arbor
Pathogenesis and Therapy of HIV-Related Neuropathic Pain

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The Role of Nicotinic Receptors in Nicotine Withdrawal

Tarantino, Lisa M. -- University of North Carolina (Chapel Hill)
Organismal and Genetic Networks in Drug Reward and Reinforcement

Taxman, Faye S. -- George Mason University
Action Research to Advance Implementation in the CJS: CJ-DATS 2 Continuation

Taylor, Jane R. -- Yale University
Incentive Motivation and Addiction: PKA Mechanisms

Terman, Gregory W. -- University of Washington
Modulation of Pruritus by Spinal Cannabinoids

Teruya, Cheryl -- University of California (Los Angeles)
Exploring Proposition 36 as a Turning Point in Life Course Drug Use Trajectories

Tesche, Claudia Denke -- University of New Mexico
The Neuroscience of Motivational Interviewing Change Talk

Thakur, Ganeshsingh Arjunsingh -- Northeastern University
Allosteric Modulators of CB1 Cannabinoid Receptor

Tidey, Jennifer W. -- Brown University
Smoking Abstinence and Lapse Effects in Smokers with Schizophrenia and Controls

Tiedge, Henri -- SUNY Downstate Medical Center
Small RNAs in Neurons

Tolma, Eleni L. -- University of Oklahoma Health Sciences Center
A Longitudinal Analysis of Gender, Youth Assets and Adolescent Substance Use

Tracy, Elizabeth M. -- Case Western Reserve University
Role of Personal Social Networks in Post Treatment Functioning

Trickett, Penelope K. -- University of Southern California
From Child Maltreatment to Adolescent Substance Abuse: Risks, Protective Factors

Tsao, Jennie C. -- University of California Los Angeles
Pain, Psychological Symptoms, and Prescription/Illicit Drug Use in the MACS

Vandrey, Ryan G. -- Johns Hopkins University
Efficacy and Safety of Dronabinol (Oral THC) for Treating Cannabis Dependence

Vaughan, Roxanne A. -- University of North Dakota
Phosphorylation and Regulation of Dopamine Transporters

Visher, Christy A. -- University of Delaware
Implementing Effective HIV/Drug Treatment in Corrections - MidStates CJ-DATS Center

Vitaliano, Gordana D. -- Mc Lean Hospital (Belmont, MA)
New Dopamine Transporter MRI Nanoprobes for Addiction Research

Vorel, Stanislav R. -- New York State Psychiatric Institute
NMDA Glutamate Receptor Transmission in Extinction of Cocaine-Seeking Behavior

Vulchanova, Lyudmila H. -- University of Minnesota (Twin Cities)
The Neurosecretory Protein VGF: Contributions to Pain

Wagner, Eric F. -- Florida International University
Brief Intervention for Marijuana Use among Latino Youth

Wagner, John J. -- University of Georgia (UGA)
Cocaine-Induced Metaplasticity in the Hippocampus

Wakschlag, Lauren S. -- University of Illinois at Chicago
Prenatal Smoking and the Substrates of Disruptive Behavior in Early Life

Walker-Schramm, Denise D. -- University of Washington
Marijuana Dependence Treatment PRN

Walsh, Sharon L. -- University of Kentucky
New Neural Targets for Opioid Use Disorders: Human Studies

Wang, Fan -- Duke University
Genetically Encoded Anatomical Probes for Neuronal Activity and Plasticity

Wang, Gene-Jack -- Brookhaven Science Associates - Brookhaven Lab
Studies in Cocaine Abuse

Warren, Keith Leverett -- Ohio State University
Maintenance and Correlates of Cooperative Behavior in Therapeutic Communities

Weiss, Stanley Jerome -- American University
Incentive Properties of Abused Drugs

Werch, Chudley E. -- University of Florida
Multiple Behavior SBIRT Model of Drug Abuse among Emerging Adults in Primary Care

Whistler, Jennifer L. -- Ernest Gallo Clinic and Research Center
Trafficking and Signaling of Opioid Receptor Subtypes and Heterodimers

Whiteaker, Paul -- St. Joseph's Hospital and Medical Center
Construction & Expression of Concatemeric Alpha6beta2 Nicotinic Acetycholine Recept

Wiebe, Sandra A. -- University of Nebraska (Lincoln)
Prenatal Tobacco Exposure, Self Regulation, Externalizing Behaviors in Early Childhood

Wilcox, George Latimer -- University of Minnesota (Twin Cities)
Phosphoproteomics of Opioid Tolerance

Wiley, Jenny L. -- Virginia Commonwealth University
Endogenous Cannabinoids and Brain Function

Williams, Chyvette -- University of Illinois at Chicago
Formative Research to Understand High-Risk Community Sex Networks

Williams, Jill M. -- University of Medicine/Dentistry of New Jersey
Double-Blind Placebo-Controlled Trial of Nicotine Nasal Spray

Williams, John T. -- Oregon Health and Science University
Agonist Selective Activation of Mu-Opioid Receptors

Winder, Danny G. -- Vanderbilt University
Physiology of Periaqueductal Gray Dopamine Neurons

Wood, David A. -- Beth Israel Deaconess Medical Center
Neural Mechanisms of the Methamphetamine-Sensitive Circadian Oscillator

Woodall, W. Gill -- University of New Mexico
Web-Based Substance Abuse STD/HIV Prevention

Woodward, John J. -- Medical University of South Carolina
Neural Actions of Toluene

Woody, George E. -- University of Pennsylvania
Suboxone and Methadone for HIV Risk Reduction in Subutex Injectors

Woolverton, William L. -- University of Mississippi Medical Center
Temporal Discounting of Punishment of Drug Choice

Wu, Li-Tzy T. -- Duke University
Classification of Substance Use Severity and Treatment Outcomes: NIDA CTN Studies

Wu, Ping -- New York State Psychiatric Institute
Drug Abuse, Criminal Justice System Involvement and Health Disparities in Youth

Xu, Ming -- University of Chicago
Extinction of Cue-Elicited Cocaine Seeking

Yang, Xinmai -- University of Kansas (Lawrence)
The Assessment of Brain Functional Alterations Due to Drug Abuse/Addiction with PAI

Yin, Hang -- University of Colorado at Boulder
Transforming Clinical Pain Control by Targeting a Novel Non-Neuronal Receptor

Yin, Hang -- University of Colorado at Boulder
Optimizing the Clinical Efficacy of Opioids by TLR4 Blockade

Yoder, Karmen K. -- Indiana University (Purdue University at Indianapolis)
Assessment of the Dopamine System in Fibromyalgia

Zahniser, Nancy Rutledge -- University of Colorado Denver
Individual Differences in Cocaine Activation/Reward and the Dopamine Transporter

Zhang, Yan -- Virginia Commonwealth University
Non-Peptide Mu Opioid Receptor Selective Antagonists

Zhang, Yanan -- Research Triangle Institute
Bivalent Ligands as Molecular Probes for CB1/OX1 Receptor Heterodimers

Zhdanova, Irina V. -- Boston University Medical Campus
Circadian System and Prenatal Cocaine in Zebrafish

Zheng, Guangrong -- University of Kentucky
Development of Antagonists for M5 Muscarinic Acetylcholine Receptor

Zhu, Jun -- University of South Carolina at Columbia
Role of Dopamine Transporter: HIV-1 Tat Protein and Nicotine Sensitization

Zhu, Jun -- University of South Carolina at Columbia
Role of DARPP-32: Individual Responsiveness to Nicotine

Zjawiony, Jordan K. -- University of Mississippi
Chemistry and Pharmacology of Newly Emerging Psychoactive Plants

Zucker, Robert A. -- University of Michigan at Ann Arbor
Brain Endophenotypes Modulating Drug Abuse Risk

Zule, William A. -- Research Triangle Institute
The Role of Dead Space Syringes in HIV Epidemics Amount IDU's - Drug Abuse Aspect

Zule, William A. -- Research Triangle Institute
A Tailored Cue-Card Driven HIV/STI Intervention for High Risk Groups Pilot Study

Director's Report to the National Advisory Council on Drug Abuse - September, 2009

Extramural Policy and Review Activities

Receipt, Referral, and Review

NIDA received 2,868 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 2,005 applications, including 580 Challenge Grant Applications (RC1) and 127 Grand Opportunity Grant Applications (RC2).

OEA arranged and managed 37 grant review meetings in which 737 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 18 contract proposal review meetings.

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 33 Special Emphasis Panels to review grant applications for a variety of reasons:

- Recovery Act Limited Competitions for NIH Grants (RC2 & P30)
- Conflicts with the chartered committees
- Program Project grant applications
- Cutting-Edge Basic Research Awards (CEBRA)
- Behavioral Science Track Award for Rapid Transition (B/START)
- Imaging Science Track Award for Research Transition (I/START)
- Conference Grants (R13)
- Mechanism for Time-Sensitive Research Opportunities
- Requests for Applications (RFAs)
- Loan Repayment Program

OEA managed the following RFA reviews:

- OD09-004 - Recovery Act Limited Competition for NIH Grants: Research and Research Infrastructure Grand Opportunities (RC2)
- OD09-005 - Recovery Act Limited Competition: Biomedical Research Core Centers to Enhance Research Resources (P30)
- DA09-008/009 - Brain Imaging Studies of Negative Reinforcement in Humans (R01 & R21)
- DA09-011 - 2009 NIDA Avant-Garde Award Program for HIV/AIDS Research

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(DP1)

- DA09-012 - Exploratory Centers for Translational Research on the Clinical Neurobiology of Drug Addiction (P20)
- DA09-013/014 - Interactions Between Physical Activity and Drug Abuse (R01& R03)
- DA09-015 - The Mouse Gene Development Initiative (R01)
- DA09-016 - Behavioral Pharmacology and Genetics: Translating and Targeting Individual Differences (R03)
- DA09-020 - Secondary Data Analyses for Substance Abuse Research (R21/R33)
- DA09-022 - Biosignatures of Chronic Drug Exposure (R21)

Completed contract-related review activity from the Contracts Review Branch since the last Council includes:

R&D and non-R&D Contract Reviews

- NO1DA-9-2217 - NIDA Center for Genetic Studies
- N01DA-9-8882 - Drug Testing for Clinical Trials
- N01DA-9-8891 - In Vitro Metabolism
- N01DA-9-1139 - Communications Support
- N01DA-9-1141 - Media Support
- N01DA-10-7772 - Preparation and Distribution of Research Drug Products

Phase II SBIR Contract Reviews

- N44DA-9-8874 - Novel Azetidine CB1 Antagonists
- N44DA-9-8869 - Long Acting Buprenorphine for Opiate Maintenance

Phase I SBIR Contract Reviews

- N43DA-10-1205 - International Activities
- N43DA-10-2218 - New Technologies: Integrating Data from Prescription Monitoring Program(s) to Current Clinical Practice
- N43DA-10-2219 - Development of Innovative Techniques/Tools for the Screening, Recruitment and Follow-up of Clinical Trial Participants
- N43DA-10-2220 - Innovative Diagnostic Drug Screening Tests for Drugs of Abuse
- N43DA-10-5555 - Tools to Promote Security and Appropriate Prescribing of Scheduled Prescription Drugs
- N43DA-10-5556 - Marketing Evidence-Based Prevention Interventions for Substance Abuse Prevention
- N43DA-10-5558 - Development of State-of-the-Art Mechanisms for Epidemiological Records
- N43DA-10-5559 - Using Handheld Devices to Support Recovery
- N43DA-10-7774 - Rapid and Sensitive Method for the Determination of Nicotine & its Major Metabolites Cotinine and trans-3'-hydroxycotinine, in Biological Fluids: A Personalized Medicine Approach for Smoking Cessation
- N43DA-10-7776 - Development of Alternate Drug Delivery Dosage Forms for Drug Abuse Studies

CTN-Related Review Activities

The Protocol Monitoring Board met May 7, 2009 to discuss study proposal CTN 0046, Smoking-Cessation and Stimulant Treatment (S-CAST): Evaluation of

the Impact of Concurrent Outpatient Smoking-Cessation and Stimulant Treatment on Stimulant-Dependence Outcomes.

The Data and Safety Monitoring Board(s) met:

- May 5, 2009, to discuss the progress of study protocol 0032, HIV Rapid Testing and Counseling in Drug Abuse Treatment Programs in the U.S.
- May 26, 2009 to discuss study proposal CTN 0037, Exercise as a Treatment for Substance Use Disorders.
- June 8, 2009, to discuss study proposal CTN 0044, Web-delivery of Evidence-Based, Psychosocial Treatment for Substance Use Disorders.

Certificates of Confidentiality

Between March 7, 2009 and August 10, 2009, OEA processed 125 Certificate of Confidentiality applications, including 29 amendments for either extension of expiration date or protocol change.

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Congressional Affairs (Prepared September 4, 2009)

Appropriations

(Thanks to Anne Houser of NIH/OLPA for the bulk of this information)
As of the beginning of the August recess, the FY2010 Appropriations action for NIH is as follows: the House passed its bill, H.R. 3293, on July 24. The Senate companion, bearing the same number, was reported from the Senate Appropriations Committee on July 30. Floor action in the Senate will occur after the recess.

- The House bill would appropriate $31,258,788,000 to NIH, which is $941,764,000 above the comparable FY2009 level and $500,000,000 above the President's budget request; rather than provide a specific funding level for cancer and autism as requested in the President's budget, recommends a funding level which provides "a comparable inflationary adjustment to the fiscal year 2009 levels for each institute and center to offset biomedical research inflation." The House bill would also provide a 2 percent stipend increase for research training grants; $534,066,000 for the Common Fund; $194,400,000 for the National Children's Study [NCS]; and $5,000,000 for the new bioethics research and training initiative. The House bill allocates $1,069,583,000 to NIDA, an increase of $36,824,000, or approximately 3.5%, over the FY 2009 level.
- The Senate bill would appropriate $30,758,788,000 to NIH, an increase of $441,764,000 over the level in the FY 2009 health appropriations bill, and equal to the President's budget request. This bill rejects the administration's proposals to earmark an increase of $268,000,000 for research on cancer and an increase of $19,000,000 for research on autism; would provide $549,066,000 for the Common Fund, the same amount as the budget request; did not provide a specific amount of funding for the NCS, stating that a decision about specific funding level, if any, for the NCS would be decided at conference. The Senate bill allocates $1,050,091,000 to NIDA, an increase of 17,332,000, or approximately 1.7%, over the FY 2009 level.

NOTE: (text from NIH) For the House bill, the rule under which debate occurred permitted five amendments to the bill, two of which pertain in some way to NIDA.

- Issa (R-CA)--Accepted without vote--Would defund three National Institutes of Health grants that support behavioral research on preventing the transmission of HIV/AIDS. The grants focus on: (1) the factors that put Thai prostitutes at special risk of HIV (a NIDA grant); (2) decreasing high-risk HIV behaviors among Russian alcoholics; and (3) an intervention program targeting HIV risk and alcohol use among Chinese prostitutes. (The Senate bill does not include this language. Final resolution will occur when the House and Senate "conference" their respective bills.

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- Souder (R-IN)--Defeated--Would have prohibited funding in the Act from being used to carry out needle exchange programs. Mr. Obey mentioned that many prominent scientific and public health leaders have endorsed needle exchange programs as an effective public health intervention, based on scientific research, to reduce the incidence of HIV and other diseases, including Dr. Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases; Thomas Frieden, the Director of the CDC; former NIH Director Harold Varmus; former Surgeons General C. Everett Koop and David Satcher; and former HHS Secretary, Dr. Louis Sullivan. Dr. Fauci, who is one of the world's leading experts on HIV/AIDS very succinctly stated in Congressional testimony in 2008, "Clearly needle exchange programs work. There is no doubt about that." The underlying bill permits Federal funds to be used for needle exchange programs, provided that such programs are NOT located within 1,000 feet of a day care center, school, college or university, or any public swimming pool, park, playground, video arcade, or youth center, or an event sponsored by any such entity."

Transition - Executive Branch

The Senate has confirmed:

- Dr. Francis S. Collins to be Director, National Institutes of Health
- Gil Kerlikowske to be Director, Office of National Drug Control Policy
- Dr. A. Thomas McLellan to be Deputy Director, Office of National Drug Control Policy

Legislation of Particular Interest

Health Reform - This topic has recently trumped most others in the current Congress. Future Reports to Council will include more detail specific to issues of particular relevance to the substance abuse and addiction field. Text below is provided by NIH/OLPA:

H.R. 3200 - On July 31, the House Committee on Energy and Commerce approved, by a vote of 31 - 28, an amendment in the nature of a substitute to H.R. 3200, the America's Affordable Health Choices Act of 2009, after multiple mark-up sessions and after many amendments were adopted. H.R. 3200 was approved by the House Committees on Ways and Means and Education and Labor on July 17th. NIH provisions are as follows:

- Division B, Title IV, Subtitle A contains comparative effectiveness research (CER) provisions which would establish a Center for CER within AHRQ, a CER Commission to oversee and evaluate the Center's activities, and a trust fund to pay for the research the Center would support. The following three CER amendments were adopted by voice vote which would:
    - prohibit research conducted, supported, or developed by the Center, the Commission, or the Federal Coordinating Council for Comparative Effectiveness Research (established by ARRA-NIH has representatives on this Council) from being used to deny or ration care. [Offered by Representative Mike Rogers (R-MI)].
    - prohibit CMS from using Federally-funded CER data to make coverage determinations on the basis of cost. [Offered by Representative Phil Gingrey (R-GA)].
    - require that, in developing best practices, the Commission or Center consult with "specialty colleges and academies of medicine." Any recommendations made or best practices developed by the Commission or Center must be based upon evidence-based medicine and must not violate standards and protocols of clinical excellence of the specialty

colleges and academies. [Offered by Representative Tim Murphy (R-PA)]

- Division C, Title III, would require CDC, NIH, and other HHS agencies conducting or supporting prevention and wellness research to take into consideration the "National Prevention and Wellness Strategy" report also required under the bill as well as take into consideration recommendations of the Task Force on Clinical Preventive Services and the Task Force on Community Preventive Services.

    - The substitute amendment contains new language in Division C that NCMHD be represented on both these task forces.
    - An amendment offered by Representative Mike Doyle (D-PA) and agreed to by voice vote, adds a new subtitle to Division C that would require the Secretary of HHS, in consultation with the Interagency Autism Coordinating Committee, to award national training initiative supplemental grants to University Centers for Excellence in Developmental Disabilities.
- An Amendment En Bloc offered by Representative by Pallone, agreed to by voice vote, would add the following pain and postpartum depression research provisions to Division C, Title V:

    - Subtitle M of Division C, as added by this amendment, would amend the PHS Act to encourage the Director of NIH to continue and expand, through the Pain Consortium, an aggressive research program on the causes of and potential treatments for pain. The Pain Consortium, in consultation with DPCPSI, would be required to make recommendations on pain research initiatives that could be paid for by the Common Fund. In addition, the Secretary would be required to hold a conference and to establish an interagency pain research consortium and be required to establish a pain research national education outreach and awareness campaign.
    - Subtitle N contains a sense of the Congress that the Director of NIMH may conduct a longitudinal study on the relative mental health consequences for women of resolving a pregnancy in various ways. Provisions in this subtitle also would encourage the Secretary to continue research to expand the understanding of the causes of, and treatments for, postpartum conditions and require the Secretary to conduct a study on the benefits of screening for postpartum conditions.

Bills of Interest

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

H.R. 2354 - On May 12, Representative Janice Schakowsky (D-IL) introduced the Health Promotion Funding Integrated Research, Synthesis, and Training Act or the Health Promotion FIRST Act. Provisions relevant to NIH would require the Director of NIH, acting through OBSSR, to develop a plan on how best to develop the science of health promotion at the agency. The plan must provide for the allocation of resources for the research. The bill would also require the Director of NIH, acting through OBSSR, to conduct or support early research programs and research training regarding health promotion. The bill was referred to the House Committee on Energy and Commerce. See S. 1001

H.R. 2369 - On May 12, Representative Patrick Kennedy (D-RI) introduced the Improving the Quality of Mental and Substance Use Health Care Act of 2009, to improve mental and substance use health care. The bill was referred to the Energy and Commerce Committee.

H.R. 2502 - On May 19, Representative Kurt Schrader (D-OR) introduced the

Comparative Effectiveness Research (CER) Act of 2009. The bill would establish a nonprofit corporation called the Health Care Comparative Effectiveness Research Institute to contract with appropriate Federal agencies or the private sector to conduct comparative effectiveness research. The Institute would be responsible for (1) establishing and carrying out a research project agenda [in carrying out a research agenda, Institute is authorized to enter into contracts with Federal government agencies with experience in conducting CER], (2) establishing a methodology committee to develop scientifically-based methodological standards for comparative clinical effectiveness research [would be required to consult or contract with IOM, AHRQ, NIH (can contract with one or more) in developing and updating standards], and (3) ensuring that there is a process for peer-review of the research [Institute would be authorized to use existing peer-review processes used by entities with which the Institute contracts]. Provisions would also establish a Board of Governors comprising 21 members, including the Secretary of HHS, the Director of AHRQ and the Director of NIH, to over-see the Institute's activities. The legislation would create the Comparative Effectiveness Research Trust Fund in the U.S. Treasury. The Trust Fund would be financed through fees on Medicare and private health insurance plans, in addition to transferring CER funds in ARRA (P.L. 111-5) not already obligated or expended. Funding for the Institute would sunset after 10 years. H.R. 2502 was jointly referred to the House Committees on Energy and Commerce and Ways and Means.

H.R. 2835 - On June 11, Representative Barney Frank (D-MA) introduced the Medical Marijuana Patient Protection Act, to provide for the medical use of marijuana in accordance with the laws of the various States. The bill was referred to the Energy and Commerce Committee.

H.R. 2818 - On June 11, Representative Jerry McNerney (D-CA) introduced the Methamphetamine Education, Treatment, and Hope Act of 2009, to amend the Public Health Service Act to provide for the establishment of a drug-free workplace information clearinghouse, to support residential methamphetamine treatment programs for pregnant and parenting women, to improve the prevention and treatment of methamphetamine addiction, and for other purposes. The bill was referred to the Energy and Commerce Committee.

H.R. 2906 - On June 16, Representative Jim Moran (D-VA) introduced the Comprehensive Problem Gambling Act of 2009, to amend the Public Health Service Act to specifically include problem and pathological gambling in programs of the Substance Abuse and Mental Health Services Administration and to establish a national program to address the harmful consequences of problem gambling. The bill was referred to the Energy and Commerce Committee.

H.R. 2943 - On June 18, Representative Barney Frank (D-MA) introduced the Personal Use of Marijuana by Responsible Adults Act of 2009, to, eliminate most federal penalties for possession of marijuana for personal use, and for other purposes. The bill was referred to the Judiciary and Energy and Commerce Committees.

H.R. 2965 - On July 8, by a vote of 386-41, the House passed H.R. 2965, the Enhancing Small Business Research and Innovation Act of 2009, which was introduced by Representative Jason Altmire (D-PA). The House adopted 5 amendments to the reported bill, which included the Manager's Amendments (to give priority to rural businesses, renewable energy, water conservation technology, places hardest hit by the economic downturn, and improve oversight of the SBIR program). Other amendments adopted would (1) require GAO to examine and report to Congress on the effect that venture capital (VC) ownership restrictions in the bill (VC operating companies investment in small businesses) have on eligibility and participation under this act (Rep. Brown-Waite); (2) require agencies with space shuttle activities to help small businesses (Rep. Kosmas); (3) give preference to organizations that are

located in underrepresented states and regions, or are owned by women, minorities, or disabled veterans when awarding grants for SBA outreach efforts (Rep. Reichert); and (4) add medical technology to the list of topics that deserve special consideration as SBIR research topics (Rep. Paulson).

As reported from the House Committee on Small Business and the House Committee on Science and Technology, the bill would permit VC capital-backed small businesses to receive funding from the SBIR and Small Business Technology Research (STTR) programs. The bill does not include any set-aside increases as does the Senate reauthorization bill, S. 1233. H.R. 2965 contains a short time-limited reauthorization for the SBIR and STTR programs, only through Fiscal Year 2011 (the current extension of the SBIR/STTR programs expired July 30, 2009). As reported, the bill would increase small business award levels as follows: $250,000 from $100,000 for participation in the Phase I level and $2 million from $750,000 for participation in Phase II. The bill would also allow small businesses to receive more than one Phase II award and require that in order to receive a Phase II award, the business must have already received a Phase I award. Additionally, the agency would have to engage with small business awardees that received multiple Phase I awards, but no Phase II awards, in order to develop performance measures with respect to progression in the SBIR program. Other features include the following:

- Eligibility Requirements for Venture Capital. The bill would provide that for determining eligibility for SBIR and STTR programs, the following must apply:
    - A business cannot have more than 500 employees.
    - Venture capital operating company (VCOC) backed small businesses would qualify for the program only if the VCOC does not own more than 50 percent of the small business or employees of that VCOC do not constitute a majority of the board of directors for that business.
    - If the VCOC is controlled by a business with more than 500 employees, the small business would be eligible to receive funds if no more than two such VCOC's (that have more than 500 employees) back that small business and those VCOC's do not control more than 20 percent of the small business.
- The bill would provide special consideration for small business projects that include energy-related research, rare disease-related research, transportation and infrastructure research and research related to nanotechnology.
- The bill has a number of other provisions including new criteria for awards; a requirement for SBA to create by regulation a process in which each agency conducts at least two rounds of SBIR research solicitations per year and would render a decision on each proposal within 90 days; and new reports and databases, one of which would require that the government database of SBIR and STTR programs include information on the ownership structure of award recipients. It would require that small businesses participating in the program provide updated information on structure.
- An amendment offered in the Small Business mark up would incorporate an evaluation program within both the SBIR and STTR programs to measure performance and track development of individual agency programs.

H.R. 3001 - On June 23, Representative Tammy Baldwin (D-WI) introduced the Ending LGBT Health Disparities Act. H.R. 3001 would require the collection of sexual and gender minority data from each health related program operated by or that receives funding from the Department of Health and Human Services. The bill also would require the Secretary, acting through the Secretary of LGBT Health (a position that would be established by the bill), and

the Directors of the Agency for Health Quality and Research and the NIH, to develop plans to expand existing research into health disparities to include those experienced by sexual and gender minority populations. H.R. 3001 was referred to the House Committees on Energy and Commerce, Armed Services, Judiciary, Ways and Means, Oversight and Government Reform, House Administration, Veterans' Affairs, Transportation and Infrastructure, Intelligence and Foreign Affairs.

H.R. 3002 - On June 23, Representative John Boehner (R-OH) introduced the Preserving Access to Targeted, Individualized, and Effective new Treatments and Services (PATIENTS) Act of 2009. The bill would prohibit the Secretary of HHS from using data obtained from comparative effectiveness research (CER), including CER research funded by P.L. 111-5, the American Recovery and Reinvestment Act (ARRA), to deny coverage under a Federal health care program. The Secretary would also be tasked with ensuring that CER conducted or supported by the Federal Government accounts for factors contributing to differences in the treatment response and treatment preferences of patients, including patient-reported outcomes, genomics and personalized medicine, the unique needs of health disparity populations, and indirect patient benefits. The bill was jointly referred to the House Committees on Energy and Commerce and Ways and Means. See S. 1259

H.R. 3065 - On June 26, Representative Jan Schakowsky introduced the Mental Illness Chronic Care Improvement Act of 2009, to establish a chronic care improvement demonstration program for Medicaid beneficiaries with severe mental illnesses, including co-occurring substance use disorders. The bill was referred to the Energy and Commerce Committee. See S.1136

H.R. 3075 - On June 26, Representative John Lewis (D-GA) introduced the National Parents Corps Act of 2009, to establish a National Parents Corps Program, and for other purposes. The bill was referred to the Education and Labor Committee.

H.R. 3245 - On July 16, Representative Bobby Scott (D-VA) introduced the Fairness in Cocaine Sentencing Act of 2009, to amend the Controlled Substances Act and the Controlled Substances Import and Export Act regarding penalties for cocaine offences. This bill would effectively equalize federal cocaine sentencing for crack vs. powdered cocaine. The bill was reported out by the Judiciary Committee and is pending in the Energy and Commerce Committee. See H.R. 1459

H.R. 3400 - On July 30, Representative Tom Price (R-GA) introduced the Empowering Patients First Act. Section 801 would (1) prohibit the Secretary of HHS from using data obtained from CER, including research conducted or supported using funds appropriated under ARRA, to deny coverage of an item or service under a Federal health care program; (2) require the Secretary to ensure that CER conducted or supported by the Federal Government accounts for factors contribu-ting to differences in the treatment response and treatment preferences of patients, including patient-reported outcomes, genomics and personalized medicine, the unique needs of health disparity populations, and indirect patient benefits; and (3) prohibit the Federal Coordinating Council for Comparative Effectiveness Research findings from being released in final form until after consulta-tion with and approval by relevant physician specialty organizations. H.R. 3400 was jointly referred to the House Committees on Energy and Commerce; Ways and Means; Education and Labor; Oversight and Government Reform; Judiciary; Rules; Budget; and Appropriations.

H.R. 3420 - On July 30, Representative Patrick Kennedy (D-RI) introduced the SUPPORT for Sub-stance Use Disorders Act, to improve and enhance substance use disorder programs for members of the armed forces, and for other purposes. The bill was referred to the Armed Services Committee.

H.R. 3475 - On July 31, Representative Randy Forbes (R-VA) introduced H.R. 3475, the Accelerate Cures for Patients Act of 2009. The bill would amend the PHS Act to authorize to be appropriated (in addition to amounts authorized to NIH under Section 402A of the PHS Act) an equal amount for medical research that has the greatest potential for near-term clinical benefit in human patients. H.R. 3475 was referred to the House Committee on Energy and Commerce. S. 1001 - On May 7, Senator Richard Lugar (R-IN) introduced the Health Promotion Funding Integrated Research, Synthesis, and Training Act or the Health Promotion FIRST Act. Provisions relevant to NIH would require the Director of NIH, acting through OBSSR, to develop a plan on how to best develop the science of health promotion at the agency. The plan must provide for the allocation of resources for the research. The bill would also require the Director of NIH, acting through OBSSR, to conduct or support early research programs and research training regarding health promotion. The bill was referred to the Senate HELP Committee.

S. 1058 - On May 14, Senator Mark Udall (D-CO) introduced the Brewers Excise and Economic Relief (BEER) Act of 2009, to amend the Internal Revenue Code of 1986 to reduce the tax on beer to its pre-1991 level, and for other purposes. The bill was referred to the Committee on Finance. See H.R. 836

S. 1136 - On May 21, Senator Debbie Stabenow (D-MI) introduced the Mental Illness Chronic Care Improvement Act of 2009, to establish a chronic care improvement demonstration program for Medicaid beneficiaries with severe mental illnesses, including co-occurring substance use disorders. The bill was referred to the Committee on Finance. See H.R. 3065.

S. 1188 - On June 4, Senator Jack Reed (D-RI) introduced the Community Mental Health Services Improvement Act, to amend the Public Health Service Act with respect to mental health services. The bill was referred to the Committee on Health, Education, Labor and Pensions. See H.R. 1011

S. 1233 - On July 23, the Senate passed S. 1390, the National Defense Authorization Act for Fiscal Year 2010, a bill to authorize appropriations for military activities of the Department of Defense, for military construction, and for defense activities of the Department of Energy, to prescribe military personnel strengths for such fiscal year. Included in this authorization bill, as an amendment, was the full text of the Senate passed bill S. 1233, the SBIR/STTR Reauthorization Act of 2009. This latter measure includes an increase of the SBIR set-aside from 2.5 to 3.5 percent and the increase of the STTR from 0.3 to 0.6, which would bring the total for the program to 4.1 percent. The House passed its version of the National Defense Authorization Act in June; its bill does not include setaside increases. See H.R. 2965

S 1259 - On June 15, Senator John Kyl (R-AZ) introduced the Preserving Access to Targeted, Individualized, and Effective new Treatments and Services (PATIENTS) Act of 2009. The bill would prohibit the Secretary of HHS from using data obtained from comparative effectiveness research (CER), including CER research funded by P.L. 111-5, the American Recovery and Reinvestment Act (ARRA), to deny coverage under a Federal health care program. The Secretary would also be tasked with ensuring that CER conducted or supported by the Federal Government accounts for factors contributing to differences in the treatment response and treatment preferences of patients, including patient-reported outcomes, genomics and personalized medicine, the unique needs of health disparity populations, and indirect patient benefits. The bill was referred to the Committee on Health, Education, Labor and Pensions. See H.R. 3002

S. 1373 - On June 25, Senators Joseph Lieberman (I-CT) and John Cornyn (R-TX) introduced the Federal Research Public Access Act (FRPAA), to require every federal department and agency with an annual extramural research budget of $100 million or more to make their research available to the public

within six months of publication. Senators Cornyn and Lieberman first introduced this legislation in the 109th Congress. The NIH Public Access Policy was established statutorily with the passage of the Consolidated Appropriations Act of 2008, (P.L. 110-161), and became permanent upon passage of the Fiscal 2009 Omnibus Appropriations (P.L. 111-8). The NIH policy requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central (PMC) upon acceptance for publication, and be accessible to the public on PubMed Central no later than 12 months after publication.

Specifically, the FRPAA would:

- Require every researcher with an annual extramural research budget of $100 million or more, whether funded totally or partially by a government department or agency, to submit an electronic copy of the final manuscript that has been accepted for publication in a peer-reviewed journal.
- Ensure that the manuscript is preserved in a stable digital repository maintained by that agency or in another suitable repository that permits free public access, interoperability, and long-term preservation.
- Require that each taxpayer-funded manuscript be made available to the public online and without cost, no later than six months after the article has been published in a peer-reviewed journal. The bill has been referred to the Senate Committee on Homeland Security and Governmental Affairs.

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International Activities

Funding Initiatives

Binational Research Project Builds on NIDA International Fellowships to Study Effectiveness of Counseling and Methadone Maintenance Treatment in Jakarta

Researchers at the University of Pennsylvania and former NIDA IP Fellows from Indonesia have been awarded an R01 grant to conduct a prospective randomized trial to evaluate the effectiveness of integrated drug and HIV counseling among injecting drug users beginning methadone treatment in Indonesia. The team hypothesizes that the structured, low-intensity, cognitive-behavioral drug and risk counseling approach will be more cost effective and result in higher rates of retention in treatment, lower rates of drug use, and lower rates of HIV risk than methadone maintenance treatment as usual. To test these hypotheses, the research team in Jakarta will recruit 300 injecting drug users as they enter treatment at the Drug Dependence Hospital and its five satellite programs. The work expands the collaboration established between the Indonesian Principal Investigator, Adhi Nurhidayat, M.D., during his NIDA INVEST Fellowship at the University of Pennsylvania, and the U.S. Principal Investigator, David Metzger, Ph.D. It will also extend findings from a World Health Organization study on substitution therapy of opiates and HIV/AIDS that was completed by former NIDA Hubert H. Humphrey Fellow Ms. Riza Sarasvita, M.S., M.H.S., and her colleagues at The Drug Dependence Hospital in Jakarta.

Binational Agreement

NIDA and Taipei Medical University Sign Binational Agreement

NIDA and Taipei Medical University, Taiwan, have agreed to cooperate on research into neuroprotection and drug abuse. NIDA Director Dr. Nora D. Volkow and Taipei Medical University President Dr. Wen-Ta Chiu signed a binational agreement to foster research training and research collaborations of mutual interest; further scientific and academic interactions between the two institutions; exchange researchers, trainees, and materials; and to promote lectures, conferences, workshops, and seminars on neuroscience and drug abuse.

NIDA International Forum

NIDA International Forum Focuses on Commonalities of Diseases of Addiction

Drugs. Sex. Gambling. Obesity. Plenary Session speakers at the 14th NIDA International Forum documented the commonalities among these "Disorders of

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Desire," citing clear overlap in implicated brain regions and similar patterns of compulsive self-administration, tolerance, craving, comorbidity, disruption of inhibitory control, and impaired decision-making. NIDA Deputy Director Dr. Timothy Condon reviewed the Institute's priority research areas and reported on the Institute's signature projects to eradicate tobacco addiction and elucidate the genetics of brain development, and initiatives to prevent and treat substance abuse among military personnel and veterans. IP Director Dr. Steven W. Gust chaired the meeting, which was held June 19 - 23, 2009, in Reno, Nevada, as a satellite to the Annual Scientific Meeting of the College on Problems of Drug Dependence (CPDD). More than 250 participants from 48 countries participated in the plenary session, workshops, and networking activities. A joint CPDD/NIDA International Forum poster session featured presentations by 150 U.S. and international researchers. Those abstracts are now available online in the new NIDA International Forum Abstract Database, which permits users to search for abstracts from 2003 through the present by author, title/subject, year, research category (basic science, epidemiology, prevention, or treatment), country, or geographic region (http://www.international.drugabuse.gov /information/abstracts/). Representatives from 10 NIDA components (IP, ARP, CCTN, DBNBR, DCNBR, DESPR, DPMCDA, IRP, Special Populations, and Women and Sex/Gender Differences Research Program) and the Fogarty International Center presented posters summarizing the units' goals, research interests, international focus, and international funding priorities.

Dr. Joseph Frascella, DCNBR, chaired the plenary session on the disorders of desire, which featured presentations by him, Dr. Wim van den Brink, University of Amsterdam, and Dr. Anna Rose Childress, University of Pennsylvania. Concurrent workshops focused on ethical issues in the conduct of research, chaired by Dr. Linda B. Cottler, Washington University; multinational assessment and prevention of inhalant abuse, chaired by Ms. Debra Dell, Canadian Youth Solvent Addiction Committee; new formulations and indications for the pharmacotherapy Naltrexone, co-chaired by Dr. Ivan Montoya, DPMCDA, and Dr. David R. Gastfriend, Alkermes, Inc.; and the interaction of violence and substance use affecting women's treatment and interventions in the global arena, chaired by Dr. Wendee M. Wechsberg, RTI International.

The International Society of Addiction Journal Editors (ISAJE) presented two concurrent breakout sessions focused on practical and ethical issues in publishing addiction science. The session on practical issues, chaired by Dr. Robert L. Balster, editor of *Drug and Alcohol Dependence*, was designed to help published and unpublished researchers choose an appropriate journal, avoid common pitfalls between submission and acceptance, and understand what editors want most from prospective authors. Dr. Thomas F. McGovern, editor-in-chief of *Alcoholism Treatment Quarterly*, chaired the session on ethical issues, which addressed issues such as good citation practices, how to deal with authorship credits, and conflict of interest related to funding sources. Participants received a copy of the newly revised book, *Publishing Addiction Science* (second edition, Babor et al., 2008).

The alumni meeting of the NIDA International Fellowship Programs was co-chaired by Ms. Dale Weiss, IP, and Dr. J. Randy Koch, Virginia Commonwealth University. Dr. David Otiashvili, Union Alternative Georgia, and Dr. George Woody, University of Pennsylvania, discussed how NIDA international fellowships and funding initiatives helped them build a productive international research team. Dr. James E. Herrington, Fogarty International Center, reviewed National Institutes of Health funding opportunities to support global health research.

NIDA/CPDD Satellite on Treating Addiction During Pregnancy

The NIDA International Program also supported a second CPDD satellite, Treating Addiction During Pregnancy: Exploring Multinational Perspectives To

Build a Treatment Approach Consensus. Invitees to the NIDA/CPPD satellite on treating addiction during pregnancy completed a premeeting survey that attracted enthusiastic responses from researchers in 22 different countries on six continents. More than 90 percent of respondents agreed with 11 of 13 proposed principles of drug treatment for pregnant women. Dr. HendrŽe Jones of Johns Hopkins University chaired the meeting; Dr. Gabriele Fischer of the Medical University of Vienna was co-chair. Dr. Marianne Springer-Kremser, Medical University of Vienna, reviewed ethical considerations involved in conducting addiction research with pregnant participants. Three other speakers reviewed research findings on studies of pregnant women in their countries: from Australia, Dr. Lucy Burns, National Drug and Research Centre; from France, Dr. Laurent Gourarier, Maison Blanche Hospital; and from Israel, Dr. Einat Peles, Tel Aviv Sourasky Medical Center.

NIDA International Program Presents Awards of Excellence

During the 2009 NIDA International Forum, the NIDA International Program presented awards to honor mentors, researchers, and binational collaborative teams whose efforts support the International Program mission.

The *Excellence in Mentoring* award was presented to James C. Anthony, M.Sc., Ph.D., Michigan State University, in recognition of his drug dependence epidemiology training programs for U.S. and international researchers. Dr. Anthony has forged a unique partnership with Universidad Peruana Cayetano Heredia in Lima, Peru, where he has made significant contributions to that university's public health research training program, as well as epidemiology research throughout Latin America.

Ian Stolerman, B.Pharm., Ph.D., King's College London, United Kingdom, was honored for *Excellence in International Leadership* for his work as president of the International Society of Addiction Journal Editors, where he helped to establish PARINT.org, which helps authors and peer-reviewers share research results across national and language borders, promotes international recognition of research published in non-English-language journals, and advances international communication within addiction science.

A trio of researchers working to understand HIV risk behaviors among drug users and sex workers on the Mexico-U.S. border was honored for *Excellence in Collaborative Research:* Steffanie A. Strathdee, Ph.D., University of California San Diego; Mar'a Remedios Lozada Romero, M.D., Baja California State, Mexico; and Carlos Magis-Rodr'guez, M.D., M.P.H., CENSIDA, Mexico. An outstanding example of cross-border cooperation, the three have worked effectively to document factors that significantly impact the evolving HIV epidemic in Tijuana. Their public health approach to shared responsibility for recognizing and treating sexually transmitted diseases between bordering countries contributes significantly to improved cross-border HIV prevention, clinical practice, and multidisciplinary global health training programs.

NIDA-Supported Meetings

NIDA Supports International Poster Session at Society for Prevention Research as SPR Launches International Networking Effort

More than 30 scientists from around the world presented their research at the International Poster Session cosponsored by the NIDA IP and DESPR Prevention Research Branch in conjunction with the 17th Annual Meeting of the Society for Prevention Research (SPR), which was held May 26-29, 2009, in Washington, DC. NIDA provided travel awards for 12 international researchers who presented the results of drug abuse prevention research completed in international settings. DESPR Director Dr. Wilson M. Compton told SPR participants that NIDA supported the international poster session because international research helps the Institute explore and extrapolate the commonalities of addiction and develop international scientists. Representing

the IP, Ms. Dale Weiss cited international researchers' important roles in addressing the public health impact of drug abuse and addiction.

Responding to the SPR decision to focus on international research during its 2011 Annual Meeting, 30 scientists from 10 countries met to suggest ways that SPR can help create more effective international research networks. The group suggested that SPR create a social networking site for international prevention researchers; develop an international structure modeled on the SPR Early Career Preventionists Network; diversify the editorial board of the SPR journal Prevention Science and prepare a special issue on international research; organize workshops on publishing research results, grant writing, or international collaboration; provide Continuing Medical Education credits for both U.S. and international participants; propose 2011 conference themes or paper sessions highlighting international research topics such as case studies on the process of building a successful collaboration, prevention in cross-border areas, and prevention among immigrant populations; and cosponsor events with European Union prevention groups.

Dr. Brenda Miller, Prevention Research Center, and Dr. Sven AndrŽasson, Swedish National Institute of Public Health, co-chaired the International Networking session. Dr. Jean Schensul, Institute for Community Research, moderated the discussion of cross-cultural differences; Dr. Harold Holder, Prevention Research Center, moderated the discussion of natural experiments that arise due to national differences in policy; and Dr. Seth Kalichman, University of Connecticut, moderated the discussion of ways to successfully establish international collaborations. Representatives of NIDA, the National Institute on Alcohol Abuse and Alcoholism, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development also participated in the meeting. Prevention scientists interested in participating in the SPR International Network are invited to contact Dr. Miller at bmiller@prev.org or Dr. AndrŽasson at sven.andreasson@ghi.se.

Fellowships

First IAS/NIDA Research Fellows in Drug Abuse and HIV/AIDS Selected

NIDA and the International AIDS Society (IAS) have announced the first two IAS/NIDA Research Fellows in Drug Abuse and HIV/AIDS. Michah Ongeri Oyaro, Ph.D., a research scientist at the University of Nairobi, Kenya, was selected for the 18-month postdoctoral fellowship. Maria Gudelia Rangel, Ph.D., a research associate and professor at El Colegio de la Frontera Norte in Tijuana, Mexico, was selected for the 8-month professional development fellowship for an established HIV researcher not currently working in the drug abuse field. The two $75,000 awards were announced at the IAS Conference on HIV Pathogenesis, Treatment and Prevention, which took place in Cape Town, South Africa, July 19 to 22, 2009. Dr. Oyaro will work with John Wylie, Ph.D., University of Manitoba, Canada, to design and conduct a study of social networks, serostatus, and molecular epidemiology of HIV, hepatitis B, and hepatitis C infections among drug abusers in Kenya. The research findings will inform future vaccine development and immediate intervention measures to address viral transmission through education, immunization, provision of condoms, and treatment strategies. Dr. Rangel has spent more than 15 years working in the field of HIV and migration, and now wishes to re-orient her career to study HIV in the context of substance abuse. She will work with Dr. Steffanie Strathdee, University of California San Diego, to investigate HIV prevalence among clients in substance abuse rehabilitation centers in Baja California, Mexico. The project findings will add significantly to the limited data on HIV among Mexican drug users, with potential implications for Mexican state and national drug policies.

Former HHH Fellow Joins UNAIDS in Bangladesh

Dr. Munir Ahmed, recipient of a 2008-2009 Hubert H. Humphrey (HHH) Drug Abuse Research Fellowship, was recently appointed as the UNAIDS Partnerships and Social Mobilization Adviser for Bangladesh under the Joint United Nations Programme for HIV/AIDS. Dr. Ahmed previously worked with CARE's harm reduction program for injection drug users and heroin smokers and led operations for CARE's HIV program. During his fellowship year, he focused on drug treatment modalities, including self-help groups and treatment for drug overdoses, prevention programs, and drug control policy and legislation. Dr. Ahmed credits his HHH Fellowship with enhancing his competitiveness for the UNAIDS position, which represents a significant career advancement.

Former HHH Fellow Leads Drug Advisory Program for Colombo Plan

Former Humphrey Fellow Mr. Duc Cuu Nguyen, Vietnam, has been named Director of the Drug Advisory Program (DAP) of the Colombo Plan Secretariat. Founded in 1951, the 26-country Colombo Plan is one of the oldest regional intergovernmental organizations in the world and is based in Colombo, Sri Lanka. The Colombo Plan launched DAP in 1973 to strengthen regional capability to participate effectively in international drug control efforts and to prevent drug abuse and illicit drug trafficking. Mr. Nguyen formerly worked on national drug control policy in the Standing Office on Drug Control of Vietnam, responsible for precursor control and international cooperation in the Greater Mekong subregion, and as officer in charge of binational relations with the United States. He focused on drug control issues as well as drug abuse treatment and prevention during his 2006-2007 Humphrey Fellowship.

Travel Support

American Association for the Treatment of Opioid Dependence

NIDA IP provided partial support for 12 scientists from 7 countries to participate in the American Association for the Treatment of Opioid Dependence National Conference, held April 25 - 29, 2009, New York, New York. NIDA-supported participants included: Dr. Orlin Todorov and Dr. Alexander Kantchelov, Bulgaria; Dr. Pascal Courty, Dr. Andre Remy, and Dr. Michel Bourquin, France; Dr. Albrecht Ulmer, Germany; Dr. Icro Maremmani, Italy; Dr. Thomas Clausen, Norway; Dr. Vladimir Mendelevich, Russia; and Dr. Andrej Kastelic, Dr. Barbara Lovrecic, and Dr. Nusa Segrec, Slovenia.

Substance Abuse Librarians and Information Specialists

NIDA IP supported the participation of two speakers at the Substance Abuse Librarians and Information Specialists Conference, Setting Sail: Best Practices for the Next Decade, which was held May 6 - 9, 2009, in Nova Scotia, Canada. Bette Reimer, Research Associate, Centre for Addictions Research of British Columbia, discussed bringing the principles and skills of information science to knowledge exchange activities aimed at supporting evidence-based substance abuse services and decision-making. Anne Welsh, Lecturer in Library and Information Studies, University College, London, reviewed the drug sector's use of Web 2.0 technologies.

Behavioral and Mental Health Research in the Arctic: Strategy Setting Meeting

NIDA provided partial travel support for three researchers who participated in the Behavioral and Mental Health Research in the Arctic: Strategy Setting Meeting, which was held June 2-3, 2009, in Anchorage, Alaska. The NIDA-supported travelers included Lawrence Hamilton, Ph.D., University of New Hampshire; Spero Manson, Ph.D., Director, American Indian and Alaska Native Programs, University of Colorado at Denver and Health Sciences Center; and Lisa Wexler, Ph.D., University of Massachusetts. IP Director Dr. Steven W. Gust also participated in the meeting.

Virtual Seminar Series Features NIDA Division Directors

The NIDA International Program has produced recorded talks to introduce the mission, goals, and international research priorities of each NIDA Division. The online NIDA Division Directors Virtual Seminar Series is a valuable tool for learning more about NIDA, identifying potential research topics of interest to NIDA, or preparing for meetings with NIDA staff.

Video Highlights Online Resources for Communications, Research Collaboration, & Training Tools

A 5-minute video available on the IP Website (http://www.international.drugabuse.gov/collaboration/index.html) highlights four online resources developed for the international drug abuse research community:

- NIDA International Virtual Collaboratory (NIVC), which supports live audio/video virtual meetings, discussion forums linked to an e-mail list-serv, user-built document libraries, secure document-writing and -editing tools, and a searchable Collaboration Matching Service.
- International Drug, Alcohol and Tobacco (IDAT) Research Community, which collects and disseminates research news, provides online training and databases, supports networking tools to facilitate collaborative work, and publishes an online, peer-reviewed journal.
- DrugAbuseResearchTraining.org, which provides free, online courses in biostatistics, evaluating drug and substance abuse programs, and designing and managing clinical trials. Each course includes self-assessment questions, practical examples, and links to resources. Continuing medical education credit and printable copies of the course materials are available for a modest fee.
- Methadone Research Web Guide and Tutorial, which presents U.S. research outcomes about methadone maintenance treatment, reviews best practices in treatment program design and implementation, and disseminates evidence-based treatment protocols. It is designed to answer the most frequently posed questions by the international community regarding the path of research inquiry used by the United States, which could be used by other countries to support approval of methadone as a treatment therapy (www.international.drugabuse.gov/methadone).

International Visitors

Under the auspices of the U.S. Department of State's International Visitor Leadership Program, a group of visitors from Russia came to NIDA on June 25, 2009. The main objective of the program is to provide an opportunity for the visitors to become acquainted with the various addiction prevention and treatment programs in the United States including outreach interventions, mediciation assisted therapy, mental health and psycho-social services. Staff from NIDA that met with the group included Jag Khalsa, Ph.D., DPMCDA, Peter Hartsock, Ph.D., DESPR, Elena Koustova, Ph.D., DBNBR, Jan Lipkin, OSPC, and Dale Weiss, IP. Staff from the NIH Office of AIDS Research, Natalie Tomitch and Amelia Hall also joined the meeting.

Other International Activities

The National Institute on Drug Abuse is recruiting fellows for the 2009 INVEST/CTN research fellowship program. Clinical trial researchers from all non-U.S. countries are encouraged to apply for this opportunity to work with a research mentor at one of the sixteen CTN Regional Research and Training Centers. The deadline for submission of applications was September 1, 2009.

Dr. Shoshana Kahana, along with members of DESPR and DPMCDA, took part in the ARP-sponsored meeting with the CDC and NIMH on Wednesday, June 24,

2009. The meeting was meant to provide participants with an opportunity to meet one another and to encourage future communication and collaboration as well as to facilitate planning of projects and to avoid duplicative research.

Dr. Meyer Glantz, DESPR, represented NIDA and NIH at the World Mental Health Consortium Meeting held in Saratoga Springs, New York, July 22-July 27, 2009. The WMH Consortium is a coordinated multi-national psychiatric epidemiology survey using a standardized assessment and analysis approach. Dr. Glantz presented an analysis of the prevalence and concomitants of the DSM-IV alcohol abuse criteria with particular attention to the implications of including the social consequences criteria in cross national research. The findings suggest that the variability associated with these criteria might be a valuable asset, particularly in economically developing countries, rather than a weakness.

Dr. Peter Hartsock, DESPR, represented NIDA at the Fogarty International Center annual AITRP/ICOHRTA network conference, May 26-27, 2009 held in Bethesda, MD. Dr. Hartsock presented on NIDA/DESPR's latest AIDS modeling research on expanded HIV testing, circumcision, the "HIV Superhighway" (multiple concurrent sexual partnerships), impact of HAART in Russian drug users who are HIV positive, identification and research on TB rates among Mexican drug users who are also HIV positive, and research on influenza (H1N1) risks in this same population.

Dr. Peter Hartsock met with Russian researchers visiting NIDA on June 25, 2009 to discuss NIDA/DESPR's AIDS research program, especially research that focuses on Russian drug abuse and AIDS and on potential opportunities for research applications on the Russian drug abuse and HIV/AIDS problem.

Dr. Ivan Montoya gave a one-day workshop on funding opportunities at NIH at the Colombian Psychiatric Association, in Bogota, Colombia on August 1, 2009.

Dr. Ivan Montoya gave a lecture at the CES Medical School and the Colegio Montessori in Medellin, Colombia on August 3 and 4, 2009, respectively.

Dr. David Gorelick, IRP, served on the International Scientific Program Committee for the 9th World Congress of Biological Psychiatry, held in Paris, France June 28-July 2, 2009.

Dr. David Gorelick met July 3, 2009 with scientists at the Fernand Widal Hospital, Paris, France to discuss their collaborative research on cannabis dependence and gave a scientific presentation on "Brain mu-opioid receptors in cocaine addiction."

Dr. David Gorelick staffed the NIDA IRP poster at the International Poster Forum at the CPDD annual meeting June 22, 2009 in Reno, Nevada, and answered questions from foreign scientists.

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Meetings/Conferences

On July 15, 2009, NIDA's Deputy Director, Dr. Timothy Condon, CTN Director, Dr. Betty Tai, and John Hamilton, CEO of Regional Network of Programs co-chaired a meeting titled: **Program Response to Patient Relapse**. This event provided the opportunity to discuss current treatment policies on relapse; learn more about how the drug abuse and addiction field views and responds to patient relapse across various treatment settings; and provided guidance to NIDA regarding how research and treatment approaches can best serve addicted patients who relapse. This meeting was organized by Drs. Denise Pintello (OD), Harold Perl (CCTN) and Petra Jacobs (CCTN).

Drs. Roger Sorensen, Susan Volman and Da-Yu Wu, DBNBR, organized a workshop entitled: **"Sensory Coding in Drug Abuse"**, that was held on June 9, 2009 in Bethesda, MD. The goal of the Workshop was to bring together drug abuse and non-drug abuse researchers to discuss the current state of knowledge for processing environmental information within sensory system, especially as relevant to the recognition and awareness of drug-related cues that may trigger thoughts of drug seeking and relapse after prolonged abstinence to drug use, and to identify potential future areas of research on brain processing of drug-related sensory cues.

Drs. William A. Corrigall and David Shurtleff, Director, DBNBR, organized and co chaired a symposium entitled: **"Nicotinic Cholinergic Mechanisms in Drug Dependence: Receptor Subtypes and Ligands"** at the annual meeting of the College of Drug Dependence on June 25, 2009. This symposium described novel aspects of nicotinic cholinergic mechanisms at the receptor level. The speakers for this symposium were:Sharon Grady, University of Colorado, Boulder, Boulder, CO; Jon Lindstrom, University of Pennsylvania, Philadelphia, PA; Roger Papke, University of Florida, Gainesville, FL; and Thorgeir Thorgeirsson, deCode, Reykjavik, Iceland.

Drs. Joni Rutter, David Shurtleff, Cheryl Boyce, and Jim Bjork co-chaired a workshop entitled, **Not Just a Matter of Gray and White: Exploring the Importance of Evolution, Genes, and Experience on Brain Development** on July 9-10, 2009. The main purpose of the meeting was to explore approaches towards understanding the interplay between genes and environment in shaping human brain development. The discussion centered around The National Children's Study (NCS), a longitudinal cohort of 100,000 children to examine the effects of environmental and genetic influences on the health and well-being of children. This study, along with other valuable resources, may provide a comprehensive look into the developing brain by linking genetic variation with brain morphology, and subsequently generating informative biological patterns of normative data for understanding factors related to brain development, as well as to provide a reference for further disease-specific analyses. The goal of this workshop was to explore the

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possibility of devising a multi-disciplinary large-scale project to examine genetic and brain morphology differences that advance our understanding of brain development.

Drs. Elena Koustova, Minda Lynch, Paul Schnur and David Shurtleff organized and co-chaired a workshop on **Validation of in vivo screening for Drug Discovery and Development: Focus on Smoking Cessation**, held August 3-4, 2009 at the at the Hilton Washington DC/Rockville. The workshop participants presented and discussed up-to-date knowledge about the mechanisms of nicotine addiction, derived from controlled laboratory studies and from clinical experience with available pharmacotherapies, and provided new approaches and screening tools for medications discovery and development.The goals of the workshop were to: (1) identify individual animal behavioral paradigms that have been proven to have clinical efficacy in smoking cessation; and (2) to evaluate the theoretical and practical justification of a developing a behavioral battery for medications discovery and development in order to significantly improve the predictive validity of in vivo screening.

Drs. Kristen Huntley organized and chaired and Drs. Davis Shurtleff, Belinda Sims, Cheryl Boyce , Harold Perl and Kristen Huntley presented in a symposium entitled **"Navigating Change at the NIH/NIDA- Exciting Opportunities in Tight Times"** held at the annual meeting of the American Psychological Association on August 7, 2009, Toronto, Canada.

Drs. Paul Schnur and David Shurtleff co-organized and co-chaired a symposium entitled **"Drug Addiction and Learning - What are the underlying connections?"** held at the annual meeting of the American Psychological Association on August 8, Toronto, Canada. Presenters discussed issues related to the idea that drug addiction is a chronic relapsing disorder in which compulsive drug use dominates and supersedes the pursuit of otherwise rewarding activities. The realignment of motivational priorities Ð a form of neural plasticity - reflects multiple and varied long-term neuroadaptations. This symposium highlighted the work of scientists who use interdisciplinary approaches to understand the connections between processes of addiction, motivation and learning, homeostatic regulation and their neurobiological substrates. Speakers for this symposium were Dr. Gary Aston-Jones, University of South Carolina College of Medicine; Dr. Colleen McClung, University of Texas South Western Medical center Dallas; Dr. Patricia Grigson, Pennsylvania State University College of Medicine; and Dr. Peter Kalivas University of South Carolina College of Medicine.

Drs Nehal Vadhan and David Shurtleff co-organized and co-chaired a symposium entitled **"Using Behavioral and Cognitive Assessments to Inform Addiction Treatment"** held at the annual meeting of the American Psychological Association on August 9, 2009, Toronto, Canada. Presenters addressed issues related to the notion that the process of becoming addicted to drugs of abuse involves long-term neuroadaptations in the brain regions that underlie learning and memory consolidation. Moreover, exposure to drugs of abuse may cause epigenetic changes, changes in gene expression, and protein modifications leading to neurobiological changes that may alter cognitive and behavioral abilities such as learning, decision-making, and inhibitory control, as well as motivational processes. The level and severity of alteration in these processes varies among addicted individuals and may not always correlate with frequency of drug use. However, basic laboratory-based procedures are successfully being used to assess and characterize specific cognitive and behavioral alterations in these individuals. Not only can these measures be used to assess specific drug-induced deficits across different cognitive and behavioral domains in drug-addicted individuals, they can assess between-subject individual differences in drug-induced cognitive deficits as well. Importantly, these intermediate phenotypes may serve as valuable predictors

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of treatment compliance, ability to stay abstinent, and propensity to relapse, and thus may prove to be useful in guiding and selecting treatment interventions for individuals. This symposium highlighted recent research that has successfully targeted these issues. Speakers for the symposium were Rita Z. Goldstein, Ph.D., Brookhaven National Laboratory, Upton, NY; Nehal P Vadhan, PhD Columbia University/NYSPI, New York, NY; Anna E Goudriaan, Ph.D., University of Amsterdam, Academic Medical Center, Amsterdam, The Netherlands, Netherlands; and W . Miles Cox, Ph.D., Bangor University, Bangor, England, United Kingdom.

In collaboration with Drs. David Shurtleff and Joni Rutter, DBNBR, Drs. Cheryl Anne Boyce and James Bjork (DCNBR) co-chaired the NIDA sponsored workshop, entitled **"Anatomical MRI Scans with the National Children's Study: Exploring Opportunities and Challenges,"** on July 9-10, 2009, at the Bethesda North Marriot in Bethesda, Maryland. The goal of the workshop was to explore the possibility of developing a multi-disciplinary large-scale project to examine genetic and brain morphology differences that advance our understanding of brain development and provide a comprehensive look into the developing brain by linking genetic variation with brain morphology, generating informative biological patterns of normative data for understanding factors related to brain development, as well as to provide a reference for further disease-specific analyses.

NIDA awarded 30 **Director's Travel Awards** for the annual meeting of the College on Problems of Drug Dependence (CPDD), June 20-25, 2009, Reno/Sparks, NV. These awards are given to NRSA trainees and fellows, and Diversity Supplement recipients to attend the CPDD meeting and the NIDA Tutorials Workshop. The Tutorials Workshop enlists several T-32 Training Directors to present on a range of topics in drug abuse and addiction research, designed to broaden the perspective of new researchers in the drug abuse field.

NIDA's **Women & Sex/Gender Differences Research Program awarded 27 Women & Gender Junior Investigator Travel Awards** for the annual meeting of the College on Problems of Drug Dependence (CPDD), June 20-25, 2009 in Reno/Sparks, Nevada. These $750 awards provide travel support to first author junior investigators who make presentations on the topic of women and/or sex/gender differences. These travel awards have been made annually beginning in 1999, and are designed to promote entry of junior investigators into drug abuse research on women and sex/gender differences. A brochure listing all the awardees since 1999 was made available at CPDD. 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 presentations, announcement of the travel award program for CPDD 2010, and information on current NIDA funding opportunity announcements in this area. These efforts were led by Drs. Cora Lee Wetherington and Samia Noursi who were assisted by Dr. Lynda Erinoff and Dr. Joe Frascella.

Dr. Vishnu Purohit, DBNBR, organized a symposium on **Placental Transfer of Therapeutic Drugs**, which was held on March 31, 2009, Rockville, Maryland. The following research areas were discussed in the meeting: Transport of Nutrients and Drugs Across the Human Placental Barrier: Role of Transporters (Dr. Vadivel Ganapathy, Medical College of Georgia); and Placental P-Glycoprotein Activity and Gestational Age: Implications for HIV-1 Infected Pregnant Women (Dr. Jashvant Unadkat, University of Washington). Dr. Rao Rapaka, DBNBR, chaired the discussion of the symposium.

Dr. Vishnu Purohit organized a workshop on the **Endocannabionoid System**

and HIV which was held on June 15, 2009, Rockville, Maryland. The following topics were discussed in the meeting by three speakers: Novel Ligands to Modulate the Endocannabinoid System (Dr. Alexandros Makriyannis, Northeastern University); Protective Effects of Cannabinoids on HIV-1 Gp120-Mediated Insult to the Blood Brain Barrier (Dr. Shalom Avraham, Harvard Medical School); and Cannabinoids Prevent Gp120-Induced Damage on Neural Progenitor Cells (Dr. Hava Avraham, Harvard Medical School). In this workshop, opening remarks were presented by Dr. Jacques Normand and the discussion was led by Dr. Rao S. Rapaka.

Dr. Vishnu Purohit and Dr. Rao S. Rapaka organized a symposium on **Cannabinoids and Liver Diseases: Molecular Mechanisms and Drug Development** at the International Cannabinoid Research Symposium (ICRS) Meeting, St. Charles, Illinois, USA, July 8-11, 2009. The following topics were covered by four speakers: Endocannabinods, the Liver, and Metabolic Syndrome (Dr. George Kunos, NIAAA/NIH); Cannabinoids, Liver Inflammation, and Cancer (Dr. Prakash S. Nagarkatti, University of South Carolina); Endocannabinoids and Hemodynamic Consequences of Liver Cirrhosis (Dr.Sandor Batkai, NIAAA/NIH); The Endocannabionoid System as a Regulator of the Hepatic Wound Healing Process (Dr. Sophie Lotersztajn, INSERM, France). The symposium was opened by Dr. Cecilia Hillard, President, ICRS; introduced by Dr. Vishnu Purohit, NIDA; and chaired by Dr. George Kunos, NIDA, and Dr. Sophie Lotersztajn, INSERM, France.

Drs. Cora Lee Wetherington, Coordinator, Women and Sex/Gender Differences Research Program, and Wendy Lynch (University of Virginia) co-organized and co-chaired the symposium, **"Biological Basis of Sex Differences in Drug Abuse: A Translational Perspective,"** at the annual meeting of the American Psychiatric Association, May 16-21, 2009 in San Francisco, CA. Presenters were Wendy Lynch, Ph.D. (University of Virginia), Jill Becker, Ph.D. (University of Michigan), Karen Berman, M.D. (NIMH), Marc Potenza, M.D., Ph.D. (Yale University School of Medicine), and Larry Cahill, Ph.D. (UC Irvine).

Drs. Cora Lee Wetherington and Jill Becker (University of Michigan) co-organized and co-chaired the symposium, **"Preclinical studies of sex differences in response to cocaine in adolescents: Are they different from adults?"** at the annual meeting of the College on Problems of Drug Dependence (CPDD), June 20-25, 2009 in Reno/Sparks, Nevada. Speakers were: Wendy Lynch, Ph.D. (University of Virginia); Marilyn Carroll, Ph.D. (University of Minnesota); Sari Izenwasser, Ph.D. (University of Miami Miller School of Medicine); Cynthia Kuhn, Ph.D. (Duke University Medical Center); and Jill Becker, Ph.D. (University of Michigan).

Drs. Cora Lee Wetherington and Sherry McKee (Yale University School of Medicine) co-organized and co-chaired the symposium, **"Role of Sex and Stress in Smoking Maintenance and Relapse,"** at the annual meeting of the American Psychological Association, August 6-9, 2009 in Toronto, Canada. The panel included: Mariella De Biasi, Ph.D. (Baylor College); Sherry A. McKee, Ph.D. (Yale); Sudie Back, Ph.D. (Medical University of South Carolina); Mustafa al'Absi, Ph.D. (University of Minnesota Medical School). Rajita Sinha, Ph.D. (Yale) will be discussing the presentations.

Dr. Allison Hoffman, DBNBR, with Dr. Ruben Baler, OSPC, organized a joint NIDA-ODS symposium entitled **"Caffeine: Is the next problem already brewing"**, July 7-8, 2009.

Dr. Allison Hoffman hosted a webinar entitled **"The 2008 Public Health Service Guideline: Treating Tobacco Use and Dependence"**, presented by Dr. Michael Fiore. This was hosted by the NIDA Nicotine/Tobacco Interest Group, in partnership with the NIH Tobacco and Nicotine Research Interest Group, July 29, 2009.

On June 16, 2009, Dr. Richard Denisco, DESPR, and Dr. Petra Jacobs, CCTN, co-chaired a Prescription Opioids and Pain Workgroup meeting on June 16, 2009 at the Rockville Hilton in conjunction with SAMHSA entitled **Cardiac Effects of Opioid Medications Ð Planning a Research Agenda**.

Dr. James Bjork, DCNBR, organized a Cutting Edge Seminar on **Connectivity of the Human Brain: Foundations and Alterations in Psychiatric Disorder**, which was sponsored by the NIDA Neuroscience Consortium and held on July 15, 2009 in the Neuroscience Center. This well-attended seminar highlighted advances in the use of fMRI to study inter-regional connectivity of the brain and its potential to uncover endophenotypes of psychiatric disease.

Dr. Yu (Woody) Lin, DCNBR, organized a Cutting Edge Symposium on **Science in NeuroAIDS Research and their Implications**, which was sponsored by the NIDA Neuroscience Consortium and held on September 1, 2009 at the Neuroscience Center. This cutting-edge seminar introduced 1) early biomarkers of compromised neurocognitive capacity in apparently cognitive asymptomatic HIV+ patients who remain medically stable and clinical significance of neural efficacy in daily functioning, resilience and treatment adherence; 2) HIV clade-dependent activation of NMDA receptors and its implications in future mechanistic and clinical studies of neuroAIDS; 3) macrophage delivery of nanoformulated drugs for HIV encephalopathy.

On July 29, 2009, **NIDA Clinical Trials Network and NIDCR PEARL Network joint Dental SBIRT Partnership** held their first meeting as a group, with participants from NIDA, NIDCR, PEARL Network, CTN nodes, and EMMES, to discuss protocol development for the Dental SBIRT project.

On April 23-24, 2009, the Special Populations Office hosted a two-day **Research Development Seminar Series Workshop** in Bethesda, Maryland. Chaired by Pamela Goodlow, the workshop was geared to new investigators interested in becoming funded through NIDA and the NIH. During the two-day session, participants met with funded NIDA investigators and senior NIDA program officials, participated in a mock review of submitted draft research grant applications, and learned about the NIH grants submission and review processes.

The Special Populations Office (SPO) provided support for the **2009 Hawai'i Addictions Conference/AAPI Workgroup Scientific Conference** May 11-12, 2009 in Honolulu, Hawaii. The Asian American/Pacific Islander (AAPI) Workgroup of the SPO convened this meeting in order to discuss drug abuse and addiction research and treatment issues among Asian Americans and Pacific Islanders. Ana Anders attended this meeting and presented welcome remarks on behalf of the SPO.

On May 11, 2009, the Special Populations Office (SPO) convened a meeting of **NIDA grantees participating in the Summer Research with NIDA program**. Chaired by Flair Lindsey, the purpose of the meeting was to (1) familiarize investigators/mentors with the program's expectations, (2) provide information on strategies of running an effective mentoring program with students from diverse backgrounds, and (3) provide helpful information on NIH and NSF resources. Additionally, participants had an opportunity to hear from research sites that have had successful summer programs/experiences through the Summer Research with NIDA program.

The Special Populations Office (SPO) and the African American Researchers and Scholars Workgroup (AARSWG) convened a **"Mini Medical School"** centered on the theme of **Marginalized African American Males** on July 20, 2009 at the Morehouse School of Medicine in Atlanta, Georgia. The one-day meeting joined health care professionals, researchers, and members of the community interested in understanding the needs of substance abusers and addiction in the African American community. Scientists and physicians lectured on topics

that covered the process of addiction, psychopharmacology, addiction treatment and services, issues arising from substance abuse and its research implications, HIV/AIDS and other related co-morbidities. The AARSWG presented an award of exemplary leadership to Ms. Pamela Goodlow, Special Populations Office, and NIDA.

The Special Populations Office and the AARSWG conducted the **2nd Annual Addiction Research Training Institute** on July 21-24, 2009 at Morehouse School of Medicine in Atlanta, Georgia. The ARTI was designed to train early/new investigators to become funded researchers in the area of substance abuse and addiction. The trainees included fourteen post-doctoral fellows and junior faculty members from several academic institutions. Training sessions included presentations on an array of current research findings and opportunities, NIDA/NIH support mechanisms, proposal development and a mock review of trainees' research proposals.

Members of **NIDA's Native American/Alaska Native Researchers and Scholars Workgroup** convened in Portland, Oregon, during the week of June 8, 2009 to meet and discuss plans for research activities during the upcoming year. A major focus of the workgroup meeting was developing mentoring activities for their "Native to Native Mentoring Program" developed to increase the number of Native Americans and Alaska Natives pursuing research careers in substance abuse research.

Dr. Timothy P. Condon, Deputy Director, NIDA, presented "The Science of Addiction: Implications for Treatment" at the Massachusetts Bureau of Substance Abuse *Innovations in Addictions: From Research to Recovery* conference in Boston, Massachusetts on May 4, 2009.

Dr. Timothy P. Condon presented "Addiction: It's a Brain Disease Beyond a Reasonable Doubt - *The Neuroscience of Addiction*" at the Court Services and Offender Supervision Agency for the District of Columbia, in Washington, D.C. on May 7, 2009.

Dr. Timothy P. Condon chaired "Addressing Substance Abuse and Mental Health Needs in Military Personnel and their Families: An Opportunity for Prevention" at the Society for Prevention Research Symposium, in Washington, D.C. on May 27, 2009.

Dr. Timothy P. Condon delivered the open plenary"Effects of Nicotine on the Developing Brain" at the 10th National Synar Workshop - *Raising the Bar: Integrating Youth Access Into Comprehensive Tobacco Control*, in Phoenix, Arizona on June 9, 2009.

Dr. Timothy P. Condon presented "Treatment is the Key: Addressing Drug Abuse in Criminal Justice Settings" at the National Association of Drug Court Professional's (NADCP) 15th Annual National Drug Court Training Conference, in Anaheim, California on June 11, 2009. He also presented at the opening plenary panel session "20 Years of Getting it Right" on June 12, 2009.

Dr. Timothy P. Condon delivered the keynote presentation "The Young and the Restless: The Role of Adolescent Brain Development in Drug Addiction" at a University of Wisconsin, Madison's Conference, *Boys and Girls at Risk: The Emerging Science of Gender Differences - Blending Science with Promising Practices*, in Middleton, Wisconsin on June 16, 2009.

Dr. Timothy P. Condon presented "Research on Addiction: What Have We Learned?" at the American Academy of Child & Adolescent Psychiatry (AACAP)-NIDA K12 Program in Reno, Nevada on June 19, 2009.

Dr. Timothy P. Condon presented "Implementing Evidence-Based Practices for Adolescent Treatment" at the Center for Substance Abuse Treatment Satellite

Session, *Implementing Evidence-Based Practices for Adolescent Treatment*, in Sparks, Nevada on June 20, 2009.

Dr. Timothy P. Condon presented "National Institute on Drug Abuse: Progress, Priorities & Plans for the Future" at the 2009 NIDA International Forum, *Commonalities Among the Diseases of Addiction: Implications for Treatment and Prevention*, in Reno, Nevada on June 20, 2009.

Dr. Timothy P. Condon presented "National Institute on Drug Abuse: Institute Update" at the Addiction Studies Program meeting in Reno Sparks, Nevada on June 20, 2009.

Dr. Timothy P. Condon participated in the Community Anti-Drug Coalitions of America's (CADCA) 1 hour television show entitled "The War Within: Helping Returning Veterans" in St. Petersburg, Florida on July 1, 2009.

Dr. Timothy P. Condon presented "Returning Military Personnel, Veterans & Their Families: *How Research is Effecting Positive Change*" at the Friends of NIDA Congressional Briefing and Panel Discussion in Washington, D.C. on July 14, 2009.

Dr. Timothy P. Condon presented "The Juvenile Justice System: Identification of the Problems of Alcoholism, Substance Abuse and Related Mental Illness" at the American Bar Association Annual Meeting and Council on Racial and Ethnic Justice symposium, *The Juvenile Justice System Youth, Drug & Mental Illness Resources and Policies: Identification of Reforms Needed to Eliminate Discrimination Disparities* in Chicago, Illinois on July 30, 2009.

Dr. Timothy P. Condon delivered the plenary presentation "National Institute on Drug Abuse: Institute Update" at the 2009 NIATx Summit and SAAS National Conference in Tucson, Arizona on July 31, 2009.

Dr. Timothy P. Condon presented "On the Cutting Edge: Trends in Alcohol and Drug Abuse and Prevention" and served as a panelist at the 2009 Office of Safe and Drug-Free Schools (OSDFS) National Conference on *The Power of Change: Healthy Students, Safe Schools and Engaged Communities*, in National Harbor, Maryland on August 3, 2009.

Dr. Timothy P. Condon presented "The Science of Addiction: Implications for Prevention, Treatment and Policy" at the American Sociological Association Annual Meeting, *The New Politics of Community*, in San Francisco, California on August 9, 2009. He also served as a panelist on the "*Science Policy, National Priorities, and Opportunities for the Social Sciences*" panel. At the ASA Science Policy breakfast Dr. Condon was honored with the "Science Leader of the Year" award.

Dr. Timothy P. Condon delivered a keynote presentation on "Addiction as a Brain Disease: Implications for Recovery" at the NAADAC, the Association for Addiction Professionals, Sowing the Seeds of Recovery Conference, in Salt Lake City, Utah on August 19, 2009.

Dr. Cindy Miner, Ms. Carol Krause, and Dr. Gaya Dowling, OSPC, presented a workshop entitled "What do teens really want to know about drug and alcohol abuse?" at the National Conference of the Office of Safe and Drug Free Schools on August 3, 2009 in National Harbor, MD.

Dr Susan Weiss, Chief, Science Policy Branch, OSPC conducted a briefing on marijuana for the Office of National Drug Control Policy on April 23, 2009 in Washington DC.

Dr. Susan Weiss presented "NIDA's Screening and Treatment Resources for Medical Health Professionals" at a meeting of the Inter-American Drug Abuse Control Commission (CICAD) on May 7, 2009 in Washington DC.

Dr. Susan Weiss presented "Preventing Drug Abuse and Addiction: What You Need To Know" at the National Association of School Nurses Meeting on June 26, 2009, in Boston, Massachusetts.

Dr. Ruben Baler, Science Policy Branch, OSPC, presented a keynote address entitled "Brain Awareness as Drug Abuse Prevention" at the 2009 Spring Academy on Prevention and Treatment Exchange hosted by the University of Nevada, Reno. (CASAT). May 18-20, 2009, Reno NV.

Dr. Mimi Ghim, Science Policy Branch, OSPC, presented on "Funding Opportunities for Junior Investigators" at the American Psychological Association's Psychology Summer Institute on July 21, 2009.

Dr. Mimi Ghim presented on "NIH Extramural Loan Repayment Programs" at the NIH Loan Repayment Program Session at the Society for Prevention Research Meeting on May 28, 2009.

Dr. Mimi Ghim coordinated the following activities at CPDD, June 20-25, 2009, in Reno/Sparks, NV: [1] NIDA Tutorials Workshop, chaired by Dr. Ghim, where four NIDA Training Directors presented either their research or a career building/training mini-workshop; [2] NIDA Training Networking Event, chaired by Dr. Susan Weiss, that provided a forum for training directors, trainees, and NIDA staff to learn about the different training programs that NIDA supports and for trainees to find future training/employment opportunities; [3] and NIDA Grant Writing Workshop, chaired by Dr. Susan Weiss, that provided information on NIDA Research opportunities, Program interests, review procedures, and grant writing tips to prospective candidates. Topics were presented by Drs. Mimi Ghim, David Shurtleff, Gerald McLaughlin, and Scott Lukas.

Dr. Lula Beatty, Director, Special Populations Office, participated as a planning committee member and faculty at the 2nd annual Leadership Institute for Women in Psychology on August 4, 2009 in Toronto, Canada.

Dr. Lula Beatty, with Dr. LeShawndra Price, DESPR, hosted a roundtable discussion on research grant development at the Quantitative Training for Underrepresented Groups program held at Ryerson University, August 5, 2009 in Toronto, Canada.

Dr. Lula Beatty participated in the annual convention of the American Psychological Association, August 6 Ð 9, 2009 in Toronto, Canada. She chaired and presented a session titled "Women leading health disparities research for women Ð career development moves" presented with NIDA grantees, A. Kathy Burlew, Ph.D. and Scyatta Wallace, Ph.D. She hosted roundtable discussions for Division 50 (on health disparities), the Society for the Psychology of Women (on early career development), and the APA Women's Program Office (on federal funding opportunities and strategies).

Dr. Lula Beatty served as a reviewer for the awards program (Carolyn Payton Early Career Award and Graduate Student Research Paper Award) of the Section on the Psychology of Black Women, Society for the Psychology of Women and American Psychological Association in May, 2009 in Washington, D.C.

Dr. Lula Beatty participated in a symposium on health disparities chaired by Rumi Price, Ph.D., at CPDD in June, 2009 in Reno, Nevada.

Dr. Lula Beatty was an invited participant in a plenary session titled "Health and Healing: The Federal Government Initiatives on Reducing Health Disparities" held at the annual meeting of the Association of Black Psychologists, on July 29, 2009 in Atlanta, Georgia.

Dr. Lula Beatty was a presenter in a session titled "Access to Mental Health and

Substance Abuse Services: What's Happening in the African American Communities" held at the annual meeting of the Association of Black Psychologists, on July 30, 2009 in Atlanta, Georgia.

Dr. Lula Beatty participated in the Robert Woods Johnson New Connections meeting as a mock reviewer, speed mentor and research grants panelist on June 25 - 26, 2009 in Princeton, New Jersey.

Dr. Lula Beatty participated as a planning committee member and participant in the 2009 4th Annual Connecting Marriage Research to Practice Conference: The Black Family in the 21st Century held June 17-19, 2009 at the University of North Carolina, sponsored by the African American Healthy Marriage Initiative, Administration for Children and Families/HHS.

Ana Anders, M.S.W., SPO, participated in the Hawai'i Addictions Conference and AAPI Workgroup Scientific Conference on May 11-13, 2009 in Honolulu, Hawaii.

Ana Anders was a speaker at the NIH National Hispanic Youth Initiative on July 13, 2009 in Bethesda, Maryland.

Dr. David Shurtleff gave an invited presentation at the Committee on Animal Research and Ethics (CARE) mentoring session entitled: "How to Navigate the NIH" on August 6, 2009 at the annual meeting of the American Psychological Association, Toronto, Canada.

Dr. Jonathan D. Pollock, DBNBR, organized a weekly webinar from January thru July 2009 on the Genetics of Nicotine Addiction, Lung Cancer, and COPD.

Dr. Jonathan D. Pollock chaired the founding meeting of the Consortium for the Genetics of the Analysis of Smoking Phenotypes (CGASP), June 15, 2009. The purpose of the consortium is to conduct a meta-analysis as well as integrate data on the genetics of nicotine addiction, lung cancer, and COPD.

Dr. Jonathan D. Pollock presented a seminar entitled, The NIDA Genetics Program and Important Research Resources" at the Cold Spring Harbor Laboratory, Cellular Biology of Addiction course.

Drs. Cora Lee Wetherington, DBNBR, and Sherry McKee (Yale University School of Medicine) co-organized and co-chaired the symposium, "Role of Sex and Stress in Smoking Maintenance and Relapse," at the annual meeting of the American Psychological Association, August 6-9, 2009 in Toronto, Canada. The panel included: Mariella De Biasi, Ph.D. (Baylor College); Sherry A. McKee, Ph.D. (Yale University School of Medicine) Sudie Back, Ph.D. (Medical University of South Carolina); Mustafa al'Absi, Ph.D. (University of Minnesota Medical School). Rajita Sinha, Ph.D. (Yale University School of Medicine) was the discussant for the presentations.

At the annual meeting of the American Psychological Association (APA), August 6-9, 2009 in Toronto, Canada, Drs. Cora Lee Wetherington and Rajita Sinha (Yale University School of Medicine) were invited by APA's Division on Addiction to serve as co-hosts for the Conversation Hour, "Addiction, Men and Women" chaired by Dr. Nancy Piotrowski, Capella University.

A workshop was organized by Rao Rapaka, DBNBR, entitled, "Fishing for the Hidden Proteome in Health and Disease (drug abuse)at the Hilton Hotel, Rockville, Bethesda MD, May 21-22, 2009.

A workshop on "Chemical Genomics", July 17-18, Portland, Oregon, Benson Hotel was organized by Rao Rapaka as a satellite meeting to the International Narcotic Research Conference's (INRC) Annual Meeting.

Dr. Vishnu Purohit co-chaired and co-organized a NIH STEP symposium on Mind-Body Medicine Ð Fact or Fiction, Bethesda, Maryland, May 7, 2009. The

following areas were presented by four speakers: Overview of the Science (Dr. Esther Sternberg, NIMH/NIH); Science of Meditation and Health (Dr. Frederick Hecht, University of California at SF); Science of Biofeedback (Dr. Lynda Thompson, Biofeedback Institute of Toronto, Canada); and Traditional Taiji and Qigong (Dr. Yang Yang, University of Illinois at Champaign-Urbana). Dr. Page McDonald, NCI, and Dr. Deborah Hayes, NCCAM, were discussants for the symposium.

Dr. Roger Sorensen, DBNBR, represented NIDA and the NIH at the 2009 NIH Regional Seminars on Program Funding and Grants Administration held on April 16 - 17, 2009 in Atlanta, GA, co-hosted by Georgia State University and the Georgia Institute of Technology; and on June 25 - 26, 2009 in Las Vegas, NV, co-hosted by the University of Nevada, Las Vegas and the University of Nevada, Reno. The Regional Seminar program provides institution administrators and scientific investigators with an inside look at processes and policies at the NIH. He gave two presentations; "Grant Writing for Success", and "Working with NIH Program Officials: PreAward & PostAward", as well as providing insight into the NIH granting process.

Dr. Nancy Pilotte, DBNBR, chaired a session entitled "Response to Social Stress Predicts Vulnerability to Drug Abuse" at the American Psychiatric Association Annual Meeting on May 19, 2009, in San Francisco, CA.

Drs. Nancy Pilotte and Jerry Frankenheim, DBNBR, co-chaired entitled "Hot Topics at NIDA" at the INRC Annual Meeting on July 15, 2009, in Portland, OR.

Dr. Allison Hoffman, DBNBR, with many colleagues from NIDA, served on the planning committee for the National Hispanic Science Network Annual Meeting, held October 29-31, 2009, Miami, FL.

Dr. Allison Hoffman with Lucinda Miner, OSPC, served on the planning committee for the 2nd Menthol Conference, held Oct 19-20, 2009, Atlanta, GA.

Dr. Samia Noursi presented a poster at NIDA's International Forum at the College on Problems of Drug Dependence (CPDD), June 20-25, 2009 in Reno/Sparks, Nevada. The poster described NIDA's Women and Sex/Gender Differences Research Program: program history, goals, and research interests.

Dr. Wilson Compton, Director, DESPR, and Dr. Meyer Glantz, DESPR co-chaired a symposium titled, "Spotting the Wolf in Sheep's Clothing: Clinical Challenges Identifying and Treating Unpresented Comorbidity" at the American Psychiatric Association Meeting held in San Francisco, California, May 18, 2009. The presentations and discussion focused on psychiatric patients presenting for mental health treatment who have concurrent substance abuse disorders (SUD) which go unidentified and untreated.

Dr. Wilson Compton and Moira O'Brien, DESPR, co-chaired a workshop on, "The Diversion of Prescription Stimulants," for the American Psychiatric Association Meeting held in San Francisco, California, May 18, 2009.

Dr. Wilson M. Compton presented on implementation science and on the epidemiology of comorbid drug abuse and PTSD at the annual meeting of the American Society of Addiction Medicine, New Orleans, Louisiana, May 1-3, 2009.

Dr. Wilson M. Compton presented two lectures on epidemiology and neuroscience at Transylvania University, Lexington, Kentucky, May 5, 2009.

Dr. Wilson M. Compton participated in and presented at the American Psychiatric Association's annual meeting, San Francisco, California, May 26-28, 2009.

Dr. Wilson M. Compton participated in the Society for Prevention Research

annual meeting, Washington, D.C., May 26-28, 2009.

Dr. Wilson M. Compton presented to the Boston Federal Re-entry Court, Boston, Massachusetts, June 16, 2009.

Dr. Wilson M. Compton presented at the annual meeting of the College on Problems of Drug Dependence, Reno, Nevada, June 25, 2009.

Dr. Wilson M. Compton participated in the ONDCP Inter-agency Workgroup for Demand Reduction, meetings have been held on an ongoing basis since March 2009.

Dr. Wilson M. Compton presented a keynote address to the National Youth Leadership Forum-Medicine, College Park, Maryland, July 6, 2009.

Drs. Redonna Chandler and Dionne Jones, DESPR, co-presented a New Investigators' Workshop via Adobe Connect for faculty and graduate students at the University of South Florida, June 15, 2009.

Dr. Elizabeth Ginexi, PRB, DESPR served as Co-Chair along with Dr. Michael Bardo of the University of Kentucky on an invited Paper Symposium at the annual meeting for the Society for Prevention Research in Washington, DC on May 27, 2009 titled "Neural and Behavioral Mechanisms of Inhibitory Control: Implications for Drug Abuse Prevention." Dr. David Jentsch of UCLA, Dr. Mark Fillmore of University of Kentucky, Dr. Carl Lejuez of University of Maryland presented papers, and Dr. Donald Lynam of Purdue University served as the discussant.

Dr. Elizabeth Ginexi served as the discussant for a Paper Symposium at the annual meeting for the Society for Prevention Research in Washington, DC on May 28, 2009 titled "Methods of Examining Peer and Social Networks in Prevention Research." Drs. Paul Juarez of Meharry Medical College, Michael Mason of Villanova University, and Isabella Lanza of Temple University presented papers.

Dr. Elizabeth Ginexi served as the discussant for a Paper Symposium at the annual meeting for the Society for Prevention Research in Washington, DC on May 29, 2009 titled "One Size Does Not Fit All: The Next Generation in Drug Prevention Communications Research." Drs. William Crano of Claremont Graduate University, William Shadel of RAND Corporation, and Rick Zimmerman of the University of Kentucky presented papers.

Dr. Elizabeth Ginexi served as Co-Chair along with Dr. Amy Goldstein, NIMH on a Paper Symposium at the annual meeting for the Society for Prevention Research in Washington, DC on May 29, 2009 titled "Methods in Longitudinal Prevention Research: Who, What, When." Drs. David MacKinnon of Arizona State University, Getachew Dagne of the University of South Florida, Hanno Petras of Johns Hopkins University, and Elizabeth Stuart of Johns Hopkins University presented papers.

Dr. Jacqueline Lloyd, PRB, DESPR, organized and chaired a symposium titled "The Role of Social Networks in HIV and STI Transmission Risk and Prevention in High Risk Drug Using Populations" at the Society for Prevention Research Annual Meeting in Washington D.C., May 26 Ð May 29, 2009. The symposium discussant was Dr. Richard Jenkins and the presenters were Drs. Carl Latkin of Johns Hopkins Bloomberg School of Public Health, Jianghong Li of the Institute for Community Research, and Thomas Valente of the Keck School of Medicine, University of Southern California.

Drs. Jacqueline Lloyd and Eve Reider of PRB, DESPR co-moderated a plenary roundtable session titled "Sexual Health and Risk Reduction: Theory to Practice" at the Society for Prevention Research Annual Meeting in Washington D.C., May 26 Ð May 29, 2009. The presenters were Dr. John Delamater of the

University of Wisconsin, Dr. Janet S. St. Lawrence of Mississippi State University, and Kevin Cranston of the Massachusetts Department of Public Health.

Dr. Aleta Meyer, PRB, DESPR, organized and chaired a paper symposium titled "Utilizing Bidirectional Paths of Influence between Consumers, Practitioners, and Researchers to Design Prevention Strategies" at the Society for Prevention Research Annual Meeting in Washington D.C., May 26 Ð May 29, 2009. The symposium discussant was Dr. Abraham Wandersman from the University of South Carolina. The presenters were Dr. Margaret Weeks of the Institute for Community Research, Dr. Jerry Schultz of Kansas University, and Ms. Amy Syvertsen of the Pennsylvania State University.

Dr. Aleta Meyer served as Co-Chair along with Dr. LeShawndra Price, ERB, DESPR, for a paper symposium at the Society for Prevention Research Annual Meeting in Washington D.C., May 26 Ð May 29, 2009 titled "Problematic Relationships as Shared Risk Factors for Adolescent Dating Violence and Substance Use." The symposium discussant was Dr. David Wolfe. The presenters were Dr. Luz McNaughton Reyes of the University of North Carolina-Chapel Hill, Dr. Terri Sullivan of Virginia Commonwealth University, and Dr. Debra Capaldi of the Oregon Social Learning Center.

Dr. Aleta Meyer organized and chaired a paper symposium titled "Working Relationships with Cooperative Extension: A Gold Mine for Translating Science into Practice at the National Level" at the Society for Prevention Research Annual Meeting in Washington D.C., May 26 Ð May 29, 2009. The symposium discussant was Dr. Suzanne LeMenestrel, National Leader for Youth Development Research at Cooperative State Research, Education, and Extension Service (USDA). The presenters were Dr. Louise Parker of Washington State University, Dr. Richard Spoth of Iowa State University, and Mr. Brian Bumbarger of the Pennsylvania State University.

Dr. Eve Reider represented NIDA on June 2, 2009 at meeting entitled "U.S. Army Suicide Reduction and Prevention Research," held by the Military Operational Medicine Research Program (MOMRP), U.S. Army Medical Research and Materiel Command (USAMRMC).

Dr. Eve Reider was a member of the program planning committee for the 17th Annual Society for Prevention Research Annual Meeting that was held May 26-29, 2009 in Washington, DC.

Dr. Eve Reider was an organizer and theme reviewer for the 2nd Annual NIDA International Poster Session, held May 26, 2009 at the 17th Annual Society for Prevention Research Annual Meeting, Washington, DC.

Dr. Eve Reider organized an invited symposium for NIDA at the 17th Annual Meeting of the Society for Prevention Research. The symposium was co-chaired by Dr. Timothy Condon, Deputy Director, NIDA, and Dr. Joan Hall, Senior Program Manager, U.S. Army Military Operational Medicine Research Program. The symposium was entitled Addressing Substance Abuse and Mental Health Needs in Military Personnel and their Families: An Opportunity for Prevention. Presenters were Christopher Spera, Ph.D., ICF International, Richard E. Heyman, The Research Foundation of State University of New York Stony Brook, and Richard Keller, R.N., U.S. Army Battlemind Program Walter Reed Army Institute of Research. The discussion was led by Michael Kilpatrick, M.D., Director of Strategic Communications Military Health System, Office of the Assistant Secretary of Defense for Health Affairs. The symposium was held May 27, 2009 in Washington, D.C.

Dr. Eve Reider served as moderator and discussant for the Paper Symposium "The Protective Effects of Parent-Adolescent Communication Against Substance Abuse" which was held May 29th, 2009 at the 17th Annual Meeting for the

Society for Prevention Research in Washington D.C. Presenters included Nikola Zaharakis, B.A., Virginia Commonwealth University, Kate Ralston, Ph.D., Iowa State University, and Peggy S. Meszaros, Ph.D., Virginia Tech.

Drs. Belinda Sims and Aria Crump, DESPR, organized an NIH Update Session at the Society for Prevention Research Meeting in Washington DC on Thursday, May 28, 2009.

Drs. Belinda Sims and Elizabeth Robertson, DESPR, co-chaired a research roundtable titled, "Advancing Prevention Research at the National Institute on Drug Abuse" at the annual meeting of the Society for Prevention Research on Thursday, May 28, 2009. The discussants were Irwin Sandler, Anthony Biglan, Mark Greenberg, Eve Reider (NIDA/DESPR), Mary Jane Rotheram-Borus, and Zili Sloboda.

Dr. Belinda Sims chaired a symposium titled, "Intervening with High Risk Youth and Young Adults in Service Settings and Systems" at the annual meeting of the Society for Prevention Research on Friday, May 29, 2009. The presenters were Dr. Janet Kilian, Touro College Graduate School of Psychology, and Dr. Benjamin VanVoorhees, University of Chicago (presented by Patrick DeGregorio).

Dr. Richard Jenkins, DESPR, gave a plenary presentation titled, "Applied Roles and the Future of Community Psychology" at the Biennial Meeting of the Society for Community Research and Action in Montclair, NJ, June 18 Ð June 21, 2009.

Dr. Richard Jenkins facilitated a mentoring session titled, "Opportunities for Funding and Employment in the Federal Government" at the Biennial Meeting of the Society for Community Research and Action in Montclair, NJ, June 18 Ð June 21, 2009.

Drs. Richard Jenkins, Jacqueline Lloyd and Eve Reider, DESPR, chaired and co-organized a plenary session titled "Sexual Health and Risk Reduction: Theory to Practice" at the Society for Prevention Research Annual Meeting in Washington D.C., May 26 Ð May 29, 2009. The presenters were John Delamater, Janet St. Lawrence, and Kevin Cranston.

Dr. Richard Jenkins served as the discussant for a panel on "Advanced Statistical Modeling of Risk Behavior Over Time" at the annual meeting of the Society for Prevention Research in San Francisco, May 28-30, 2009. Panelists included Ed Smith, Donna Coffman, Megan Patrick, and Stephanie Lanza, all from Pennsylvania State University.

On March 5 and 6, 2009, Dr. LeShawndra Price, DESPR, presented "NIDA Initiatives, Collaborations, and Research Activities" at the U.S. State Department Meeting Promoting Resiliency & Protecting Children from the Psychological Consequences of Violence: Recent Findings and Future Directions.

On May 22, 2009, Dr. LeShawndra Price, DESPR, served as a panelist for a Workshop entitled, "Show Me the Money: Grant-Getting for Graduate Students and New Faculty" at the annual meeting of the Association for Psychological Science in San Francisco, CA.

On May 27, 2009, Drs. Aleta Meyer and LeShawndra Price of DESPR co-chaired a paper symposium at the Society for Prevention Research annual meeting in Washington, DC entitled, "Problematic Relationships as Shared Risk Factors for Adolescent Dating Violence and Substance Use." Drs. Deborah Capaldi of the Oregon Social Learning Center, Luz Reyes of the University of North Carolina at Chapel Hill, and Terri Sullivan of the Virginia Commonwealth University presented papers. Dr. David Wolfe of the University of Toronto served as discussant.

Dr. Naimah Weinberg, DESPR, chaired a symposium entitled "The Genes, Environment, and Development Initiative (GEDI) of the Minnesota Center for Twin and Family Research" at the annual meeting of the Behavior Genetics Association in Minneapolis, MN, on June 19, 2009.

Dr. Dionne Jones, DESPR, presented on "Funding Opportunities through NIDA/NIH" and served as faculty/mentor in NIDA's Addiction Research Training Institute held in Atlanta, GA, July 20-24. 2009.

Dr. Dionne Junes organized and chaired a symposium, "Making Health Care and Treatment Services Work for Abused Women" at the American Psychological Association Annual Meeting, August 6-9, 2009, Toronto, Canada.

Dr. James Bjork attended the Annual Meeting of the Organization for Human Brain Mapping in San Francisco on June 22, 2009, where he gave a presentation entitled Changes in NIH Peer Review: Implications for Neuroimaging.

Dr. James Bjork attended the Annual Meeting of American Psychiatric Association in San Francisco on May 20, 2009, where he gave a presentation entitled Rewards, Risk, and the Teenage Brain: Insights from functional MRI as part of a workshop entitled "Teen Risk-Taking: Translating Neuroscience Into Real Life Choices."

Dr. Joseph Frascella, Director, DCNBR, participated in the 2009 NIDA International Forum and gave a presentation ("Common Brain Mechanisms in Addiction and Obesity"). This meeting was a satellite to the Annual CPDD meeting in Reno, NV on June 20, 2009.

Dr. Joseph Frascella, DCNBR participated in the CPDD "Brunch with Champions" session at the annual meeting of the College and spoke with junior investigators about their research and career plans in Reno, NV on June 25, 2009.

Dr. Nicolette Borek, DCNBR, attended the Pediatric Academic Societies (PAS) annual meetings in Baltimore, MD held May 2-5, 2009. The PAS Annual Meeting is a unique forum for pediatrics which provides an opportunity for representatives from almost all pediatric subspecialty areas to collaborate, exchange findings and share ideas that propel the future of child health. The PAS is comprised of four sponsoring organizationsÐthe American Pediatric Society, the Society for Pediatric Research, the Academic Pediatric Association and the American Academy of Pediatrics.

Dr. Cheryl Anne Boyce, DCNBR, attended the Clinical Translational Science Awards (CTSA) CTSA Consortium Child Health Oversight Committee (CC-CHOC) Face-to-Face Meeting, in conjunction with the PAS Meetings on May 1, 2009. The CC-CHOC is the national forum for CTSA investigators and NIH scientists to identify collaborative opportunities to facilitate child health clinical and translational research through the CTSA program.

Dr. Nicolette Borek, DCNBR, was a co-organizer and participant for the Consultation on the Inclusion of Adolescents in HIV Prevention Clinical Trials which was held on June 18 and 19, 2009 in Washington, DC. The meeting was sponsored by NIDA, NICHD, NIMH, NIAID, and the Forum for Collaborative HIV Research and brought together staff from NIH and FDA, domestic and international experts from academia, industry, HIV-affected communities, Foundations, Advocacy groups and the WHO to discuss adolescents' participation in biomedical HIV prevention trials including microbicides, PrEP, and HIV vaccine trials.

Dr. Cheryl Anne Boyce, DCNBR attended the Society for Neuroscience first sponsored summit meeting entitled, "Neuroscience Research in Education

Summit" held at the Center for the Neurobiology of Learning and Memory at UC Irvine on June 22 to 23, 2009. The meeting was held to encourage and catalyze dialogue between educators and scientists to positively influence pre-KÐ12 student development and learning. Participants included leaders in neuroscience and education, including researchers, practitioners, and policymakers, as well as representatives of foundations, associations, and the media.

At the invitation of the Psychiatry and Behavioral Sciences section, Dr. Cheryl Anne Boyce participated as an expert speaker for the educational program presented on "Transformative Neurodevelopmental Research Priorities and the NIDA Strategic Plan" at the 2009 National Medical Association convention in Las Vegas, NV.

At the 2009 American Psychological Association (APA) Convention in Toronto, Canada, Dr. Cheryl Anne Boyce presented at various grant workshop and scientific sessions. She chaired an invited plenary by NIH grantee Dr. Dante Cichetti on "Developmental Psychopathology in Action: Nature, Nurture, and Change." She presented on DCNBR divisional priorities in the session, "Navigating Change at NIH/NIDA---Exciting Opportunities in Tight Times" chaired by Kristen Huntley (DEA) and with fellow NIDA presenters David Shurtleff (DBNBR), Belinda Sims (DESPR) and Harold Perl (CTN). She highlighted NIDA and NIH funding initiatives in her presentation "Financial Support Opportunities for Minority Students" at a graduate student symposium. For the presentation which described the community based participatory research project the AAKOMA project, she served as a discussant to highlight the important role of the community and recent NIH initiatives in this area. Finally, as a speaker for a symposium focused on the measurement of stress and trauma, she presented on "Youth Stress and Trauma Measurement Across Multiple Levels of Analysis" to review models integrating clinical neuroscience, behavioral and sociocultural considerations.

Dr. Lisa Onken, DCNBR, with representatives from multiple ICs, including NIMH, NIA, and NIAAA, co-organized a trans-NIH Roadmap meeting on the Science of Behavior Change that took place on June 15-16, 2008 in Bethesda, Maryland. Dr. Onken moderated the panel on "Changing Existing Behaviors."

Dr. Lisa Onken assisted in planning a meeting led by Dr. Melissa Riddle of NIDCR. The meeting, "Behavioral Intervention Research at a Crossroads: Where Do We Go From Here?" took place at NIDCR on July 23-24, 2009 in Bethesda, Maryland. Dr. Onken moderated a panel called "Starting Points for Intervention Development Research."

Dr. Lisa Onken helped to plan a planning meeting for the Advanced Training Institute on Health Behavior at the National Cancer Institute on July 28-29, 2009. In addition, Dr. Onken presented NIDA's research portfolio on theoretically-drive intervention research.

On April 26, 2009, Dr. David McCann, Acting Director, DMPCDA, chaired the "NIDA Medications Development Workshop: Smoking Cessation and Beyond" as a satellite to the annual meeting of the Society for Research on Nicotine and Tobacco in Dublin, Ireland. The workshop entailed a presentation by Dr. Elbert Glover, University of Maryland, entitled Evaluation of Selegiline Transdermal System for Smoking Cessation: Preliminary Results of NIDA's 246 Subject, Multi-Site Trial, a presentation by Dr. Celia Jaffe Winchell (FDA) entitled Medications to Treat Tobacco Dependence: An FDA Perspective, and presentation by Dr. McCann entitled Medications Development for Polydrug Addiction Treatment: A NIDA Perspective.

Dr. Ivan Montoya, DPMCDA, led the workshop entitled: "Funding Opportunities at NIH" at the Latino Mental Health Conference in New Brunswick, New Jersey on June 11-13, 2009.

Dr. Ivan Montoya gave the lecture entitled "Treatment Update: What Works/What's Ready? Pharmacotherapies" at the NASADAD meeting in Syracuse, New York on June 3, 2009.

Dr. Ivan Montoya chaired the symposium entitled "The New World of Naltrexone: New Formulations, New Indications" at the NIDA International Satellite Conference, in Reno, Nevada on June 20, 2009. It included presentations by Dick Hawks (History and Pharmacology of Naltrexone), Sandra Comer (New formulations of naltrexone in the U.S.A.), Evgeny Krupitsky (Evaluation of new formulations of naltrexone for opioid dependence in Russia), David Gastfriend (Naltrexone for alcohol dependence around the world) and Johan Franck (Naltrexone for methamphetamine addiction in Scandinavia). The discussant was Chuck O'Brien.

Dr. Ivan Montoya gave an oral presentation entitled "Impact of inclusion and exclusion criteria on clinical trials of drug abuse pharmacotherapies" at the symposium entitled: "From clinical trials to practice: The implications of inclusion and exclusion criteria in clinical trials of pharmacotherapies to treat drug dependence", at the CPDD meeting in Reno (NV), on June 25, 2009.

Dr. Jag Khalsa, DPMCDA, presented/participated in the Annual Meeting of the American Society of Addiction Medicine (ASAM), New Orleans, April 2009. He chaired three symposia: "Substance Abuse Associated Comorbidity", covering the physiological and biochemical systems impacted by drug abuse and infections; (2) "Medical Marijuana: Revisited", where panelists discussed the current status of medical marijuana research; (3) "International Collaborations Between ASAM and ISAM: Unique Treatment Models for Substance Abuse", where speakers from Iceland (Dr. Tyrfingsson), Russia (Dr. Krupitsky), and UK (Dr. Strang) presented drug addiction treatment programs in their respective countries.

Dr. Jag Khalsa attended the Annual Meeting of the American Association for the Oro-maxillary Surgeons (AAOM), Chicago, IL, May 2009, and encouraged the members to conduct research on oromaxillary/dental consequences of drug addiction.

Dr. Jag Khalsa participated in the Annual Meeting of the ACTHIV (American Conference on Treatment of HIV Treatment) in Denver, CO), May 2009.

Dr. Jag Khalsa gave an invited lecture at the Inauguration of a newly established Institute of NeuroImmune Pharmacology at the Florida International University, Miami, June 1, 2009, and also attended the 9th International Conference on NeuroVirology (ICNV), Miami, June 2-3, 2009.

Dr. Jane B. Acri, DPMCDA, participated in a workshop entitled "Evaluating the Abuse Potential of Novel Compounds and Abuse Resistant Formulations," at the College on Problems of Drug Dependence. The workshop was chaired by Michael A. Nader, and Dr. Acri's presentation was entitled, "The role of NIDA in the evaluation of emerging drugs of abuse." Her presentation described data generated by NIDA on emerging drugs of abuse as identified by the DEA.

Dr. Petra Jacobs, CCTN, chaired a pre-conference session at the American Association for the Treatment of Opioid Dependence (AATOD) meeting on April 26, 2009 in New York, NY. This session provided an overview of new research findings addressing opioid analgesic dependence including assessment, co-occurring pain, patient characteristics, and treatment approaches.

The 30th Annual Meeting of the Society for Clinical Trials took place May 3-6, 2009, in Atlanta, GA. CCTN staff participated in the following sessions.

1) Dr. Paul Wakim organized and chaired an invited session titled, "Is a Null Result a Failure? Can Anything Good Come out of Null Results?" 2) Joint work by Ms. Carmen Rosa and Dr. Paul Wakim on "Participation in Substance Abuse

Clinical Trials: Comparing Gender and Racial/Ethnic Groups" was presented as part of a Contributed Paper Session titled, "Patient Recruitment, Enrollment and Retention".

Dr. Betty Tai, Director, CCTN, co-chaired a symposium on "International and Global Issues in Drug Abuse Treatment" at the NIDA 2009 Hawaii Addictions Conference/AAPI Workgroup Scientific Conference on Addiction and Related Issues: Focusing on Recent Research and Culturally Relevant Treatments Among Asian Americans and Pacific Islanders, May 11-12, 2009 Honolulu, Hawaii.

Dr. Udi E. Ghitza, CCTN, co-chaired a NIDA-sponsored symposium entitled Integrating Treatment for Substance Use and Post-Traumatic Stress Disorders in Patients with Co-occurring Conditions at the American Psychiatric Association Annual Meeting in San Francisco, CA, May 16-21, 2009. The purpose of this symposium was to examine the challenges and opportunities for advancing an integrated medical care approach concurrently treating functional impairments associated with both substance use and post-traumatic stress disorders in patients with co-occurring conditions.

The Regional Dissemination Workshop Series promotes and encourages adoption and implementation of the CTN products. The Oregon/Hawaii and Pacific Northwest Nodes with the Northwest Frontier Addiction Technology Transfer Center and the CCTN hosted the first CTN Regional Dissemination Workshop June 3-4, 2009 in Portland, Oregon. The workshop highlighted treatment products tested in the clinical trials conducted by the CTN. There were 135 registered participants. The workshop featured speakers from the CTN and ATTC Networks. Dr. Betty Tai delivered the plenary presentation. Dr. Harold Perl and Ms. Michele Straus also attended.

Dr. Petra Jacobs and Dr. Richard Denisco (DESPR) co-chaired the NIDA/Prescription Opioid and Pain WorkgroupÐsponsored workshop entitled "Opioid Agonist Medications Effects on Cardiovascular System." This workshop was held on June 16, 2009 in Rockville, MD.

Dr. Mary Ellen Michel, CCTN, presented an overview of the CCTN's research to representatives from other NIDA divisions, NIMH and the CDC. The meeting was organized by NIDA's Office of AIDS Research on June 24, 2009.

The College on Problems of Drug Dependence (CPDD) held its 71st annual meeting June 20-25, 2009, in Reno/Sparks, Nevada. CCTN staff participated in the following:

1. Dr. Raul Mandler chaired a mini symposium entitled, "HIV Risk Prevention in the CTN." Dr. Susan Tross, Chief of the CTN-HIV-SIG from the CTN LI Node, Dr. Donald Calsyn, from the Pacific Node and Dr. Lisa Metsch from the FL Node discussed Comparative Effectiveness Research of HIV Prevention Protocols done in the CTN, focusing of gender and minority differences.
2. A poster presentation by Ms. Carmen Rosa and Dr. Paul Wakim on "Participation in Substance Abuse Clinical Trials: Comparing Gender and Racial/Ethnic Groups" was presented on June 25, 2009.
3. A poster presentation by Drs. Steven Sparenborg, Udi Ghitza, and Betty Tai on "Comparative effectiveness research in the National Drug Abuse Treatment Clinical Trials Network (CTN)" was presented on June 25, 2009.

Drs. Udi E. Ghitza, Steven Sparenborg, Betty Tai, and Ms. Michele Straus, organized a NIDA-sponsored two-day meeting entitled, "Narrowing the Research-Practice Divide in Evidence-Based Medicine with Adoption of Electronic Health Record Systems: Present and Future Directions" on July 13-14, 2009 in Rockville, MD. The purpose of the meeting was to explore the prospects and challenges of using electronic health record systems to bridge the gap between specialized substance abuse treatment and mainstream

medical care.

Drs. Michelle Leff and Betty Tai organized a health Economics workshop on July 30-31, 2009. There were four specific goals for this workshop: 1) Raise awareness of the feasibility and potential value of economic evaluation in addiction treatment clinical trials. 2) Address design issues to improve the feasibility of these studies, such as a standard inventory of cost analysis measures to integrate into addiction treatment RCTs. 3) Address the perspectives of the various stakeholders and identify meaningful metrics for communicating results. 4) Develop a white paper with recommendations from this workshop to serve as initial guidance for future CTN trials.

Ms. Carmen Rosa attended the 2009 21st Annual Native Health Research Conference in Portland, OR, August 3-6. During the conference, she visited the Suquamish tribe in Washington on August 3. She also conducted site visits to two of the CTN study sites, the Native American Rehabilitation Association (NARA), in Portland, and the Warm Springs reservation in Oregon, August 5-6, 2009.

NIDA CCTN staff participated in the 117th Annual Convention of the American Psychological Association Meeting, held August 6-9, 2009 in Toronto, Canada as follows:

1. On August 5, 2009, Dr. Harold Perl taught a half-day workshop (with Dr. Kristen Huntley of OSA) as a pre-convention workshop titled, "Unlock the Mysteries of NIH Funding: Improve Your Application and Improve Your Chances at Success."
2. On August 6, 2009, Dr. Perl gave a talk titled, "What Really Matters in Turning Evidence into Impact? NIDA Programs to Advance Drug Abuse Treatment Practice," as part of a symposium session titled, "Evidence Based Practices: What Do We Mean By Evidence?"
3. On August 7, 2009, Dr. Perl gave a talk titled, "Exciting Opportunities in Tight Times: Grant Mechanisms and Academic/Business Partnerships," as part of a symposium session titled, "Navigating Change at NIH/NIDA: Exciting Opportunities in Tight Times."

Dr. Teresa Levitin, Director, OEA, co-organized a workshop for the annual meeting of the American Sociological Association on funding opportunities at NIDA and presented a paper at that session on changes in review policies and procedures at NIH and NIDA.

Dr. Jose Ruiz, OEA, co-organized and moderated the "Career Development Workshop" at CPDD, June 2009.

Dr. Gerald McLaughlin, OEA, co-organized and co-presented at three workshops: "What's New at NIDA and NIH", "Career Development" and "Grant Writing" at the June 2009 CPDD meeting.

Dr. Kristen Huntley, OEA, organized and chaired a symposium titled "Navigating Change at NIH/NIDA: Exciting Opportunities in Tight Times" and presented "Policy Updates and Changes in Peer Review" at the American Psychological Association 117th Convention, Toronto, August 2009.

Dr. Scott Chen, OEA, was a judge for medical student research posters at Georgetown University School of Medicine's 23rd Annual Student Research Days Competition and Exposition 2009.

Dr. Gerald McLaughlin, OEA, was a judge at the graduate student research competition of the Georgetown University School of Medicine, June, 2009.

Dr. Nadine Rogers, OEA, presented "De-Mystifying NIH Grants Review" at the Mini Medical School & Summer Research Training Institute at Morehouse

School of Medicine, Atlanta, GA, July 22, 2009.

Dr. Jose Ruiz, OEA, was a speaker at the "What's New at NIDA" Symposium at CPDD, June 2009.

Dr. Kristen Huntley co-chaired a Pre-Meeting Workshop titled "Unlock the Mysteries of NIH Research Funding-Improve Your Grant Application and Improve Your Chance at Success" at the American Psychological Association 117th Convention, Toronto, August 2009.

Dr. Kristen Huntley was a planning committee liaison to three Institutes for the Office of Behavioral and Social Science Research Capitol Hill Poster Session: "National Institutes of Health: Improving the Nation's Health through Behavioral and Social Sciences Research", April 28, 2009.

Dr. Scott Chen was a co-organizer and co-presenter at the "What's New at NIDA" symposium at the 2009 CPDD Annual Meeting.

Dr. Amy Newman, IRP, was invited to give a seminar entitled "Molecular Tools to Study Drug Addiction" at the Center for Drug Discovery's "7th Annual Current Trends in Drug Abuse Research" Northeastern University, Boston MA, May 2009.

Jonathan Katz, IRP, was invited to give a talk entitled: "Behavioral Pharmacology of Atypical Dopamine Uptake Inhibitors: Potential for Understanding the Dopamine Transporter and as Treatments for Stimulant Abuse" to the Department of Pharmacology, Drexel University College of Medicine, January 2009.

Director's Report to the National Advisory Council on Drug Abuse - September, 2009

Media and Education Activities

NIDAMED Launch

April 20, 2009 - A press conference was held at the National Press Club to announce NIDA's first comprehensive Physician's Outreach Initiative, NIDA**MED**. NIDA**MED** gives medical professionals tools and resources to screen their patients for tobacco, alcohol, illicit and nonmedical prescription drug use. The initiative stresses the importance of the patient-doctor relationship in identifying unhealthy behaviors before they evolve into life-threatening conditions. The NIDA**MED** resources include an online screening tool, a companion quick reference guide, and a comprehensive resource guide for clinicians. The news conference featured NIDA Director Dr. Volkow, Acting Director of the Office of National Drug Control Policy Ed Jurith, J.D., Sen. Carl Levin of Michigan, Acting Surgeon General Steven K. Galson, M.D., and representatives from the World Health Organization, the American Medical Association, and other organizations committed to helping patients who struggle with drug-related medical issues.

A patient-tested postcard, designed to complement the physician screening materials, encourages patients to discuss any and all drug use with their doctors to help ensure proper medical care. Physicians are encouraged to place the postcards in their waiting rooms. Media coverage of the event included articles by the Associated Press, the *Washington Post, BHC Journal, Alcoholism & Drug Abuse Weekly,* and ABC Radio. The Associated Press article was picked up by more than 15 newspapers nationwide. In addition, a NIDA**MED** radio announcement produced by the North American Precis Syndicate (NAPS), was broadcast 121 times in 29 different states with an audience of 14,237,420 (as of 8/19/09).

Addiction Science Fair Awards

In May 2009, NIDA presented Addiction Science Awards to students participating in the INTEL International Science and Engineering Fair (ISEF), the world's largest competition for high school science students. This is the second year that NIDA has participated in the Special Awards Program, bestowing 1st, 2nd and 3rd place honors for projects that advance addiction research. This year, more than 1,500 students from more than 50 countries participated in the ISEF competition at the Reno Sparks Convention Center, which is coordinated by the Society for Science and the Public. Winners of the Addiction Science Award received cash awards provided by Friends of NIDA, with a $2,500 scholarship for the first-place honoree. In addition, the students travelled to NIDA on August 3, 2009 to present their innovative projects to NIDA Director Dr. Nora Volkow and NIDA program staff.

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Planned Meetings

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ARRA Publicity

NIDA's Public Information and Liaison Branch (PILB) has provided technical assistance to the press information officers (PIOs) at several institutions that have received the first American Recovery and Reinvestment Act (ARRA) stimulus grants from NIDA. A sample press release, newsworthy details about the grants, and boilerplate language about NIDA and ARRA were provided to PIOs at 15 universities and institutes across the country. Several of these institutes have subsequently issued press releases to local media about their new grants.

Press Releases

April 20, 2009 - **NIDA Launches Drug Use Screening Tools for Physicians.** NIDA unveiled its first comprehensive Physicians' Outreach Initiative, NIDA**MED**, which gives medical professionals tools and resources to screen their patients for tobacco, alcohol, illicit, and nonmedical prescription drug use. See NIDA**MED** Launch description in this report for details.

May 13, 2009 - **NIDA Study Reveals Widespread Effects of Cocaine on Genome Structure and Function.** Repeated use of addictive drugs such as cocaine causes long-lasting changes in parts of the brain involved in motivation and reward, among others, yet the precise mechanisms by which these changes are maintained are poorly understood. A new NIDA-supported study, published May 14, 2009 in the journal *Neuron*, sheds light on this process by providing fundamental new insights into the effects of cocaine on the structure and function of the genome, the complete set of DNA instructions needed to make an organism.

May 15, 2009 - **NIDA Study Suggests Low-Key Anti-Smoking Ads Are More Likely to Be Remembered than Attention-Grabbing Messages.** For the first time, preliminary research using brain-imaging technology has shown that low-key and attention-grabbing anti-smoking public service announcements stimulate different patterns of activity in smokers' brains and that smokers are more likely to remember seeing the low-key PSAs. The study, published May 15, 2009 in the journal *NeuroImage*, was supported by NIDA and the National Cancer Institute.

May 15, 2009 - **The Impact of Third Hand Smoke on Risk for Genetic Mutations Wins First Place Addiction Science Award at 2009 Intel ISEF Competition.** A resourceful study into the effect of third hand smoke upon the risk for genetic mutations in fruit flies won the top Addiction Science Award at this year's Intel International Science and Engineering Fair (ISEF), the world's largest science competition for high school students. The Intel ISEF Addiction Science Awards were presented at an awards ceremony by NIDA and Friends of NIDA, a group that supports NIDA's mission and educates policy makers, health professionals and the general public about advances achieved from the investments in biomedical and behavioral research related to finding a cure for and eliminating drug dependence.

June 18, 2009 - **NIDA Study Shows School-Based Prevention Program Reduces Problem Behaviors in Fifth Graders By Half.** A study suggests that school-based prevention programs begun in elementary school can significantly reduce problem behaviors in students. Fifth graders who previously participated in a comprehensive interactive school prevention program for one to four years were about half as likely to engage in substance abuse, violent behavior, or sexual activity as those who did not take part in the program. The study, supported by NIDA, appeared in the August 2009 print issue of the *American Journal of Public Health*.

July 30, 2009 - **NIH and VA Announce $7 Million Partnership for**

Substance Abuse Research among Military Personnel, Veterans and their Families. Two federal departments have joined forces to create a first-time collaborative funding project to support research on substance abuse and associated problems among U.S. military personnel, veterans and their families. NIDA, in partnership with two other NIH Institutes—the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the National Cancer Institute (NCI)—are jointly collaborating with the Department of Veterans Affairs (VA), on a seven million dollar funding opportunity announcement for research in this area.

Research News

Full NewsScans can be seen at http://www.nida.nih.gov/NIDANews.html#newsscan.

June 2, 2009 - **NIDA NewsScan #61** - Research News

- Persistent Brain Changes in Response to Cocaine Depend on Expectation of Reward
- Antibiotic Improves Efficacy of Morphine and Reduces Reward Response
- New Analytic Method to Test Effectiveness of Open-Enrollment Group Interventions
- Middle School Interventions Reduce Nonmedical Use of Prescription Drugs
- Stress Hormone Levels Altered in Maltreated Foster Children
- Deep Brain Stimulation Decreases Cocaine Seeking in Rats
- Immune System Proteins Interfere With Painkilling Effects of Opioids
- Functional Embryonic Stem Cells Isolated From Rats

July 8, 2009 - **NIDA NewsScan #62** - Research News

- Time to Hepatitis C Infection in Injection Drug Users Lengthening in Developed Countries
- Male, Female Injection Drug Users in Tijuana Have Different Risk Factors for HIV Infection
- HIV Prevalence at the United StatesÐMexico Border May Change the HIV Epidemic in Mexico
- Varenicline Improves Learning Deficits Caused by Nicotine Withdrawal in Mice
- Denicotinized Cigarettes Affect Nicotine Receptors in Smokers' Brains
- Family-Based Intervention Helps Male Children of Drug Users Avoid Substance Use Disorders
- Computerized Cognitive-Behavioral Therapy Has Enduring Effects on Drug Use
- Vigabatrin Prevents Relapse to Methamphetamine Use in an Animal Model of Addiction

Interviews & Articles of Interest

March 11, 16, & 17, 2009 - *Philadelphia Inquirer, USA Today*, Associated Press, Thomson Reuters, and several trade publications - Interviews with Dr. Nora Volkow regarding published paper in the *Journal of the American Medical Association* on the effects of modafinil on dopamine and dopamine transporters in the male human brain.

March 19 & 20, 2009 - Grayscale Productions - Interviews with Drs. David Shurtleff, David McCann, Gaya Dowling, Wilson Compton, and Joe Frascella for inclusion in a 10-part video series called *Drugs: The Straight Facts*.

March 26, 2009 - *Los Angeles Times* - Interview with Dr. Nora Volkow about studies on obesity for a story about bad habits and how hard it is to break them.

April 7, 2009 - *Christian Science Monitor* - Interview with Dr. Nora Volkow about the use of cognitive enhancing drugs in healthy adolescents and adults.

April 14, 2009 - Indiana Public Radio - Interview with Dr. Timothy Condon about risk for substance abuse among baby boomers.

April 15, 2009 - **Washington Post** - Interview with Dr. Nora Volkow about the science of addiction.

May 15, 2009 - *Time* - Interview with Dr. Wilson Compton about naloxone distribution to addicts and pain patients to reverse overdose.

May 18, 2009 - Associated Press - Interview with Dr. Wilson Compton about illicit drug trends.

May 19, 2009 - Federal News Radio - Interview with Dr. Nora Volkow about NIDA**MED** initiative.

May 29, 2009 - *Chicago Tribune* - Interview with Dr. Nora Volkow about cognitive enhancing drugs.

June 17, 2009 - *New York Magazine* - Interview with Drs. Joe Frascella and Redonna Chandler regarding the long-term effects of illicit drugs.

June 22, 2009 - *Ladies Home Journal* - Interview with Dr. Joe Frascella about the biochemical reasons behind why women overeat/crave certain foods, link between drug addiction and obesity, and how exercise can curb the dopamine response.

June 25, 2009 - ESPN - Interview with Dr. Wilson Compton about prescription drug abuse.

June 25, 2009 - *New York Times* - Interview with Dr. Nora Volkow about growing concerns and evidence of rising rates of marijuana addiction.

July 1, 2009 - Voice of America - Interview with Dr. Wilson Compton about the problem of prescription drug abuse in America.

July 14, 2009 - ABC Network News - Interview with Dr. Nora Volkow about whether healthy people should be allowed to take performance enhancing drugs.

July 17, 2009 - WedMD - Interview with Dr. Susan Weiss about pain medication addiction.

July 21, 2009 - *Mental Health Weekly* - Interview with Dr. Cindy Miner about two ARRA grants studying smoking cessation in schizophrenics.

July 29, 2009 - Channel One News - Interview with Dr. Wilson Compton about teen addiction to painkillers and other prescription drugs.

August 3, 2009 - ABC News online - Interview with Dr. Nora Volkow about use, addiction and potency of marijuana.

Outreach Activities

NIDA Teen Blog - http://teens.drugabuse.gov/blog/
NIDA has launched the "Sara Bellum Blog" on its Teen Web site. The blog content is managed by NIDA's Office of Science Policy and Communications. This new format gives NIDA an opportunity to respond more quickly to public

events that capture the attention of teens.

Recognition for *NIDA NOTES* Science Writing
NIDA Notes received First Place in Science Writing in the 2009 Blue Pencil & Gold Screen Awards Competition of the National Association of Government Communicators (NAGC). The award, which recognized the article, "Basic Science Discoveries Yield Novel Approaches to Analgesia" (*NIDA Notes*, Vol. 22 No. 1), named Senior Science Writer Lori Whitten, Managing Editor Andrew Keegan, Deputy Editor Julie Ann Miller, and Editor David Anderson.

NIH Plain Language Gold Award
On June 2, 2009 OSPC received an NIH Plain Language Gold Award for an editorial about stigma that was published in *Science News*. The editorial, entitled "It's Time for Addiction Science to Supersede Stigma," focused on how stigma associated with substance use disorders poses a huge obstacle to the effective translation of science-based principles into practice. The authors of the piece included Dr. Volkow, Ruben Baler, Susan Weiss, Gaya Dowling, Jessica Palmer, & Jennifer Elcano.

Recent and Upcoming Conferences/Exhibits

National Medical Association Annual Convention and Scientific Assembly July 25-30, 2009 -- Las Vegas, NV

2009 State Associations of Addiction Services and the Network for The Improvement of Addiction Treatment Summit -- July 29-August 1, 2009 -- Tucson, AZ

American Psychological Association 117th Annual Convention August 6-9, 2009 -- Toronto, Ontario, Canada

NAADAC the Association for Addiction Professionals Annual Conference August 19-22, 2009 -- Salt Lake City, UT

Blacks in Government 31st Annual National Training Conference August 24-28, 2009 -- Baltimore, MD

Latino Behavioral Health Institute 15th Annual Conference September 23-25, 2009 -- Los Angeles, CA

American Academy of Family Physicians Scientific Assembly October 14-18, 2009 -- Boston, MA

American Academy of Pediatrics National Conference and Exhibition October 17-20, 2009 -- Washington, DC

Society for Neuroscience 39th Annual Meeting October 17-21, 2009 -- Chicago, IL

Employee Assistance Professionals Association Conference October 22-24, 2009 -- Dallas, TX

13th Annual United States Conference on AIDS October 29-31, 2009 -- San Francisco, CA

American Association of Medical Colleges Annual Meeting November 6-11, 2009 -- Boston, MA

American Public Health Association 137th Annual Meeting and Exposition November 7-11, 2009 -- Philadelphia, PA

National Association for the Education of Young Children 2009 Annual Conference & Expo November 18-20, 2009 -- Washington, DC

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Director's Report to the National Advisory Council on Drug Abuse - September, 2009

Planned Meetings

Dr. Da-Yu Wu has organized and will chair the first NIDA symposium at the **2009 World Molecular Imaging Congress** to be held on September 23 to 26, 2009 in Montreal Canada, titled "NIDA/NIH Mini-Symposium: MI in Drug Addiction". Speakers and titles are: 1) Joanna S. Fowler, Brookhaven National Laboratory, "Imaging Brain Chemistry in Diseases of Addiction"; 2) Christina Liu, Mass General Hospital/Harvard University, "Live Brain Gene Imaging of Drug Addiction"; 3) Brian D. Ross, Huntington Medical Research Institutes, "Glutamate Neurotransmitter Function in the Human Brain: A Multinuclear MRS Approach to Drug Addiction, Recovery and Relapse"; 4) Dean F. Wong, Johns Hopkins Medical Institutions, "SPECT Imaging in Living Brains of Smokers."

The next **National CTN Steering Committee Meetings** are planned for October 20-22, 2009 in Bethesda, MD. In the spring, the Steering Committee Meetings will be held April 19-21, 2010 in conjunction with the NIDA Blending Conference in Albuquerque, New Mexico.

The **CTN Regional Dissemination Workshops** are scheduled for October 28-29, 2009 in Pittsburgh, PA and November 2, 2009 in Charleston, SC.

NIDA will host a **T32 Training Directors' Meeting** on November 2, 2009 at the Pooks Hill Bethesda Marriott Hotel in Maryland. This meeting will offer a forum for training directors to discuss any challenges they are facing as well as ways to enhance their research training programs. The central theme of this meeting will be on sustaining training programs for the 21st century, and topics will include recent peer review changes, recruitment and retention, mentorship, evaluation and tracking, and other best practices.

A NIDA-OSPC meeting entitled, **Exploring Interconnections: A Network Dynamics Workshop for Understanding and Preventing Adolescent and Young Adult Substance Abuse**, will be held at NIH's main campus on January 13-14, 2010. Drs. Bethany Griffin Deeds, Elizabeth Ginexi, and Thomas Brady of DESPR are co-chairs of the event. This workshop focuses on bringing researchers utilizing network dynamics together with a select group of drug abuse epidemiologists, prevention, and services researchers to: share findings from social network research and to discuss obstacles and opportunities for stimulating scientific advancements and translating these findings to understand, prevent, and deliver treatment services/ recovery support for adolescent and young adult substance abuse.

NIDA's eighth **Blending Conference** will be convened at the Albuquerque Convention Center in Albuquerque, New Mexico on April 22-23, 2010. This 2-day conference is designed to bring clinicians and researchers together to jointly present the most recent scientific drug abuse and addiction findings and their application to clinical practice. NIDA's Deputy Director, Dr. Timothy Condon, is overseeing all conference planning activities and Drs. Cindy Miner

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(OSPC) and Denise Pintello (OD) are working closely with the two CTN Node PIs co-hosting the Blending Conference: Drs. James Sorenson (California-Arizona Node) and Michael Bogenschutz (Southwest Node).

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NIDA Publications

Epidemiologic Trends in Drug Abuse - Community Epidemiology Work Group -
Volume I: Executive Summary - January 2009 (Publication Date: August 2009)
NIH Pub. No.: 09-7420
This report provides descriptive information on the most recent significant trend, emerging problems and populations at risk within and across areas participating in the Community Epidemiology Work Group. This report provides program administrators and officials with specific indicator data in tabular and graphic format, and ethnographic information on current patterns and trends as well as emerging problems.

Heads Up: Real News about Drugs and Your BodyÑYear 7 Compilation for Teachers
HURN09-07TC (Publication Date: September 2009)
This booklet provides skill-building extension activities and further resources to those included for students in Publication # HURN09-07SC. The topics covered in this compilation of teacher editions published in Scholastic magazines during the 2008-2009 school year include: the risk factors for addiction, the heath consequences of drug abuse, and the treatment of addiction and its relationship to other mental health disordersÑas well as profiles of student researchers and their addiction science projects.

Heads Up: Real News about Drugs and Your BodyÑYear 7 Compilation for Students
HURN09-07SC (Publication Date: September 2009)
This booklet is a collection of articles that were originally published in Scholastic magazines as well as supplemental articles published on Scholastic's website for the 2008-2009 school year. Together these articles teach students about the full spectrum of drug abuse and addiction including the risk factors for addiction (Genetics and Addiction & Do You Know Your Risk for Addiction), the health consequences of drug abuse (Stimulant Addiction & Health Effects of Stimulants), and the treatment of drug addiction and its relationship to other mental health disorders (The Truth About "Rehab" and Drug Addiction & Overlapping Illnesses). Also included are articles highlighting the addiction research of remarkable teens (Teen Science Investigators & In Their Own Words: Teen-Science Investigators).

Mind Over Matter: The Brain's Response to Cocaine (Rev.)
(Publication Date: September 2009) NIH Pub. No.: 09-3857
Explains how cocaine changes the way nerve cells communicate and affect neurotransmission.

Mind Over Matter: The Brain's Response to Opiates (Rev.)
(Publication Date: September 2009) NIH Pub. No.: 0909-3856
Explains how opiates affect the brain stem, the spinal cord, and the limbic system. Discusses dependency and the results of long-term exposure to opiates.

Mind Over Matter: The Brain's Response to Hallucinogens (Rev.)
(Publication Date: September 2009) NIH Pub. No.: 09-3858
Explains how hallucinogens affect the brain's communication centers as well as its ability to control sleep and emotions.

Mind Over Matter: The Brain's Response to Steroids (Rev.)
(Publication Date: September 2009) NIH Pub. No.: 09-3860
Shows how anabolic steroids can cause liver damage, cancer and weaken the immune system.

Mind Over Matter: The Brain's Response to Prescription Drugs
(Publication Date: September 2009) NIH Pub. No.: 09-7423
This brochure contains scientific information on how various prescription drugs act in the body and brain to elicit their effects. It provides this information in a format that uses drug information to teach science and engender student interest in science, while also providing messages of the harmful effects associated with the abuse of prescription drugs.

Principles of Drug Abuse Treatment for Criminal Justice Populations: A Research-Based Guide (Rev.) (Publication Date: September 2009) NIH Pub. No.: 09-5316
This booklet provides treatment principles and research findings that are of particular relevance to the criminal justice community and to treatment professionals working with drug-abusing offenders.

Mentoring: A Guide for Drug Abuse Researchers - Tips for Mentors and Mentees
(Publication Date: September 2009) NIH Pub. No.: 09-5770
This publication will describe "best practices" for recruiting, training, mentoring, and advancing the careers of highly talented scientists focused upon drug abuse epidemiological, services, and prevention research.

The Brain: Understanding Neurobiology Through the Study of Addiction (Rev.)
(Publication Date: September 2009)
This educational supplement was developed for high school teachers to use when teaching neurobiology to high school students. It uses drug abuse and addiction to teach neurobiology topics such as neurotransmission, brain chemistry, etc. Included are 5 lessons, correlations with the National Science Education Standards and a website.

Brain Power! K-1 (Rev.) (Publication Date: September 2009)
This educational supplement provides teachers with 5 days of lessons and activities that can be incorporated into the kindergarten-first grade classroom. The lessons cover what it means to be a scientist, the amazing brain, and how to keep your brain healthy.

In June 2009, the Special Populations Office published *NIDA-Supported Research on Drug Abuse and Addiction in Racial/Ethnic Minority Populations; A Resource Guide*, designed to share information on the progress that NIDA has made in developing and supporting drug abuse research and resources related to racial/ethnic minority populations.

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The lead story describes how computer-based interventions can promote drug abstinence by reinforcing and expanding the well-established benefits of therapy delivered by a counselor. The story presents three groundbreaking examples of interactive multimedia therapies that may reduce costs and extend access to treatment. Also included in the issue are features reporting an immunotherapy that shows promise as a treatment for methamphetamine overdose; evidence that a person's genetic makeup influences success in quitting smoking and also which smoking cessation technique works best; and a new technique that uses dime-size arrays of tiny needles to painlessly deliver naltrexone and other medications. Another feature explores how extended cocaine exposure impairs attention in rats. In the Director's Perspective, Dr. Nora Volkow describes NIDA coalition with other federal agencies to assess and find solutions to the problems of substance abuse among service men and women, veterans, and members of military families.

***NIDA NOTES,* Vol. 22, No. 6**
This issue begins with a description of research from several laboratories that links contrasting smoking patterns with variations in half a dozen genes that dictate the structure of the brain receptor to which nicotine binds. The results suggest that genes for several receptor subunits drive different aspects of the multi-step process of nicotine addiction. Also included in the issue is a feature reporting that a checkup system provided after treatment for substance abuse may be especially beneficial for clients with co-occurring mental disorders. Another feature presents evidence that highly active antiretroviral therapy (HAART) is as useful in combating HIV in people who use illicit injection drugs as in other people infected with the virus. The issue also includes a report that proliferation of a rare receptor may underlie the intensification of craving that cocaine abusers experience during their first weeks of abstinence. In the Director's Perspective, Dr. Nora Volkow notes NIDA's 35th Anniversary, listing the Institute's major accomplishments and describing current challenges.

CTN-Related Publications

Eight editions of the CTN Bulletin Board were distributed. The Bulletin Board is an electronic report on the progress of the protocols, committees, and node activity in the CTN. The Bulletin has wide readership within and outside the CTN and NIDA.

Data from 19 CTN trials are now available on the CTN Data Sharing Web Site. Over 300 research scientists have downloaded one or more data sets. These data sets are in compliance with HIPAA and CDISC (Clinical Data Interchange Standards Consortium) standards in support of the interoperability required by the NIH Roadmap.

International Program-Related Publications

NIDA International Program Issues 2008 Annual Report
The 2008 Annual Report demonstrates how the NIDA International Program links the Institute to research organizations and scientists throughout the world, providing the opportunity for collaborators develop knowledge jointly that neither partner could have developed independently. The report is available on the IP Website, http://www.international.drugabuse.gov/.

Other Publications

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Staff Highlights

Staff Honors and Awards

The following NIDA staff received the **2009 NIH Director's Award: Wilson Compton** "for his significant & important contributions to the implementation of new community-based drug abuse prevention & treatment approaches".

Group Award for National Center on Minority Health and Health Disparities: "for contributions made in planning and coordinating the first NIH Summit: The Science of Eliminating Health Disparities".
NIDA Recipients: **Lula Beatty, Pamela Goodlow** and **LeShawdra Price**

Group Award for Early State Investigator Workgroup: "for conceiving, developing, and implementing NIH policy encouraging biomedical scientists and their institutions to accelerate postdoctoral training completion and early application for independent research support."
NIDA Recipient: **Teri Levitin**

Group Award for The RTX Development Project Team: "for advancing resiniferatoxin to a successful IND approval, enabling its evaluation in clinical trials as a tx for intractable pain".
NIDA Recipients: **Nate Appel, Jamie Biswas, Nora Chang, Marta DeSantis, Roberta Khan, David McCann, Moo Park, Amrat Patel, James Terrill, David Thomas & Robert Walsh**

The following NIDA staff received the **2009 NIDA Director's Award:**

Carol Cushing, CCTN
Myriam Selmane, DBNBR
Cecelia Spitznas, DCNBR
Elizabeth Lambert, DESPR
Carlo Contoreggi, IRP
Kandi Culbertson, IRP
Bruce T. Hope, IRP
Flair Lindsey, SPO
Nadine Rogers, OEA

The NIDA 2008 Employee Recognition Event
Janelle Barth, James Bjork, Nicolette Borek, Carol Cushing, Tracey Coleman-Rawlinson, Edith Davis, Jennifer Elcano, Joseph Frascella, Stacy Gardner, Deborah Grossman, Aida Klun, Donna Inman, Mary Kautz, Diane Loeb, Marsha Lopez, Lisa Onken, Gerald McLaughlin, Montrue Nelson, Nancy Pilotte, Karen Sirocco, Laurence Stanford, David Thomas, Carolyn Tucker, Barbara Usher, & Michael Wright

The Prevention Research Branch

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Aria Crump, Augusto Diana, Syreeta Evans, Elizabeth M. Ginexi, Richard A. Jenkins, Jacqueline Lloyd, Aleta Meyer, Eve Reider, Elizabeth Robertson, and Belinda Sims

The SAETRS Team, DPMCDA
Ann Anderson, Marta De Santis, Roberta Kahn, Erin Iturriaga, Ivan Montoya, and Robert L. Walsh

The Station Support Branch
Tonya Mansfield, Liem Nguyen, Susan Nsangou, Idella Simpson, and Jasmine Snoddy

The NIDAMed Team
Pat Anderson, Ericka Boone, Tom Brady, Redonna Chandler, Usha Charya, Wilson Compton, Tim Condon, Jessica Cotto, Elisabeth Davis, Richard Denisco, Gaya Dowling, Jennifer Elcano, Mark Fleming, Carol Krause, Geoff Laredo, Jan Lipkin, Brian Marquis, Sheryl Massaro, Cindy Miner, Joan Nolan, Stephanie Older, Lisa Onken, Jane Smither, Cecelia Spitznas, Anna Staton, Susan Weiss

The following NIDA staff received the **2009 NIDA Director's Award for EEO, Diversity and Quality of Worklife:**
John Hamill
Massoud Vahabzadeh

The following NIDA staff received the **2009 NIDA Director's Innovator Award:**
Boris Y. Mileykovskiy
"For development of innovative techniques to measure electrophysiological activities in mid-brain dopamine pathways and their inputs".

The following NIDA staff received **Length of Service Awards:**

30 Years of Government Service Awards
Patricia Anderson, Diana Haikalis, Susan Harrelson, Sharan Jayne, Elizabeth Lambert, Lawrence Raigrodski, Ming Shih & James Quinn

40 Years of Government Service Award
Marc Brodsky

Dr. David Gorelick, IRP, was among the first group of diplomates selected April, 2009 by the American Board of Addiction Medicine.

Takato Hiranita, IRP, received a FARE2010 award.

Staff Changes

Jeff Levine, M.J., joined the Public Information and Liaison Branch, OSPC as the NIDA Press Officer in June 2009. Mr. Levine's extensive journalist and broadcast background includes an 18-year career with CNN and several public relation firms, including Porter Novelli and Ketchum where he worked on a great deal of press outreach for health related issues. He also had a three-year stint as the Washington, D.C., Bureau Chief of *Web*MD at the time the powerhouse online health information site catapulted into national prominence.

Kevin Lin started his summer internship at NIDA CCTN on June 8, 2009 and is currently pursuing his B.S. in Finance. He currently holds a B.S. in Physiology and Neurobiology from the University of Maryland, College Park. Mr. Lin is enrolled in the Gemstone Honors program at University of Maryland and completed a research project which earned him the Howard Hughes Undergraduate Medical Institute Research Grant and a separate research grant from Becton-Dickinson. Mr. Lin wishes to combine his prior intramural research experience at NIAAA with his NIDA internship to gain a comprehensive understanding of NIH operations.

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Dr. Geetha Subramaniam joined the Behavioral & Integrative Treatment Branch, DCNBR, on July 6, 2009. Dr. Subramaniam was until very recently a full-time faculty member (Assistant Professor) in the department of Psychiatry at the Johns Hopkins University School of Medicine and the Associate Medical Director at Mountain Manor Treatment Center (MMTC) in Baltimore, MD. She attended the Government Medical College, Bellary, Karnataka, India and received a M.B.B.S. degree from Gulbarga University. She completed a residency in general Psychiatry at the University of Missouri Kansas City (WMMHC) and a fellowship in Child and Adolescent Psychiatry at Johns Hopkins University of Medicine. She is American Board of Psychiatry and Neurology (ABPN) certified in Child and Adolescent Psychiatry, Addiction Psychiatry and General Psychiatry. Dr. Subramaniam has had extensive experience in the treatment of adolescents with substance use disorders, particularly opioid use disorders and integrated treatments for adolescents with co-occurring psychiatric disorders. She was a recipient of a NIDA-AACAP K-12 award focusing on the treatment needs of opioid dependent adolescents; and served as the site Principal Investigator for two of NIDA Clinical Trials Network studies: Buprenorphine/naloxone for the treatment of opioid dependent adolescents and young adults and OROS methylphenidate vs. placebo treatment of ADHD in adolescents with substance use disorders. Dr. Subramaniam has authored peer-reviewed journal articles and has presented her research findings at numerous national conferences.

Dr. David Clark, DESPR, has accepted a Health Scientist Administrator position with the National Institute of Dental and Craniofacial Research (NIDCR). At NIDCR, Dr. Clark will build a research portfolio that examines the behavioral determinants of oral health both at the provider and patient levels as well as social and community aspects. He will also be active in coordinating and conducting scientific meetings, and performing other core programmatic activities to develop his scientific portfolio. Fortunately for NIDA, Dr. Clark will continue to collaborate with NIDA/DESPR on the Screening and Brief Intervention and Referral to Treatment (SBIRT) initiative for nicotine dependence, and on trans-NIH workgroups.

William "Jim" Glass, M.S. retired from NIDA on July 2, 2009 with over 30 years of federal service. Jim was the Chief of the Informatics Unit and was responsible for developing the Informatics program in the Division of Pharmacotherapies and Medical Consequences of Drug Abuse. Under Jim's leadership, a Clinical Data Repository that houses electronic data collected from many of NIDA's clinical research projects was developed. He also led the development of applications such as Livelink (a document management system currently in use by several divisions in NIDA), a Serious Adverse Events Tracking and Reporting System (SAETRS) for NIDA clinical trials, a Global Library of standardized clinical trial case report forms, and the Addiction Treatment Development Program Discovery and Development application for tracking, analyzing and managing data on compounds of interest to medications development.

Dorie Hightower, former NIDA Press Officer, accepted a position within the NIH Office of Research on Women's Health in May 2009.

Jessica Palmer, Ph.D., ended her 2 year rotation as a AAAS Science and Policy Fellow in OSPC in July 2009. Dr. Palmer's main focus while at NIDA was new media communications strategies and how we can use new technologies such as Twitter, Facebook, virtual games and other online platforms to reach broader audiences. Dr. Palmer's will begin Harvard Law School in the fall.

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R. Dale Walker, M.D., director of the One Sky Center and Center for American Indian Health Education Research at Oregon Health & Science University has been named the **2009 Indian Physician of the Year**. Dr. Walker was honored by the Association of American Indian Physicians for "distinguished service and commitment to improving the quality of health care for Native Americans and Alaska natives." He received the award at the organization's 38th annual meeting and conference in Alexandria, VA. Walker, who is Cherokee, also was honored as Indian Physician of the Year in 1989. He is one of two American Indian psychiatrists in the nation certified in addictions treatment. He is a professor of psychiatry and public health and preventive medicine in the OHSU School of Medicine. Throughout his career, he has served locally and nationally as an advocate for health care access and elimination of the stigma of mental illness and substance use disorders. His research is focused on addictions and mental health issues among American Indians. His current efforts address the low number of Indian students in the health care fields and draws attention to best practices for the prevention and treatment of addition and mental health disorders among American Indians.

Dr. Michael Hecht, Distinguished Professor, Department of Communication Arts and Sciences and the Department of Crime, Law and Justice at The Pennsylvania State University, has been selected as the recipient of the 2009 D.A.R.E. Champion award. His selection for the honor was based upon unique and notable work on behalf of substance use prevention for youth throughout the world.

Dr. David Olds, Professor of Pediatrics and Director of the Prevention Research Center for Family and Child Health at the University of Colorado, Denver, received the 2009 Presidential Award of the Society for Prevention Research annual meeting. The award was given for recognition of Dr. Olds' major, lifetime contribution to prevention; in particular, for his body of research on the Nurse Family Partnership, one of the most widely disseminated preventive interventions targeting high risk first-time mothers during pregnancy and through the child's second birthday.

Dr. John Lochman, Professor and Doddridge Saxon Chair in Clinical Psychology, and Director of the Center for the Prevention of Youth Problem Behavior, at the University of Alabama, received the International Collaborative Prevention Research Award at the 2009 Society for Prevention Research annual meeting. Dr. Lochman received this award due to his international collaborative prevention research; in particular, for his work on aggressive behav-iors and substance use disorders in collaboration with researchers in the Netherlands. He has also provided intervention training in Poland, Belgium, Great Britain, Italy, Ireland, Spain, and Puerto Rico.

NIDA researcher **Samuel Friedman, Ph.D.**, of the National Development and

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Research Institutes, New York City, N.Y., was honored with the prestigious International Rolleston Award of 2009 on April 22, 2009 in Bangkok, Thailand. The award was in recognition of Dr. Friedman's outstanding contributions to reducing the harms of psychoactive substances at an international level. This award is named after Sir Humphrey Rolleston, President of the Royal College of Physicians who chaired the UK Departmental Committee on Morphine and Heroin Addiction. It was first presented in Melbourne, Australia in 1992.

NIDA grantees **Dr. Bruce Hinds**, Associate Professor and William Bryan Professor of Chemical Engineering at the University of Kentucky, and **Dr. Gonzalo E. Torres**, Assistant Professor, Department of Neurobiology, University of Pittsburgh were honored by the White House for the 2008 Presidential Early Career Award for Scientists and Engineers Program.

CTN Delaware Valley Node

Dr. A. Thomas McLellan, Co-PI of the Delaware Valley Node, has been confirmed as the Deputy Director of the White House Office of National Drug Control Policy (ONDCP).

CTN Southern Consortium Node

Dr. Kathleen Brady, the PI of the CTN Southern Consortium Node, received a CTSA award. The National Institutes of Health's Clinical and Translational Science Award (CTSA) consortium is a unique network of medical research institutions across the nation. Launched in 2006, this network now includes awardees in 26 states, and is led by the National Center for Research Resources (NCRR). When the program is fully implemented, it will support approximately 60 CTSAs across the nation. Dr. Brady is the first psychiatrist PI in the CTSA consortium.

CTN Florida Node

Dr. Jose Szapocznik has been appointed Associate Dean for Translational Research and Community Development at the Miller School of Medicine of the University of Miami. Dr. Szapocznik is being recognized by his peers for substantial progress in the University of Miami application for a CTSA Award. Dr. Szapocznik will continue as Professor with Tenure and Chair of the Department of Epidemiology/Public Health at Miller.

The Florida Department of Children and Families and the Florida Alcohol and Drug Abuse Association announced that **The Village** and **Gateway Community Services** are two of the recipients of the 2009 Substance Abuse Services Best Practices Awards. The Village South, Inc., in Miami, received the EXEMPLARY PROGRAM award for its post CTN 0015 extension and sustaining of its Seeking Safety Program, and Gateway Community Services, Independence Village, in Jacksonville received third place for the Best Practice TREATMENT PROGRAM. The Best Practices Recognition Program provides recognition for programs that exemplify "best practice" methods in substance abuse prevention and treatment services. These programs' efforts are shown to measurably improve service outcomes and the quality of life for program participants. Award winners were highlighted during an award ceremony at the **FADAA Annual Conference** on August 13, 2009 in Orlando FL.

CTN Mid-Atlantic Node

Dr. Dace Svikis, Lead Investigator for CTN 0020 (Job Seekers Training in Drug Abuse Treatment) has been named recipient of the VCU College of Humanities and Sciences Distinguished Scholar Award for 2009. This is the

most prestigious award given by the College of Humanities at VCU, which encompasses a variety of academic departments. Dr. Svikis' selection is based on her leadership and scientific contributions to perinatal addiction research and effective addiction treatment for drug abusing mothers. Her multi-disciplinary research approach and her efforts toward translating research into practice were cited as contributing to the selection.

A luncheon appreciation celebration was held on May 12, 2009, in Richmond VA, to honor **Mr. Ned Snead** and the **Chesterfield Community Service Board Treatment Program**. Under Mr. Snead's leadership, the Chesterfield program has made substantive contributions to the CTN over the years, having participated effectively in several protocols dating back to the CTN 0004 Motivational Interviewing study and continuing unabated to the present CTN 0032 HIV Rapid Testing and Counseling study. The celebration marks a well deserved recognition.

CTN Texas Node

Dr. Robrina Walker, at the Texas Node RRTC, was selected to receive a NIDA Travel Award to present her poster "Outcomes and Lessons Learned: Disseminating Contingency Management and Motivational Interviewing in Substance Abuse Treatment Programs" at the 2009 American Psychological Association Convention's Early Career Poster Session co-sponsored by NIDA, NIAAA, and APA's Divisions 28 and 50. Homeward Bound, Inc., Mental Health and Mental Retardation of Tarrant County, Nexus Recovery Center, and Phoenix House were participating CTPs in the projects.

Ms. Becca Crowell, the Executive Director of Nexus Recovery Center in Dallas, was selected from more than 130 nominations to be one of the 18 Associates for the first SAMHSA CSAT Women's Addiction Services Leadership Institute. Associates were selected based on their individual accomplishments, future aspirations, attributes and contributions they are likely to bring to the first class of Associates.